

# Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions

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**Neural correlates of the often-powerful emotional responses to music are poorly understood. Here we used positron emission tomography to examine cerebral blood flow (CBF) changes related to affective responses to music. Ten volunteers were scanned while listening to six versions of a novel musical passage varying systematically in degree of dissonance. Reciprocal CBF covariations were observed in several distinct paralimbic and neocortical regions as a function of dissonance and of perceived pleasantness/unpleasantness. The findings suggest that music may recruit neural mechanisms similar to those previously associated with pleasant/unpleasant emotional states, but different from those underlying other components of music perception, and other emotions such as fear.**

Music has an extraordinary ability to evoke powerful emotions. This ability is particularly intriguing because, unlike most other stimuli that evoke emotion, such as smell, taste or facial expression, music has no obvious intrinsic biological or survival value. Although changes in certain physiological processes have been characterized in response to music<sup>1,2</sup>, neural correlates of emotional responses to music, their relation to music perception and their relation to other forms of emotion have not been well studied. Here we present a novel approach to the study of music and emotion, using positron emission tomography (PET) to measure cerebral correlates of affective and perceptual responses to musical dissonance. Although music may often evoke positive emotions, individual differences in musical preference may obscure any systematic neural correlates. Instead, we opted to study the negative affective reactions elicited by dissonance, which appear to be relatively consistent and stable. Listeners who have been exposed to the Western tonal idiom typically respond readily to dissonance, even in the absence of formal musical training. This phenomenon presumably indicates that listeners have internalized the tonal rules of music in their culture and react to violations of these rules<sup>3</sup>.

Many aspects of melodic processing depend on the integrity of superior temporal and frontal cortices. More specifically, both lesion and functional imaging studies indicate that regions of auditory cortex within the right superior temporal gyrus are specifically involved in analysis of pitch and timbre<sup>4–8</sup>, and that working memory for pitch entails interactions between temporal and frontal cortices<sup>6,9</sup>. Few data are available concerning the affective component of musical processing. A recent case study of a patient with amusia, however, has suggested that perceptual and emotional analysis of music may be dissociated<sup>10</sup>. In parallel with visual face processing, judgments of affective content of a melody (happy versus sad) can be made even in the complete absence of any ability to identify or recognize a melody. Here our purpose was to investigate whether such dissociations could be under-

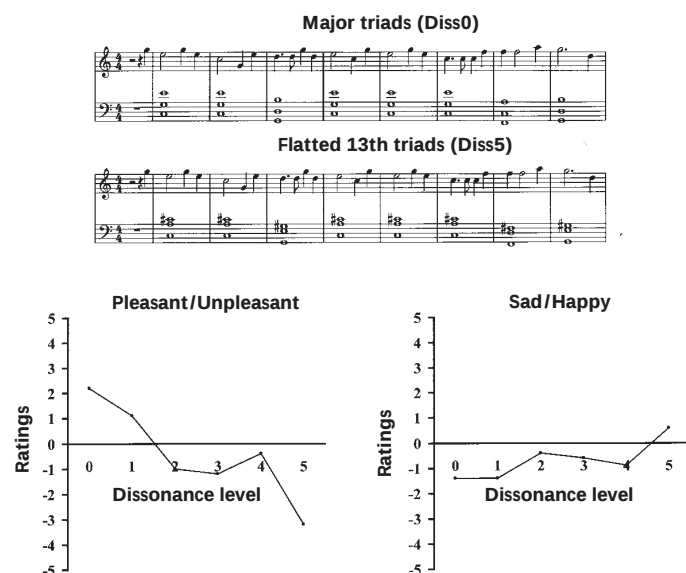
stood in terms of distinct neural mechanisms engaged by musically induced affect and to establish their functional anatomy.

Identifying neural correlates of affective responses to music may also prove advantageous in coming to a more general understanding of emotion. Unlike many other stimuli, music can often evoke emotion spontaneously, in the absence of external associations<sup>11–14</sup>. Our choice of the dissonance paradigm was predicated on this aspect, because dissonance directly elicits feelings of unpleasantness in novel passages without any prior associations.

