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Representation of Perceived Sound Valence in the Human Brain

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Abstract: Perceived emotional valence of sensory stimuli influences their processing in various cortical and subcortical structures. Recent evidence suggests that negative and positive valences are processed separately, not along a single linear continuum. Here, we examined how brain is activated when subjects are listening to auditory stimuli varying parametrically in perceived valence (very unpleasant–neutral–very pleasant). Seventeen healthy volunteers were scanned in 3 Tesla while listening to International Affective Digital Sounds (IADS-2) in a block design paradigm. We found a strong quadratic U-shaped relationship between valence and blood oxygen level dependent (BOLD) signal strength in the medial prefrontal cortex, auditory cortex, and amygdala. Signals were the weakest for neutral stimuli and increased progressively for more unpleasant or pleasant stimuli. The results strengthen the view that valence is a crucial factor in neural processing of emotions. An alternative explanation is salience, which increases with both negative and positive valences. *Hum Brain Mapp* 00:000–000, 2011. © 2011 Wiley-Liss, Inc.

Key words: emotion; valence; fMRI; amygdala; auditory cortex; prefrontal cortex



INTRODUCTION

Across more than a century of emotion research, the unpleasantness vs. pleasantness dimension, i.e. valence, has been considered to be at the core of human emotion processing [Russell and Barrett, 1999; Russell and Mehre-

bian, 1977; Schlosberg, 1954; Wundt, 1902]. Many previous parametric functional Magnetic Resonance Imaging (fMRI) studies on processing of emotional valence have suggested that valence is processed in bipolar fashion in key emotional regions in the human brain [Anderson et al., 2003; Colibazzi et al., 2010; Cunningham et al., 2004; Grabenhorst et al., 2007; Grimm et al., 2006; Heinzel et al., 2005]. That is, activity in specific brain areas varies linearly according to valence from the most negative (unpleasant) through neutral to the most positive (pleasant). These findings have been challenged by studies reporting evidence that different brain areas are involved in processing of negative and positive valences, and that in some brain areas the valence-related activity is U-shaped [Lewis et al., 2007; Viinikainen et al., 2010]. In a U-shaped activation pattern, activation increases towards positive and negative valence end points and is lowest for the neutral valence. Both upright and inverted U-shaped activation patterns have been reported in the previous studies.

Brain mechanisms underlying processing of valence of auditory stimuli have been investigated in one parametric

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positron emission tomography (PET) study [Blood et al., 1999]. Music was used as stimuli with valence modulation obtained by varying the degree of dissonance in the music. The authors observed positive linear correlation between regional cerebral blood flow (rCBF) and valence in the right orbitofrontal and medial subcallosal cingulate cortex and negative linear correlation in the right hippocampal gyrus and posterior cingulate cortex. However, it remains to be seen whether these results generalize to a wider range of auditory stimuli.

Previous results suggest that activity in the amygdala and auditory cortex is enhanced by both negative and positive valences of the auditory stimuli, at least for vocalizations. Human vocalizations of happiness, sexual pleasure, sadness and fear, compared to neutral vocalizations such as coughs, increase activity in the bilateral amygdala, and auditory cortex [Fecteau et al., 2007]. Sander and Scheich [2001] found increased activity in the same areas for both laughing and crying. Ethofer et al. [2006] found essentially a U-shaped dependency between valence of intonation of speech and blood oxygen level dependent (BOLD) signal in the associative auditory cortex in superior temporal sulcus (STS). Increased activity to emotional compared to neutral speech prosody has been observed also in the bilateral amygdala [Wiethoff et al., 2009].

