

Cognitive and Emotional Modulation of Brain Default Operation

Karen Johanne Pallesen¹, Elvira Brattico², Christopher J. Bailey¹,
Antti Korvenoja³, and Albert Gjedde¹

Abstract

■ Goal-directed behavior lowers activity in brain areas that include the medial frontal cortex, the medial and lateral parietal cortex, and limbic and paralimbic brain regions, commonly referred to as the “default network.” These activity decreases are believed to reflect the interruption of processes that are ongoing when the mind is in a restful state. Previously, the nature of these processes was probed by varying cognitive task parameters, but the presence of emotional processes, while often assumed, was little investigated. With fMRI, we studied the effect of systematic variations of both cognitive load and emotional stimulus connotation on task-related decreases in the default network by employing an auditory working memory (WM) task with musical sounds. The performance of the WM

task, compared to passive listening, lowered the activity in medial and lateral, prefrontal, parietal, temporal, and limbic regions. In a subset of these regions, the magnitude of decrease depended on the memory load; the greater the cognitive load, the larger the magnitude of the observed decrease. Furthermore, in the right amygdala and the left precuneus, areas previously associated with processing of unpleasant dissonant musical sounds, there was an interaction between the experimental condition and the stimulus type. The current results are consistent with the previously reported effect of task difficulty on task-related brain activation decreases. The results also indicate that task-related decreases may be further modulated by the emotional stimulus connotation. ■

INTRODUCTION

The current study addresses the question of the relationship between stimulus-independent activity during situations characterized by rest, also commonly referred to as default activity or resting state activity, and stimulus-related goal-directed activity in the human brain. During selective attention and stimulus-related cognitive operations, the default activity of the brain decreases in several cortical, limbic, and paralimbic locations. These decreases, which are believed to reflect the interruption of processes that are characteristic of a task-independent state (Gusnard & Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997), could be of two kinds: (i) task-dependent decreases in areas not engaged in the current task, such as regions processing input generated by other stimulus modalities (Laurienti et al., 2002; Lewis, Beauchamp, & DeYoe, 2000; Haxby et al., 1994), or (ii) task-independent decreases across different types of tasks and stimuli (first described by Shulman et al., 1997). Brain regions representative of the posited task-independent decreases include the posterior cingulate gyrus, precuneus, lateral parietal regions,

medial and orbital prefrontal cortex, anterior cingulate gyrus, inferior frontal cortex, and lateral frontal regions (Tomasi, Ernst, Caparelli, & Chang, 2006; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Mazoyer et al., 2001; Binder et al., 1999; Petersen, van Mier, Fiez, & Raichle, 1998; Raichle, 1998; Shulman et al., 1997; Haxby et al., 1994; Raichle et al., 1994).

Psychological evidence suggests that the mind, in the absence of external stimulation, is occupied with the stimulus-independent thoughts of “mind-wandering” (Teasdale et al., 1995; Antrobus, Singer, & Greenberg, 1966) that may involve cognitive operations similar to those employed during the execution of exogenously imposed tasks (Teasdale et al., 1995). Hence, stimulus-independent thoughts may be the psychological baseline of the resting mind (Smallwood & Schooler, 2006). To further probe the nature of these processes, task-related decreases were studied during different types of tasks with a main focus on the variation of cognitive parameters. Evidence from brain imaging studies include semantic processes (McKiernan et al., 2003; Binder et al., 1999) and episodic memory (Mazoyer et al., 2001) in this baseline state. Another view has as its main premise the observation that consistent task-related decreases do not reflect specific activations

¹University of Aarhus, Denmark, ²University of Helsinki, Finland,
³Helsinki University Central Hospital, Finland

(defined as activity elevation compared to the average brain activity during rest) in the resting state. This insight led to the formulation of a theory of a “default mode of brain function” that is functionally engaged in the general mental task of monitoring the external and internal environment. The default mode according to this theory critically involves the posterior cingulate gyrus (BA 31), the precuneus (BA 7), the medial prefrontal cortex (PFC, BAs 10, 32), the lateral parietal cortex (BAs 39, 40) (Raichle et al., 2001), and, as a more recent addition, the hippocampal formation (Vincent et al., 2006, 2007; Greicius, Srivastava, Reiss, & Menon, 2004).

Task-related decreases of activity in medial prefrontal and limbic cortices suggest that processing of self-referential and emotional materials occurs generally when more pressing tasks are not imposed from the outside (Gusnard et al., 2001; Raichle et al., 2001). Simpson, Snyder, Gusnard, and Raichle (2001) tested the influence of the emotional state of subjects performing a cognitive task on the magnitude of decreases in the medial PFC, a brain region assigned a general role in emotion processing (Steele & Lawrie, 2004; Phan, Wager, Taylor, & Liberzon, 2002). Task-related decreases of activity in the medial PFC (BAs 9, 10 and 32) were less when performance anxiety accompanied a word-generation task (compared to passive vision). The attenuation suggested an interaction between increased emotional activity and decreased cognitive activity in this region (Simpson et al., 2001).

The amygdala is critically involved in the experience of emotional valence (Habel, Klein, Kellermann, Shah, & Schneider, 2005; Kim et al., 2004; Anderson & Phelps, 2001; Blood & Zatorre, 2001; Isenberg et al., 1999; Morris et al., 1996, 1998; Bechara, Tranel, Damasio, & Damasio, 1996; Adolphs, Tranel, Damasio, & Damasio, 1994; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990). During processing of emotionally charged visual stimuli, the amygdaloid responses were lowered during naming compared to superficial matching (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Hariri, Bookheimer, & Mazziotta, 2000), during rating compared to recognition (Liberzon et al., 2000), during explicit compared to implicit processing, and during the task of describing negative visual scenes in unemotional terms (Ochsner, Bunge, Gross, & Gabrieli, 2002). There is also evidence of increased responses in the amygdala during introspective emotion reappraisal compared to passive (task unrelated) perception (Ochsner, Ray, et al., 2004).

Temporary reallocation of resources saved by the task-related decrease of brain activity implies competition (McKiernan et al., 2003; Drevets & Raichle, 1998; Haxby et al., 1994) and predicts that the cognitive demand dictates the magnitude of the decrease. In a meta-analysis, Shulman et al. (1997) found no evidence that matched this prediction, but other studies found evidence of reduced activity of the default network in pro-

portion to task difficulty during auditory discrimination and presentation rate detection (McKiernan et al., 2003), and visual tracking and visual working memory [WM] (Tomasi et al., 2006).