In the present study, we used a novel melody, which was made to sound more or less consonant or dissonant by varying the harmonic structure of its accompanying chords (Fig. 1a). PET scans were obtained while subjects with no more than amateur musical training listened to six versions of this stimulus (termed Diss0 through Diss5), designed based on pilot studies to spontaneously elicit a continuum of pleasant to very unpleasant emotional responses. In addition, acoustically matched noise stimuli were presented as a sensory control condition, allowing us to examine the complete activation pattern related to processing of the stimuli<sup>9</sup>. Regression analysis was used to correlate rCBF with degree of dissonance; this analysis was complemented by conventional subtraction analysis. Regional covariation analyses were then used to identify possible functional interactions between specific cerebral structures. Subjects also rated the emotional quality of the music, using a rating scale with eight pairs of adjectives. We hypothesized that the variations in affective quality of the stimuli would correlate with rCBF changes in regions involved in emotional processes, and that these regions would differ from those involved in perceptual analysis of music.

## RESULTS

Regional CBF changes in paralimbic and neocortical areas were associated with both increasing dissonance and increasing consonance. However, distinct structures were activated by dissonance versus consonance. Activity in right parahippocampal



**Fig. 1.** Examples of music stimuli and average subject ratings of unpleasant versus pleasant and happy versus sad for each version. **(a)** Excerpts from the most consonant version (major triads, Diss0) and the most dissonant version (flatted 13th triads, Diss5) of music stimuli used in the PET study. **(b)** Line graphs demonstrating averaged subject ratings following scans for each of the six versions, Diss0 through Diss5. Ratings of very pleasant (+5) versus very unpleasant (−5) demonstrated significant interactions (ANOVA;  $p < 0.001$ ) and a high correlation coefficient ( $r = 0.57$ ) with dissonance level. Ratings of very sad (+5) versus very happy (−5) did not demonstrate significant interactions and had a lower correlation coefficient ( $r = 0.33$ ) with dissonance level.

gyrus and precuneus regions correlated with increasing dissonance, whereas activity in orbitofrontal, subcallosal cingulate and frontal polar cortex correlated with decreasing dissonance (equivalent to increasing consonance). Regional covariation analyses demonstrated inverse correlations between these two sets of regions. Right parahippocampal, right orbitofrontal and medial subcallosal cingulate activity was confirmed by subtraction analysis. The unpleasantness of increasing dissonance was confirmed by subjects' analog ratings; these ratings also covaried with rCBF changes in similar paralimbic regions.

An analysis examining rCBF changes as a function of increasing dissonance (see Methods) identified significant positive correlations in right parahippocampal gyrus and right precuneus regions (Table 1 and Fig. 2a). Significant negative correlations, corresponding to increasing consonance, were found in large areas of orbitofrontal cortex bilaterally, medial subcallosal cingulate region (3 mm to the right of the midline) and right frontal pole (Table 1 and Fig. 2b).

Subtraction of images obtained during the most consonant (Diss0) version from those obtained during the most dissonant (Diss5) version confirmed activity in right parahippocampal gyrus (Table 2). Decreases in activity (corresponding to increased consonance) were found in right orbitofrontal and medial subcallosal cingulate regions (Table 2), also confirming findings in the regression. No activity was observed in precuneus or frontal polar regions with subtraction analysis, nor were any additional regions identified.

To investigate the entire pattern of activity elicited by the stimuli (as opposed to that related specifically to the variation in dissonance), we compared rCBF in conditions Diss0 and Diss5 to the matched noise control condition. This subtraction revealed,

as expected, activity in superior temporal cortices bilaterally (Table 2). These regions were similar across both dissonance conditions and were found outside of primary auditory areas, consistent with the use of the noise stimulus as a baseline, which would be expected to control for nonspecific auditory stimulation. In addition, this comparison yielded patterns of activity very similar to those found in regression analyses, including reciprocal activation of the parahippocampal gyrus, also observed in the regional covariation analyses described below. Increased orbitofrontal cortex rCBF was observed in the Diss0 comparison, whereas decreased rCBF was found in medial subcallosal cingulate in the Diss5 condition.

