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NeuroImage

NeuroImage 20 (2003) 2142–2152

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# Musical structure is processed in “language” areas of the brain: a possible role for Brodmann Area 47 in temporal coherence

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Received 16 June 2003; revised 1 August 2003; accepted 1 August 2003

## Abstract

The neuroanatomical correlates of musical structure were investigated using functional magnetic neuroimaging (fMRI) and a unique stimulus manipulation involving scrambled music. The experiment compared brain responses while participants listened to classical music and scrambled versions of that same music. Specifically, the scrambled versions disrupted musical structure while holding low-level musical attributes constant, including the psychoacoustic features of the music such as pitch, loudness, and timbre. Comparing music to its scrambled counterpart, we found focal activation in the pars orbitalis region (Brodmann Area 47) of the left inferior frontal cortex, a region that has been previously closely associated with the processing of linguistic structure in spoken and signed language, and its right hemisphere homologue. We speculate that this particular region of inferior frontal cortex may be more generally responsible for processing fine-structured stimuli that evolve over time, not merely those that are linguistic.

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Several important parallels exist among music, speech, and American Sign Language (Cooper and Paccia-Cooper, 1980). In all three forms of communication, the sensory input evolves over time in a coherent structure. Theories of structure in all three domains are in fact theories of temporal coherence and how elements are grouped over time (Cooper and Meyer, 1960; Cooper and Paccia-Cooper, 1980; Krumhansl, 1990, 1991; Lerdahl, 2001; Lerdahl and Jackendoff, 1971, 1983; West et al., 1985; Zatorre et al., 2002). A second parallel concerns the specific order of constituents in revealing meaning. The sentences of all human languages (spoken and signed) are composed of words in a certain linear order (Akmajian et al., 1990); although some languages display considerable freedom of word order, in no human language may the words of a sentence occur in a random order. This is also the case with music: musical phrases are composed of notes and/or chords, but these are not randomly ordered (Lerdahl, 2001; Patel, 2003). In the

pitch domain, *la-ti-do* has a very different meaning and implication than *ti-la-do*; the chord progression IV–V–I (which resolves) implies a different set of expectations than I–V–IV (which sounds unresolved). The four opening notes of Beethoven's Fifth Symphony provide an additional example from the rhythmic domain: the main motive, three short notes followed by a long one, takes on a completely different meaning if the rhythmic elements are changed to be long-short-short-short, or indeed, any other transformation (in the Chomskian sense) of the elements (Cooper and Paccia-Cooper, 1980). Thus there exist parallels in the formal generative structure of these three communication forms and as well, all three exhibit specific and relatively fixed developmental time courses (Brown, 1991; Klima and Bellugi, 1988; Poizner et al., 1990; Trehub, 2001).

The neural underpinnings of spoken and signed sentences in humans have been explored (Brown and Hagoort, 1999; Dapretto and Bookheimer, 1999; Gazzaniga et al., 1998; Just et al., 1996; Meyer et al., 2000; Neville et al., 1998; Petersen et al., 1988, 1989; Poldrack et al., 1999; Tettamanti et al., 2002), and the left inferior frontal cortex (LIFC) has been generally implicated in the comprehension

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of sentences (Dapretto and Bookheimer, 1999; Poldrack et al., 1999), and specifically in the control of semantic retrieval (Wagner et al., 2001), the selection of semantic information (Thompson-Schill et al., 1997), and rehearsal and maintenance of linguistic as well as nonlinguistic verbal materials (Petrides et al., 1993a, 1993b). Anatomically, the ventrolateral prefrontal cortex comprises, caudally, the pars opercularis (area 44) and, more anteriorly, the pars triangularis (area 45) and pars orbitalis and the immediately adjacent cortex (area 47/12). Areas 45 and 47/12 have been referred to as the mid-ventrolateral prefrontal region (Petrides, 2000). Different operations appear to be subserved by distinct subregions of the LIFC, with the ventral-anterior regions of LIFC (BA 47) involved in semantic/syntactic processing and the dorsal-posterior (BA 44/45) regions involved in phonological processing (Demonet et al., 1996; Fiez et al., 1995; Poldrack et al., 1999; Roskies et al., 2001; Zatorre et al., 1992, 1996). Less is currently known about the involvement of these regions in processing musical structure. Patel's (2003) "shared syntactic integration resource hypothesis" (SSIRH) proposes that syntax in language and music share a common set of processes instantiated in frontal brain regions.

The concept of structure pertains to whole systems, not to isolated components (Pomerantz and Lockhead, 1991). Just as visual structure is manifested in the way visual elements group over space, musical structure manifests itself in the way musical elements are grouped over time (Bent and Pople, 2000). Based on theoretical discussions of what constitutes structure most generally, we operationally define *musical structure* as that which exists when musical elements are bound, through temporal coherence, in a way that leads to informational redundancy and expectation (Garner, 1974; Pomerantz and Lockhead, 1991). More simply stated, structure exists when one can differentiate an ordered sequence from a random sequence of musical events (see also Patel, 2003). Thus, in the present experiment we randomized ("scrambled") musical excerpts within a piece of music in order to disrupt musical structure and to examine those neural structures within the IFC that are involved in the processing of musical stimuli.