Here we test the hypothesis that both the cognitive load and the emotional stimulus connotation modulate the pattern of task-related activity decreases, especially that the emotional induction prevents the reassignment of neuronal resources that would otherwise be disengaged by a cognitive task. We designed an auditory experiment with systematic variation of the cognitive load and the emotional stimulus connotation. The stimuli were major, minor, and dissonant musical chords, characterized by happy, sad, and unpleasant emotional connotations, respectively (Pallesen, Brattico, & Carlson, 2003; Trainor & Heinmiller, 1998; Zentner & Kagan, 1998; Crowder, Reznick, & Rosenkrantz, 1991; Crowder, 1985). The emotional unpleasantness, or dissonance, of the sound stimuli had three levels, with major and dissonant chords representing the extremes. Processing of dissonance in musical stimuli was previously associated with the amygdala (Gosselin, Peretz, Johnsen, & Adolphs, 2007; Koelsch, Fritz, von Cramon, Muller, & Friederici, 2006), the parahippocampal gyrus (Gosselin et al., 2006; Koelsch et al., 2006), and the precuneus (Blood, Zatorre, Bermudez, & Evans, 1999). Hence, we predicted that cortical and limbic brain areas are deactivated during auditory cognition compared to a resting state of passive perception, and specifically, (i) that the decreases during the cognitive task depend on the cognitive load, and (ii) that the activity decrease in the amygdala, parahippocampal gyrus, and precuneus would be smaller in response to the negatively charged than to the positively charged auditory stimuli, resulting from the hypothesized countermodulation of task-related decreases by the emotional stimulus properties. Three experimental conditions varied the cognitive load: (1) passive listening (PL), (2) 1-back pitch WM (1B), and (3) 2-back pitch WM (2B). Because the subjects were required to perform a cognitive task on the chord stimuli, we thought that the emotional connotations implicitly would enter all experimental conditions. To allow wide generalization of the results, we presented the chords to musically untrained subjects while fMRI recorded the responses.

METHODS

Subjects

The 10 volunteers (age range = 22–31 years, mean = 25 years, 5 women) had minimal musical training, obtained exclusively as obligatory primary school music education. All subjects were right-handed and had no history of neurological disease or hearing deficit. The volunteers gave informed consent to the study as approved by the ethics committee of the Helsinki University Central Hospital.

Stimuli

The stimuli were nine sound combinations (chords) belonging to three different chord categories according to the Western tonal music theory (“major,” “minor,” and “dissonant”), and each spanning three frequency levels separated by an octave (frequency ratio 1:2, in musical notation the lowest pitches of the chords were A3, A4, and A5; see Figure 1). Each chord was produced with the grand-piano (Piano 1) timbre of the Roland Sound Canvas SC-50 synthesizer with built-in samples, and played using the ENCORE software. The chords were then edited by CoolEdit and SoundForge programs to be balanced in the loudness level and have the same duration (870 msec). The relatively long duration for single piano chords was chosen to maximize the emotional effects. The major chords consisted of A, C \sharp , E, A, C \sharp and, as such, were characterized mostly by consonant intervals. The minor chords consisted of A, C, E, A, C, including the minor third interval, which is considered an imperfect consonance in music theory (cf. Schön, Regnault, Ystad, & Besson, 2005). The dissonant chords were made of A, B, G, A, C, including a minor second, the interval considered the most dissonant in the literature (Fishman et al., 2001; Kameoka & Kuriyagawa, 1969; Plomp & Levelt, 1965), and several other dissonant intervals.

Experimental Conditions

The three experimental conditions included two *n*-back task conditions in which subjects memorized the pitch of the chords, and a passive listening condition in which subjects listened to the stimuli with no cognitive evaluation. The subjects responded to each stimulus by pressing the left or right button of a response pad, with their right index and middle finger, respectively. In the 1B task, subjects pressed the left button when the pitch of the chord was the same as in the previous trial and in the 2B task when the pitch was the same as presented two trials back. The right button was pressed in all other trials. In the PL condition, subjects pressed the right button after each chord.

Magnetic Resonance Imaging

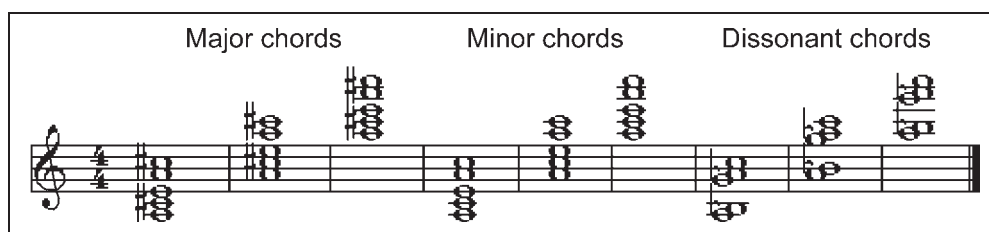
Magnetic resonance imaging measurements were performed in the Department of Radiology, Helsinki Uni-

versity Hospital, on a Siemens Sonata 1.5-T scanner. A 3-D T1-weighted anatomical image was acquired of each subject with the Magnetization Prepared Rapid Gradient Echo sequence [MP-RAGE; TR = 1900 msec, TE = 3.86 msec, TI = 1100 msec, flip angle = 15°, FOV = 256 mm, 256 × 256 mm² matrix, 176 sagittal slices, 1 mm³ isotropic voxel dimension]. For the functional imaging, a T2*-weighted, gradient-echo echo-planar sequence was used [EPI; TR = 3660 msec, TE = 40 msec, flip angle = 90°, FOV = 224 mm, 64 × 64 mm² matrix, 4 mm slice thickness (no gaps), 36 slices]. A single functional volume was acquired in 2790 msec, introducing a period of scanner silence (870 msec; no gradient noise) during which the stimuli were presented. The slices were oriented axially and placed according to an initial scout image to cover the whole brain and the cerebellum.

Experimental Procedure

Subjects were informed of the experimental conditions with written and oral descriptions. They practiced the button presses in the scanner room until they felt confident in performing the WM tasks. With respect to the PL condition, subjects were told to rest their mind from the task while still pressing a button after each stimulus. The chords were presented binaurally with MR-compatible head phones (Commander XG, Resonance Technology). The chords were played at an intensity of approximately 80 dB, individually adjusted, so that subjects could clearly hear the sounds and did not feel any related discomfort. In order to assure optimal perception of the sounds, stimulus presentation was interleaved with image acquisition. The experiment was divided into two sessions, each session containing 18 blocks of 20 trials. Each trial consisted of a stimulus (870 msec) followed by scanning (2760 msec) and silence (30 msec), with a total trial duration of 3660 msec. The blocks lasted 73.2 sec and were separated by 4-sec intervals. In addition to the task condition (PL, 1B, or 2B), each block was characterized by a chord category (i.e., major, minor, or dissonant). Thus, there were nine types of blocks: (1) PL, major; (2) 1B, major; (3) 2B, major; (4) PL, minor; (5) 1B, minor; (6) 2B, minor; (7) PL, dissonant; (8) 1B, dissonant; (9) 2B, dissonant. Each block was presented four times in a counterbalanced design. An instruction figure (“Passive Listening,” “1-Back,” or “2-Back”) was presented on a screen for a period of 4 sec before each

Figure 1. The stimuli were nine piano chords belonging to three different chord categories: major, minor, and dissonant. Each chord spanned three frequency levels separated by an octave; the lowest pitches of the chords were A3, A4, and A5. The duration of the chords was 870 msec.



block. The subjects viewed the instructions through a mirror placed on the head coil. During task performance, subjects were asked to fixate on a central cross on the screen. Between the two sessions there was a 2-min break, during which subjects stayed quietly in the scanner but were allowed to move the eyes freely or close them. A short sound at the end of the break told subjects to be ready for the next session. Image acquisition followed immediately after each stimulus. The imaging part lasted 54 min, and the anatomical scan lasted approximately 7 min, thus the total time in the scanner was approximately one hour.