The human amygdala responds to many types of emotionally valenced stimuli [for a review, see Sander et al., 2003]. For example, in auditory domain, Anders et al. [2008] found using fMRI that the left amygdala responds to negative emotional sounds, whereas Sander et al. [2005] found the right amygdala to respond to angry speech prosody. In their lesion study, Anderson and Phelps [2001] provided evidence that the amygdala, especially of the left-hemisphere, enhances perception of emotionally valenced stimuli. Subjects with left amygdala damage showed no difference in attentional blink during presentation of neutral and negative words, whereas for control subjects the attentional blink effect decreased for negative words. Additional findings of the role of amygdala in processing emotionally valenced stimuli have been found for negative and positive words [Hamann and Mao, 2002], faces [Yang et al., 2002], baby faces [Baeken et al., 2009], and pictures [Garavan et al., 2001; Hamann et al., 2002]. A recent meta-analysis found stronger amygdala responses to positive rather than to negative stimuli [Sergerie et al., 2008].

The aim of the present study was to focus on the processing of perceived valence of auditory stimuli using a very wide range of different types of stimuli to decrease the possibility that stimulus-specific auditory features can explain results found. We used stimuli from the International Affective Digital Sounds (2nd Edition; IADS-2; Bradley and Lang, 2007) collection, parametrically modulating valence of the presented stimuli. Based on previous findings, we hypothesized that such stimuli would modulate activity in the amygdala and auditory cortex. Specifically, we expected that activity in the amygdala and auditory

cortex would be modulated as a U-shaped (quadratic) function of valence [Ethofer et al., 2006; Fecteau et al., 2007]. We expected to find valence-related activity modulations also in other brain areas known to be related to emotional processing, particularly in the prefrontal cortex [Viinikainen et al., 2010]. Rather than linear, valence dependencies were hypothesized to be U-shaped in these regions as well [Lewis et al., 2007; Viinikainen et al., 2010].

METHODS

Participants

Seventeen subjects, five females and 12 males, participated in the study. The mean age of the subjects was 24.3 years (range 20–32). Fifteen subjects were right- and two left-handed, each had normal or corrected-to-normal visual acuity, no self-reported hearing problems, and no neurological or psychiatric disorders. Preliminary analyses indicated that the results of left-handed participants were similar as those of the right-handed participants. The subjects were recruited amongst students of Aalto University and from a student newsgroup for job applicants. Subjects received course credit for their participation. Each subject gave a voluntary written informed consent prior to participation to the experiment, which was approved by the ethical committee of Helsinki and Uusimaa Hospital District for healthy subjects and basic healthcare.

Stimuli

The stimuli were 36 sounds (environmental sounds, sounds caused by humans and animals, and music) from the International Affective Digital Sounds (2nd Edition; IADS-2) collection. Their duration was 6 sec, and they varied in emotional content. Eight subjects participated in a pilot experiment designed for stimulus selection. They evaluated separately the positive and negative valences of all 167 IADS-2 stimuli on a 5-point scale ranging from “neutral” (1) to “very pleasant” or “very unpleasant” (5), and the credibility of the stimuli on a 3-point scale ranging from “quite credible” (1) to “very contrived” (3). Ambivalence, on scale 1–5, was defined as the minimum of negative and positive valence evaluations [Kaplan, 1972]. Ambivalence scale was included because our preliminary inspection of IADS-2 stimuli suggested that the neutral stimuli might be substantially more ambivalent than negative and positive stimuli. Credibility scale was included to select such stimuli that could exist in real life. Varying levels of ambivalence and credibility might have been significant confounds in our study. Stimuli that were highly ambivalent (mean ambivalence rating above 2.1; 14 stimuli) or not credible (mean credibility rating above 2.0; 26 stimuli) were discarded. From the rest of the stimuli 36 were selected as stimuli on the basis of previous study of Bradley and Lang [2007] so that they covered the entire

TABLE I. Summary of the subjects' evaluations for stimulus blocks with negative valence (1–4), neutral valence (4–6), and positive valence (6–9)

	<i>N</i>	Valence (mean/std)	Arousal (mean/std)	Negative valence (mean/std)	Positive valence (mean/std)
Negative blocks (valence 1–4)	4	2.89/0.64	6.52/0.34	3.52/0.41	1.52/0.19
Neutral blocks (valence 4–6)	4	4.95/0.46	5.94/0.72	2.31/0.23	2.31/0.27
Positive blocks (valence 6–9)	4	6.68/0.72	6.07/0.54	1.75/0.24	3.27/0.57
All blocks (valence 1–9)	12	4.84/1.71	6.18/0.57	2.53/0.82	2.37/0.88