Previous studies have probed the sensitivity of brain regions to musical structure by employing a paradigm of deviant musical events, or "oddball" stimuli. Participants in these experiments typically hear chord sequences designed to establish a musical context and then harmonic expectancies are either violated or fulfilled. Regions of inferior frontal cortex (IFC) including Broca's Area (BA 44) have been thus implicated in the processing of such violations of musical expectancies using both MEG (Maess et al., 2001) and fMRI (Koelsch, 2002). In related work, brain evoked-potentials elicited from the processing of musical chord-sequences have been found to be similar to those elicited by spoken language (Koelsch et al., 2000a, 2000b; 2002; Patel et al., 1998). Because expectation is necessarily dependent on temporal coherence, these studies are relevant to the

present investigation, although there are important differences. These previous studies tap into neural structures involved with surprise, tonal dissonance, and shifting attentional focus from a tonal center, and accordingly they serve as tests of processing associated with local structural incongruities in music. We were interested in building on this prior work to go beyond focal incongruities using a new paradigm that violated temporal coherence more globally.

Petitto et al. (2000) demonstrated that the LIFC is recruited for the processing of visual signs in natural signed languages. Both the ventral-anterior region of the LIFC (pars orbitalis, BA 47) and Broca's area (BA 44)—previously implicated in semantic and phonological processing of spoken language, respectively—showed significant activation in response to visual signs. Two important conclusions follow from this: first, that the LIFC participates in stimulus processing beyond just spoken and written language; and second, that it has a much greater degree of plasticity than was previously imagined, sufficient to allow new representations of linguistic meaning to develop in the absence of sound and written alphabets. This converges with the neuropsychological evidence that lesions to the lateral regions of LIFC (including BA 47) lead to difficulties in consciously representing sequences of speech or behavior (Luria, 1970). Tallal and co-workers (Merzenich et al., 1996; Tallal, 1980; Tallal et al., 1996) and Temple et al. (2000) have suggested that the LIFC is involved in the processing of those aspects of acoustic stimuli that change over time. The findings of Petitto et al. (2000) suggest that these changing stimuli need not even be acoustic; we wondered if they need even be linguistic.

We presented participants with excerpts from the standard classical music repertoire and with scrambled versions of those excerpts, in a paradigm analogous to studies of scrambled sentences (Marks and Miller, 1964; Miller, 1962; Miller and Selfridge, 1950; Vandenberghe et al., 2002). The scrambled music was created by randomly reordering 250- to 350-ms fragments of the regular music. This yielded quasi-musical stimulus examples that retained the pitch distribution, loudness profile, and timbre/spectral distribution of an actual piece of music, but lacked temporal coherence. In the scrambled version, those musical attributes that manifest themselves across time are disrupted, such as melodic contour, the navigation through tonal and key spaces (as studied by Janata et al. 2002), and any rhythmic groupings lasting longer than 350 ms.<sup>1</sup> Consequently, the stimulus comparison was between sounds that shared low-level

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<sup>1</sup> Of the eight attributes of a musical signal—pitch, loudness, timbre, spatial location, reverberant environment, rhythm, tempo, and contour (Levitin, 1999; Pierce, 1983), we were able to match the first five of those that are not time dependent, and we disrupted the remaining three. The five we matched are low-level aspects of the auditory system, the other three (rhythm, tempo, and contour) are not acoustic, but, rather, invoke higher order cognitive operations. Future studies will be required to tease apart the relative contributions of these musical attributes.

acoustic properties (pitch, loudness, timbre) but differed in high-level cognitive properties—the temporal coherence (and hence structure) of the music (Dowling and Harwood, 1986; Meyer, 1956). Thirteen adult volunteers, all of whom were nonmusicians, were tested using functional magnetic resonance imaging (fMRI) and the blood oxygenation level-dependent (BOLD) response was measured.

We hypothesized that if the IFC is involved in processing temporal coherence in music, it would show greater BOLD activation during music listening than listening to our scrambled stimuli. However, unlike previous studies of IFC with linguistic stimuli, we expected to find activation bilaterally in pars orbitalis, with the left hemisphere processing the temporal components of music, and the right hemisphere processing pitched components, both of which contribute to structural coherence as manifested across time in music (Zatorre et al., 2002).

## Methods

### *Subjects*

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

### *Stimuli*

The stimuli for the music conditions consisted of digitized sound files (22,050 sampling rate, 16 bit mono) presented in a random order taken from compact disc recordings of standard pieces in the classical repertoire. The first 23 s of the pieces was used. Scrambled versions were created by randomly drawing 250- to 350-ms variable-sized excerpts from each piece and concatenating them with a 30-ms linear cross-fade between excerpts. The stimuli used are listed in the Appendix.