A questionnaire and a behavioral test followed the imaging part. The questionnaire involved evaluation of memory strategies by ticking one or several of the following options: auditory rehearsal, verbal rehearsal, visual imagery, somatosensory imagery, movement, no specific strategy. The task difficulty level was evaluated as: 1 = very easy, 2 = easy, 3 = intermediate, 4 = difficult, and 5 = very difficult. In the behavioral test, subjects were asked to rate the emotional connotation of each stimulus (the major, minor, and dissonant chords) along a happy–sad scale and along a pleasant–unpleasant scale. Each scale had 11 values, from –5 to +5, with –5 denoting the most negative rating and +5 the most positive rating, and zero denoting “neutral.” The chords were rated twice, with chords presented in a randomized sequence.

Analysis of Behavioral Data

All statistical analyses were performed using the R project for statistical computing (www.r-project.org/). Two-way repeated measures analysis of variance (RM-ANOVA) was applied to the log-transformed reaction time (RT) data, with task condition and chord category as within-subject factors, and subject treated as a random effect. The RM-ANOVA was implemented as a linear mixed effects model (R function `lme`), and *t* tests were used post hoc to assess significant differences within factors. Task performance was measured as the ratio (*r*) of correct responses over total (*n*) responses. The ratio was then transformed using the following formula: $r' = 2 \times \pi \times \arcsin(p)$, where $p = 1/(4 \times n)$, if $r = 0$; $p = r$, if $0 < r < 1$; $p = (n - 1/4)/n$, if $r = 1$. The arcsine transformation is used to homogenize the variance of a binomial response variable (*r*). The transformed ratios (*r'*) and the emotional chord ratings were subjected to the same statistical test (RM-ANOVA) as the log-transformed RTs.

Analysis of fMRI Data

All analysis of functional and anatomical data was performed using the FMRIB Software Library (FSL, version 3.2b), Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, UK (www.fmrib.ox.ac.uk/fsl/). Non-

brain tissue was removed from the T1-weighted anatomical images using the Brain Extraction Tool (BET) of FSL (Smith, 2002). The MNI/ICBM-152 average brain was used as the standard stereotaxic space template in group analyses (Collins et al., 1998; Collins, Neelin, Peters, & Evans, 1994; Evans & Collins, 1993). Each individual's brain volume was coregistered to the template using affine transformations (12 degrees of freedom) estimated by FMRIB's Linear Registration Tool, FLIRT (Jenkinson & Smith, 2001).

Functional data were processed using FMRIB's Expert Analysis Tool (FEAT). During the experiment, 896 volumes were collected, of which the first five were discarded allowing T1 effects in the signal to saturate. The functional volumes were realigned to the midpoint of the experiment using rigid-body transformations (MCFLIRT; Jenkinson, Bannister, Brady, & Smith, 2002). Spatial smoothing was performed using a low-pass Gaussian filter with a full width at half maximum of 8 mm. A piecewise linear temporal high-pass filter (longest period passed: 805 sec) was used to remove low-frequency components of the data.

The general linear model (GLM) implementation of FEAT was used for model fitting of preprocessed data. The design matrix consisted of nine columns representing each of the possible blocks: permutations of memory load (2B, 1B, or PL) and chord category (major, minor, or dissonant). All columns were convolved with the “canonical” double-gamma hemodynamic response function. Autocorrelations in the model fit residuals were estimated and removed using the FILM prewhitening step in FEAT (Woolrich, Ripley, Brady, & Smith, 2001). First-level contrast images between the PL and WM conditions were calculated separately within each chord category: PL (major) versus 2B (major), 1B (dissonant) versus 2B (dissonant), and so forth. In addition, the regressors for each of the nine stimulation blocks were contrasted to the implicit baseline of the study, the instruction periods between blocks, in order to evaluate effects of chord type on the neuronal responses.

Group results were obtained using full mixed effects (ME) modeling, thus allowing generalization to the subject population. Higher-level parameter estimates and the ME variance were estimated implicitly within FEAT using FMRIB's Local Analysis of Mixed Effects (FLAME) (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004; Beckmann, Jenkinson, & Smith, 2003). The inputs to group analyses consisted of first-level contrast images categorized by chord, for instance, PL (major) versus 2B (major), PL (minor) versus 2B (minor), and PL (dissonant) versus 2B (dissonant) for each subject. One-sample *t* tests were implemented across subjects and chord types to test for specific load effects (nonzero means) in the planned contrasts. In addition, we implemented an “omnibus” ANOVA model in FEAT at the group level with the factors “load” and “chord,” each at three levels. The inputs to the analysis were the

nine regressors per subject representing the experimental blocks.

SPMs of the group contrasts of interest were created for “Gaussianized” t values, the so-called Z -scores. To control for the effects of multiple comparisons (type I error), Gaussian random field (GRF) theory was employed to assign p values to SPM peaks surviving the $Z > 3.0$ threshold (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992). All results and conclusions are based on clusters that reached at least the $p < .05$, corrected significance level. Tables of local Z -score maxima produced by FSL

for each contrast were translated to anatomical names using a structural parcellation of the MNI single-subject brain (Collins et al., 1998), and the extended naming procedure described in Tzourio-Mazoyer et al. (2002).

Chord category-specific effects were evaluated at standard-space coordinates selected as described in Results (cf. Table 1). A spherical ROI of 8 mm radius was created, centered on each coordinate, and resampled to each subject’s functional data space using transformations estimated during intrasubject analysis. Mean percent BOLD signal changes were then extracted for the nine contrasts representing the experimental blocks

Table 1. Group Activations for PL versus 2B Contrast; List of Local Maxima

Region of Activation	Hemisphere	Coordinates (MNI)			Peak Z Score
		x	y	z	
Medial superior frontal gyrus	left	−8	58	18	7.28
	right	0	62	6	8.58
Orbital middle frontal gyrus	right	6	56	−2	8.10
Gyrus rectus	left	−4	28	−12	8.03
Precuneus	left	−8	−52	16	7.21
Middle cingulate gyrus	left	−10	−44	36	7.12
Posterior cingulate gyrus	left	0	−44	30	6.39
Angular gyrus	left	−46	−68	30	7.08
Calcarine gyrus	left	−6	−64	22	6.89
Rolandic operculum	right	58	−4	10	6.57
Superior frontal gyrus	left	−16	30	56	6.55
Middle temporal gyrus	right	56	−4	−22	6.51
Precentral gyrus	right	28	−26	74	6.26
Lingual gyrus	right	6	−50	4	6.26
Inferior temporal gyrus	right	52	−6	−30	6.22
Fusiform gyrus	left	−24	−38	−14	6.14
	right	28	−32	−20	6.22
Temporal pole	left	−36	10	−38	6.20
	right	44	18	−36	6.21
Hippocampus	right	26	−10	−18	6.12
Orbital inferior frontal gyrus	left	−32	34	−12	6.03
Postcentral gyrus	right	36	−30	70	6.01
Middle frontal gyrus	left	−26	22	46	5.88
Parahippocampal gyrus	left	−26	−20	−20	5.75
Insula (long gyrus)	right	38	−16	6	5.69
Superior temporal/inferior parietal gyrus	right	54	−30	22	5.49
Amygdala	right	28	0	−20	4.95

(vs. instruction baseline). Two-way RM-ANOVA was used for statistical analysis, implemented as described above for the RT data.

