Despite intersubject variability, dramatic impairments of socio-communicative skills are core features of autistic spectrum disorder (ASD). A deficit in the ability to express and understand emotions has often been hypothesized to be an important correlate of such impairments. Little is known about individuals with ASD’s ability to sense emotions conveyed by nonsocial stimuli such as music. Music has been found to be capable of evoking and conveying strong and consistent positive and negative emotions in healthy subjects. The ability to process perceptual and emotional aspects of music seems to be maintained in ASD. Individuals with ASD and neurotypical (NT) controls underwent a single functional magnetic resonance imaging (fMRI) session while processing happy and sad music excerpts. Overall, fMRI results indicated that while listening to both happy and sad music, individuals with ASD activated cortical and subcortical brain regions known to be involved in emotion processing and reward. A comparison of ASD participants with NT individuals demonstrated decreased brain activity in the premotor area and in the left anterior insula, especially in response to happy music excerpts. Our findings shed new light on the neurobiological correlates of preserved and altered emotional processing in ASD.

**Keywords:** Asperger, autism spectrum disorders, emotion, fMRI, music

**Introduction**

Autism spectrum disorders (ASDs)—including autism, Asperger syndrome (AS), and pervasive developmental disorders not otherwise specified (ICD-10, WHO 1993; Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), APA 1994)—are neurodevelopmental disorders with an estimated incidence of 6:1000 (Chakrabarti and Fombonne 2001; CDC 1994)—are neurodevelopment disorders with an estimated incidence of 6:1000 (Chakrabarti and Fombonne 2001; CDC 1994)—are neurodevelopment disorders with an estimated incidence of 6:1000 (Chakrabarti and Fombonne 2001; CDC 1994)—are neurodevelopment disorders with an estimated incidence of 6:1000 (Chakrabarti and Fombonne 2001; CDC 1994)– are characterized by impairments in social interaction, communication, and repetitive and restricted interests or behaviors. Despite intersubject variability, dramatic impairments of interpersonal behavior, communication, and empathy are core features of ASD (APA 1994; Pelphrey et al. 2002). A deficit in the ability to express and understand emotions has often been hypothesized to be an important correlate of such social impairments (Hobson 1986; Trevarthen 1998; Pelphrey et al. 2002). Behavioral studies on ASD have documented difficulties in the recognition of facial expressions of emotions (Weeks and Hobson 1987; Celani et al. 1999; Adolphs et al. 2001; Dawson et al. 2004; Boraston et al. 2008) and of emotional prosody (Rutherford et al. 2002; McCann and Peppé 2003; Golan et al. 2006, 2007). Deficits in the processing of nonverbal emotional cues have been found to relate with the level of social dysfunction of individuals with ASD (Braverman et al. 1989). Moreover, poor or unusual emotional prosody often characterizes speech productions of individuals with ASD (Paul et al. 2005), and the atypical expression of emotions is included as criteria in the most used diagnostic observation tool for ASD (Autism Diagnostic Observation Schedule-Generic [ADOS-G], Lord et al. 2000).

Neuroimaging studies enable the exploration of the neurobiological correlates of such a core deficit in emotion processing. The majority of studies have concentrated on responses to facial expressions, highlighting in most cases hypoactivation of fusiform gyrus and amygdala (Crichtley et al. 2000; Pierce et al. 2001; Hall et al. 2003, 2010; Hubl et al. 2003; Schultz et al. 2003; Piggot et al. 2004; Wang et al. 2004; Deeley et al. 2007; Hadjikhanli et al. 2007). However, the observation of atypical brain responses in ASD during visual exposure to facial expressions of emotions could be explained by their abnormal visual inspection of faces (Boucher and Lewis 1992; Klin et al. 2002; Corden et al. 2007) or by the disruptive value that such a social-salient stimulus exerts on individuals whose diagnosis specifically impairs the social domain (Klin 2008). Furthermore, although studying brain responses to affective facial expressions helps to elucidate emotional reactions induced by others in an interpersonal context, it does not capture the whole features of emotional processing that could be elicited by nonsocial affective stimuli.

To date, little is known about individuals with ASD’s ability to perceive emotions conveyed by nonsocial stimuli. Only recently Silani et al. (2008) investigated brain response to emotionally arousing stimuli in AS using pictures from the International Affective Picture System (IAPS; Lang et al. 2008) that includes images of various kinds of emotional scenes. In response to unpleasant compared with neutral pictures, the authors found greater activity in the inferior orbitofrontal cortex, but not amygdala, in control participants, suggesting a stronger basic response to emotions in this group.