The differences between the control and the experimental conditions were as follows. Both retain, over the course of the 23-s excerpt, the same distribution of pitch and loudness (this must logically be true, since elements were simply reordered) and the same spectral information (as shown in Fig. 1). Fast Fourier transforms (FFTs) between the normal and scrambled versions correlated significantly (Pearson's  $r = 0.99$ ,  $P < 0.001$  for all selections). What is different between the two versions is temporal coherence. In the scrambled version, those elements that manifest themselves across time are disrupted, such as melodic contour, the navigation through tonal and key spaces (as studied by

Janata et al. 2002), and any rhythmic groupings lasting longer than 350 ms.

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

### *fMRI acquisition*

Images were acquired on a 3T GE Signa scanner using a standard GE whole-head coil (software Lx 8.3). Images were acquired every 2 s in a single run that lasted 8 min and 48 s. A custom-built head holder was used to prevent head movement. Twenty-eight axial slices (4.0 mm thick, 0.5 mm skip) parallel to the ACPC line and covering the whole brain were imaged with a temporal resolution of 2 s using a T2\*-weighted gradient-echo spiral pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 70°, 180 time frames, and 1 interleave; Glover and Lai, 1998). The field of view was 200 × 200 mm, and the matrix size was 64 × 64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss arising from field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring functional MRI scans (Kim et al., 2000). Images were reconstructed, by gridding interpolation and inverse Fourier transform, for each time point into 64 × 64 × 28 image matrices (voxel size 3.125 × 3.125 × 4.5 mm). A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (Glover and Lai, 1998).

To aid in localization of functional data, a high-resolution T1-weighted spoiled grass gradient recalled (SPGR) inversion-recovery 3D MRI sequence was used with the following parameters: TI = 300 ms, TR = 8 ms; TE = 3.6 ms; flip angle = 15°; 22 cm field of view; 124 slices in sagittal plane; 256 × 192 matrix; 2 averages, acquired resolution = 1.5 × 0.9 × 1.1 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9-mm spatial resolution. Structural and functional images were acquired in the same scan session.

### *Stimulus presentation*

The task was programmed using Psyscope (Cohen et al., 1993) on a Macintosh (Cupertino, CA) computer. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a CMU Button Box microprocessor (<http://poppy.psy.cmu.edu/psyscope>) connected to the Macintosh. Auditory stimuli were presented binaurally using a custom-built magnet-compatible system. This pneumatic delivery system was constructed using a piezoelectric loudspeaker attached to a cone-shaped funnel, which in turn was connected to flexible plastic tubing leading to the participant's ears. The tubing passed through foam earplug

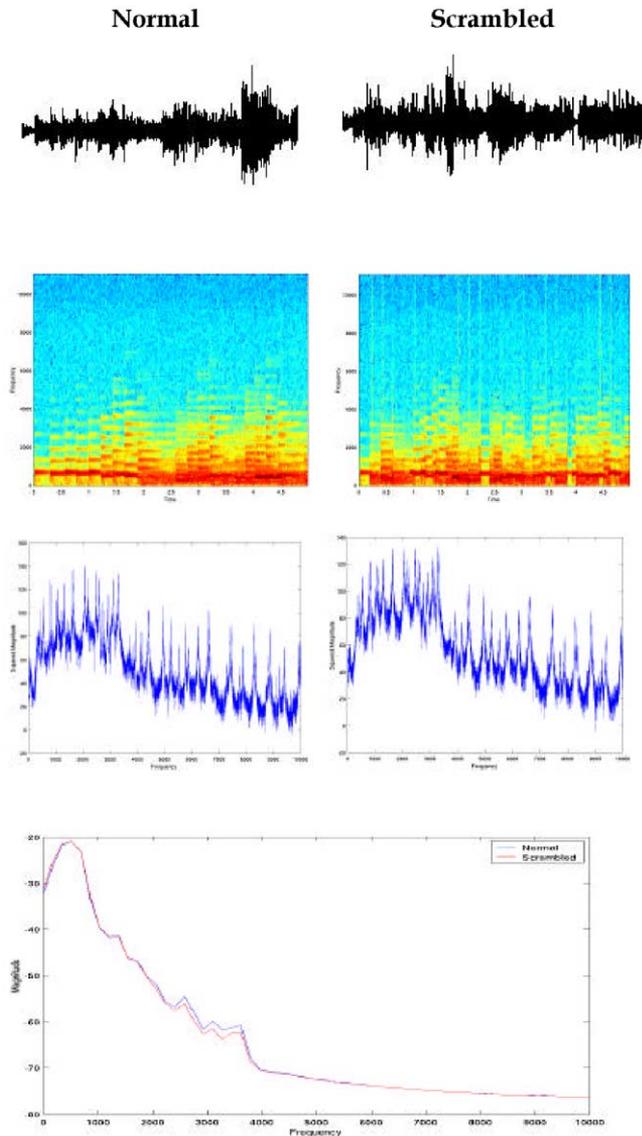


Fig. 1. Normal (left) vs scrambled music (right) stimulus comparisons for the first 5 s of a typical musical piece (Für Elise) used in the present experiment. Top panel: amplitude vs time. Second panel: Spectrogram. Third panel: Power spectrum. Bottom: Fast Fourier transform. The stimuli are spectrally equivalent and contain the same power over the duration of the excerpt presented.