The columns show means and standard deviations (std) for valence, arousal, negative valence, and positive valence evaluations. The three stimulus classes differed significantly in valence properties but not in arousal (*t*-test $P < 0.05$).

valence scale. These stimuli were grouped into 12 blocks containing three stimuli. Table I shows the properties of the negative, neutral, and positive stimulus blocks as evaluated by the subjects who participated in the fMRI experiment (see “Behavioral Measures” section). Valence variation worked as intended, and negative, neutral, and positive blocks differed significantly from one another with respect to valence, negative valence, and positive valence (*t*-test $P < 0.05$). The aim was to have minimal arousal variation in order to make the valence analyses simple. This was also successful, since all differences in arousal evaluations between negative, neutral, and positive blocks were non-significant: negative vs. neutral $t = 1.469$, $P = 0.216$; negative vs. positive $t = 1.482$, $P = 0.198$; neutral vs. positive $t = 0.309$, $P = 0.769$. On scale 1–9, arousal level of the stimuli ranged from 4.95 to 7.08 [Bradley and Lang, 2007].

Scanning Paradigm

During fMRI scanning, the stimuli were presented in blocks, each block containing three different 6-sec sounds with similar valence and arousal. The IADS-2 code numbers of the used stimuli per block are presented in Table II. Valence of the stimuli was varied across the blocks, so that valence space was covered as well as possible. Each block was repeated three times in the scanner, and all the blocks as well as stimuli within blocks were presented in random order. The sounds were lead to subjects' ears with pneumatic earpieces. During the presentation of stimuli subjects fixated at a white cross on the center of their visual field, displayed against black background. This was implemented with a mirror positioned on the head coil, which allowed the subjects to see a translucent screen onto which the visual image was projected. At the end of every block the subjects were presented with a forced-choice response screen for 6 sec, during which they had to press either left or right button depending on whether the block contained more sounds by inanimate or animate entities. Number of inanimate and animate blocks was same, and their respective classification accuracies were 89.3% and 85.6%. The total duration of each block was 24 sec. The subjects were asked not to move except for the button

press at the end of every block. Their head movements were minimized using padding and restraint.

Behavioral Measures

Traditionally, emotional valence is considered as a bipolar continuum from very unpleasant to very pleasant [e.g., Russell and Barrett, 1999]. However, recent evidence from single-cell [Paton et al., 2006] and fMRI studies [Lewis et al., 2007; Viinikainen et al., 2010] suggests that neural basis for representing negative and positive valences may differ. There is also behavioral evidence for separate negative and positive valence dimensions [e.g., Cacioppo and Berntson, 1994; Cacioppo et al., 1997]. This is why, in addition to using a general valence scale, we asked our subject also to evaluate positive and negative valences separately.

After scanning, the subjects participated in a separate behavioral experiment, in which they evaluated each of the presented 36 sounds by their valence, arousal, positive valence (pleasantness), and negative valence (unpleasantness). This was done in two sessions: the other included evaluations of valence and arousal on scale 1–9 (unpleasant–pleasant, and calm–aroused) and the other evaluations of positive and negative valences on scale 1–5 (neutral to pleasant or unpleasant). The sessions were counterbalanced across subjects. After presentation of each stimulus

TABLE II. IADS-2 code numbers of the used stimuli in different blocks

Block	IADS-stimulus number		
1	284	420	255
2	261	703	242
3	502	730	116
4	134	133	380
5	320	500	710
6	114	410	722
7	425	120	403
8	363	378	808
9	601	221	802
10	355	820	816
11	352	351	353
12	811	110	815

TABLE III. Correlations between different ratings for our 36 stimuli

	Arousal	Negative valence	Positive valence	Valence (IADS-2)	Arousal (IADS-2)
Valence	-0.233	-0.946	0.927	0.930	-0.348
Arousal		0.347	-0.066	-0.087	0.762
Negative valence			-0.807	-0.869	0.450
Positive valence				0.854	-0.214
Valence (IADS-2)					-0.265