During the past years, neuroscience research has demonstrated that music is a valuable tool to study emotion (Koelsch 2005a, 2005b). Music has been found to be capable of inducing strong and consistent positive and negative emotions in neurotypical (NT) individuals (Koelsch et al. 2006; Mitter-schiffthaler et al. 2007). Moreover, the emotional responses evoked by music are quite comparable across different musical categories and subjects (Peretz and Hebert 2000; Trehub 2003; Fritz et al. 2009). Neuroimaging studies on NT adults have brought to light the neural correlates of music processing that include a network of limbic and paralimbic structures implicated in reward and emotion. Specifically, activations of amygdala, hippocampus, parahippocampal gyrus, insula, temporal poles, ventral striatum, orbitofrontal cortex, and cingulate cortex were observed in response to music (Blood and Zatorre 2001; Salimpoor et al. 2009).
Following the clinical insights of a particular interest and disposition for music in individuals with ASD, researchers have empirically documented that music does represent a domain of preserved or even enhanced abilities in ASD (Sloboda et al. 1985; Treffert 1989; Young and Nettlesbeck 1995; Mottron et al. 1999, 2000; Heaton et al. 2001). As an example, individuals with ASD show intact or superior musical pitch processing (Mottron et al. 2000; Bonnel et al. 2003; Heaton 2003, 2005). Although such musical abilities have been mostly observed in autistic musical savants, there are also indications about spared musical skills and potential in autistic individuals who are not savants (Heaton 2009). Moreover, behavioral studies have reported on the ability of individuals with ASD to properly identify the positive and negative emotional valence of sad and happy music stimuli (Heaton et al. 1999; Allen et al. 2009) and, recently, Quintin et al. (forthcoming) demonstrated the preserved ability of adolescents with AS to recognize musical emotion as belonging to one of 4 categories: happy, sad, scared, or peaceful. Although emotional reactions to music seem to be essentially preserved in ASD, the access to a full range of emotion words to describe them is impaired (Allen et al. 2009, 2010). Consistently, previous studies on alexithymia in ASD reported that high-functioning ASD individuals have difficulties in high-level analysis of their own emotional states and reactions (Hill et al. 2004; Berthoz and Hill 2005; Bird et al. 2010).

Possible relations between ASD preserved ability of basic emotion recognition in music and their unusual pattern of emotional responsiveness and behavior within the interpersonal domain have been discussed according to 2 of the main theories about ASD (Heaton et al. 1999; Quintin et al. forthcoming). Hobson’s theory (1993), hypothesizing a basic deficit in interpersonal relatedness—early spontaneous ability to read others emotional expressions—to be the core dysfunction of ASD, would explain a preserved ability to experience emotions through music that does not imply direct interpersonal interaction (Heaton et al. 1999). In a similar fashion, difficulties in meta-representations of others mind posited to be the ASD core deficit according to the theory of mind hypothesis (Baron-Cohen et al. 1985; Baron-Cohen 1995) would not apply to music as no mental representations are needed to appreciate the affective aspects of music (Heaton et al. 1999). More generally, the emotion processing deficits in ASD arising in response to social situations as specified in the DSM-IV (APA 1994) but not in response to nonprimarily social stimuli, such as music, may be thus specific to the social domain (Quintin 2010).

Hence, emerging evidence emphasizes the role of musical stimuli in studying emotion processing in ASD at a neurobiological level. As music is not primarily social in its nature, investigation of the emotional response to music may deepen our knowledge about the neurobiological bases of emotion processing in ASD, going beyond the impaired interpersonal domain.

In an attempt to identify the neural correlates of emotion processing in ASD, we used functional magnetic resonance imaging (fMRI) during the processing of happy and sad music excerpts. Our goal was to investigate emotion processing in individuals with ASD within the music domain, which represents an area of interest and preserved abilities. Based on previous behavioral data (Heaton et al. 1999; Allen et al. 2009; Allen and Heaton 2010; Quintin et al. 2010), we hypothesize that music induces activity in some of limbic and paralimbic structures usually connected to reward and emotion (Blood and Zatorre 2001; Salimpoor et al. 2009) in individuals with ASD. However, in line with recent neuroimaging studies focusing on the brain response to emotional scenes with social as well as nonsocial valence (Silani et al. 2008; Bird et al. 2010), we expected to find decreased activity in individuals with ASD compared with NT controls in areas involved with high-level awareness of own emotional states.

Two methodological consideration regarding this study should be noted. First, considering the possible variability in music preferences across individuals, participants were asked to select their preferred happy and sad music pieces, which were then employed as stimuli in our experiment together with validated musical pieces used in previous fMRI investigations (Mitterschiffthaler et al. 2007). We expected that self-selected stimuli would enhance the emotional response compared with the “standard” musical excerpts. Second, to increase sample homogeneity, we included in the study only participants with AS, enabling us to conduct our investigation on individuals with a clearer diagnosis compared with pervasive developmental disorder not otherwise specified, and a less severe symptomatology compared to classic autism.

Results from this inquiry promised to enhance our knowledge of emotional skills and deficit in ASD and provide the neurobiological bases for the interventions based on music therapy which seem to facilitate communication in these patients (de Falco and Venuti 2006; Kern and Aldridge 2006; Kern et al. 2007).

Materials and Methods

Participants

Altogether 22 individuals voluntarily participated in this study. Eight were individuals with AS (6 men; age range 19–37 years; mean age 23.40 years, SD 7.03) and 14 were NT participants (6 men; age range 19–32 years; mean age 24.30 years, SD 3.02). Participants were recruited through Internet advertisement. They had no history of major psychiatric disorders (other than AS) or medical illness affecting brain function (e.g., psychosis or epilepsy) and did not have intellectual delay. They were nonmusicians and received no specific music education. All participants with AS received a clinical diagnosis from an independent clinician based on the DSM-IV and ICD-10 criteria. To confirm the diagnosis, all participants were also administered with the ADOS-G (Lord et al. 2000) and, when age appropriate (n = 6), with the Asperger Gilliam Asperger’s Disorder Scale (GADS, Gilliam 2001) and the Krug Asperger’s Disorder Index (KADI, Krug and Arick 2003). Six participants met the diagnostic criteria for AS at the ADOS and reached a high probability of AS at GADS and/or KADI scales; the other 2 participants reached a high probability of AS at both GADS and KADI scales.

Intelligence was measured through the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981). All participants gave written informed consent for their participation in the study. The experimental procedures were approved by the ethical committee for experiments involving humans at the University of Trento.