inserts that attenuate external sound by approximately 28 dB. The loudness levels at the head of the participant due to the fMRI equipment during scanning was approximately 98 dB (A), and so after the attenuation provided by the ear inserts, background noise was approximately 70 dB (A) at the ears of the listener. The experimenters set the stimuli at a comfortable listening level determined individually by each participant during a test scan.

### Image preprocessing

fMRI data were preprocessed using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm>). Images were corrected for

movement using least-squares minimization without higher order corrections for spin history (Friston et al., 1996), and were normalized to stereotaxic Talairach coordinates using nonlinear transformations (Ashburner and Friston, 1999; Friston et al., 1996). Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4-mm Gaussian kernel to reduce spatial noise.

### Statistical analysis

Statistical analysis was performed using the general linear model and the theory of Gaussian random fields as implemented in SPM99. This method takes advantage of multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data (Friston et al., 1995). Activation foci were superimposed on high-resolution T1-weighted images and their locations were interpreted using known neuroanatomical landmarks (Duvernoy and Bourgouin, 1999). MNI coordinates were transformed to Talairach coordinates using a nonlinear transformation (Brett, 2000).

A within-subjects procedure was used to model all the effects of interest for each subject. Individual subject models were identical across subjects (i.e., a balanced design was used). Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 s) was applied to the fMRI time series to enhance the temporal signal to noise ratio. We then defined the effects of interest for each subject with the relevant contrasts of the parameter estimates. Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. This model estimates the error variance for each condition of interest across subjects, rather than across scans and therefore provides a stronger generalization to the population from which data are acquired (Holmes and Friston, 1998). In the first stage, contrast images for each subject and each effect of interest were generated as described above. In the second stage, these contrast images were analyzed using a general linear model to determine voxelwise  $t$  statistics. One contrast image was generated per subject, for each effect of interest. Finally, the  $t$  statistics were normalized to  $Z$  scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent of  $Z$  scores (Poline et al., 1997), with height ( $Z > 2.33$ ;  $P < 0.01$ ) and extent thresholds ( $P < 0.05$ ).

### Results

We analyzed fMRI activation for the normal music versus the scrambled music conditions: the difference between these two conditions (Normal - Scrambled) should index