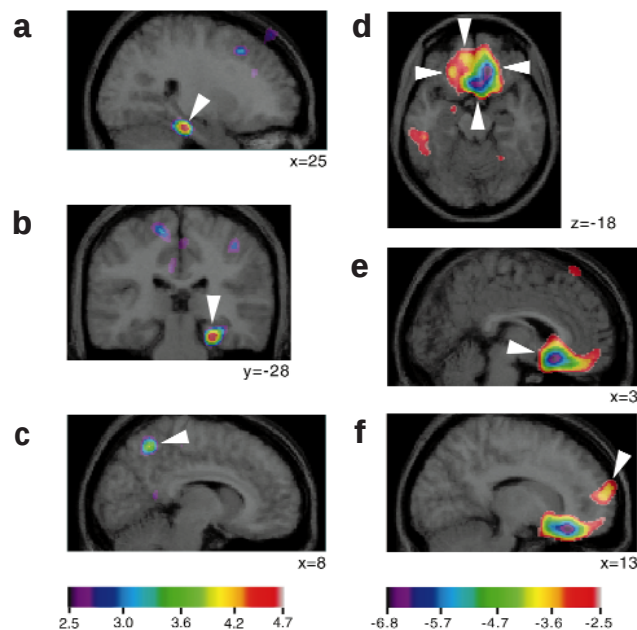
Regional covariation analyses (Table 3) were used to determine whether activity in any other brain regions correlated either positively or negatively with activity in right parahippocampal, right orbitofrontal and medial subcallosal cingulate regions identified in the original regression (Table 1). Bilateral orbitofrontal and frontal polar activity were found to covary negatively with activity in right parahippocampal gyrus, whereas right parahippocampal activity was found to covary negatively with activity in right orbitofrontal and medial subcallosal cingulate regions (Table 3). Activity in right and medial precuneus regions covaried positively with activity in right parahippocampal gyrus. Bilateral frontal polar activity covaried positively with activity in both right orbitofrontal and medial subcallosal regions.

Using a one-way ANOVA, behavioral ratings of unpleasant versus pleasant, tense versus relaxed, irritated versus uninterested, annoying versus uninteresting, dissonant versus consonant and angry versus calm were found to interact significantly ( $p < 0.05$ ) with dissonance level. These ratings also had positive correlation coefficients with dissonance level, ranging from 0.62 to 0.39 (Fig. 1b). Higher levels of dissonance were correlated with higher average ratings of adjectives associated with negative emotions (that is, unpleasant, tense, irritated, annoying, dissonant and angry), whereas higher levels of consonance were correlated with higher average ratings of adjectives associated with positive emotions (pleasant, relaxed, uninterested, uninteresting, consonant and calm). Ratings of bored versus interested and sad versus happy did not show significant interactions with amount of dissonance and had correlation coefficients of 0.18 and 0.33, respectively (Fig. 1b).

**Table 1. Regression of rCBF with dissonance level.**

| Region                   | Brodmann<br>Area | Coordinates |     |     | t Value |
|--------------------------|------------------|-------------|-----|-----|---------|
|                          |                  | x           | y   | z   |         |
| Positive Correlations    |                  |             |     |     |         |
| R. parahippocampal gyrus | 28/36            | 25          | −28 | −21 | 4.73    |
| R. precuneus             | 7                | 17          | −52 | 59  | 4.01    |
| R. precuneus             | 7                | 8           | −57 | 53  | 3.92    |
| Negative Correlations    |                  |             |     |     |         |
| R. orbitofrontal cortex  | 14*              | 13          | 30  | −18 | −6.84   |
| M. subcallosal cingulate | 25               | 3           | 18  | −15 | −6.81   |
| L. orbitofrontal cortex  | 13*              | −24         | 32  | −14 | −4.00   |
| L. orbitofrontal cortex  | 14*              | −5          | 41  | −21 | −3.75   |
| R. frontal pole          | 10               | 13          | 65  | 14  | −3.53   |

Positive correlations denote increasing dissonance; negative correlations denote increasing consonance. Coordinates refer to location in stereotaxic space<sup>15</sup>. \*Nomenclature following ref. 16.