RESULTS

Behavioral Results

Reaction Time and Task Performance

The task condition had a significant effect on RT [$F(2, 6786) = 2107.62, p < .001$], which increased as a function of cognitive load: The median 2B RT of 1001 msec exceeded the median 1B RT of 835 msec which, in turn, exceeded the median PL RT of 540 msec (PL vs. 1B: $t = 45.58, p < .001$; 1B vs. 2B: $t = 17.24, p < .001$). There was a significant effect of chord category [$F(2, 6786) = 12.61, p < .001$]: RTs were significantly shorter in response to dissonant chords (median 760 msec) than to both major (median 794 msec; $t = 3.29; p < .01$) and minor (median 798 msec; $t = 3.40; p < .001$) chords, whereas there was no significant difference of RTs to major and minor chords ($t = 0.11, p > .05$). Interactions between load and chord were not significant [$F(4, 6782) = 0.91, p > .05$], and were thus removed from the model. The effect of task condition on the RTs is illustrated in Figure 2, in which the effect of dissonance is present at all WM loads.

The mean error rates were 0.1%, 5.3%, and 10.4% for PL, 1B, and 2B, respectively. We used the arcsine-transformed ratio of correct-over-total responses (cf. Methods) to measure the effects of load and chord category on task performance. Neither the main effect of chord category [$F(2, 72) = 0.18, p > .05$] nor the Load-by-

Chord interaction [$F(4, 72) = 0.06, p > .05$] significantly improved the ANOVA model fit, and both were removed from the regression. Providing evidence that the cognitive demands of the three WM conditions were indeed different, the main effect of WM load on performance was highly significant with an F ratio of $F = 45.30, p < .001$: Subjects performed better in PL than in 1B WM ($t = 5.18, p < .001$), and better in 1B than 2B ($t = 4.32, p < .001$).

Ratings of Difficulty Level and Employed Task Strategies

Nine of the 10 subjects rated the 1B task “very easy” or “easy” and 8 of 10 rated the 2B task as “difficult” or “intermediate.” Most subjects used several different task strategies (7/10 subjects). The “auditory rehearsal” strategy (explained to subjects as “keeping the tones in mind”) was used as a memory strategy by 8/10 subjects. “Verbal rehearsal” (explained to subjects as for example keeping in mind the tones as “low,” “middle,” or “high”) was used by 6/10 subjects. “Visual imagery” (explained to subjects as “for example imagining the high sound as being placed on a high location”) was used by 3/10 subjects.

Emotional Ratings of the Chords

During scanning, tasks were never related to the emotional connotations of the stimuli. After scanning, subjects’ attention for the first time explicitly turned toward the emotional valence of the stimuli. As illustrated in Figure 3, chord type significantly influenced the perceived happiness of the stimuli [$F(2, 75) = 34.70, p <$

Figure 2. Detailed analysis of reaction times (RTs) as a function of WM load and chord type. The box-and-whisker plots illustrate the extent of variation of the RTs in the nine experimental conditions. Each box is drawn from the first (Q1) to the third (Q3) quartile around the median (solid horizontal line), and the whiskers extend to the robust extremes of the distribution, that is, 3/2 times the interquartile (Q1–Q3) range. The median values for each condition, and the across-chord averages at each load level, are shown above the plots. Significant differences are highlighted for the dissonant versus minor and dissonant versus major chord-type comparisons ($*p < .05$).

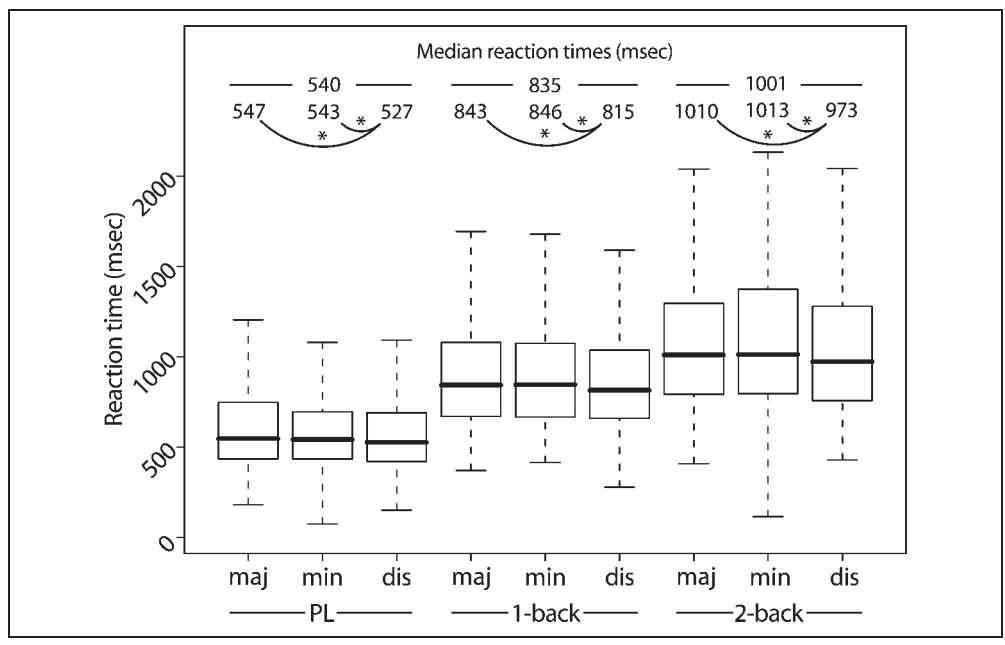
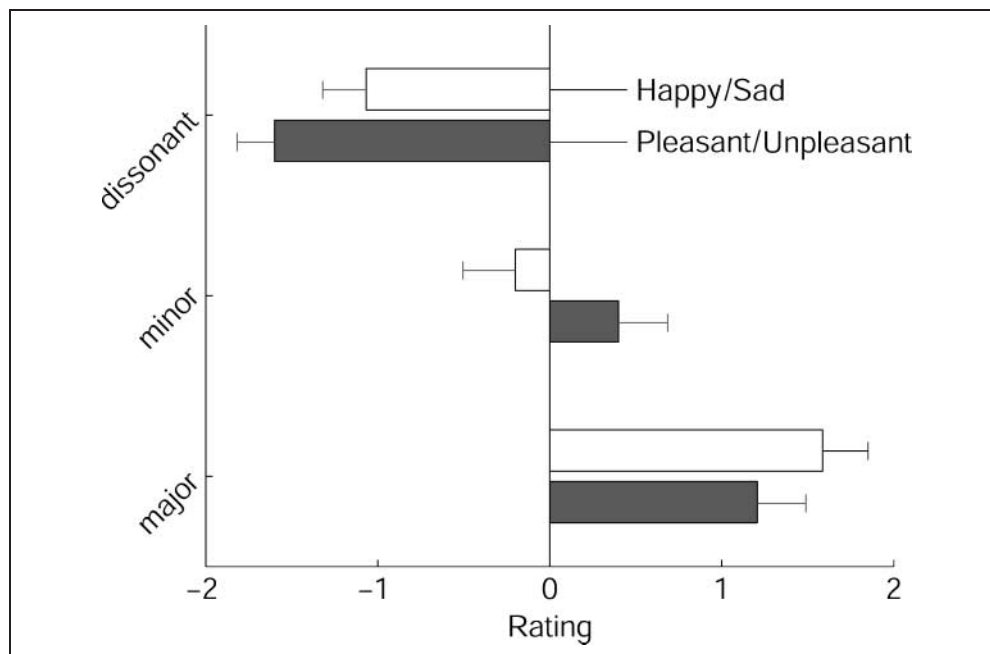


Figure 3. Emotional ratings by chord type. Dissonant chords were judged more sad and unpleasant than both minor and major chords. Major chords were judged happier and more pleasant than minor chords. Bars represent the standard error (see Results section for statistical analysis).