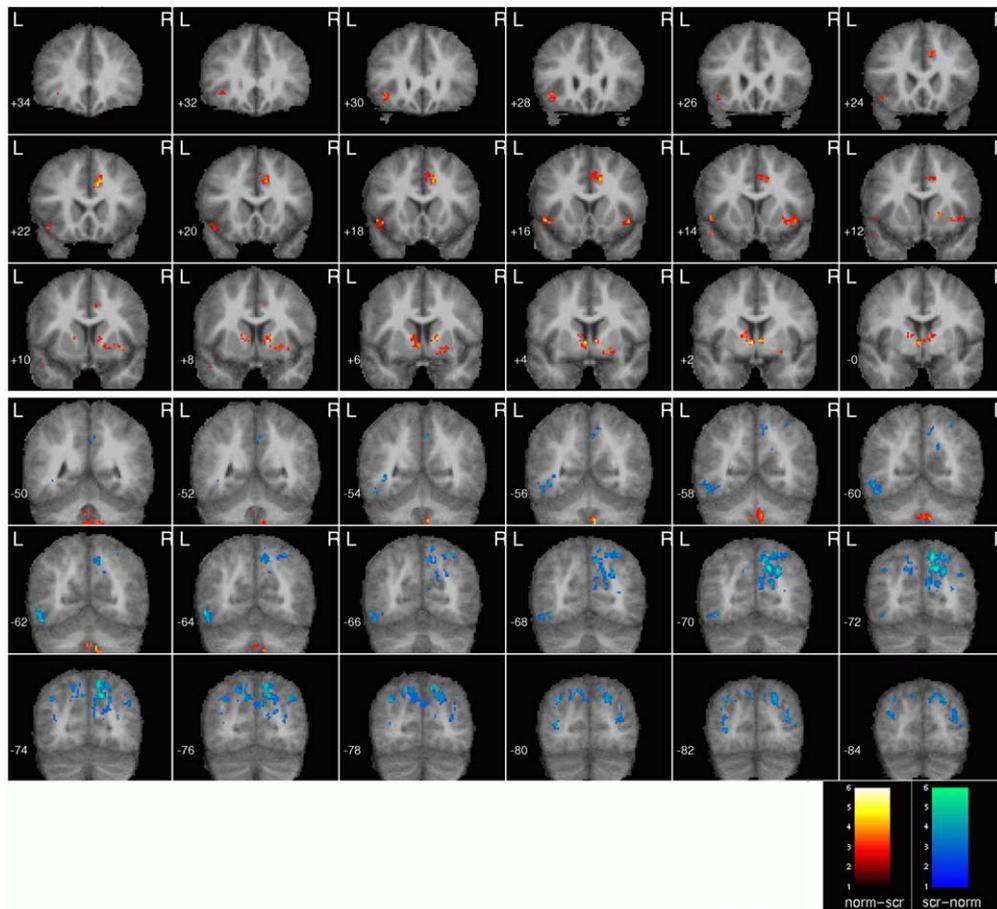


Fig. 2. Coronal sections showing BOLD activations and deactivations to normal compared to scrambled music. Activation is shown superimposed on group-averaged ( $N = 13$ ), spatially normalized, T1-weighted images. In each hemisphere, activation of the pars orbitalis region of the left inferior frontal cortex (BA 47) was observed, although activation was more extensive in the left hemisphere. Refer to Tables 1 and 2 for a list of principal coordinates for, respectively, the Music–Scrambled and Scrambled–Music comparisons.

neural processes associated with the perception of musical structure, but not with any features that the two conditions had in common with one another. Comparing music and scrambled music in fact revealed no differential activation in primary or secondary auditory cortices, serving as a validation that the two conditions were well matched for low-level acoustical features believed to be processed in these structures, such as loudness, pitch (Zatorre et al., 2002), and timbre (Menon et al., 2002). As hypothesized, we found significant ( $P < 0.01$ , corrected) activation in the pars orbitalis region of LIFC (BA 47) and the adjoining anterior insula as well as their right hemisphere homologues (see Fig. 2). The right hemisphere activation was less extensive than activation in the left; activation there was primarily confined to the posterior pars orbitalis section of the IFC (BA 47), immediately adjoining the anterior insula. In addition, we found significant ( $P < 0.01$ , corrected) activation in the anterior cingulate cortex, the nucleus accumbens, brainstem, and the posterior vermis (see Table 1 for a complete list of activations and their Talairach coordinates).

We also examined brain areas that showed greater acti-

vation in the scrambled, compared to normal, music condition (represented as deactivation in Fig. 2). No activation was observed in either the left or the right IFC or any other region of the prefrontal cortex (Table 2).

One might argue that our results were an artifact of the nonscrambled music sounding somewhat familiar and the scrambled music being unfamiliar. That is, the activations we observed may have been due to differing cognitive operations invoked due to familiarity (Platel et al., 1997). To address this possibility, we presented participants both familiar and unfamiliar selections (confirmed individually by each participant), unscrambled. A direct statistical comparison of these conditions revealed no differences in activation in BA 47 or any other IFC regions, confirming that familiarity was not a confound for the prefrontal activations. A second concern might be raised that the lack of significant activation in the auditory cortex occurred because scanner noise was so loud as to activate auditory cortex at ceiling levels in both conditions and thus account for them canceling each other out. To counter this claim, we compared the music condition to a no music resting condition in a separate group of participants, and found statistically significant ac-

Table 1  
Brain regions that showed significant activation during normal, as compared to scrambled music

Regions	<i>P</i> value (corrected)	No. of voxels	Maximum <i>Z</i> score	Peak Talairach coordinates (mm)
Left inferior frontal cortex, pars orbitalis (BA 47) and adjoining insula	0.019	100	3.70	−48 16 −6
Right inferior frontal cortex, pars orbitalis (BA 47), anterior insular cortex	0.010	110	3.15	44 16 −8
Anterior cingulate cortex (BA 24)	<0.007	116	3.88	10 22 32
Nucleus accumbens	<0.001	194	4.61	−4 2 0
Brainstem	0.040	89	4.00	−8 −26 −14
Posterior vermis/Brainstem	<0.001	245	3.97	6 −46 −40

Six significant clusters of activation were found ( $P < 0.01$  height,  $P < 0.05$  extent). For each cluster, the brain region, significance level, number of activated voxels, maximum *Z* score, and location of peak in Talairach coordinates are shown.

tivation in primary and secondary auditory cortex (Levitin et al., 2003), indicating that the effect of scanner noise was not at ceiling levels when no music was being played.