Stimuli

Stimuli consisted of 10 happy musical excerpts, 10 sad musical excerpts, and 10 control stimuli. Half of the emotional stimuli were the happy and sad musical pieces used in a previous study (Mitterschiffthaler et al. 2007) and consisting of famous classical musical pieces from 18th, 19th, and 20th century Western, herein named “standard.” The second half of the stimuli were preferred happy and sad musical pieces selected by the participants, herein named “favorite.” Participants were asked to select their favorite happy and sad instrumental pieces. As for the control stimuli, we did not employ noise stimuli in order to minimize experimental group’s discomfort. Stimuli consisting of random sequences of tones with no rhythmic structure
and no melodic contour (Deutsch 1999; Janata, Birk et al. 2002; Levitin and Menon 2003) were instead used. All the auditory stimuli were digitized sound files (sampling rate = 22 050 kHz, 16 bit resolution, stereo) normalized to the same root mean square level and presented at a comfortable loudness level. Participants were asked to assess their individual emotional state induced by the selected stimuli prior to the functional MRI data acquisition so that we also reduced novelty effects of auditory material. During stimuli assessment and fMRI data acquisition, participants passively attended to the musical excerpts.

**Experimental Protocol**

Two different pseudorandom sequences of stimuli, one starting with happy music and one starting with sad, were administered to the participants to exclude that the order of presentation had an effect on the emotional response. The selected stimuli were randomly presented in a block design consisting of 30 s epochs of musical excerpts (happy and sad alternated) and 30 s of control stimuli interspersed with 16 s of rest. To minimize interference effects due to rapid switching between one affective state to another, 2 stimuli with the same emotional characteristics were presented consecutively. The same order of the stimuli presentation was used for each participant during both the stimuli assessment and fMRI data acquisition (Supplementary Material). The former, performed out of the scanner room, was based on the subjective emotional valence and arousal measured with the Self-Assessment Manikin (SAM) (Bradley and Lang 1994). SAM is a nonverbal pictorial assessment for measuring pleasure, aversion, and arousal associated with a person’s affective reaction; valence and arousal dimensions vary along a 9-point scale (valence: from 1 = extremely negative to 9 = extremely positive; arousal: from 1 = calm to 9 = exciting). Several studies have found that individuals with high-functioning autism (Baron-Cohen et al. 1997; Neumann et al. 2006) can recognize facial expressions of basic emotions. Moreover, previous studies have successfully administered SAM to adults with high-functioning ASD (Wilbarger et al. 2009); schematic pictorial representations of facial expressions have also been used as self-report tool in studies on children with ASD (Heaton et al. 1999).

Before the experiment, participants were briefed about the experimental tasks and SAM ratings and were trained to execute the ratings. After listening to each music piece, subjects were presented with the 2 SAM valence (6 s) and arousal (6 s) scales in close succession. The final selection of subjective rating was performed by positioning a red outline on the chosen level of the scale. Participants were provided with 2 buttons allowing movements of the cursor in the left and right directions.

**Behavioral Data Analysis**

Our purpose was to verify how participants with AS, compared with the control group, explicitly rated the emotional valence and arousal of the stimuli for both happy and sad music. Moreover, we wanted to investigate if preference influenced the scores attribution. Separate analyses of variance (ANOVA) were carried out on the valence and arousal scores to reach these objectives, with either Group (AS vs. NT) and Preference (favorite vs. standard) or group and connotation (happy vs. sad) as factors. Statistical analysis of the behavioral data was performed with the statistical package SPSS 14.0 (SPSS Inc.).

**fMRI Analysis**

Functional data were first preprocessed using standard routines (Supplementary Material). For each participant, an analytic design matrix was constructed modeling onsets and duration of each trial as epochs convolved with a canonical hemodynamic response function. At the first level, for each single subject, the different types of music corresponding to the 5 experimental conditions (favorite happy and sad music—FH and FS, standard happy and sad music—SH and SS and control stimuli CS) were modeled as separate regressors and interrogated to derive contrast images for second-level group analysis. All regressors were then incorporated into a general linear model. Motion correction parameters created during the realignment stage were included in the analysis as a covariate of no interest to model residual effects due to head motion. Contrast images of each class of stimuli compared with control stimuli were created. The main contrasts of interest were happy music (favorite + standard) > control stimuli, sad music (favorite + standard) > control stimuli, favorite > standard within happy and favorite > standard within sad. Second-level analysis in the AS group was obtained using a fixed-effect analysis following guidelines provided in Friston et al. (1999). The reason for performing a fixed-effect analysis was based on several aspects: the reduced number of participants being too small to perform a random-effect analysis, the good reproducibility between participants of the activation patterns, the minimal intersessions variability as a single fMRI session was acquired, and the homogeneity of the selected group in terms of age and diagnosis.

As for the NT group, a second-level random-effects analysis was performed to allow inferences across participants that generalize to the population. The resulting contrast t-maps obtained from the first-level (intrasubject) analysis were entered into a full factorial design in SPM5 with preference (favorite and standard) and valence (happy and sad) as within-subject factors. The same contrasts of interest considered for the AS group were assessed in the NT group analysis. SPM {t}maps of the AS and NT groups were corrected for multiple comparisons across the whole brain. Significance levels were set at P < 0.05, corrected using cluster-wise false discovery rate (FDR) correction (Genovese et al. 2002; Chumbley and Friston 2009); only clusters with a size of k ≥ 10 voxels were considered. The surviving activated voxels were superimposed on high-resolution magnetic resonance scans of a standard brain (MNI); brain regions were labeled anatomically according to Tzourio-Mazoyer et al. (2002).

Group differences between AS and NT were assessed performing t-tests for independent samples on the first-level contrast images generated for each group. Threshold significance for functional imaging data was P < 0.01, corrected for multiple comparisons at the cluster level (k = 10). For helping clarity and readability of the manuscript, NT results are considered only for comparisons with AS group.