**Fig. 2.** Cortical regions demonstrating significant rCBF correlations with dissonance level. Regression analyses were used to correlate rCBF from averaged PET data with dissonance level (Diss0 – Diss5). Correlations are shown as *t*-statistic images superimposed on corresponding averaged MRI scans (see **Table 1**). The *t*-statistic ranges for each set of images are coded by color scales below each column, corresponding to images (a–c) and (d–f). (a–c) Positive correlations with increasing dissonance demonstrated rCBF activity in right parahippocampal gyrus (a, sagittal section,  $x = 25$  mm; b, coronal section,  $y = -28$  mm) and right precuneus (c, sagittal section,  $x = 8$  mm). (d–f) Negative correlations with increasing dissonance (equivalent to positive correlations with increasing consonance) demonstrated rCBF activity in bilateral orbitofrontal cortex (d, horizontal section,  $z = -18$  mm; also shows medial subcallosal cingulate), medial subcallosal cingulate (e, sagittal section,  $x = 3$  mm) and right frontal polar regions (f, sagittal section,  $x = 13$  mm).

Individual subject ratings of unpleasantness versus pleasantness of the music were also regressed against rCBF changes (Table 4 and Fig. 3a and b). Ratings of increasing unpleasantness correlated, albeit weakly, with rCBF activity in right parahippocampal gyrus, but in the identical location to that found in the regression with dissonance level. Increasing unpleasantness also correlated with activity in posterior cingulate, whereas ratings of increasing pleasantness correlated with activity in right orbitofrontal and medial subcallosal cingulate cortex.

## DISCUSSION

The data presented here demonstrate that rCBF changes in specific paralimbic and neocortical areas known to be involved in affective processing correlate with increasing dissonance or consonance. These include right parahippocampal gyrus, right precuneus, bilateral orbitofrontal, medial subcallosal cingulate and right frontal polar regions. Different groups of structures correlated positively with dissonance as opposed to consonance. The presence of inverse regional covariations suggests that reciprocal functional interactions exist between parahippocampal and frontal regions. Furthermore, dissonance was associated with certain positive or negative emotional ratings, suggesting that the regions in question are involved specifically in response to these emotions, rather than other emotions that did not change as a function of dissonance. The paralimbic and neocortical regions identified are distinct from areas of secondary auditory cortex that emerged in control subtractions. Activity in these auditory cortical areas likely represents perceptual processes, including operations related to processing consonance and dissonance; however, activity in these regions was very similar for Diss0 and Diss5 conditions, suggesting that similar perceptual processes were elicited.

Right parahippocampal gyrus activity was found consistently throughout regression, subtraction and

covariation analyses. Although the parahippocampal gyrus has been traditionally associated with learning and memory processes<sup>17–19</sup>, it has strong reciprocal connections with the amygdala<sup>20</sup>, suggesting involvement of this region in emotional processes as well. Previous findings support this conjecture; for example, rCBF increases in parahippocampal gyrus are associated with unpleasant emotions evoked by pictures with negative emotional valence<sup>21</sup>. The precuneus region is active in response to a variety of stimuli, including memory-related and selective attention processes<sup>22,23</sup>,

**Table 2. Subtraction analyses.**

| Region                     | Brodman<br>Area | Coordinates |     |     | t Value |
|----------------------------|-----------------|-------------|-----|-----|---------|
|                            |                 | x           | y   | z   |         |
| Diss5 – Diss0              |                 |             |     |     |         |
| rCBF increases             |                 |             |     |     |         |
| R. parahippocampal gyrus   | 28/36           | 25          | -28 | -21 | 4.73    |
| rCBF decreases             |                 |             |     |     |         |
| R. orbitofrontal cortex    | 14*             | 12          | 32  | -18 | -5.82   |
| M. subcallosal cingulate   | 25              | 0           | 18  | -15 | -4.99   |
| Diss5 – noise              |                 |             |     |     |         |
| rCBF increases             |                 |             |     |     |         |
| R. superior temporal gyrus | 22              | 50          | 12  | −9  | 3.55    |
| L. superior temporal gyrus | 41/22           | −46         | −9  | 5   | 3.69    |
| R.parahippocampal gyrus    | 28/36           | 28          | −37 | −18 | 2.86    |
| rCBF decreases             |                 |             |     |     |         |
| M. subcallosal cingulate   | 25              | 4           | 18  | −21 | −4.06   |
| Diss0 – noise              |                 |             |     |     |         |
| rCBF increases             |                 |             |     |     |         |
| R. superior temporal gyrus | 22              | 50          | 10  | −3  | 3.70    |
| L. superior temporal gyrus | 41/22           | −47         | −13 | 5   | 3.42    |
| R. orbitofrontal cortex    | 14*             | 12          | 32  | −15 | 5.42    |
| rCBF decreases             |                 |             |     |     |         |
| R. parahippocampal gyrus   | 28/36           | 28          | −25 | −20 | −3.48   |