One might argue that a confound in our experimental design could have emerged if the normal and scrambled music differed in the salience of the tactus, that is, the pulse or beat to which one might tap one's feet (or at least the feet in one's mind). To counter this, we ran a control condition in which four participants tapped their feet to the normal and scrambled versions of two different pieces chosen at random. The scrambled versions were presented first so as not to bias the participants. We calculated the percentage coefficient of variation (*cv*) in each case and compared them statistically, the variability is the appropriate measure since mean tapping may be different across the examples, and it is the steadiness of pulse that is of interest (Drake and Botte, 1993; Levitin and Cook, 1996). The results were: *William Tell Overture*: *cv* = 3.34 (normal) and 4.55 (scrambled),  $z = 0.45$ ,  $P \sim 0.66$  (n.s.); *Eine Kleine Nachtmusic*: *cv* = 4.54 (normal) and 4.18 (scrambled),  $z = 0.13$ ,  $P \sim 0.90$  (n.s.). We performed an analysis of note length distributions between the two versions for two songs chosen at random, and they were found to be not statistically different (by Wald-Wolfowitz runs test,  $P \sim 0.10$  for both comparisons). One piece of converging neural evidence that the strength of pulse was matched across conditions was the lack of cerebellar activation.

## Discussion

Our subjects listened with focused attention to music from the standard classical repertoire, and we compared brain activations in this condition with listening to scrambled versions of those same musical pieces. The objective of presenting scrambled music was to break temporal coherence; the comparison condition consisted of “nonmusical music,” balanced for low-level factors. Previous investigations of musical structure have disrupted musical expectations by introducing unexpected chords, and consequently these manipulations examined only a more narrow notion of musical structure and expectation, and involved cognitive operations related to surprise, tonal dissonance, and the shifting of attentional focus to an incongruity. Our findings of no differential activation in auditory cortex confirmed that the two conditions in the present experiment were well matched for low-level acoustical features (even a multidimensional one such as timbre that by itself activates both primary and secondary auditory cortices; Menon et al., 2002). We hypothesized that we would obtain significant activation in IFC; in particular in BA 47 and the anterior insula adjoining it, if this region were involved in the processing of temporal coherence in music. This is in fact what we found, and is consistent with Patel's (2003) SSIRH hypothesis that musical and linguistic syntax may share common neural substrates for their processing.

Table 2  
Brain regions that showed significant activation during scrambled, as compared to normal music

Regions	<i>P</i> value (corrected)	No. of voxels	Maximum <i>Z</i> score	Peak Talairach coordinates (mm)
Right superior parietal lobule, intraparietal sulcus (BA 7), posterior cingulate (BA 23), precuneus (BA 19)	<0.001	1118	4.82	16 −68 40
Left inferior temporal gyrus, inferior occipital gyrus (BA 37)	<0.001	207	4.27	−52 −60 −10
Left superior parietal lobule, intraparietal sulcus (BA 7), angular gyrus (BA 39)	0.003	132	3.64	−34 −76 36
Right middle occipital gyrus (BA 19)	<0.001	199	3.56	34 −86 18

Five significant clusters of activation were found ( $P < 0.01$  height,  $P < 0.05$  extent). For each cluster, the brain region, significance level, number of activated voxels, maximum *Z* score, and location of peak in Talairach coordinates are shown.

Compared to normal music, scrambled music showed greater activation in the posterior cingulate cortex, the precuneus, cuneus, superior and middle occipital gyrus, and the inferior temporal gyrus. It is unlikely that activation in these regions directly reflects processing of scrambled music. First, many of these regions, including the cuneus, superior and middle occipital gyrus, and the inferior temporal gyrus are in fact involved in various aspects of visual processing. It is relevant to note here that these regions are strongly “deactivated” in response to auditory stimuli (Laurienti et al., 2002). Although auditory stimuli in our study were closely matched, it is likely that the two types of stimuli evoke different levels of “deactivation” for reasons that are not entirely clear at this time. Other regions, such as the posterior cingulate cortex, the precuneus, and anterior aspects of the cuneus, are known to be deactivated during both auditory and visual processing. Deactivations in these two regions are typically observed when activation during demanding cognitive tasks is compared with a low-level baseline, such as “rest” (Greicius et al., 2003; Schulman et al., 1997). Based on available data we therefore conclude that most of these activation differences arise from “deactivation,” and many more experimental manipulations, including the use of a low-level-baseline task (such as rest or passive fixation) are needed to tease out the brain and cognitive processes underlying the observed effects.

Our finding is consistent with a large number of studies linking LIFC to semantic processing of spoken language (Binder et al., 1997; Bokde et al., 2001; Dapretto and Bookheimer, 1999; Demb et al., 1995; Fiez et al., 1995; Ni et al., 2000; Poldrack et al., 1999; Roskies et al., 2001; Shaywitz et al., 1995) and signed languages (Bavelier et al., 1998; Neville et al., 1998; Petitto et al., 2000), with a study associating BA 47 activation to discrimination of musical meter by nonmusicians (Parsons, 2001) and with research implicating the BA 47 region in dynamic auditory processing (Poldrack et al., 1999). They provide regional specificity to claims that there exists a unique cognitive system dedicated to the processing of syntactic structure (Caplan, 1995), and that prefrontal cortex may be central to dynamic prediction (Huettel et al., 2002).

