A Functional MRI Study of Happy and Sad Affective States Induced by Classical Music

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Abstract: The present study investigated the functional neuroanatomy of transient mood changes in response to Western classical music. In a pilot experiment, 53 healthy volunteers (mean age: 32.0; SD = 9.6) evaluated their emotional responses to 60 classical musical pieces using a visual analogue scale (VAS) ranging from 0 (sad) through 50 (neutral) to 100 (happy). Twenty pieces were found to accurately induce the intended emotional states with good reliability, consisting of 5 happy, 5 sad, and 10 emotionally unevocative, neutral musical pieces. In a subsequent functional magnetic resonance imaging (fMRI) study, the blood oxygenation level dependent (BOLD) signal contrast was measured in response to the mood state induced by each musical stimulus in a separate group of 16 healthy participants (mean age: 29.5; SD = 5.5). Mood state ratings during scanning were made by a VAS, which confirmed the emotional valence of the selected stimuli. Increased BOLD signal contrast during presentation of happy music was found in the ventral and dorsal striatum, anterior cingulate, parahippocampal gyrus, and auditory association areas. With sad music, increased BOLD signal responses were noted in the hippocampus/amygdala and auditory association areas. Presentation of neutral music was associated with increased BOLD signal responses in the insula and auditory association areas. Our findings suggest that an emotion processing network in response to music integrates the ventral and dorsal striatum, areas involved in reward experience and movement; the anterior cingulate, which is important for targeting attention; and medial temporal areas, traditionally found in the appraisal and processing of emotions. *Hum Brain Mapp 28:1150–1162, 2007.* © 2007 Wiley-Liss, Inc.

Key words: ventral striatum; dorsal striatum; amygdala; hippocampus; music; emotions; mood

INTRODUCTION

Previous research has shown that music evokes comparable emotional responses across different musical categories and cultures [Peretz and Hebert, 2000; Trehub, 2003]. It has also been argued that affective states induced by music are stronger, longer lasting, and more pervasive than affective states induced through other modalities [Krumhansl, 1997].

However, only a small number of studies have focused on the neural correlates of emotions elicited by music in

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healthy individuals [Blood and Zatorre, 2001; Blood et al., 1999; Brown et al., 2004; Koelsch et al., 2006; Menon and Levitin, 2005; Peretz et al., 1998]. A prominent finding of these studies has been an increased engagement of the ventral striatum in response to pleasant emotional music [Blood and Zatorre, 2001; Brown et al., 2004; Koelsch et al., 2006; Menon and Levitin, 2005].

The ventral striatum is involved in reward generation, attention, and motivation, whereas the dorsal striatum is thought to be involved in the initiation of movement towards potentially rewarding stimuli in humans and animals [Elliott et al., 2004; Roitman et al., 2005; Schultz, 2000; Tobler et al., 2003]. Dorsal striatal activation has also been found during suppression of motor reactions [Raemaekers et al., 2002]. The mesolimbic dopaminergic system plays an important role in mediating the activation of neurons in this region through nucleus accumbens afferents [Carelli and Wightman, 2004], thus regulating the reinforcing effect of reward stimuli. In primates, neural firing in the ventral and dorsal striatum occurs immediately prior to approach behavior and continues until the reward has been obtained [Berns et al., 2001; Schultz and Romo, 1990]. Activation in these structures has also been observed during mating/copulation in rodents [Pfaus et al., 1995], in humans in association with stimulants such as food [Small et al., 2001], recreational drugs [Breiter et al., 1997] and while viewing pleasant pictures or facial images [Aharon et al., 2001; Lane et al., 1999; Morris et al., 1996, 1998; Phillips et al., 1998].

Another structure of interest in the context of emotion research is the anterior cingulate cortex (ACC) with its afferents from the midline thalamus and brainstem nuclei [Paus, 2001]. Cytoarchitecture and function suggest a division into a dorsal cognitive area and a rostral–ventral affective area [Bush et al., 2000]. Neuroimaging research has reported ACC activation during positive emotions [Morris et al., 1996; Phillips et al., 1998], sad affect [George et al., 1995; Levesque et al., 2003], as well as across both happy and sad affects [Killgore and Yurgelun-Todd, 2004]. Using musical pieces, Blood and Zatorre [2001] found a positive correlation with ACC activation and the intensity of the physiological experience of a highly rewarding sensation with a selection of music. Moreover, Blood et al. [1999] found that activity in the ventral portion of the ACC showed an association with decreases in levels of tonal dissonance.

A further region that is frequently reported with positive and negative emotional processing is the amygdala [Phan et al., 2002; Zald, 2003]. Amygdala engagement has been reported in response to fearful [Breiter et al., 1996; Morris et al., 1996; Whalen et al., 1998] and sad [Blair et al., 1999; Goldin et al., 2005; Killgore and Yurgelun-Todd, 2004; Posse et al., 2003] emotional stimuli. Interestingly, Blood et al. [2001] observed decreased cerebral blood flow in the amygdala in relation to increased “chills” induced by highly pleasurable classical music, while Koelsch et al. [2006] found greater amygdala activation with unpleasant musical excerpts. Additional structures recruited during processing of emotional music include the hippocampus [Koelsch et al., 2006], parahippocampal gyrus [Blood et al., 1999] and orbitofrontal cortex [Blood and Zatorre, 2001; Blood et al., 1999; Menon and Levitin, 2005].