Coordinates refer to location in stereotaxic space<sup>15</sup>. \*Nomenclature following ref. 16

suggesting that this region may be related to processes not specific to emotion. The finding that emotional responses, particularly negative ones, activate regions related to both memory and attention may indicate that these processes are interrelated<sup>24</sup>. However, subject ratings of 'bored' versus 'interested' in the present study did not vary systematically with dissonance level, suggesting that any differences in arousal between conditions were minimal.

Orbitofrontal cortex, subcallosal cingulate and frontal polar regions have all been implicated in emotional processing<sup>21,25–35</sup>. For example, orbitofrontal cortex damage in monkeys disinhibits control of affective processing<sup>30</sup>. Identification of emotional expression is impaired in patients with lesions in subcallosal and other ventral medial prefrontal regions<sup>31</sup>; these impairments often occur independently of perceptual impairments in recognition of stimuli presented. The ventromedial portion of prefrontal cortices is proposed to be involved in making judgments about stimuli based on their emotional valence<sup>28,29</sup>. Finally, the subcallosal cingulate region exhibits decreased baseline rCBF in depressed patients compared to normals<sup>32</sup>; the present data agree with this finding, because activity in the subcallosal region decreased with unpleasantness, whereas it increased with pleasantness of the stimuli.

Regional covariations, both positive and negative, suggest there may be functional interactions between regions associated with negative versus positive emotions. Reciprocal regional activation was found between increasing versus decreasing dissonance conditions, as well as in control subtractions. Thus, increasing activity in certain regions during negative emotions seems to be associated with a corresponding decrease in activity in regions that are active during positive emotions. Positive correlations of orbitofrontal and subcallosal cingulate activity with activity in bilateral frontal polar cortex during more consonant conditions also suggest functional interactions between regions within a given type of affective response.

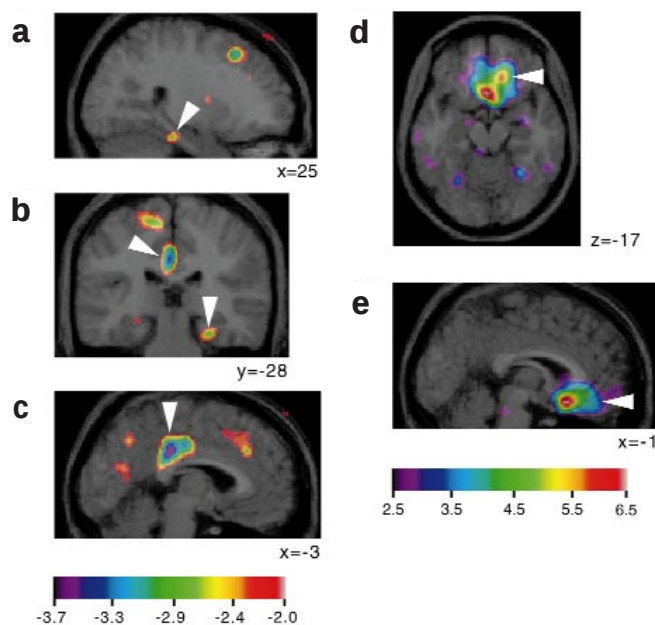
**Fig. 3.** Cortical regions demonstrating significant rCBF correlations with ratings of increasing unpleasantness and increasing pleasantness. Regression analyses were used to correlate rCBF from averaged PET data with individual subject ratings of unpleasantness versus pleasantness. Correlations are shown as *t*-statistic images superimposed on corresponding averaged MRI scans (see **Table 2**). The *t*-statistic ranges are coded by color scales below each column, corresponding to images (a–c) and (d, e). (a–c) Positive correlations with increasing unpleasantness (equivalent to negative correlations with increasing pleasantness) demonstrated rCBF activity in right parahippocampal gyrus (a, sagittal section, *x* = 25 mm; b, coronal section, *y* = –28 mm; also shows left posterior cingulate) and left posterior cingulate (c, sagittal section, *x* = –3 mm). (d, e) Positive correlations with increasing pleasantness demonstrated rCBF activity in right orbitofrontal cortex (d, horizontal section, *z* = –17 mm) and medial subcallosal cingulate (e, sagittal section, *x* = –1 mm).