IADS-2 ratings refer to the normative ratings in Bradley and Lang [2007] study, whereas other ratings are from the current experiment. Significant correlation values ($P < 0.05$) have been presented in bold case.

the subjects gave their ratings by clicking an integer value (e.g., valence 8, arousal 6) with a mouse. Two scales (valence and arousal or positive and negative valence) were shown simultaneously and the subjects were able to give their ratings of the two in self-preferred order. After rating of the stimulus, the subjects clicked the next button and the subsequent stimulus was presented. The subjects were asked to make their evaluations based on their first impression. In addition, it was stressed that positive valence and negative valence were considered as separate entities that could be non-reciprocally connected. The subjects were able to replay the sounds, if they saw it necessary. Table III summarizes the correlations between different ratings, significant correlations being highlighted with bold case. Correlations of our valence and arousal ratings with those of Bradley and Lang [2007] were 0.930 and 0.762. Negative valence and positive valence showed strong linear dependency on valence, absolute values of correlation being over 0.9.

Scanning Procedure and Image Analyses

Scanning was performed on a 3.0 Tesla GE Signa MRI system with Excite upgrade and eight-channel head coil. Functional scans were acquired with a gradient-echo T2*-weighted echo-planar imaging (TR = 2.0 s, TE = 32 ms, flip angle = 75°, matrix = 64 × 64, field of view (FOV) = 20 cm). Thirty-three oblique slices with 3.0-mm slice thickness covered the entire brain apart from the cerebellum. Four hundred thirty-six volumes were obtained. However, the four initial volumes were discarded to account for T1-saturation effects. After functional EPI, T1-weighted anatomical images were acquired with 1 mm × 1 mm × 1 mm resolution.

fMRI data analysis was done with random effects (RFX) analysis in BrainVoyager QX [Goebel, 2006]. Prior to statistical measures each subjects' scans were motion corrected and filtered spatially and temporally. We used a 6 mm full-width-at-half-maximum Gaussian kernel and a high pass filter with cutoff frequency 1/288 sec, which allowed frequencies above three cycles in time course. After pre-processing the fMRI-volumes were co-registered with the corresponding individual MRI-image of the brain and transformed into Talairach space. Separate RFX-analyses were made for valence (linear and quadratic terms), arousal, positive valence, and negative valence. The pre-

dictors were derived from the individual evaluations of valence, arousal, positive valence, and negative valence of each subject. The predictors were calculated from subject-wise averages over each block and convolved with a canonical hemodynamic response function (HRF). For each RFX-model, a z-transform was performed. As described in the "Results" section, RFX-models were run also with nuisance covariates "arousal," "ambivalence," and "number of human vocalizations" to verify their possible influence on each model's results. False discovery rate (FDR) level 0.05 was applied to voxel-wise *t*-scores in the group analysis, together with a 135 voxel cluster size constraint (resampled 1 mm × 1 mm × 1 mm voxels, corresponding to 5 original 3 mm × 3 mm × 3 mm voxels).

Granger Causality

Granger causality is a measure first introduced in econometrics by Nobelist C.W.J. Granger [Granger, 1969]. The idea is to test, whether one time series X helps to linearly predict the behavior of another time series Y , or vice versa. In the simplest first order case, also applied here for BOLD time series, $Y(t) = A_{YY}Y(t-1) + A_{YX}X(t-1) + E_Y(t)$ and $X(t) = A_{XY}Y(t-1) + A_{XX}X(t-1) + E_X(t)$, where $E_Y(t)$ and $E_X(t)$ are the error terms or residuals and A_{ij} are the regression coefficients. The main question is whether $A_{YX} = A_{XY} = 0$ (null hypothesis) minimizes the error or not. If yes, then information about $X(t-1)$ does not help to predict $Y(t)$ and information about $Y(t-1)$ does not help to predict $X(t)$. However, if this null hypothesis does not hold, then there is said to be Granger causality between X and Y . The direction of Granger causality is determined by the strength of A_{YX} and A_{XY} .