.001]. Major chords were rated happier than both minor ($t = 5.55, p < .001$) and dissonant ($t = 8.24, p < .001$) chords, and minor chords were rated happier than dissonant chords ($t = 2.72, p < .001$). We also observed a significant effect of octave [$F(2, 75) = 5.77, p < .005$]: The fifth octave was judged happier than the third (the lowest in frequency; $t = 3.38, p < .005$).

The subjects' evaluations of the pleasantness of the stimuli were also affected by both chord type [$F(2, 75) = 37.70, p < .001$] and octave [$F(2, 75) = 4.38, p < .05$]. Major chords were rated more pleasant than minor ($t = 2.37, p < .05$) and dissonant ($t = 8.35, p < .001$) chords, and minor chords were rated more pleasant than dissonant chords ($t = 6.03, p < .001$). The fifth octave (the highest in frequency) was rated more pleasant than the third ($t = 2.41, p < .05$) and fourth ($t = 2.71, p < .01$) octave. The chord ratings confirm the distinct emotional connotations of the three chord types, which are not influenced by MR scanner noise (Pallesen et al., 2003).

Functional Imaging Results

Group-level parametric activation maps of the planned contrasts revealing WM load-dependent BOLD signal changes were calculated across chord categories. The group mean PL versus 2B contrast located the responses to the ventral and dorsal parts of the medial PFC (BAs 11, 32, 10, 9, 8), the middle/posterior cingulate gyrus (BAs 23/31), the precuneus (BA 7/31), the lateral parietal cortex (angular gyrus/BA 39), the temporal gyri (BAs 20, 21, 42), the temporal pole (BA 38), the Rolandic operculum (BA 43), the posterior insula, the hippocam-

pal formation, and the right amygdala (Figure 4A, blue color scale and Table 1). The group mean PL versus 1B results (Table 2) mainly revealed the same areas found in the PL versus 2B contrast (Table 1), with the exception of the ventral medial PFC (gyrus rectus), which did not reach the significance criterion in the PL versus 1B contrast.

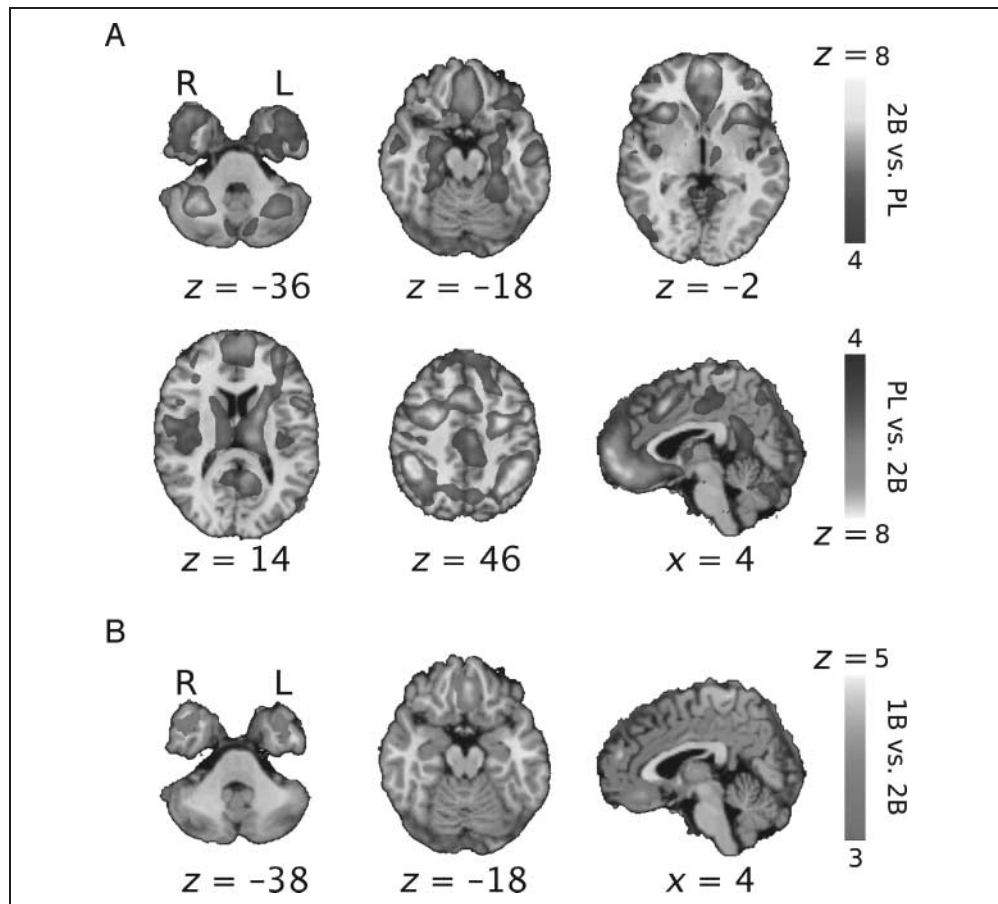
The opposite contrast, 2B versus PL, located responses to areas typical of WM tasks with a high level of executive demand such as the *n*-back WM task, as documented in other studies employing it (Figure 4A, red color scale and Table 4) (Rämä et al., 2001), including the dorsolateral PFC (BAs 6, 9), the superior and inferior lateral parietal cortex (BAs 7, 40), the striatum, the thalamus, the anterior insula, and the cerebellum.

To test the hypothesis of load-dependent attenuation of responses during WM, we determined the group-mean 1B versus 2B contrast across chord categories. Several brain regions were more active during 1B than 2B tasks, including the medial PFC (BAs 11, 25, 32, 10, 9), the cingulate gyrus/paracentral lobule (BA 23/31), the lateral parietal cortex (angular gyrus/BA 39), the temporal gyri (BAs 20, 21, 41/42), the temporal pole (BA 38), the Rolandic operculum (BA 43), and the posterior insula (Figure 4B and Table 3).

ROI Analysis

A chord category effect on emotional evaluations of the major, minor, and dissonant sounds was observed in the behavioral data (Figure 3). We wished to test whether neural correlates of this effect could be detected in the BOLD signal, and whether the effect depended on the

Figure 4. Significant BOLD signal modulations by WM. (A) WM increased (2B vs. PL; light-to-dark) and decreased (PL vs. 2B; light-to-dark) brain activity in distinct networks. (B) In a subset of the deactivated brain regions, the strength of down-regulation was WM load dependent (1B vs. 2B; green); (A and B) Activity maps were corrected for multiple comparisons at the cluster level ($p < .05$). The coordinate in MNI standard space is given below each image slice. The underlying structural image is the so-called MNI single-subject brain, which is displayed in radiological orientation.