**Table 3.** Inter-regional covariation of rCBF with regions of interest from **Table 1**.

| Region of Interest                                                                                 | Regions of Covariation | Brodmann Area | Coordinates |     |     | t Value |
|----------------------------------------------------------------------------------------------------|------------------------|---------------|-------------|-----|-----|---------|
|                                                                                                    |                        |               | x           | y   | z   |         |
| R. Parahippocampal Gyrus                                                                           |                        |               |             |     |     |         |
|                                                                                                    | Positive correlations  |               |             |     |     |         |
|                                                                                                    | R. precuneus           | 7             | 7           | −54 | 53  | 5.18    |
|                                                                                                    | M. precuneus           | 7             | 0           | −49 | 36  | 4.85    |
|                                                                                                    | Negative correlations  |               |             |     |     |         |
|                                                                                                    | R. orbitofrontal       | 14*           | 8           | 20  | −17 | −12.83  |
|                                                                                                    | L. orbitofrontal       | 14*           | −7          | 20  | −17 | −10.64  |
|                                                                                                    | R. frontal pole        | 10            | 23          | 61  | −3  | −7.31   |
|                                                                                                    | L. frontal pole        | 10            | −28         | 56  | −5  | −5.70   |
| R. Orbitofrontal Cortex                                                                            |                        |               |             |     |     |         |
|                                                                                                    | Positive correlations  |               |             |     |     |         |
|                                                                                                    | R. frontal pole        | 10            | 17          | 67  | 5   | 6.73    |
|                                                                                                    | L. frontal pole        | 10            | −4          | 68  | 5   | 5.20    |
|                                                                                                    | Negative correlations  |               |             |     |     |         |
|                                                                                                    | R.parahippocampal g    | 28/36         | 32          | −28 | −20 | −6.89   |
|                                                                                                    | M. precuneus           | 7             | 0           | −45 | 39  | −6.79   |
| M. Subcallosal Cingulate                                                                           |                        |               |             |     |     |         |
|                                                                                                    | Positive correlations  |               |             |     |     |         |
|                                                                                                    | R. frontal pole        | 10            | 11          | 67  | 11  | 7.93    |
|                                                                                                    | L. frontal pole        | 10            | −4          | 68  | 5   | 6.19    |
|                                                                                                    | Negative correlations  |               |             |     |     |         |
|                                                                                                    | M. precuneus           | 7             | 1           | −42 | 39  | −6.69   |
|                                                                                                    | R.parahippocampal g    | 28/36         | 31          | −28 | −20 | −6.29   |
| Coordinates refer to location in stereotaxic space <sup>15</sup> . *Nomenclature following ref. 16 |                        |               |             |     |     |         |

Coordinates refer to location in stereotaxic space<sup>15</sup>. \*Nomenclature following ref. 16

The regions activated in this study differ from those activated during perceptual analysis of music<sup>4–8</sup>, supporting the hypothesis that there may be a dissociation between perceptual and emotional responses to music. This hypothesis is supported by the lack of significant activity in these regions in regression analyses, as well as by the anatomical similarity of auditory cortical regions