This body of evidence thus suggests an important role of musical stimuli in studying human emotion processing [Blood and Zatorre, 2001; Blood et al., 1999; Brown et al., 2004; Koelsch et al., 2006; Menon and Levitin, 2005; Peretz et al., 1998]. The present study sought to investigate the neural correlates of happy and sad affective states induced by music using fMRI. Baseline neural activity was measured during presentation of musical pieces of emotionally unevocative, neutral valence. An important methodological consideration of the present study concerns the choice of musical stimuli. As humans actively choose to listen to certain types of music in different settings, we believed that utilizing existing musical pieces may be advantageous in provoking emotional reactions similar to those encountered in natural environments. The present research aimed to first establish a set of musical pieces that can reliably induce affective states in healthy individuals. In a pilot behavioral validation study, musical pieces reliably inducing happy, sad, and neutral affective states were determined. These musical stimuli of happy, sad, and neutral valences were then presented to a separate group of healthy volunteers to investigate the neural correlates of music of an emotive nature, using fMRI.

We hypothesized that music from these emotional categories would evoke neural activation in cortical and subcortical regions associated with processing of relevant emotional stimuli. We expected that the happy musical pieces would be associated with greater activation in the ventral striatum [Blood and Zatorre, 2001; Elliott et al., 2004; Koelsch et al., 2006; Menon and Levitin, 2005; Roitman et al., 2005; Schultz, 2000; Tobler et al., 2003] and anterior cingulate [Blood et al., 1999; Morris et al., 1996; Phillips et al., 1998] and the sad stimuli would elicit greater activity in the amygdala [Blair et al., 1999; Killgore and Yurgelun-Todd, 2004; Koelsch et al., 2006; Posse et al., 2003], compared to emotionally neutral musical excerpts.

METHODS

Participants

Sixteen right-handed healthy participants (eight males: mean age = 30.86, SD = 6.01; eight females: mean age = 28.13, SD = 5.03; group: mean age = 29.5, SD = 5.5) were recruited through local newspaper advertisement. All participants signed written informed consent and were screened for neurological disorder, head injuries, and current or past psychiatric disorders by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, nonpatient version) [First et al., 1997]. The study was approved by the Institute of Psychiatry and South London and Maudsley NHS Trust Research Ethics committee.

Immediately before scanning, participants completed the BDI [Beck et al., 1961], Fawcett-Clark Pleasure Scale (FCPS) [Fawcett et al., 1983], and Eysenck Personality Questionnaire – Revised (EPQ-R) [Eysenck and Eysenck, 1991]. The BDI [Beck et al., 1961] is a self-evaluation measure of depressed state where higher scores reflect a greater presence of depressive symptoms. The trait systems of the FCPS [Fawcett et al., 1983] and EPQ-R [Eysenck and Eysenck, 1991] are based on psychobiological models of personality, which postulate that personality traits predict mood states [Cuijpers et al., 2005].

Stimulus Selection

Fifty-three healthy volunteers (22 males: mean age 30.86, SD = 8.16; 31 females: mean age 32.23, SD = 11.40; group: mean age = mean age: 32.0; SD = 9.6; mean years of education: 16.86 (SD = 2.95) for males and 16.56 (SD = 4.59) for women) participated in this pilot study rating mood changes in relation to 60 musical pieces on a unidimensional VAS. None of these volunteers participated in the subsequent fMRI study. One minute sections of 60 classical musical pieces from 18th, 19th, and 20th century Western composers were selected for their perceived emotional content. Twenty pieces were considered happy, 20 sad, and 20 neutral, respectively. The selection was based on findings from previous music research [Levitin et al., 2003; Peretz et al., 1998;] and individual judgement.

Participants were instructed to judge whether a particular piece of music would have an impact on their emotional state. If they felt a piece would change the way they felt, they should express this by placing the cursor on the rating scale at the appropriate position. They were also made aware of the fact that some of the pieces were composed to express happy or sad emotions, but they should only judge their individual emotional experience in response to the music.

While listening to each piece, volunteers rated their mood state by moving a cursor along a computerized VAS, ranging from 0 (sad) through 50 (neutral) to 100 (happy). Each piece was rated by every participant. Data were continuously sampled with one data point for every 1 s. Musical pieces were presented in a different random order for every participant, with rest intervals of 7 s between pieces. After each piece the cursor on the rating scale was automatically reset to the "neutral" position.

Mean ratings and SD were calculated from the ratings of the first 30 s of each musical piece for each participant in order to match the stimulus display requirements of the subsequent fMRI experiment.

To investigate whether musical stimuli selected on the basis of these data represented the hypothesized emotional dimensions of happy, sad, and neutral valence, a principal component analysis (PCA) [Cattel, 1996] was carried out on the Pearson correlation matrix of participants' mean ratings for all stimuli. Three factors were requested in accordance with the hypothesis. Factors with an Eigenvalue of larger than one were accepted, following standard procedures [Coolican, 1994]. An orthogonal rotation was used (Varimax), resulting in uncorrelated factor scores, in order to maximize the statistical independence and interpretation of the expected emotional dimensions [Kaiser, 1958]. The PCA yielded three factors that could clearly be identified from the rotated component matrix and the scree plot. These factors were labeled as "Happy" (Factor 1: Eigenvalue 13.17), "Neutral" (Factor 2: Eigenvalue 9.21), and "Sad" (Factor 3: Eigenvalue 4.47) musical stimuli. The factor structure accounted for 45% of the variance. Items that did not load onto its expected factor and had low communality (<0.3) were excluded from the stimulus selection.

To examine the robustness of the induced mood states to repeated exposure, 20 of the volunteers rated the musical pieces on a second occasion after a period of at least 4 weeks. Intraclass correlations (ICC) [Bartko, 1991] were used to assess reliability of ratings of both time points by comparing the variability of different ratings of the same subject to the total variation across all ratings and all subjects. ICCs (Table I) for selected items were higher than 0.43, suggesting substantial temporal stability.