**Results**

**Behavioral Data**

**Valence**

Mean valence scores are reported in Figure 1. No main effect for group emerged in any of the ANOVAs carried out on the valence scores with either Group and Preference or Group and Connotation as factors. Specifically, no group differences emerged in the ability to accurately rate more positive the happy excerpts compared with the sad ones both within favorite (F_{1,19} = 130.57, P < 0.01) and within standard music (F_{1,19} = 645.61, P < 0.01). However, a Group × Connotation interaction effect was found for standard music (F_{1,19} = 8.50, P < 0.05); Although a main effect of connotation was found at an univariate level in both groups, this effect was stronger in NT group compared with AS group.

**Arousal**

Mean valence scores are reported in Figure 1. No main or interaction effect for group emerged in any of the ANOVAs carried out on the arousal scores except for a Group × Connotation interaction for favorite music (F_{1,19} = 4.57, P < 0.05). In particular, within favorite music, although no significant differences in the arousal scores between sad and happy excerpts were found in either group, a trend of increased arousal for happy excerpt was found in AS group only. Also, within standard music, participants in both groups
equally rated arousing the happy excerpts compared with the sad ones ($F_{1,19} = 0.89$, ns). Moreover, arousal scores attributed to favorite happy music were higher compared with the standard ones in both groups ($F_{1,19} = 12.50$, $P < 0.005$), and both groups rated standard sad music as less arousing compared with favorite sad music ($F_{1,19} = 27.56$, $P < 0.001$).

**fMRI Results of the AS Group**

fMRI analysis revealed significant blood oxygenation level-dependent (BOLD) responses ($P < 0.05$, FDR) in cortical and subcortical brain regions (Tables 1 and 2, Fig. 2) underlying music perception and emotional processing.

**Happy Music**

Happy music, with respect to control stimuli activated the left supramarginal gyrus (Brodmann’s area, BA40), the primary auditory cortex (BA42) bilaterally, and the right auditory association area (BA21). Enhanced BOLD response was also observed in the inferior frontal gyrus (BA44, 45) and the cerebellum bilaterally, the right insula (BA47), the putamen, and caudate nucleus (Table 1, Fig. 2a). When favorite musical pieces were contrasted to standard, enhanced activity in several bilateral brain regions was observed (Table 1, Fig. 2b). Specifically, active regions were the medial prefrontal cortex (mPFC) (BA8, 9), the posterior cingulate cortex (BA31, 26) and precunes (BA30) the left posterior insula, the ventromedial (BA11) and frontopolar (BA10) cortices, and the lingual gyrus (BA17). In addition, activity in the primary (BA41) and secondary auditory cortex (BA21) was also measured.

**Sad Music**

While AS participants listened to sad music in comparison with control stimuli, a significant activation was observed only in the right cerebellum using the cluster-wise FDR corrected $P$ value (Table 2, Fig. 2c). On the contrary, sad favorite excerpts activated bilaterally temporal regions (BA22, 38), the inferior frontal gyrus (BA44, 45) and the cerebellum, the right supramarginal gyrus (BA40), the right ventral tegmental area (VTA)/substantia nigra, the right hippocampus, the left insula, the left precuneus, the right medial and frontopolar prefrontal cortex (BA8, 10), and the right premotor regions (BA6) (Table 2, Fig. 2d).

Results on NT of the same contrasts of interest are shown in Tables 3 and 4 and Figure 2.

**Between Group fMRI Analysis**

While listening to happy music with respect to control stimuli, NT individuals compared with AS participants activated the right premotor cortex, the supplementary motor area and the cerebellum bilaterally (Fig. 3a, Table 5). Favorite happy musical excerpts compared with standard activated in NT group more than AS group the supplementary motor area and the left anterior insula/frontal operculum (BA47, 48) (Fig. 3b, Table 5). While listening to sad music with respect to control stimuli, NT individuals compared with AS participants activated the right supramarginal gyrus, the right superior temporal gyrus, the supplementary motor area, the left frontal operculum, and the left cerebellum (Fig. 3a, Table 5). Favorite sad musical excerpts compared with standard activated in NS group more than AS
group the left and right premotor cortex only (Fig. 3b, Table 5). No significant activations were observed when AS group was compared with healthy controls.

Discussion

The present fMRI study investigated the neural correlates of emotional processing in AS individuals during listening to happy and sad music. A comparison with NT individuals aimed to describe functional and dysfunctional brain circuits underlying music-evoked emotions in ASD. The experimental design entailed the presentation of a set of validated happy and sad musical pieces (Mitterschiffthaler et al. 2007) and a set of self-selected favorite happy and sad musical excerpts. By using favorite pieces, we hypothesized an enhanced emotional response to music in AS and reduced potential confounds due to variability of musical preference. Behavioral ratings of the music pieces, collected before the scanning procedure, overall indicated no differences between the 2 groups in the ability to correctly identify the valence of the stimuli, although the distinction of happy and sad music was more extreme in NT individuals. Explicit arousal in response to the music excerpts was also similar in the 2 groups. Moreover, an effect of preference was found in both groups, that is, self-selected excerpts were generally rated more arousing and with stronger emotional valence than standards ones. Our behavioral results are in line with the literature depicting music as a domain of preserved ability and interest in ASD (Heaton et al. 1999, 2008; Bonnel et al. 2003; Heaton 2003, 2009). Our findings also support those of a recent investigation by Quintin and colleagues (2010) which revealed no differences between adolescents with AS and NT controls in their ability to correctly identify the emotional valence of music excerpts. It appears that although ASD individuals have prominent deficits in processing complex emotional cues within the social context, their ability to appropriately identify the emotional content of music—a complex nonsocial affective stimulus—is largely preserved.