**Table 4. Covariation of rCBF with ratings of stimulus pleasantness.**

| Region                   | Brodmann Area | Coordinates |     |     | t Value |
|--------------------------|---------------|-------------|-----|-----|---------|
|                          |               | x           | y   | z   |         |
| Positive Correlations    |               |             |     |     |         |
| M. subcallosal cingulate | 25            | −1          | 17  | −15 | 6.53    |
| R orbitofrontal cortex   | 14*           | 12          | 32  | −17 | 5.76    |
| Negative Correlations    |               |             |     |     |         |
| L posterior cingulate    | 23/31         | −3          | −33 | 32  | −3.69   |
| R. parahippocampal gyrus | 28/36         | 25          | −28 | −21 | −2.68   |

Positive correlations denote increasing pleasantness; negative correlations denote increasing unpleasantness. Coordinates refer to location in stereotaxic space<sup>45</sup>. \*Nomenclature following ref. 16.

activated in the control stimulus (noise) subtraction for Diss0 and Diss5 (Table 2). Although the specific structures involved differ between perceptual and emotional responses to music, both the present study and some previous studies of music perception<sup>5-7</sup> have suggested a relative hemispheric specialization favoring right temporal and frontal structures. This suggests that circuitry related to the emotional components of music may be anatomically proximal to that used during more perceptual processes. It is also possible that right hemisphere dominance of responses in this study is due to a general dominance of right hemisphere activity underlying emotional processes<sup>36,37</sup>.

The present study also suggests dissociations between neural correlates of different emotions. Many studies of emotion have examined fear perception and conditioning. The amygdala, particularly in the left hemisphere, has been clearly implicated as a key structure in fear processing<sup>38-41</sup>. In the present study, amygdala activation was not detected, and activated structures were found primarily in the right hemisphere. In addition, sites of rCBF change in the present study differed between negative versus positive emotions. These findings suggest that the processing or experience of different emotions is associated with distributed activity in different cerebral structures. Because dissonance is only one way of eliciting emotional responses to music, it is possible that music that induces different types of emotions would recruit different neural substrates. This may be especially likely if emotion is elicited through memory or association, rather than spontaneously.

In summary, the findings in this study identify activity in paralimbic and neocortical regions correlated with degree of musical dissonance, and thus begin to characterize the neural basis for emotional responses to music. These regions have been previously shown to be associated with certain emotional processes. However, these regions differ from those that are active during perceptual aspects of music processing, as well as from those attributed to processing different emotions. The findings of this study not only begin to define a neural network associated specifically with emotional responses to music, but also demonstrate dissociations from other important cognitive processes.

## METHODS

**Subjects.** Ten normal, right-handed volunteers, five male and five female, participated in this study. Subjects were screened to verify that they had no more than amateur musical training. Before the PET studies, 11 additional subjects (not used in the PET study) were used in pilot studies to verify that the stimuli produced the desired emotional responses.

**Stimuli.** A novel melody was made to sound more or less consonant or dissonant by varying the harmonic structure of its accompanying chords, pro-

ducing six otherwise-identical versions of a music passage. Each version consisted of a melody, which remained constant between versions, and a three-note chord accompaniment (major triads, dominant 7ths, 9ths, 11ths, 13ths or flatted 13ths, corresponding to dissonance levels 0 through 5, denoted as Diss0 through Diss5), used to produce the varying amounts of dissonance (Fig. 1a). Dissonance level increased incrementally between versions, and was uniform throughout a given version, such that there was no resolution of dissonance in any music passage. The pieces were composed specifically for this experiment so that they were unfamiliar to all subjects, thus eliminating the possibility of personal associations contributing to the emotional value of the music. Acoustically matched noise bursts<sup>9</sup> were played as a baseline control stimulus; to be comparable to the music stimuli, they were constructed to approximate the duration, intensity and onset-offset shape of the melody.

Musical stimuli were created as General MIDI files on a PC platform with Cubase VST 3.5 by Steinberg Software and were presented via a Kurzweil<sup>®</sup> MASS[ies]<sup>®</sup> synth engine using the default patch set. At a tempo of 160 beats per minute, the complete melody lasted approximately one minute, 13 seconds. The acoustically matched noise burst stimulus was created with Cool Edit Pro 1.1 by Syntrillium Software and Mitsyn by W.L.H. Music stimuli were played for pilot subjects in both a piano and an organ version to determine which timbre produced the strongest correlation between dissonance level and ratings of unpleasantness.