To characterize functional connections of the most significantly activated brain regions, we performed both Granger causality and seed volume of interest (VOI) correlation mappings using these regions as seeds (all activated voxels were selected to form a seed VOI for each region, respectively). For Granger causality analysis, one time step (i.e., volume) regression was used. The measures were calculated between seed region and all other voxels in the brain. The Granger causalities were thresholded with uncorrected $P < 0.001$ and the seed VOI correlations were thresholded with uncorrected $P < 0.000001$. In addition, 135-voxel cluster-size constraint was used.

RESULTS

In the analyses, the fMRI blocks were divided into perception-related (9 first volumes, i.e. 18 sec) and judgment-related (during 3 last volumes, i.e. 6 sec) periods. These periods were examined using four different models: valence (linear and quadratic terms), arousal, negative valence, and positive valence. None of our study predictors showed any significant correlations with BOLD signal during the judgment period. Neither did any linear covariate, valence, arousal, positive valence, or negative valence, show significant correlations during the perception of sounds. The only predictor which showed significant correlations during sound perception was the second-order non-linear relation with respect to valence. For this predictor robust activations were found in several regions of the brain.

The most significant second-order correlations are depicted in Figure 1. Correlations were highly significant across voxels in the bilateral auditory cortices, amygdala, and dorsomedial prefrontal cortex (DMPFC). Significant correlations were additionally found in the right inferior frontal gyrus (IFG), left middle occipital gyrus, left ventromedial prefrontal cortex (VMPFC), right medial geniculate nucleus (MGN) of thalamus, and left precuneus, as well as in white matter anterior to hippocampus. All significant correlations are presented in Table IV.

The BOLD signal exhibited quadratic rather than linear dependency on valence. This explains also the lack of significant correlations for the negative valence and positive valence models, since both of them had a strong (> 0.9) correlation with linear valence. Variation between stimuli in arousal dimension was small ($\text{std} = 0.96$) and even this variation was not effectively used in the block design, since the stimuli within blocks were selected solely on the basis of valence. It is hence not surprising that we did not find significant arousal effects in the brain.

Next, we performed Granger causality and seed VOI correlation analyses using bilateral amygdala and auditory cortex as seeds. No significant Granger causalities were found with $P < 0.001$ and 135 voxel cluster-size constraint (connection from the left amygdala to the right anterior nuclei of thalamus was significant but did not survive the cluster-size correction). The seed VOI correlation analysis showed that activity in bilateral auditory cortex and bilateral amygdala were significantly correlated ($P < 0.000001$ and 135 voxel cluster size). In addition, the bilateral thalamus showed significant correlation with the bilateral amygdala and left auditory cortex. Retrosplenial cortex (RSC) showed correlation with the left amygdala and auditory cortex. Table V summarizes all significant seed VOI correlations.

Ambivalence of the stimuli showed a significant negative second-order correlation with valence ($R^2 = 0.766$; $F(2,9) = 14.73$, $P < 0.01$). In addition, there was a positive, although not significant, correlation between the number of vocalizations by humans and valence ($R^2 = 0.249$; $F(2,9)$

$= 1.49$, $P = 0.10$). Since these dependences could in principle affect the statistical parametric maps (SPMs), calculated with general linear model (GLM) for actual study predictors, we tested our model including these features as nuisance covariates. Also arousal was included as a nuisance covariate. The nuisance covariates did not, however, have an effect on the SPMs of the study predictors, indicating that the results were robust against variations in ambivalence, number of human vocalizations, and arousal. Systematic differences in the acoustic features of different valence blocks could also have affected our results. The following acoustic parameters were available for the research stimuli [Bradley and Lang, 2007]: minimum and maximum sample value in dB; peak amplitude in dB; minimum, maximum, and average root mean square power in dB. None of these parameters had significant linear or quadratic correlations with valence ratings.