fMRI results indicated that while listening to music individuals with AS-activated brain regions known to be involved in the processing of syntactic, temporal, rhythmic and pitch information such as the left supramarginal gyrus, the superior temporal gyrus and pole bilaterally, the supplementary motor area, and the cerebellum (Riecker et al. 2000; Maess et al. 2001; Janata et al. 2002; Koelsch et al. 2002, 2005; Tillmann et al. 2003; Callan et al. 2006; Peck et al. 2009). This is line with the literature reporting preserved ability in AS individuals to perceive musical structure and increased sensitivity to musical pitch and timbre (Heaton et al. 1999, 2008; Bonnel et al. 2003; Heaton 2003, 2009). More interestingly, several emotion- and reward-related brain areas were also observed in the main contrasts of interest as discussed below.

During happy excerpts presentation, enhanced brain activity was observed in the right anterior insula, anterior part of superior temporal pole, putamen, and caudate nucleus. The right anterior insula has been associated with subjective perception of emotional states (Craig 2002, 2003) and awareness of emotionally salient stimuli (Critchley et al. 2004, Craig 2009). It has been posited that anterior insula, along with anterior cingulate cortex, is a key substrate for conscious emotion experience and for central representation of autonomic arousal as it seems to integrate visceral, attentional, and emotional information (Dagleish 2004). The right insular cortex is also involved in sound detection, nonverbal processing, and auditory temporal processing (Bamiou et al. 2003; Levitin and Menon 2003). Consistently, activity in the right anterior insula was already observed in previous studies when healthy individuals listened to pleasant music (Koelsch et al. 2006). Moreover, activity within the anterior part of superior temporal pole (BA38) seems to play a role in emotional processes, in particular in high-level processing of perceptual inputs to visceral emotional responses (Olson et al. 2007). Activity in the dorsal striatum, caudate nucleus and putamen, has been shown to be involved in reward-related responses (Balleine et al. 2007). The observed activations in the anterior insula as well as in the dorsal striatum indicate that happy music represents a strong emotional and rewarding stimulus for AS individuals as also confirmed by behavioral data.

Within happy music, favorite with respect to standard excerpts, besides activating brain areas involved in musical structure processing, also elicited activity in the dorsal regions of the mPFC (BA8, 9), the left precuneus, the right posterior cingulum, the medial orbitofrontal cortex (BA10, 11), the left posterior insula and the right thalamus. The mPFC is involved in the perception of pleasant stimuli and judgments regarding self-relevance and affect (Aharon et al. 2001; Bartels and Zeki 2004; Ochsner et al. 2004). Recent evidence (Janata 2009) indicates that the mPFC represents a neural substrate for associating music, emotions, and memory. Activity within the retrosplenial cortex, the precuneus and the posterior cingulate cortex, has been also associated with memory retrieval (Cabeza and Nyberg 2000; Janata et al. 2007), autobiographical memory (Fink et al. 1996; Maguire 2001; Piefke et al. 2003), and episodic memory processes (Krause et al. 1999) in healthy individuals. Whether these processes are related to recall music descriptors, such as the tonality or melodic passages or to recall of autobiographical memories, or both, cannot be here discerned. Studies on memory on high-functioning ASDs, although not

Table 2

Asperger group—sad music

<table>
<thead>
<tr>
<th>Location group—sad music</th>
<th>Side</th>
<th>Coordinates (MNI)</th>
<th>Brodmann area (BA)</th>
<th>r value</th>
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<tbody>
<tr>
<td>Standard and favorite &gt; control stimuli</td>
<td>Cerebellum</td>
<td>R 51, −54, −39</td>
<td>5.55</td>
<td></td>
</tr>
<tr>
<td>Favorite &gt; standard</td>
<td>Middle temporal gyrus</td>
<td>R 69, −30, 3</td>
<td>9.16</td>
<td></td>
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<tr>
<td></td>
<td>Superior temporal pole</td>
<td>R 57, 6, −9</td>
<td>9.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Superior temporal gyrus</td>
<td>L −63, −42, 15</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Superior temporal gyrus</td>
<td>R 63, −42, 15</td>
<td>7.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Superior temporal gyrus</td>
<td>R 63, −42, 15</td>
<td>7.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lingual gyrus</td>
<td>L 69, −27, 21</td>
<td>6.0</td>
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<tr>
<td></td>
<td>Inferior frontal gyrus/parietal opercularis</td>
<td>R 54, 30, 15</td>
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<td></td>
<td>Inferior frontal gyrus/parietal opercularis</td>
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<tr>
<td></td>
<td>Cerebellum</td>
<td>R 36, −39, −33</td>
<td>5.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle frontal gyrus</td>
<td>R 45, 12, 54</td>
<td>6.17</td>
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<tr>
<td></td>
<td>Supramarginal gyrus</td>
<td>R 69, −33, 30</td>
<td>40</td>
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<td></td>
<td>Inferior frontal gyrus/parietal opercularis</td>
<td>L −51, 15, −3</td>
<td>45</td>
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<tr>
<td></td>
<td>Cerebellum</td>
<td>L −18, −93, −21</td>
<td>5.06</td>
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</tr>
<tr>
<td></td>
<td>VTA/substantia nigra</td>
<td>R 12, −21, −9</td>
<td>5.06</td>
<td></td>
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<tr>
<td></td>
<td>Precuneus</td>
<td>L −24, −81, 51</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medial superior frontal</td>
<td>R 6, 21, 70</td>
<td>8</td>
<td></td>
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<tr>
<td></td>
<td>Hippocampus</td>
<td>R 21, −27, −12</td>
<td>4.53</td>
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<tr>
<td></td>
<td>Superior frontal gyrus</td>
<td>R 36, 60, 12</td>
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<tr>
<td></td>
<td>Posterior insula</td>
<td>L −45, −18, 0</td>
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<tr>
<td></td>
<td>Supplementary motor area</td>
<td>R 0, 15, 69</td>
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Note: Significant enhanced activations (SPM t-maps) during processing of sad music in participants with AS.
univocally, report an impairment in certain aspects of episodic memory and memory recall (Bowler et al. 2000; Gardiner et al. 2003; Williams et al. 2005, 2006). However, no studies have thus far specifically investigated the music-evoked memory processing in these individuals.