**Pilot studies.** Eleven pilot subjects listened to each of the six tunes and rated their responses to each tune on an 11-point scale for 12 pairs of contrasting adjectives (see below). Ratings were evaluated using ANOVA and linear regression analysis to identify significant effects of the six different versions on response valence/strength and their correlation coefficients, respectively. These preliminary studies determined that dissonance stimuli produced the desired emotional responses and were thus suitable for use in the PET study. The piano version elicited more incremental unpleasant/pleasant ratings than the organ version (that is, higher correlation coefficient) and was thus chosen as the timbre to be used in the PET study. The six pairs of adjectives that demonstrated significant interactions with dissonance level in the piano version were used in the PET study to similarly identify subjects' emotional responses to the music (see below). Two pairs of non-significant adjectives also were used in the PET study to demonstrate that certain emotions were not elicited by the stimuli.

**PET study.** PET scans were done on a Siemens HR+ scanner, using the [<sup>15</sup>O] bolus water technique to measure regional cerebral blood flow (rCBF)<sup>42</sup> without arterial blood sampling<sup>43</sup>. Each subject also received an MRI scan for anatomical registration of PET data<sup>44</sup> and resampling into a standardized stereotaxic coordinate system<sup>45</sup>.

The music and matched noise stimuli described above were used in the PET study. Stimuli were calibrated at 75 dB SPL, and were presented binaurally. The melody alone was played twice for each PET subject before entering the scanner to familiarize the subject and thereby avoid responses specific to hearing novel stimuli. To avoid repetition effects, however, subjects did not hear the six different versions of the music passage until PET scans were performed. Before scanning, subjects were also familiarized with analog rating scales and instructed that we were interested in examining their emotional responses to the music.

Ten subjects were scanned during each of the six versions of the music passage, plus the noise control stimulus, for a total of seven scans per subject. Each scan lasted one minute. Stimulus onset occurred approximately 10 seconds before scan onset to establish and stabilize subjects' responses to stimuli before each scan began. Thus, each stimulus was played only once through the duration of a scan. Scan order was pseudo-randomized between subjects to minimize ordering effects. Subjects were instructed to listen carefully to each piece of music as it was played. Subjects used a bipolar analog scale of -5 to +5 immediately following each scan to rate emotional valence and intensity of stimuli. Adjectives selected for ratings in the PET study were unpleasant versus pleasant, tense versus relaxed, irritated versus un irritated, annoying versus un annoying, dissonant versus consonant, and angry versus calm, all of which varied significantly with dissonance

level in pilot testing, and bored versus interested and happy versus sad, which did not vary significantly in pilot testing.

**Data analysis.** Regression maps<sup>45</sup> were calculated to assess the significance of the relationship between dissonance level and rCBF, to detect co-variance of regional brain activity, and to assess the significance of the relationship between individual subject ratings and rCBF. Regression analysis involves correlation of incremental changes in a specific experimental variable, such as stimulus rate, with rCBF. This analysis can also be used to make inferences of functional connectivity, by identifying correlations between activity in a given volume of interest and activity in the rest of the brain, and is complementary to conventional subtraction analysis. Regressions used an analysis of co-variance (ANCOVA)<sup>46</sup>. Values equal to or exceeding a criterion of  $t = 3.53$  were considered significant ( $p < 0.01$ , two-tailed), yielding a false-positive rate of 0.58 in 182 resolution elements (each of which has dimensions  $14 \times 14 \times 14$  mm), if the volume of brain gray matter is  $500 \text{ cm}^3$ .

As a complementary method of analysis, we also used subtractions<sup>47</sup> to identify regions that may have responded nonlinearly to dissonance. Images obtained during Diss0 were subtracted from images obtained during Diss5 to isolate rCBF changes due solely to the change in dissonance. Subtraction of the noise control condition from the most dissonant (Diss5) and most consonant (Diss0) versions was used to identify rCBF responses due to generalized music perception.

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