Our findings also converge with those of Petrides and his colleagues (Doyon et al., 1996; Petrides, 1996). Using a spatial expectation paradigm developed by Nissen and Bullemer (1987) and positron emission tomography (PET), they found activation in right mid-ventrolateral frontal cortex during the performance of an explicitly trained visual sequence. The focus of their study was to ascertain whether implicit and declarative aspects of skilled performance could be dissociated at the neural level. Within the framework of our current thinking, and considering recent work on IFC as a whole, we reinterpret their finding as having isolated brain regions responsible for the processing of meaning in temporally ordered sequences. Taken together, we believe our findings provide support for the hypothesis that the pars orbitalis is involved *generally* in the processing

of stimuli that have a coherent temporal structure, and that have meaning that evolves over time, and that these stimuli need be neither auditory nor linguistic.

In a recent study of musical processing, Janata et al. (2002) investigated the cortical topography of musical keys by playing experimental participants a specially designed musical sequence that navigated through all 24 major and minor keys. Using fMRI, they found activation in right IFC with the focus of highest activation in different portions of this region than in the present findings, and that is to be expected since the two tasks were quite different. Our activations were more ventral and posterior to those reported by Janata et al., and probably index the different cognitive operations involved in the two experiments. The activations in the Janata et al. study were observed in the anteriormost aspects of the pars triangularis region of the IFC. Structuro-semantic processing in language is generally associated with the more ventral (pars orbitals and pars opercularis) regions of the IFC (Bookheimer, 2002) activated in our study. The ways in which this cortical key topography might interact with temporal coherence and musical structure is an important topic for further exploration.

Koelsch et al. (2002) found activation in the pars opercularis region in response to violations of musical expectation. Our activations, in the pars orbitalis region, are more anterior and ventral to theirs, all still within the IFC. It is believed these regions play distinct roles in language and temporal processing, and differences between our findings are to be expected. We used more conservative statistical criteria with random effects analysis and  $P < 0.01$  *corrected* for multiple spatial comparisons. Task differences existed also: their subjects were asked “to differentiate between in-key chords, clusters, and chords played by instruments deviating from piano,” a set of tasks that invokes quite different cognitive operations than our task did, including harmonic expectations, tracking of harmonic motion, music theoretical reasoning, detection of timbral change, and specific focal violations of musical structure which may have induced surprise and covert attentional shifts.

Tillmann et al. (2003) conducted a study of musical priming in which listeners were asked to detect related and unrelated musical targets at the end of musical sequences. Their activations were in the opercular and triangular regions of the IFC, more dorsal than ours. We believe that our more rigorous and conservative statistical analysis underlies the different focus and extent of activation we observed compared to their observations. Although Tillmann et al. did use a random effects analysis, they did not apply the rigorous spatial correction that we did. Such spatial corrections allow one to state with greater certainty the precise regions, and subregions, that were activated in an experiment, and it is only through the application of such corrections that one can make inferences about the true source of neural activity. We also believe that the cognitive operations tapped in our experiment were more circumscribed than in these previous two studies, and limited to the differences

between perceiving temporal structure and the lack of it in music. Our activations were thus more focused than in these previous two studies because we eliminated the ancillary cognitive operations that were invoked during their musical judgment tasks. Our study thus shows for the first time, in a statistically rigorous manner, that the pars orbitalis region is involved in processing temporal coherence in music, and by extension, those aspects of the musical signal that contain its meaning.

Our brainstem activation is consistent with the findings of Griffiths et al. (2001) who found activations there in a task involving the encoding of temporal regularities of sound. Despite the conservative random effects analyses used in our study, with corrections for multiple spatial comparisons, we detected activation in all three brainstem regions identified in the Griffiths et al. study, including the the cochlear nucleus (Talairach coordinates: 6, -46, -40), inferior colliculus (coordinates: -8, 26-14), and the medial geniculate nucleus (coordinates: -4, -26, -2). Previous research has implicated the cerebellum bilaterally (Caplan, 1995) in music listening, and this may index the rhythmic and metric aspects of the music. One cerebellar region in particular, the posterior vermis, has also been associated with music listening (Griffiths et al., 1999; Levitin et al., 2003), which we attribute along with the nucleus accumbens activation to the emotional component of listening to meaningful music (Blood et al., 1999; Schmahmann, 1997; Schmahmann and Sherman, 1988). These activations are presumably mediated by major connections linking the prefrontal cortex with the basal ganglia and the cerebellar vermis (Mesulam, 2000; Schmahmann, 1997), and are consistent with the notion that a region in the right cerebellum may be functionally related to those in the LIFC for semantic processing (Roskies et al., 2001), thus serving to link the cognitive and emotional aspects of music. Taken together, our findings and those of Griffiths suggest the involvement of subcortical auditory regions in the processing of temporal regularities in music.