Favorite happy music seems to be perceived as more intense and able to induce a stronger emotional response with respect to standard stimuli as indicated by activity in the orbitofrontal cortex and in the mPFC, which are known to be modulated by emotional responses to music and the perceived pleasantness of music (Blood et al. 1999; Blood and Zatorre 2001; Brown et al. 2004). Activity in the orbitofrontal cortex (BA10, 11) has been associated with the perception of pleasant emotional stimuli (Aharon et al. 2001; Karama et al. 2002; O’Doherty et al. 2003; Bartels and Zeki 2004; Hamann et al. 2004; Aron et al. 2005; David et al. 2005; Ferretti et al. 2005; Fisher et al. 2005; Sabatinelli et al. 2007). Orbitofrontal cortex critically contributes to emotional processing in the human brain (Kringelbach 2005) and it is supposed to be involved in monitoring the reward value of many different reinforcers (Kringelbach and Rolls 2004). Activity within the orbitofrontal cortex as well as in the right thalamus was previously observed during pleasant emotional responses to music and associated with reward and emotional arousal respectively (Blood and Zatorre 2001).

In individuals with AS, sad musical pieces, favorite and standard together, compared with control stimuli, elicited activity in the cerebellum only, whereas the right VTA/substantia nigra and the right hippocampus in addition to auditory brain areas such as BA22, 38 and musical structure analysis-related areas were activated when favorite were compared with standard pieces. Activity within a network of mesolimbic structures involved in reward/motivation and emotional processing including the VTA/substantia nigra was previously reported during listening to standard pieces in the classical repertoire (Blood and Zatorre 2001; Menon and Levitin 2005). The VTA and substantia nigra are crucial for reward processing as dopamine neuron cell bodies projecting to the nucleus accumbens are located in this mesolimbic region (Nicola et al. 2000; Berridge and Robinson 2003). As previously observed in healthy subjects (Mitterschiffthaler et al. 2007), sad stimuli, although elicited a differential pattern of activity with respect to happy music—involving the hippocampus and VTA/substantia nigra—do represent a pleasant and rewarding stimuli for AS individuals. This result also supports the observed preserved ability in AS to recognize happy and sad music (Heaton 1999; Quintin 2010).

Altogether our functional data of AS group reveal the involvement of brain regions implicated in emotion and reward and corresponding to those reported in studies on emotional processing of pleasant music in healthy individuals (Blood et al. 1999; Blood and Zatorre 2001; Menon and Levitin 2005; Koelsch 2005a; Koelsch et al. 2005; Mitterschiffthaler et al. 2007).
Social context. This pattern of results is consistent with the processing of music does take place out of interpersonal and such as music. This may be due to the strength of music in Spezio et al. 2007) and does not appear across other domains specific (Schultz et al. 2000; Pelphrey et al. 2002; Gross 2004; 2007; Salimpoor et al. 2009). Furthermore, fMRI results confirm behavior studies on emotion recognition in the musical 2007; Zatorre et al. 1994). Decreased activity in these areas in AS might reflect an altered rhythm perception and tracking or a diminished cortical motor preparation for vocalization/covert singing (Riecker et al. 2000; Callan et al. 2006; Peck et al. 2009). Functional and anatomical alterations of the cerebellum have been observed in studies of individuals with ASD (Courchesne et al. 1994; Courchesne 1995; Hashimoto et al. 1995). Moreover, motor deficit has been frequently described in AS (Green et al. 2002; Weimer et al. 2001) and motor skill impairment was also correlated with the severity of AS (Hilton 2007). The comparison between NT and AS individuals on the favorite > standard happy music contrast revealed a diminished left insula/frontal operculum activity in participants with AS. Previous studies on healthy participants reported enhanced left insula activity in response to pleasant music (Blood and Zatorre 2001; Menon and Levitin 2005). Similarly, when listening to sad music, the NT group showed increased activation in premotor areas as well as in the left frontal operculum. Therefore, hypoaactivation of the left insula/frontal operculum emerged as the only atypicality in AS individuals’ emotional processing of music.

Our findings indicate that in contrast to individuals with AS’s low performance within social and interpersonal domains, they seem to have a preserved ability in processing affect in musical stimuli (Heaton et al. 1999; Boso et al. 2009). Indeed, the observed activity within brain regions such as the mPFC, the orbitofrontal cortex, the dorsal striatum, the thalamus as well as the VTA/substantia nigra and the hippocampus suggests that affective components of music were processed at different levels. Specifically, a physiological level of emotional processing (first-order emotional experience, Damasio 1999; Critchley et al. 2001; LeDoux 2003) seems to be preserved as brain response to music was observed in the mesolimbic and limbic regions known to be involved in reward and emotion. Moreover, activity in the prefrontal cortex suggests a higher level of emotional processing which could be linked either to reward (Rolls 1990, 1996; Damasio 1996) or to top-down regulation of intense emotional responses (Davidson et al. 1990; Davidson and Irwin 1999).