WM load level. An initial “omnibus” ANOVA (cf. Methods) showed evidence only of a main effect of load—No significant activation clusters were detected for the main effect of chord or the Load-by-Chord interaction. We proceeded to select the regions (Table 1 and Figure 4A) with significant decreases during WM (i.e., the PL vs. 2B group mean contrast) for further ROI-based analysis (as described in Methods). The two-way RM-ANOVA performed on the right amygdala revealed a significant Load-by-Chord interaction [$F(4, 70) = 3.54, p < .05$]. One-way RM-ANOVAs with chord category as factor within each load level separately gave a significant chord category effect only in the passive listening condition [$F(2, 18) = 4.01, p < .05$]. During PL, a significantly larger BOLD response was observed to dissonant chords than to major chords ($t = 2.79, p < .05$), whereas the differences between dissonant and minor chords and major and minor chords were not significant. We observed a significant main effect of chord category in the left precuneus [$F(2, 72) = 3.22, p < .05$], where the BOLD signal exhibited significantly greater change during blocks of dissonant and minor stimuli than during major stimuli in both the PL [$F(2, 18) = 4.19, p < .05$; dissonant vs. major: $t = 2.24, p < .05$; minor vs. major: $t = 2.71, p < .05$] and the 2B [$F(2, 18) = 5.09, p < .05$; dissonant vs. major: $t = 2.11, p < .05$; minor

vs. major: $t = 3.13, p < .01$] conditions. The BOLD signal changes in the right amygdala and left precuneus are summarized in Figure 5 with the location and size of each ROI.

DISCUSSION

By employing an experimental design that allowed controlled manipulations of cognitive load and emotional stimulus connotation, we tested the hypothesis that task-related decreases during a cognitive task depend on both the cognitive load and the emotional stimulus connotation. The results were consistent with the hypothesis by showing a cognitive load-dependent effect on the magnitude of the decreases. As expected, the task of memorizing the pitch of musical chords deactivated medial and paleocortical regions of the brain: the posterior cingulate gyrus, precuneus, medial PFC, lateral parietal cortex, and hippocampal formation (Table 1 and Table 2), that is, areas that are core regions of the default processing mode (Raichle & Snyder, 2007). The WM load-dependent decreases (1B vs. 2B contrast) mainly occurred in areas outside key components of the default system. The results also indicated an interaction between the experimental condition and the emotional

Table 2. Group Activations for PL versus 1B Contrast; List of Local Maxima

Region of Activation	Hemisphere	Coordinates (MNI)			Peak Z Score
		x	y	z	
Medial superior frontal gyrus	left	-2	62	14	7.35
	right	10	38	54	4.33
Orbital middle frontal gyrus	left	-2	54	0	7.08
	right	0	44	-8	7.38
Precuneus	left	-6	-52	22	7.14
Middle cingulate gyrus	left	-2	-20	42	4.58
Posterior cingulate gyrus	left	0	-46	32	7.04
Angular gyrus	left	-40	-78	34	6.28
Rolandic operculum	right	52	-12	12	3.81
Superior frontal gyrus	left	-14	58	28	5.84
	right	18	40	36	4.73
Middle temporal gyrus	left	-48	-66	24	7.03
Precentral gyrus	right	18	-26	78	3.73
Lingual gyrus	right	8	-46	2	5.17
Inferior temporal gyrus	left	-48	6	-32	5.09
Fusiform gyrus	left	-26	-38	-12	6.31
	right	28	-32	-18	5.17
Temporal pole	left	-44	16	-34	5.00
	right	42	20	-38	4.96
Hippocampus	right	20	-8	-18	3.96
Orbital inferior frontal gyrus	left	-40	28	-16	4.41
Postcentral gyrus	right	38	-30	70	4.25
Middle frontal gyrus	left	-24	24	48	6.32
Parahippocampal gyrus	left	-24	-20	-20	4.08
	right	18	-32	-12	4.38
Insula (long gyrus)	right	42	-8	-2	3.96
Superior temporal/inferior parietal gyrus	right	60	-10	10	4.04
Amygdala	right	34	4	-18	3.81

stimulus connotation in the amygdala and the precuneus, both regions linked to processing of dissonance in addition to their role in default operations.

Working Memory Down-regulates Activity in the Default Network

The finding of deactivation of the medial/posterior cingulate gyrus (BAs 23/31), the precuneus (BA 7), the angular gyrus (BA 39), and regions in the medial and orbital PFC (BAs 11, 32, 10, 9, and 8) agrees with pre-

vious observations of deactivation in these areas during goal-directed behavior (McKiernan et al., 2003; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997). By comparing task-related decreases during three different auditory tasks performed on tone stimuli (a discrimination task, a stimulus presentation task, and a short-term memory task), McKiernan et al. (2003) noted an influence of the task on the deactivation pattern, which was replicated by Tomasi et al. (2006), who found deactivation in partially overlapping nets including the cingulate gyrus (BA 24, 31), the insula (BA 13), the postcentral gyrus (BA 30), and the precuneus (BA 7) in a visual

Table 3. Group Activations for 1B versus 2B Contrast; List of Local Maxima

Region of Activation	Hemisphere	Coordinates (MNI)			Peak Z Score
		x	y	z	
Gyrus rectus	left	-2	42	-16	5.05
	right	10	30	-14	3.89
Medial superior frontal gyrus	left	-2	48	26	3.87
	right	4	52	20	4.64
Precentral gyrus	right	26	-28	74	4.51
Rolandic operculum	left	-44	-24	18	4.03
	right	42	-14	20	4.38
Middle cingulate gyrus	left	-2	-24	50	4.31
	right	8	-20	48	3.89
Postcentral gyrus	right	40	-32	68	4.26
Inferior temporal gyrus	right	54	-6	-28	4.25
	left	-40	6	-38	3.73
Insula (long gyri)	left	-38	-18	4	4.12
	right	36	-18	6	4.23
Superior temporal gyrus (A1)	left	-54	-24	12	4.04
Superior temporal/inferior parietal gyrus	right	54	-30	22	4.23
Middle temporal gyrus	right	56	-6	-24	4.22
Middle temporal pole	left	-34	10	-40	4.09
	right	44	8	-34	3.95
Orbital middle frontal gyrus	left	-8	48	-4	3.97
	right	12	42	-12	4.04
Anterior cingulate gyrus	left	-10	48	0	3.91
Medial superior frontal gyrus	right	8	54	2	3.89
Supramarginal gyrus	right	60	-30	26	3.87
Supplementary motor area	left	-2	-16	52	3.86
Putamen	right	32	6	10	3.78
Paracentral lobule	left	0	-28	60	3.60

attention tracking task compared to passive viewing, and a visual WM *n*-back task compared to a passive reaction task (Tomasi et al., 2006). Although the current study describes a unique pattern of decreases, it shares the majority of deactivated regions with the aforementioned studies. These results include decreases in areas related to visual processing, as found in previous auditory studies (McKiernan et al., 2003; Laurienti et al., 2002; Lewis et al., 2000). The pattern of decrease in visual areas during auditory processing clearly depends on specific task characteristics. In our study, the task instructions were mediated visually, and the behavioral results indicated that visual imagery was part of the task strategies

used by approximately one third of the subjects. Also observed in our study, responses in the superior temporal/inferior parietal and middle temporal gyri were enhanced during low cognitive load. It may be noted that the 2B versus PL contrast also included responses in these regions (Table 4), however, at more posterior locations. A response in the anterior part of the inferior temporal gyrus was also enhanced during low cognitive load.