Based on results of the PCA, the ICCs, and mean ratings, 20 musical pieces (5 happy, 5 sad, 10 neutral) were selected that best represented the proposed emotional categories (Table I). Happy stimuli were a priori required to have a group mean rating of ≥ 60, sad stimuli were required to have a mean rating of <40, and neutral stimuli ranging from 40 to 59.

fMRI Experiment

The selected 20 musical pieces were presented in a blocked design alternating between 30 s epochs of emotional and 30 s epochs of emotionally unevocative, neutral stimuli. To avoid interference effects of one affective state on another and to establish whether order of presentation had an effect on the emotional response, two orders of stimulus presentation were used. In the first-order, participants listened to five happy musical pieces alternated with five neutral pieces and then listened to five sad pieces alternated with five neutral pieces. In the second-order, participants listened to five sad pieces alternated with five neutral pieces first and then listened to five happy musical pieces alternated with five neutral pieces. Participants were randomly assigned to one of these two orders ($N = 8$ each).

Each piece of music was followed by a 16 s quiet evaluation period during which participants were required to rate affective changes related to the most recently presented musical piece on a VAS ranging from sad (0) through neutral (50) to happy (100). The initial position of the cursor was randomized for each musical piece. Participants were instructed to concentrate on the music and to rate any changes in their emotional state related to the most recently presented piece. Similar to the procedure in

TABLE I. Musical pieces selected for the fMRI paradigm

Musical pieces	Composer		Mean ratings
Happy pieces			
Carmen: Chanson du toreador	Bizet	0.87 (0.001)	79.66 (13.45)
Allegro—A little night music	Mozart	0.90 (0.001)	82.22 (13.19)
Rondo allegro—A little night music	Mozart	0.65 (0.021)	80.70 (12.10)
Blue Danube	Strauß	0.84 (0.001)	76.82 (15.12)
Radetzky march	Strauß	0.77 (0.003)	79.66 (13.68)
Sad pieces			
Adagio in sol minor	Albinoni	0.80 (0.001)	36.24 (19.15)
Kol Nidrei	Bruch	0.60 (0.04)	33.61 (14.42)
Solveig's song—Peer Gynt	Grieg	0.79 (0.001)	36.81 (17.59)
Concerto de Aranjuez	Rodrigo	0.62 (0.03)	36.55 (18.44)
Suite for violin & orchestra A minor	Sinding	0.80 (0.001)	29.52 (16.55)
Neutral pieces			
L'oiseau prophete	Schumann	0.56 (0.02)	52.90 (12.32)
Claire de lune	Beethoven	0.57 (0.05)	50.53 (15.73)
Claire de lune	Debussy	0.79 (0.001)	44.42 (20.22)
Symphony no. 2 C minor	Mahler	0.60 (0.002)	44.55 (16.21)
La traviata—Prelude to the 1st scene	Verdi	0.56 (0.30)	53.90 (18.07)
Pictures at an exhibition	Mussorgsky	0.63 (0.01)	41.86 (12.10)
Water music—passepied	Händel	0.57 (0.02)	55.92 (13.43)
Violin romance no. 2 F major	Beethoven	0.54 (0.02)	45.12 (20.07)
Water music—minuet	Händel	0.57 (0.02)	55.30 (12.10)
The planets—Venus	Holst	0.74 (0.001)	42.13 (16.11)

the stimulus selection study, participants were asked to rate subjective changes in their affective states rather than judging the emotion a piece of music would try to convey. In order to avoid novelty effects, participants were familiarized with the musical stimuli 1 week prior to the fMRI scan. Musical stimuli were presented binaurally at ~75 dB SPL using a special MRI compatible audio system (MR Confon, Magdeburg, Germany).

fMRI Acquisition

A 1.5 Tesla General Electric Signa MR Imaging system (General Electric Medical Systems, Milwaukee, WI) was used to acquire 468 T2* weighted echoplanar images (EPI) depicting BOLD contrast. Head movement of participants was restricted by using foam padding and a Velcro strap across the forehead. For each acquired volume, 16 near-axial slices parallel to the intercomissural plane were collected allowing coverage of the entire brain (repetition time: 2,000 ms, echo time: 40 ms, flip angle 90°, slice thickness 7 mm, interslice gap 0.7 mm, matrix size 64×64, in plane resolution 3 mm $\times$ 3 mm).

Statistical Analysis

Affect ratings and psychometric measures

Multivariate analysis of variance (MANOVA) was carried out in SPSS 12 using gender (male, female) as independent variable to investigate gender differences in affect ratings and psychometric measures (dependent variables: happy, sad, and neutral ratings, BDI, EPQ-R, FCPS). Individual affect ratings during music presentation in the fMRI scanner were analyzed by extracting the mean value of happy, sad, and neutral stimuli.

A 2×3 repeated measures analysis of variance (ANOVA) was carried out using Order (happy first, sad first) as between-groups variable, Valence (happy, sad, neutral) as within-group variable and affect ratings as dependent variable.

fMRI data

Functional image preprocessing and subsequent analyses were carried out using the Statistical Parametric Mapping software package (SPM2, Wellcome Department of Cognitive Neurology, London) on a Matlab (The MathWorks, Natick, MA) platform. The functional time series was realigned, normalized into a standard stereotaxic space using a Montreal Neurological Institute EPI template and the coordinate system of Talairach and Tournoux [Talairach and Tournoux, 1988] and smoothed using an 8-mm Gaussian kernel filter FWHM to permit application of Gaussian random field theory and to facilitate intersubject averaging.

Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. The first-level analysis allowed computation of individual mean images that corresponded to the main contrasts of interest: happy > neutral, sad > neutral, neutral > sad and happy; their interaction happy > sad and sad > happy. These mean images were combined in a second level analysis. A general linear model was used to deter-

TABLE II. Summary of mean affect ratings

Group [N]	Happy	Sad	Neutral
Stimuli selection [53]	79.81 (13.51)	34.55 (17.23)	48.93 (16.04)
fMRI study total: [16]	83.88 (8.72)	26.02 (14.07)	50.30 (5.77)
fMRI study			
Happy first [8]	88.06 (7.53)	18.98 (10.16)	46.11 (4.49)
Sad first [8]	79.70 (8.14)	33.06 (14.41)	54.49 (3.36)

All values inside parentheses are SD values.

mine voxel-wise t statistics for both orders (happy first, sad first). 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 [Eugene et al., 2003]. The t statistics were normalized to Z scores and significant clusters of activation were determined. Effects of music on affect were considered significant at $P \leq 0.05$, family wise error (FWE).

Furthermore, an independent samples t-test was carried out to determine whether there were significant effects of order of stimulus presentation (happy first, sad first) by utilizing the contrasts computed with the random effects model.

A conjunction analysis (conjunction null, $P \leq 0.05$, FWE), was performed with SPM2 using statistical parametric maps of the minimum t statistics over orthogonal contrasts (main effect of happy: happy > neutral, main effect of sad: sad > neutral, main effect of neutral: neutral > happy and sad, interaction effects: happy > sad, sad > happy across both orders). Inference was based on P-values adjusted for the search volume using random field theory [Friston et al., 2005].

In order to confirm activation found in the ventral striatum and right hippocampus/amygdala volume-of-interest (VOI) analyses were performed using the VOI toolkit implemented in SPM2. A functional region of interest was drawn based on the coordinates of the ventral striatum and hippocampus/amygdala derived from the conjunction analysis results of the contrasts happy > neutral and sad > neutral. For each individual subject an 8-mm sphere was drawn around the original coordinates. BOLD was extracted for each subject and the average percent signal change between experimental and neutral conditions was calculated. This provided a representative response for changes in activation in specific brain regions over time, which was then averaged for each stimulus type. A paired-sample t-test was conducted to calculate differences between conditions.

RESULTS

Affect Ratings and Psychometric Measures

MANOVA revealed no statistically significant differences between males and females on affect ratings of musical stimuli (all $P > 0.63$) or psychometric measures (all $P > 0.35$). Hence, males and females were combined in the following analyses.

In the ANOVA for affect ratings, Mauchly's test of sphericity was significant ($P < 0.001$). Therefore, the Greenhouse-Geisser correction of degrees of freedom was used [Jennings, 1987]. There was a main effect of Stimulus ($F[1.10, 15.45] = 144.59$, $P < 0.001$), indicating highest ratings for happy stimuli, lowest ratings for sad stimuli, and neutral stimuli falling in between. There was also a main effect of Order ($F[1, 14] = 5.78$, $P = 0.03$), indicating that volunteers who started with happy music first provided lower overall ratings (153.15), compared to volunteers who started with sad music first (167.25). Finally, there was a stimulus-by-order interaction ($F[1.10, 15.45] = 5.83$, $P = 0.03$). This interaction reflects that participants who listened to happy music first had higher affect ratings for happy pieces and lower affect ratings for sad pieces (i.e. were sadder) compared to those listening to sad music first. Participants who listened to sad pieces first had higher affect ratings during sad musical pieces (i.e. were less sad), but lower affect ratings for happy pieces (i.e. were less happy). Neutral pieces received similar emotional ratings in both conditions (Table II).

fMRI Data

An independent samples t-test comparing both orders (happy first, sad first) on all relevant contrasts revealed no significant differences ($P \leq 0.05$, FWE) between different orders. The conjunction analysis revealed significant BOLD responses in subcortical and cortical brain regions (Table III–V) in the three experimental conditions (happy, sad, neutral; $P \leq 0.05$, FWE).

Main Effects of Happy Music

Significant BOLD responses associated with happy music were found in the left superior frontal gyrus (BA8),

TABLE III. Conjunction analysis ($N = 16$): Neural activity associated with processing of happy relative to neutral music ($P \leq 0.05$, FWE)

		Talairach coordinates				
Happy	BA	x	y	z	P-value	Z-score
L. superior temporal gyrus	41	−54	−34	8	0.004	4.96
R. superior temporal gyrus	41	46	−16	0	0.004	4.54
L. superior frontal gyrus	8	−20	32	46	0.007	3.93
L. ACC	32	−10	38	14	0.019	3.39
L. ACC	24	−4	−12	38	0.007	3.92
L. posterior cingulate gyrus	31	−4	−28	38	0.016	4.47
L. nucleus caudate	n/a	−12	14	16	0.008	3.80
L. ventral striatum	n/a	8	4	−6	0.018	3.41
L. parahippocampal gyrus	n/a	−14	−46	2	0.022	3.31
L. medial frontal gyrus	6	−8	−26	64	0.018	3.40
L. precuneus	7	−12	−48	44	0.025	3.26

left medial frontal gyrus (BA6), the left ACC (BA32, BA24), left posterior cingulate (BA31), bilateral primary auditory cortex (BA41), bilateral ventral striatum, left nucleus caudate, left parahippocampal gyrus, and left precuneus (Fig. 1, Table III). A paired t-test performed on the BOLD signal change during happy and neutral, extracted through VOI-analysis in the ventral striatum, indicated a significant difference between signal intensity during those conditions [$t(15) = 4.58$, $P < 0.001$].