DISCUSSION

As predicted, the auditory cortex, amygdala, and medial prefrontal cortex (DMPFC and VMPFC) showed a strong U-shaped dependency between valence and BOLD signal change. Similar dependency was found also in other brain regions (Table IV). This fulfilled our expectations that instead of a linear valence continuum, negative and positive valence processing yields a non-linear dependency of valence. Highly correlated activation of auditory cortex and amygdala time series suggests that they are strongly linked in processing auditory valence. Lacking Granger causality in their connection suggests that it is bidirectional. In addition, our results indicate that auditory thalamus and retrosplenial cortex are closely coupled to this network.

Correlation of BOLD Activity With Valence

Robust modifications in auditory cortex activations show that valence influences sensory processing of auditory stimuli. Similar observations were made by Fecteau et al. [2007] and Sander and Scheich [2001], who reported auditory cortex (and amygdala) activations for different emotion categories (both positive and negative) compared to neutral, when using human non-verbal vocalizations. Ethofer et al. [2006] showed activity as function of absolute valence (i.e., distance from neutral) of intonation bilaterally in the associative auditory cortex in STS, using different intensities of happy and angry vocalizations of single adjectives. In addition, BOLD signal increases to angry vs. neutral prosody have been reported in the bilateral associative auditory cortex in STS [Grandjean et al., 2005; Sander et al., 2005]. Ethofer et al. [2007] found bilateral increases to erotic vs. neutral prosody in the primary and associative auditory cortices in superior temporal gyrus. On the other hand, Kotz et al. [2003] reported increases, not decreases, to neutral vs. emotional (positive/negative)