The results are evidence of a stronger representation of limbic regions than seen in previous studies of task-related decreases. In addition to the frequently reported medial/posterior cingulate gyrus, medial and orbital

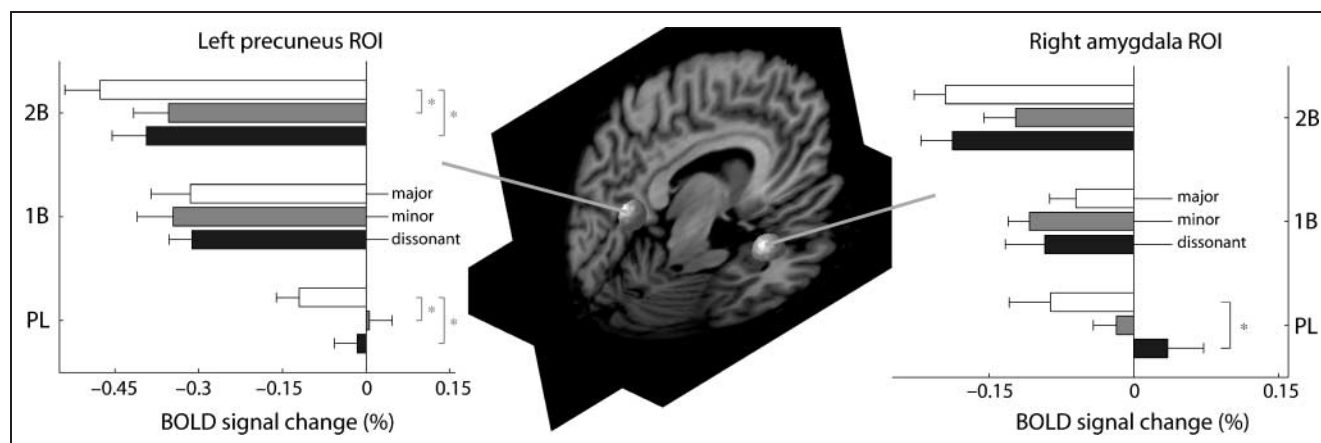


Figure 5. Mean percent BOLD signal changes within precuneus and amygdala ROIs (illustrated in the center) as a function of WM load and chord category. In the amygdala (right), the BOLD signal was significantly modulated by chord category in the PL condition, but not in either of the WM conditions. In the precuneus (left), the BOLD signal was significantly modulated by chord category in the PL condition and in the 2B condition. Note the different scales in the left and right plots. Whiskers represent the standard error; $*p < .05$.

PFC, our findings include the amygdala, the hippocampus and parahippocampal gyrus, the anterior cingulate gyrus, the insula, and temporal poles. The task-related decreases in multiple limbic structures may reflect the emotionally charged stimuli used in the present study. The same limbic areas previously were linked to processing of music (Gosselin et al., 2005, 2006, 2007; Mitterschiffthaler, Fu, Dalton, Andrew, & Williams, 2007; Koelsch et al., 2006; Khalifa, Schon, Anton, & Liegeois-Chauvel, 2005; Brown, Martinez, & Parsons, 2004; Blood & Zatorre, 2001; Blood et al., 1999). However, because no significant effect of chord type was found in most of these regions, this claim must be tested further with a greater number of subjects. Another past finding is that of decreases in limbic areas during processing of nonemotional stimuli, such as the consistent deactivation of the right amygdala in visual tasks in the meta-analysis by Shulman et al. (1997) and the parahippocampal gyrus during a visual *n*-back task compared to a passive reaction task (Tomasi et al., 2006), and during a tone task compared to rest (Binder et al., 1999), suggesting that activity in these limbic regions automatically is suspended in favor of other processing. Decreased activity in the parahippocampal gyrus and uncus during a tone WM task compared to passive listening can result from a higher level of automatic episodic memory encoding during passive listening than during WM (Zatorre, Evans, & Meyer, 1994). In other words, an automatic associative memorization of the stimuli as a whole would be contrasted with the goal-directed encoding. This interpretation is consistent with the suggestion that certain cognitive processes are prevalent at rest (Mazoyer et al., 2001; Binder et al., 1999). The present task-related decreases in the hippocampus and parahippocampal gyrus are relevant in relation to the functional connections of the hippocampal formation to the parietal cortex, both as members of

the default network, associated with episodic memory processes (Vincent et al., 2006).

Effect of Working Memory Load on the Task-related Decreases

The present finding of significant task difficulty-dependent decreases adds to previous findings (Tomasi et al., 2006; McKiernan et al., 2003). As expected, the brain areas in which the metabolic signal varies inversely with the WM load formed a subset of the areas deactivated in the PL versus 2B contrast. McKiernan et al. (2003) reported an interaction between the difficulty level of their short-term memory tone task and the magnitude of deactivation (based on ROI analysis) in the right precuneus/superior parietal lobule, the right anterior cingulate gyrus, the left anterior cingulate/superior frontal gyrus, the left middle frontal gyrus, and the right posterior cingulate gyrus. Tomasi et al. (2006) reported that enhanced brain deactivation in the cingulate gyrus and insula followed parametric increases in visual WM load (based on ROI analysis). Our present results of the 1B versus 2B contrast, examining the entire brain, provides confirming evidence to the above findings and extends the putative network exhibiting WM load-dependent task-related decreases by several brain regions previously undetected in the ROI analyses.

Of note, the WM load-dependent decreases found in our study, by contrasting directly the easy 1B with the demanding 2B task, were not significant in the posterior cingulate gyrus (although in neighboring middle cingulate gyrus), precuneus, lateral parietal cortex, and the hippocampal formation. Thus, the change in WM load did not significantly affect the task-related decreases in these areas, suggested to be key components of the default mode of brain function (Raichle et al., 2001).

Table 4. Group Activations for 2B versus PL Contrast; List of Local Maxima

Region of Activation	Hemisphere	Coordinates (MNI)			Peak Z Score
		<i>x</i>	<i>y</i>	<i>z</i>	
Inferior parietal gyrus	left	-48	-44	54	8.49
	right	44	-50	48	7.54
Superior parietal gyrus	left	-30	-64	50	8.10
	right	34	-64	56	6.20
Precentral gyrus	left	-50	0	42	7.90
	right	48	4	34	6.93
Middle frontal gyrus	left	-26	2	54	7.34
	right	28	-2	54	8.30
Middle frontal gyrus	left	-46	26	34	7.19
	right	42	36	26	7.89
Middle cingulate gyrus	right	2	14	46	7.39
Inferior frontal operculum	left	-54	10	16	6.71
	right	46	6	24	7.33
Superior frontal gyrus	left	-26	-6	62	7.31
Supplementary motor area	left	-4	2	60	6.31
Cerebellum lobule 8	right	30	-66	-58	7.29
Insula (short gyri)	left	-34	24	-2	7.09
	right	34	24	-4	6.83
Precuneus	left	-6	-64	54	6.24
	right	12	-68	54	6.86
Cerebellum crus 1	left	-32	-62	-30	6.69
	right	30	-58	-34	6.95
Cerebellum lobule 6	right	28	-62	-30	6.79
Caudate	left	-16	-10	22	6.47
Thalamus	left	-10	-18	14	6.35
Cerebellum crus 2	right	8	-76	-28	6.22
Putamen	left	-18	12	2	5.79
Superior temporal gyrus	left	-54	-44	18	4.08
Middle temporal gyrus	left	-54	-50	16	3.93