Main Effects of Sad Music

Significant BOLD responses associated with sad music were found in the left medial frontal gyrus (BA6), left posterior cingulate gyrus (BA31), bilaterally in the primary auditory cortex (BA41) and right auditory association area (BA21), right hippocampus/amygdala and left cerebellum (Fig. 2, Table IV). A paired t-test performed on the BOLD signal change during sad and neutral conditions, extracted

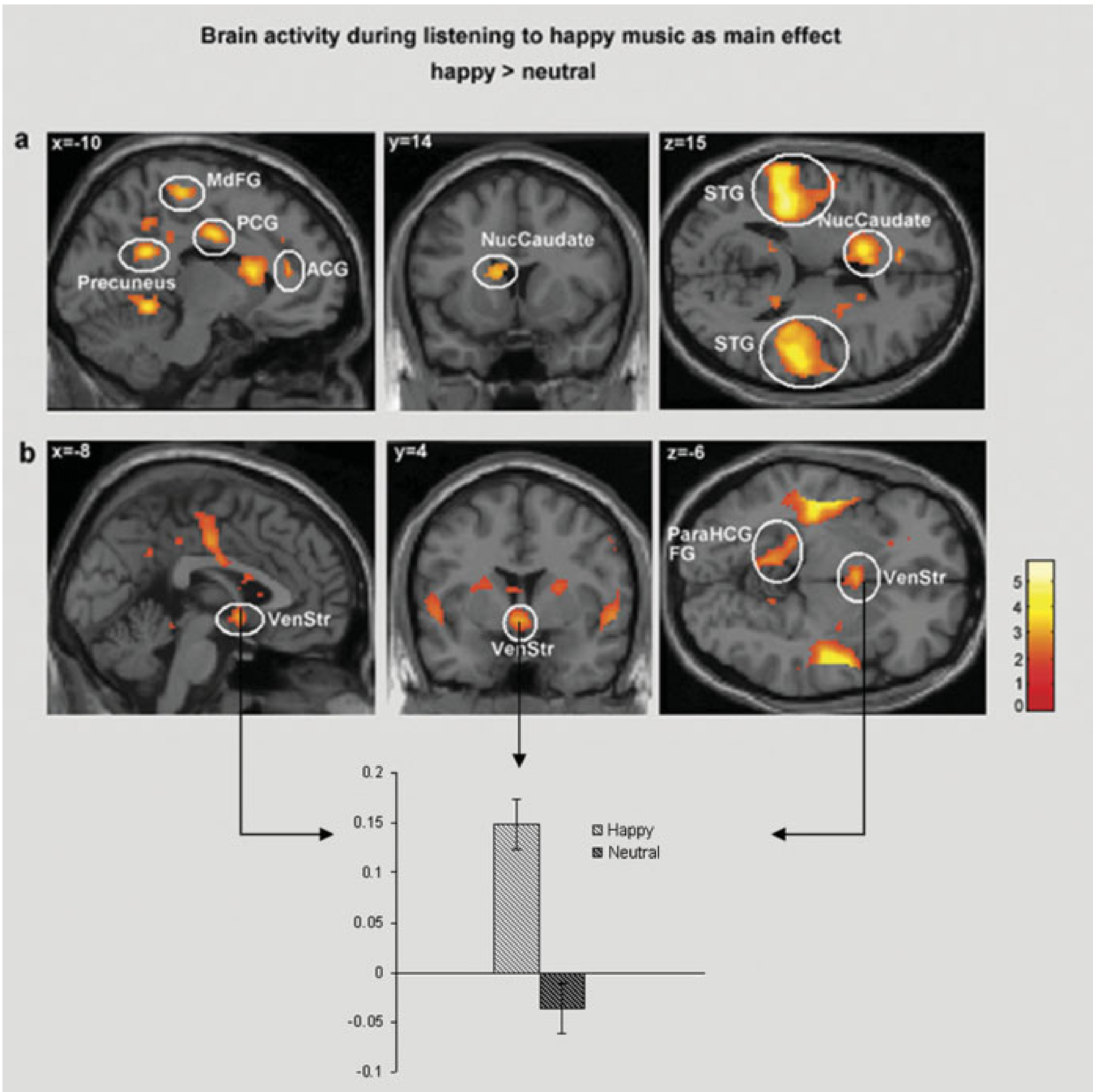

Figure 1.

Regions of increased brain activation during listening to happy classical music. Results are derived by conjunction analysis from two stimulus presentation orders ($N = 8/8$; $P \leq 0.05$, FWE) plotted on a single-subject template: (**a**) ACG, anterior cingulate gyrus; PCG, posterior cingulate gyrus; MdFG, medial frontal gyrus; NucCaudate, nucleus caudate; STG, superior temporal gyrus (**b**) VenStr, ventral striatum; ParaHCG/FG, parahippocampal gyrus/fusiform gyrus. Graph displays percent signal change during listening to happy compared to neutral music in the ventral striatum.