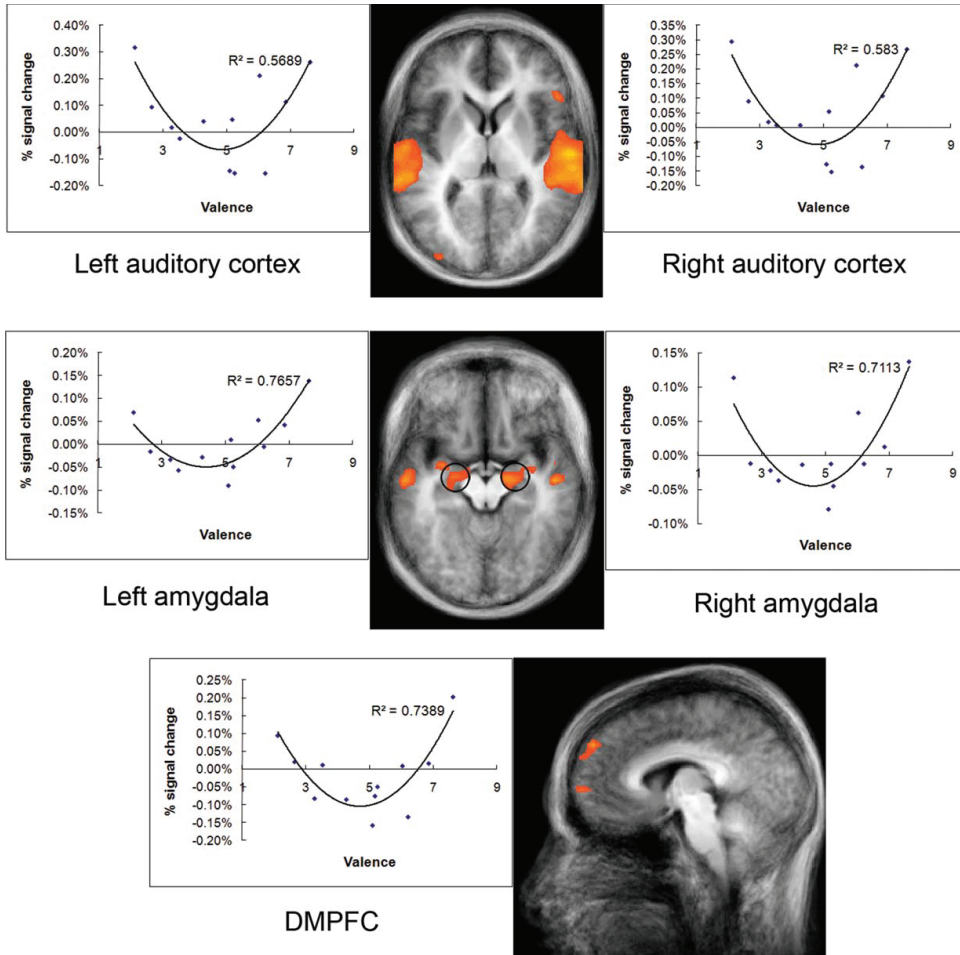


Figure 1.

BOLD signal changes are plotted as a function of valence of the auditory stimuli in bilateral auditory cortex, bilateral amygdala, and bilateral DMPFC. Second-order non-linear functions have been fitted to the data. R^2 -values show the correlation coefficient squared, indicating how much variations in valence explain variations in the BOLD signal level. Positive correlations above

threshold $FDR < 0.05$ have been displayed in the brain images. The darkest orange corresponds to t -score 4.0 and brightest yellow to 8.0. Both statistical maps and scatter plots show evidence of strong U-shaped dependency between brain activity and evaluated valence of the stimuli. In the brain image for amygdala, both amygdalae have been encircled with black.

prosody in the bilateral auditory cortex. Our present findings confirm that valence influences processing in the auditory cortex and extends these findings from non-verbal and verbal vocalizations also to non-vocal stimuli.

Also the right auditory thalamic nucleus, MGN, showed U-shaped dependency on valence of the stimuli. This suggests that valence modulates neural activity at early levels

of the auditory processing stream, possibly by feedback connections from the higher levels. This is supported by the seed VOI correlations we found between the bilateral thalamus and left auditory cortex. It has been shown in rats, that it is indeed the MGN (with inferior colliculus) that sustains conditioned emotional responses coupled to acoustic stimuli [LeDoux et al., 1983]. Amygdala is

TABLE IV. Brain regions with statistically significant (FDR < 0.05 and 135 voxel cluster size) second-order U-shaped valence dependencies

Brain region	L/R	x	y	z	t-value
Auditory cortex	R	60	-16	7	7.276607
Auditory cortex	L	-63	-16	1	6.782236
Amygdala	R	18	-13	-11	5.905139
Amygdala	L	-24	-13	-5	6.674483
DMPFC	R	9	59	34	5.221725
DMPFC	L	-6	56	37	6.154131
Inferior frontal gyrus	R	51	26	10	5.552052
Middle occipital gyrus	L	-33	-91	7	5.153540
VMPFC	L	-3	65	4	5.111476
Medial geniculate nucleus	R	15	-22	-5	5.243488
Precuneus	L	-43	-73	37	4.947390
Anterior to hippocampus (WM)	R	27	-25	4	6.344590
Supramarginal gyrus	L	-60	-58	22	4.505031
Middle temporal gyrus	L	-54	-76	16	4.828597
Posterior cerebral artery	L	-9	-31	-2	4.655397
Substantia innominata	L	-24	8	-14	4.766873

Hemispheric lateralities, peak Talairach coordinates and peak *t*-values have been reported.

essential for the development of neuronal plasticity of the MGN during auditory fear conditioning [Maren et al., 2001]. Such connection probably underlies the correlated activity of bilateral amygdala and thalamus (including MGN) found here.