On the other hand, AS showed reduced activity in the left anterior insula with respect to the healthy controls during affective music perception. Robust evidence exists about the crucial role of the anterior insular cortex in the representation of internal bodily states of arousal as well as emotional awareness or second-order (interoceptive) awareness (Critchley et al. 2001; LeDoux 2003) and alexithymia (Bird et al. 2010).

The deficits in social and empathic skills and in particular the difficulties in the cognitive processing of emotions in ASD have been connected to alexithymia (literally "being without

### Table 3

Control group—happy music

<table>
<thead>
<tr>
<th>Location</th>
<th>Side</th>
<th>Coordinates (MNI)</th>
<th>Brodmann area (BA)</th>
<th>t value</th>
</tr>
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<tbody>
<tr>
<td>Precentral gyrus</td>
<td>R</td>
<td>54, 0, 48</td>
<td>6</td>
<td>6.44</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>L</td>
<td>–6, 7, 26</td>
<td>6</td>
<td>6.15</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>R</td>
<td>6, 9, 72</td>
<td>6</td>
<td>5.68</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>–27, –60, –27</td>
<td></td>
<td>5.37</td>
</tr>
<tr>
<td>Inferior frontal gyrus/parietal gyrus</td>
<td>R</td>
<td>45, 30, 0</td>
<td>45</td>
<td>5.27</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>L</td>
<td>–51, –36, 21</td>
<td>42</td>
<td>5.26</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>30, –57, –30</td>
<td>6</td>
<td>4.63</td>
</tr>
<tr>
<td>Putamen</td>
<td>L</td>
<td>–24, 6, 9</td>
<td></td>
<td>4.51</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>R</td>
<td>48, –33, 21</td>
<td>42</td>
<td>4.33</td>
</tr>
<tr>
<td>Putamen</td>
<td>R</td>
<td>24, 9, 12</td>
<td></td>
<td>4.25</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>R</td>
<td>69, –33, 4</td>
<td>40</td>
<td>4.22</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>L</td>
<td>–48, –42, 6</td>
<td>42</td>
<td>4.20</td>
</tr>
<tr>
<td>Insula</td>
<td>L</td>
<td>–36, 12, 3</td>
<td>13</td>
<td>4.13</td>
</tr>
<tr>
<td>Inferior frontal gyrus/parietal gyrus</td>
<td>R</td>
<td>36, 33, 6</td>
<td>45</td>
<td>4.05</td>
</tr>
<tr>
<td>Inferior frontal gyrus/pars opercularis</td>
<td>R</td>
<td>6, 15, 0</td>
<td>44</td>
<td>3.98</td>
</tr>
<tr>
<td>Thalamus</td>
<td>L</td>
<td>–12, –12, 6</td>
<td></td>
<td>3.10</td>
</tr>
</tbody>
</table>

Note: Significant enhanced activations (SPM t-maps) during processing of happy music in healthy controls (NT).

### Table 4

Control group—sad music

<table>
<thead>
<tr>
<th>Location</th>
<th>Side</th>
<th>Coordinates (MNI)</th>
<th>Brodmann area (BA)</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentral gyrus</td>
<td>R</td>
<td>27, 48, 42</td>
<td>9</td>
<td>7.11</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>R</td>
<td>33, 33, 1</td>
<td>8</td>
<td>6.46</td>
</tr>
<tr>
<td>Heschl gyrus</td>
<td>L</td>
<td>39, –27, 41</td>
<td>6</td>
<td>6.05</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>R</td>
<td>33, 33, 0</td>
<td>32</td>
<td>5.75</td>
</tr>
<tr>
<td>Pons</td>
<td>L</td>
<td>–9, –24, 42</td>
<td></td>
<td>5.59</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>R</td>
<td>3, 27, 39</td>
<td>6</td>
<td>5.57</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>L</td>
<td>–30, –18, 9</td>
<td>13</td>
<td>5.55</td>
</tr>
<tr>
<td>Posterior insula</td>
<td>L</td>
<td>–36, –30, 15</td>
<td>48</td>
<td>5.53</td>
</tr>
<tr>
<td>Precuneus</td>
<td>L</td>
<td>–15, –54, 39</td>
<td></td>
<td>5.41</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>L</td>
<td>–63, –45, 18</td>
<td>22</td>
<td>5.38</td>
</tr>
<tr>
<td>Frontal superior medial gyrus</td>
<td>L</td>
<td>–9, –9, 6</td>
<td>10</td>
<td>5.34</td>
</tr>
<tr>
<td>Thalamus</td>
<td>L</td>
<td>–15, –9, 6</td>
<td>5.34</td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>L</td>
<td>–18, 12, 12</td>
<td>5.25</td>
<td></td>
</tr>
<tr>
<td>Medial temporal</td>
<td>R</td>
<td>0, –30, –18</td>
<td>5.24</td>
<td></td>
</tr>
<tr>
<td>Middle cingulate gyrus</td>
<td>R</td>
<td>0, –24, 42</td>
<td>31</td>
<td>5.08</td>
</tr>
<tr>
<td>Putamen</td>
<td>L</td>
<td>–27, 3, 9</td>
<td>5.03</td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>R</td>
<td>6, 9, 9</td>
<td>4.91</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>33, –33, 24</td>
<td>40</td>
<td>4.22</td>
</tr>
<tr>
<td>Frontal superior medial gyrus</td>
<td>L</td>
<td>12, 66, 3</td>
<td>10</td>
<td>4.82</td>
</tr>
<tr>
<td>Thalamus</td>
<td>L</td>
<td>–12, –6, 0</td>
<td>4.81</td>
<td></td>
</tr>
</tbody>
</table>