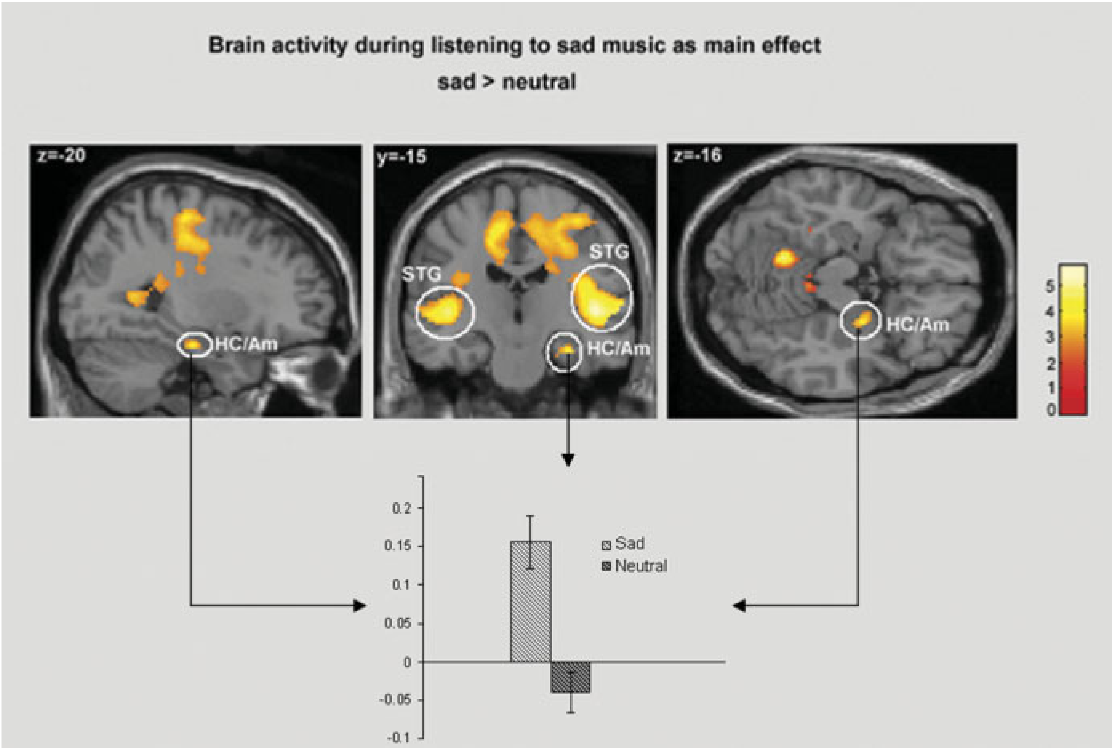

Figure 2.

Regions of increased brain activation during listening to sad classical music. Findings are derived by conjunction analysis of two different stimulus presentation orders (N = 8/8; $P \leq 0.05$, FWE) plotted on a single-subject template. Graph displays percent signal change during listening to sad compared to neutral music in the hippocampus/amygdala. HC/Am, hippocampus/amygdala; STG, superior temporal gyrus.

through VOI-analysis, indicated a significant difference between signal intensity during both conditions [$t(15) = 4.88$, $P < 0.001$].

Main Effects of Neutral Music

Emotionally neutral music was contrasted with activation during happy and sad music. Significant BOLD responses associated with neutral music in both orders were found bilaterally in the auditory association area (BA22) and left insula (Table V).

Effects of Happy and Sad Music

A comparison between happy > sad music revealed a significant difference in the left superior temporal gyrus (BA22). No significant differences at $P < 0.05$, FWE were found during sad > happy music.

TABLE IV. Conjunction analysis ($N = 16$): Neural activity associated with processing of sad relative to neutral music ($P \leq 0.05$, FWE)

		Talairach coordinates				
Sad	BA	*x*	*y*	*z*	*P*-value	Z-score
L. superior temporal gyrus	41	−40	−32	8	0.001	4.07
R. superior temporal gyrus	41	48	−20	4	0.001	3.99
R. superior temporal gyrus	21	60	6	−2	0.001	3.92
R. hippocampus/amygdala	n/a	20	−15	−20	0.051	3.25
L. posterior cingulate gyrus	31	−14	−32	40	0.041	3.71
L. medial frontal gyrus	6	−12	14	56	0.048	3.29
L. cerebellum	n/a	−14	−52	−16	0.045	3.47

TABLE V. Conjunction analysis (*N* = 16): Neural activity associated with processing of neutral relative to sad and happy music (*P* = 0.05, FWE)

Neutral	BA	Talairach coordinates x	y	z	P-value	Z-score
L. superior temporal gyrus	22	−56	−36	10	<0.001	5.15
L. insula	13	−36	−30	18	0.001	5.05

DISCUSSION

The present study was designed to investigate the neural basis of modulation of affective states through music by utilizing a set of validated happy, sad, and neutral musical pieces. Behavioral valence ratings provided during the scanning procedure point to a successful induction of happy and sad emotional states. The ratings, however, revealed that order of presentation (happy pieces first, sad pieces first) influenced the emotional experience of subsequent musical pieces. Participants who started with happy musical pieces provided more pronounced subjective ratings of happy and sad music. On the other hand, when sad musical pieces were presented first diminished affect ratings for both happy and sad musical pieces were observed. Both groups were matched for trait measures, such as extraversion, neuroticism and hedonia, factors which may affect subjective perception of emotional state. These findings are thus comparable with previous observations of permeating and lingering effects of exposure to sad stimuli on subsequent processing of happy stimuli, which has been observed in the visual modality [Ekman et al., 1980].

Given the findings in the behavioral data, it was expected that this would be reflected in the fMRI data. However, an analysis controlling for order effects found consistent activation patterns between the two groups in all contrasts of interest. The lack of differences represents a replication of the activation patterns in two independent samples; this finding thus allowed the data to be combined in a conjunction analysis.

As expected, happy emotional music showed greater activation in the ventral striatum relative to neutral music. Recruitment of the ventral striatum has been observed in many forms of positive emotional states [Aharon et al., 2001; Blood and Zatorre, 2001; Brown et al., 2004; Elliott et al., 2004; Koelsch et al., 2006; Menon and Levitin, 2005; Schultz, 2000]. Moreover, animal research [Schultz, 2000] has shown that neurons in the ventral striatum display a higher percentage of reward related responses, compared to those in the nucleus caudate or putamen. The activation found in the ventral striatum could therefore reflect the rewarding effect of music.

Although one could argue that the musical pieces used in this study were very well known and could, therefore, have been conditioned with rewarding experiences, a similar finding of ventral striatum activation was found in a recent PET study with popular musical pieces [Brown et al., 2004] in response to unfamiliar music. This finding would add support to the notion that non-natural stimulants activate our reward system. This view receives further support by a connectivity study by Menon and Levitin [2005] who found a strong correlation between activation in nucleus accumbens and the ventral tegmental area, which is the site of mesolimbic dopamine neuron cell bodies that receives input from brainstem, medial and occipital prefrontal cortices, amygdala and from striatal areas [Carelli and Wightman, 2004; Wise, 2002].