Effect of Stimulus Type on the Task-related Decreases

A strong motivation for the current study was the claim that the emotional stimulus connotation present during cognition may counteract task-related decreases. The behavioral data showed distinct effects of chord dissonance reflected both in the ratings of the emotional connotations of the chords and in the RTs, which were significantly shorter to dissonant chords than to major

and minor chords in all the experimental conditions (Figure 2). The shorter RTs to dissonant chords may reflect previously observed distressed arousal related to increased motor activity (Zentner & Kagan, 1998). The presence of this differential behavioral effect of chord types on RT not only during PL but also during WM indicates that the neural coding of emotional stimulus aspects may be upheld in structures outside the network that is generally down-regulated by cognition. In support of this suggestion, we previously found differential

responses to the chord types during PL in brain areas including, in addition to the amygdala, the retrosplenial cortex, the brainstem, and the cerebellum (Pallesen et al., 2005). We therefore expected the perceived unpleasantness of the dissonant chords to evoke the strongest emotional responses, also during cognition.

A significant Load-by-Chord BOLD signal interaction was present in the right amygdala and the left precuneus, two of the three regions hypothesized to mediate interaction effects. In the amygdala, the differential response as a function of chord type was significant during the PL condition, which required mere button presses after each stimulus. These chord-dependent responses were, however, absent in both the 1B and 2B tasks. Consistent with this observation, the pattern of task-related decreases in the amygdala showed significant changes in both the PL versus 1B and PL versus 2B contrasts (Tables 1 and 2). This suggests that differential amygdala responses to the chord types were diminished already during a low WM load. A more complex response pattern was detected in the left precuneus, in which dissonant and minor chords elicited stronger BOLD responses than did major chords. The effect was present in both the PL and 2B conditions. This indicates that the precuneus, in contrast to the amygdala, may be a part of a brain network that retains a larger part of its processing capability and function during goal-directed behavior. The conclusion from these results remains circumstantial, as the hypothesis of a countermodulation of task-related decreases by emotional processes was only partly confirmed.

The processes that mediate task-related decreases are still debated. The current results suggest that task-related decreases happen gradually in some areas while in other areas the decreases may depend on their role in information processing in relation to the particular demands imposed by current cognitive operations. Attention resources may be the critical factor that determines the need for reprioritization of ongoing processes. Although this may indeed be the case, the specific course of the progression of task-related decreases also depends on the nature of the cognitive task in question. The *n*-back task has uneven jumps in attentional and, specifically, cognitive requirements, hence, a linear progression in the decreases from PL to 1B to 2B would seem unlikely. From the perspective of the amygdala and the precuneus, the suspension of emotion-related processes would also be expected to be nonlinear, as was indeed the case.

Previous findings of a countermodulating effect of subjects' emotional state on cognitive down-regulation in the ventral region of the medial PFC (Simpson et al., 2001), which is frequently activated during emotional processing (Phan et al., 2002), inspired the current investigation similar effects related to emotionally charged stimuli. Although an up-regulating effect of the negative emotional state on task-related decreases was found by Simpson

et al. (2001), our study did not show a similar effect in relation to the dissonant chords, despite subjects characterizing them as unpleasant (Figure 3). A potential explanation suggested by Simpson et al. implies that the presence of the same emotional influences in control and active conditions minimizes the effect in the ventromedial PFC. We do not rule out the possibility that a negative emotional state during the WM task potentially canceled responses to negative emotions in the PL condition, because we did not specifically interview subjects about task-induced stress or anxiety during the active task. However, this possibility is remote, given the observation that processing of dissonance was affirmed by the increased activity of the amygdala during the PL versus 2B WM. Rather, self-referential processing may be the critical function that activates parts of the medial PFC during emotional tasks (Ochsner, Knierim, et al., 2004; Gusnard et al., 2001; Lane, Fink, Chau, & Dolan, 1997). A recent review assigned "the anterior region of the rostral medial PFC" (including approximately BAs 32, 10, 24, and the lower part of BA 9) to the mental operation of assessing self-knowledge (Amodio & Frith, 2006). A certain presentation duration of emotional stimuli, leading to the occurrence of implicit cognitive processes, rather than emotional processing per se, was also recently found to be a critical predictor of ventral medial PFC activity (Geday, Kupers, & Gjedde, 2007). In the present study, subjects did not explicitly reflect upon the passive perception of an emotional state, which led to fewer emotion-related responses that may rely on enhanced awareness of self.

Task-related Decreases and the Default Network

The formulation of the theory of a default system in the brain addressed brain regions characterized by consistent activity decreases during exogenously imposed tasks, or specific goal-directed behavior. The identity of the default system as a group of areas that are functionally connected is evident in studies of temporally coherent BOLD signal fluctuations at rest (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003) as well as in independent component analyses (Damoiseaux et al., 2006; Greicius & Menon, 2004). The membership of the default network has evolved somewhat and now includes the hippocampal formation as a candidate on the basis of the strength of functional connections to the posterior parietal cortex (Vincent et al., 2006, 2007; Greicius et al., 2003, 2004).

The functions of the default network, on the other hand, are controversial. The hippocampal–parietal link involved in episodic memory supports the claim that exogenously generated tasks and stimulus-independent thoughts have some cognitive operations in common, as in the case of the positive correlation between the degree of mind-wandering and BOLD responses in the default network (Mason et al., 2007). Other evidence,

such as the finding of an analogue of the default network in the monkey brain (Vincent et al., 2007), invokes the more fundamental function of maintenance of information needed to interpret and respond to environmental demands (Raichle & Snyder, 2007).

The claim that regions that process emotions are tonically active at rest and more active at rest than during goal-directed behavior is consistent with a fundamental role of emotions in the direction of behavior (Damasio, 2000). The evaluation of the behavioral relevance of intrinsic operations of the brain is a challenge, but better understanding of processes active at rest makes it easier to interpret activity increases and decreases during exogenously generated tasks used in functional brain imaging (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; McKiernan et al., 2003). Also, individual variation influences the observed brain responses and frequently is reflected in task-related activation as well as in intrinsic brain activity (Greicius & Menon, 2004).

In summary, the current findings support the hypothesis that the neural coding of emotional stimulus properties depends on the cognitive context, and is generally consistent with the theory of a dynamic balance between emotional and cognitive neural processes. We suggest that the specific neural signature of brain responses during mental operations depends intricately on the specific context of variables in ways that remain to be further investigated. Overall, the current findings are a strong basis for further testing of the hypothesis of countermodulation of task-related decreases by emotional stimulus connotation.

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Reprint requests should be sent to Karen Johanne Pallesen, Center of Functionally Integrative Neuroscience, Building 30 Aarhus University Hospitals, Norrebrogade 44, 8000 Aarhus C, Denmark, or via e-mail: karenjohanne@pet.auh.dk; karenjohanne.pallesen@gmail.com.

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