Note: Significant enhanced activations (SPM t-maps) during processing of sad music in healthy controls (NT).
words for emotions’), a subclinical condition characterized by difficulties in perceiving, identifying, and describing feelings and emotions. Bermond (1997) drew a distinction between “type I alexithymia” in which affective responses are reduced or absent and “type II alexithymia” in which affective arousal is present, but the individual is unable to gain cognitive awareness of the nature of the emotions. Several studies indicated a compromised emotional awareness—type II alexithymia—in ASD individuals (Hurlburt et al. 1994; Hill et al. 2004; Ben Shalom et al. 2006; Rieffe et al. 2006; Silani et al. 2008; Allen and Heaton 2010). In particular, Berthoz and Hill (2005) found a high incidence of type II alexithymia in ASD group compared with controls, but no significant difference in type I alexithymia between controls and autism group. Silani et al. (2008) reported an association between a reduced response in the anterior insula and self-reported poor awareness of own and others feelings in high-functioning autism/Asperger individuals. In a subsequent study, the same authors (Bird et al. 2010) observed a reduced activation of the left anterior insula in individuals with ASD compared with control participants when exposed to empathic pain stimuli. They reported that alexithymia, measured with the Toronto Alexithymia Scale—a standard questionnaire sensitive to type II alexithymia—mediated the empathy deficits in ASD. Hypoactivation of the left anterior insula in response to music in our AS group compared with the NT group provides further confirmation of the importance of this region as the site of differences in sensitivity to emotion-inducing stimuli in autism.

According to a recent hypothesis (Shalom 2009), a higher level of emotional processing might be used to compensate type II alexithymia in ASD. This compensatory mechanism would be mediated by the medial prefrontal regions. In this study, activity in these regions (BA10, 11) was observed during both “favorite” happy and sad musical excerpts, although no emotional assessment of our participants was specifically required.

Finally, our findings may help to explain the reported efficacy of music therapies in ASD (de Falco and Venuti 2006; Kern and Aldridge 2006). Music constitutes a domain of preserved skills and interest and a powerful and intelligible affective stimulus that emotionally captures and rewards ASD individuals as well as NTs. Although music does not have a primary social connotation, it can be regarded as a nonverbal form of communication able to consistently convey affective meaning, which can be therefore

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**Table 5**

<table>
<thead>
<tr>
<th>Location</th>
<th>Side</th>
<th>Coordinates (MNI)</th>
<th>Brodmann area (BA)</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard and favorite &gt; baseline</td>
<td>R</td>
<td>27, −15, 75</td>
<td>6</td>
<td>5.34</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>R</td>
<td>6, −15, 60</td>
<td>6</td>
<td>3.73</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>R</td>
<td>36, −84, −27</td>
<td>6</td>
<td>3.22</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>0, −87, −33</td>
<td>6</td>
<td>3.13</td>
</tr>
<tr>
<td>Favorite &gt; standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>L</td>
<td>−12, 12, 70</td>
<td>6</td>
<td>5.07</td>
</tr>
<tr>
<td>Insula</td>
<td>L</td>
<td>−39, 6, 15</td>
<td>48</td>
<td>3.29</td>
</tr>
<tr>
<td>Inferior frontal gyrus (frontal operculum)</td>
<td>L</td>
<td>−39, 24, −6</td>
<td>47</td>
<td>3.10</td>
</tr>
<tr>
<td>Sad</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard and favorite &gt; baseline</td>
<td>R</td>
<td>39, −60, 31</td>
<td>39</td>
<td>3.91</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>R</td>
<td>48, −60, −9</td>
<td>48</td>
<td>3.84</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>R</td>
<td>27, −15, 75</td>
<td>6</td>
<td>3.65</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>L</td>
<td>−15, −3, 63</td>
<td>6</td>
<td>3.61</td>
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<tr>
<td>Inferior frontal gyrus (frontal operculum)</td>
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<td>−54, 18, 15</td>
<td>47</td>
<td>3.65</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>33, −87, −30</td>
<td>48</td>
<td>3.38</td>
</tr>
<tr>
<td>Favorite &gt; standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>L</td>
<td>−21, 3, 60</td>
<td>6</td>
<td>3.99</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>R</td>
<td>21, −6, 57</td>
<td>6</td>
<td>3.61</td>
</tr>
</tbody>
</table>

Note: Significant enhanced activations (SPM t-maps) during processing of happy and sad music in healthy controls (NT) compared with individuals with AS.
used to facilitate emotion comprehension and to increase communicative skills in ASD patients.

Conclusions
This study substantially enhances our knowledge about the neurobiological correlates of emotion processing in ASD. Previous studies concentrated on emotions perceived in social stimuli, such as faces, leaving the neural correlates of emotions conveyed by nonsocial stimuli largely unexplored. By analyzing brain response to affective music, we highlighted for the first time several preserved cortical and subcortical circuits underlying affect and reward in individuals with ASD. Despite the generally impaired perception of emotions of ASD individuals in social situations, we demonstrated that they do possess relatively intact perception of emotions when listening to music. Moreover, patients with respect to control individuals showed a specific hypoactivation of the left anterior insula, which is considered pivotal for awareness of emotional states and second-level emotional process—a well-documented deficit in ASD. Our results also provide a neurobiological justification for the use of music therapies in ASD, which seem to enhance emotional skills and facilitate communication in these patients.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes
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Conflict of Interest None declared.

References