If rewards are essentially "environmental incentives we tend to approach" [Scherer, 2000], music has to be conditioned as a rewarding stimulus in order to recognize its lure. The beginnings of this reward experience could lie in early mother–child communication of prelinguistic children. Developmental research has provided evidence that mothers of different cultural backgrounds, when singing to their babies, use a repertoire of simple pitch contours [Trehub, 2003] and repetitions and that these particular melodies are recognizable as lullabies even when they are from an unknown cultural background [Trehub, 2003]. It could be argued that these early positive experiences with music within a social context have conditioned us to display an approach reaction to happy musical tunes as they signal rewarding social interactions. Furthermore, in evolutionary research the importance of music has been interpreted as a group-building agent, helpful in mating rituals and social group-building functions [Darwin, 1871; Miller, 2000]. Thus, ventral striatum activation during happy music may be connected to the anticipation of social reward in a wide variety of settings.

A main effect of happy music was also observed in the dorsal striatum, namely in the caudate. The basal ganglia system, in particular striatum and substantia nigra, are known to be involved in motor function. As the mesolimbic system is closely connected to the dopamine system in these regions, it has been argued that this structure mediates motivational and motor mechanisms [Carelli and Wightman, 2004] of behavior approach and withdrawal. Activations in the caudate and ventral striatum were only observed with happy music. This may reflect the rewarding effect of happy musical pieces and perhaps their higher incentive to move to or move towards them.

However, ventral striatum activation could also be an indication of physiological arousal in response to happy musical pieces, due to higher tempi compared to neutral or sad musical pieces. To address this possible concern, SCR data were collected from a subsample ($N = 11$). The findings suggest that mean SCR were higher during the emotional valence that was presented first (happy first, sad first). Hence, volunteers' SCR levels rose in response to the novelty of the experimental set-up rather than in response to the emotional valence of the musical pieces.

Significant activation during happy music was also observed in the rostral pregenual and dorsal ACC. The ACC is implicated in controlling of autonomic arousal, error monitoring, conflict processing, nociception, and appetitive behavior (for reviews please refer to: [Ongur and Price, 2000; Paus, 2001; Vogt, 2005; Vogt et al., 2005]). The ACC holds anatomical connections with the ventral and dorsal prefrontal cortices, parietal cortex, amygdala, striatum, and thalamus [Cavada et al., 2000; Tekin and Cummings, 2002; Vogt and Pandya, 1987; Vogt et al., 1987].

ACC activation in response to enjoyable music has previously been reported [Blood and Zatorre, 2001; Menon and Levitin, 2005]. Moreover, Blood and Zatorre [2001] found a positive correlation between ACC activation (BA24&32) and the intensity of "chills" as well as an association between physiological arousal and regional cerebral blood flow in the ACC. Furthermore, increased ACC and ventral striatum activation have been observed during drug administration in cocaine dependent individuals [Breiter et al., 1997] suggesting involvement in reward generation.

A recent study investigating reward in response to high risk behavior suggested that the anatomical links between striatum and ACC are also reflected in the functional connectivity of those areas [Cohen et al., 2005]. Bush et al. [2002] suggested an involvement of the ACC in reward based decision processes. Furthermore, a study investigating single-unit firing in ACC neurons [Shidara and Richmond, 2002] has suggested that ACC activity relates directly to reward expectation, whereas Rogers and colleagues [Rogers et al., 2004] observed pregenual ACC activation during reward-related decision processes.

In the context of the present findings, it might be that the pregenual ACC activity during listening to pleasant music is a reflection of a reward-related decision process preceding the actual rating process in the subsequent phase. An alternative explanation could be its involvement in vocalization. The ACC is involved in speech-related tasks [Paus et al., 1993; Petersen et al., 1988]. Together with the increased activation found in the supplementary motor area the findings may suggest that an analysis and reproduction of the music's melody was initiated. As inspection of Table I shows, happy musical pieces may have been better known, relative to neutral pieces. Their melodies may therefore have been easier to recognize and reproduce.

Moreover, the precuneus activation observed with happy music may have been associated with aspects of vocalization and recognition of musical melody as well as attention. The precuneus has been implicated in general episodic memory processes [Krause et al., 1999], memory retrieval [Cabeza and Nyberg, 2000] as well as mental imagery [Fletcher et al., 1995]. The increased activation of this area in the present context could be a reflection of the attempt of retrieving the episodic memories related to the musical pieces. Interestingly, Platel and colleagues [Platel et al., 2003] reported precuneus activation during a music task probing episodic memory retrieval.

We also observed recruitment of left parahippocampal gyrus activation with happy musical excerpts. The parahippocampal gyrus has been engaged by unpleasant musical stimuli [Blood et al., 1999; Koelsch et al., 2006] as well as during both happy and sad emotional states [Damasio et al., 2000; Jatzko et al., 2006; Lane et al., 1997; Tabert et al., 2001; Winston et al., 2002]. Moreover, previous studies have reported a parahippocampal engagement in processing and retrieval of spatial scenes and navigation (e.g. [Epstein and Kanwisher, 1998; Hayes et al., 2004; Mayes et al., 2004; Rosenbaum et al., 2004]) and processing of highly context-dependent information [Bar and Aminoff, 2003]. Given this evidence, it seems likely that the parahippocampal gyrus is involved in both the processing of emotional aspects of music as well as information related to the retrieval of spatial scenes. However, further research is needed to support such proposition.