In a study of musical imagery for familiar songs, and the processing of components associated with retrieval of songs from memory (Halpern and Zatorre, 1999), both activated Area 47 (right hemisphere only) and musical imagery activated Area 44 (left). When imagery involved “semantic retrieval” (here the authors are referring to semantic memory vs episodic memory, not to the notion of semantic meaning of the musical piece), they found activation in Broca’s Area (left BA 44). Our findings are consistent with these. Whereas those authors interpreted these findings as indicating Area 47’s involvement in memory, we believe in light of the current findings that their activation resulted from the structural aspects of the musical content.

Duncan et al. (2000) have implicated the BA 47 region of the LIFC in general intelligence (Spearman’s *g*). Using PET, they argue that a wide array of tasks—spatial, verbal, and perceptuo-motor—are associated with selective recruitment of these regions when compared to similar tasks that

do not require high levels of *g*. Closer inspection of the tasks they employed, however, reveals that all of the high-*g* tasks involved the processing of patterns in space or time. In light of the present findings, we are inclined to interpret their BA 47 activation as resulting from the temporal sequencing or the structuring of temporal events in the stimuli they chose to employ.

Anomaly processing involving, for example, a single focused violation of syntax or structure, has been a popular paradigm in the recent speech and music literature, but the processing of meaning and structure in a more general and fundamental sense are perhaps better addressed with the present paradigm which has a distinguished but older history, going back to Miller and Selfridge (1950).

According to theories of musical aesthetics, music does not represent specific, verbalizable emotions, such as pity or fear (Cooper and Meyer, 1960; Meyer, 1956). That is, music represents the dynamic form of emotion, not the static nor specific content of emotional life (Dowling and Harwood, 1986; Helmholtz, 1863/1954; Langer, 1951). This conveying of emotion is the essence of musical semantics, and depends on schemas and structure (Meyer, 1956). Almost without exception, theories of musical meaning are, in fact, theories of musical structure and its temporal coherence (Cooper and Meyer, 1960; Lerdahl and Jackendoff, 1971, 1983; West et al., 1985). Meaning itself, in a general sense, has been defined as the coordination of schemas and structure (Akmajian et al., 1990; Bregman, 1977; Hayakawa, 1939), the building of a consistent description based on rules that define internal consistency. We believe that a large body of evidence is now converging to suggest that Brodmann Area 47 and the adjoining anterior insula constitute a modality-independent brain area that organizes structural units in the perceptual stream to create larger, meaningful representation. That is, it may be part of a neural network for perceptual organization, obeying the rules of how objects in the distal world “go together” when they are manifested as patterns unfolding in a structured way over time.

## Acknowledgments

We are grateful to Evan Balaban, Al Bregman, Jay Dowling, John Gabrieli, Mari Reiss Jones, Carol Krumbhansl, Steve McAdams, Michael Posner, Bill Thompson, Anthony Wagner, and Robert Zatorre for helpful comments, Ben Krasnow and Anne Caclin for assistance with data acquisition, Gary Glover for technical assistance, Caroline Traube for programming the scrambler, Catherine Guastavino and Hadiya Nedd-Roderique for assistance preparing the figures, and Michael Brook for his assistance in preparing the scrambled stimuli. Portions of this work were presented at the Meeting of the Society for Music Perception and Cognition, Las Vegas, NV, June 2003, and at the Biannual Rhythm Perception & Production Workshop, Isle

de Tatihou, France, June 2003. This work was funded by grants from the Natural Sciences and Engineering Council of Canada (NSERC 228175-00), the Fonds du Recherche sur la Nature et les Technologies Quebec (FQRNT 2001-SC-70936), and by equipment grants from M&K Sound and Westlake Audio to D.J.L., and by NIH Grants HD40761 and MH62430 to V.M.

## Appendix

### *Musical stimuli employed*

Standard pieces from the classical repertoire were selected based on pilot testing. Using a separate group of 12 participants drawn from the same pool as our experimental participants, we identified 8 pieces that were known to all and 8 pieces by the same composers that were known to none. After the scanning sessions, we asked our experimental participants to indicate which of the selections were familiar and which were unfamiliar. In two cases, participants identified an “unfamiliar” piece as familiar, so for the analysis of their data we eliminated both that piece and its matched “familiar” piece.

### *Familiar*

J. S. Bach, *Jesu, Joy of Man's Desiring*  
 Beethoven, *Fifth Symphony*  
 Beethoven, *Für Elise*  
 Elgar, *Pomp and Circumstance*  
 Mozart, *Eine Kleine Nachtmusik, KV 525*  
 Rossini, *William Tell Overture*  
 Strauss, *Blue Danube*  
 Tchaikovsky, *March from the Nutcracker Suite*

### *Unfamiliar*

J. S. Bach, *Coriolan*  
 Beethoven, *First Symphony*  
 Beethoven, *Moonlight Sonata, 2nd Movement*  
 Elgar, *Symphony #1*  
 Mozart, *Ein Musikalischer Spaß, KV 522*  
 Rossini, *La Donna*  
 Strauss, *Wine, Women and Song*  
 Tchaikovsky, *First Symphony*

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