The presentation of sad emotional music relative to neutral music, was associated with recruitment of the right-sided hippocampus/amygdala region as predicted. Activation has been reported in previous neuroimaging research of emotion in healthy people in association with positive and negative stimulus material and through different channels of sensory processing [Phan et al., 2002; Zald, 2003]. A consistent finding in mood disorders is an engagement of the amygdala in the resting state, as well as during cognitive or affective challenges [Drevets, 2000]. Of particular importance for the present study are findings by Koelsch et al. [2006] who found left amygdala activation in response to unpleasant music, which underscores the specific role of this region for negative emotion processing. Increased hippocampus/amygdala activation during sad music processing could be an aspect of appraising and evaluating emotional stimuli, especially in response to sad material [Richardson et al., 2004]. There is evidence of an enhanced amygdala response to emotionally salient stimuli occurring before conscious stimulus appraisal [Phelps, 2004; Whalen et al., 1998]. The lateral nucleus of the amygdala serves as an interface for different sensory modalities and receives auditory projections from a thalamic cell group involved in auditory transmission, i.e. the medial geniculate body [LeDoux, 1992; Phelps and LeDoux, 2005]. Here, rapid processing of emotionally salient acoustic information can be made through amygdala mediation. The amygdala/hippocampus activation observed here could represent enhanced perception and attention assigned to emotionally arousing stimuli in order to determine the appropriate reaction in response to the perceived stimuli. The behavioral ratings would support the argument that volunteers perceived the musical pieces as sad. Previous neuroimaging studies investigating affect and music, however, found hippocampus activation in response to both pleasant [Brown et al., 2004] and unpleasant musical pieces [Koelsch et al., 2006]. Furthermore, Blood and Zatorre [2001] reported negative correlations between intensity of chills and activation in the hippocampus/amygdala region.

The hippocampal formation, which also receives input from the mesolimbic dopaminergic system, plays a vital role in episodic memory consolidation and has been found in association with reward processes [Wittmann et al., 2005]. The exact role of hippocampal activation during listening to emotional music deserves further investigation. However, a tentative explanation for the present finding could lie in the specific nature of sad music as well as the interconnections that the hippocampus and amygdala are holding with the mesolimbic dopaminergic system.

Anecdotal evidence and reports from the "strong experience of music project" [Gabrielsson, 2002] describe sad music often as extremely beautiful and capable of inducing euphoric reactions. It could therefore be that the neural network underlying sad emotions induced through music is different from the neural activation seen in sadness induced through other sensory modalities or experienced in depression.

An observation that integrates both happy and sad emotional states is the left sided activation during happy musical stimuli in the ventral and dorsal striatum and the right sided activation observed during sad emotional stimuli in hippocampus/amygdala, relative to neutral music.

However, when neural activity during sad and happy emotional states were compared only the superior temporal gyrus (happy greater than sad) showed a significant increase in activation. This finding is somewhat puzzling since sad and musical pieces differ not only in terms of affective valence, but also in terms of structural features (tempo, mode). It is not clear at present why this structure responded more strongly to happy than sad stimuli, but could be to do with differences in the music structure between the two types of stimuli. More notably, an fMRI study comparing major and minor classical musical pieces performed on a MIDI piano found medial and superior frontal and posterior cingulate activation during minor, i.e., sad musical pieces, whereby major, i.e. happy musical pieces, failed to reveal differences [Khalfa et al., 2005].

In previous studies of affect in music, no direct comparisons between happy and sad pieces were possible, since control conditions have involved dissonant musical stimuli [Blood et al., 1999], scrambled musical pieces [Koelsch et al., 2006; Menon and Levitin, 2005] or rest [Brown et al., 2004]. Applications comparing musically induced sad and happy states are needed to determine the extent of overlap or difference between those states.

Somewhat surprisingly, neutral stimuli were associated with increased BOLD responses in the left auditory association area and left posterior insula. Previous studies found a lateralization for auditory functions with the right hemisphere traditionally involved in processing emotional information of sound and speech, whereas the left hemisphere is concerned with the structural analyses of auditory information (for a review please refer to [Tervaniemi and Hugdahl, 2003]). As the selected stimuli had little affective content the activation observed in this area could be a reflection of an analytical listening process.

LIMITATIONS

As the primary interest was on the emotional response to music, pieces were solely selected on their likely ability to induce sad, happy, and neutral states. Therefore, other musical features such as tempo, mode, pitch, or timbre were not taken into account. It is possible that the sad musical pieces could have had a more relaxing effect on the listener, while the happy pieces could have induced arousal states. These factors should be controlled in future studies by measuring skin conductance and collecting behavioral arousal ratings. Another limitation was that the strength of emotional valence was unbalanced between happy and sad musical pieces, suggesting stronger emotional valance for happy than sad pieces. This finding could support the notion that happy music in general triggers stronger reward responses compared to sad emotional states. However, areas that have previously been observed during sad emotional processing, such as amygdala, were significantly activated during sad emotional music, which suggests a sufficiently strong emotional valence for sad pieces. Future studies might want to alternate happy, neutral, and sad pieces throughout the experiment, allowing easier within-subject comparisons, rather than having to perform between-group comparisons on a relatively small sample. However, the present design was chosen to investigate and establish whether order of presentation has an impact on the induction of affective states and to facilitate the temporary mood induction by the musical pieces.

An in-depth debriefing after the scanning procedure should also be considered in future studies employing popular pieces of music. This might be of importance as autobiographical memory retrieval could have an impact on the processing of musical pieces.

Additionally, the study might have profited from a procedure to enforce attendance to the musical stimuli. However, given the pattern of activation and the fact that music is a very pervasive stimulus it can be argued that participants in this study were in fact attentive toward the stimuli.

CONCLUSIONS

The present study investigated neural correlates of emotions induced by happy and sad emotional musical stimuli. Objectively validated happy, sad, and neutral musical pieces were determined in an initial behavioral study. The happy musical stimuli were associated with increased activation in the bilateral ventral and left dorsal striatum, left ACC and left parahippocampal gyrus. Sad musical stimuli led to increased activation in right medial temporal structures. These activations were observed without employing region-of-interest analyses frequently used in previous studies, which further underlines the strength of the present data. These findings may be integrated with recent research investigating musical emotions with familiar musical pieces.

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