There is growing evidence of U-shaped dependency of valence and activity in several brain structures. A recent study reported mainly overlapping regions processing positive and negative adjectives, when contrasted to neutral adjectives [Demirakca et al., 2009]. Especially, the amygdala has exhibited responses to both negative and positive stimuli in several experiments using different stimulus modalities, congruently with our findings. Wiethoff et al. [2009] reported increase in BOLD activity in the amygdala for angry, happy, and erotic vocalizations of single adjectives and nouns. Hamann and Mao [2002] found heightened left amygdala activity for positive and negative compared to neutral emotional words. In the study by Garavan et al. [2001], both negative and positive valence pictures were found to activate bilateral amygdala when compared to neutral pictures. Yang et al. [2002] found similar results with emotional facial expressions, and Baeken et al. [2009] with baby faces. Hamann et al. [2002] found bilateral amygdala responses for negative visual stimuli and left-hemisphere responses for positive visual stimuli. In addition, the visual cortex was, analogously to our auditory cortex activations, activated bilaterally by negative and positive pictures. Kensinger and Schacter [2006] found elevated BOLD-signal levels for highly arousing negative and positive pictures and words in the amygdala, and also in DMPFC and VMPFC. Ethofer et al. [2009] reported increases to angry vs. neutral prosody in multiple brain

regions, including the bilateral amygdala and bilateral orbitofrontal cortex.

A meta-analysis by Wager et al. [2003] has shown that the medial prefrontal cortex shows activation for both approach- and withdrawal-emotions. This is in concord with our U-shaped correlation findings in the bilateral DMPFC and left VMPFC. Several other studies have reported similar results. In the study by Fossati et al. [2003], words describing positive and negative self-referential personality traits activated the medial prefrontal cortex. Leclerc and Kensinger [2008] found activation to positive and negative pictures compared to neutral pictures in the DMPFC for both younger and older adults. However, Grimm et al. [2006] found linear correlation with BOLD signal and valence in the VMPFC and with

TABLE V. Brain regions with statistically significant ($P < 0.000001$ and 135 voxel cluster size) correlations with the seed region time series, i.e. with left and right amygdala and auditory cortex

	x	y	z	t-value
Left amygdala				
Right amygdala	26	-5	-9	14.21162
Left retrosplenial cortex	-10	-65	6	9.374434
Right retrosplenial cortex	5	-56	6	9.489069
Left superior temporal gyrus	-52	4	-3	12.56442
Right superior temporal gyrus	56	4	0	13.36767
Left auditory cortex	-61	-20	-3	10.38246
Right auditory cortex	47	-14	-9	11.39988
Left thalamus	-13	-11	6	11.40641
Right thalamus	11	-14	9	11.23098
Left precentral gyrus	-55	4	24	9.909047
Right amygdala				
Left amygdala	-28	-8	-9	14.57928
Left superior temporal gyrus	-52	7	-3	10.46817
Right superior temporal gyrus	56	4	-3	11.22058
Left auditory cortex	-64	-35	6	9.357652
Right auditory cortex	50	-5	6	10.46364
Left thalamus	-22	-14	9	10.33147
Right thalamus	5	-11	12	11.00381
Left auditory cortex				
Left amygdala	-31	-8	-9	9.38982
Right amygdala	29	-8	-9	11.69007
Right auditory cortex	53	-32	3	15.05946
Left retrosplenial cortex	-13	-56	12	10.35897
Right retrosplenial cortex	5	-44	21	10.65656
Left anterior insula	-46	24	12	8.963338
Right anterior insula	38	25	0	9.083041
Left thalamus	-13	-11	9	9.021572
Right thalamus	14	-17	9	8.807079
Right auditory cortex				
Left amygdala	-28	-11	-12	9.354454
Right amygdala	26	-5	-15	9.104115
Left auditory cortex	-58	-17	12	26.22648
Left olfactory sulcus	-13	16	-15	8.960045

Peak Talairach coordinates and peak *t*-values of the correlated regions have been reported.

BOLD signal and arousal in the DMPFC, and Heinzl et al. [2005] observed linear correlation with BOLD signal and valence in the DMPFC, with emotional pictures.

We have reported non-linear correlations between valence and bilateral DMPFC activations also in our previous study using pictures selected from the International Affective Picture System [Viinikainen et al., 2010]. In the present study, the correlations lie considerably more anterior than in the previous study. A striking difference between the present and the previous study [Viinikainen et al., 2010] is that the previous study reported opposite (i.e., inverted) U-shaped activation pattern between valence and brain activations than the present study. It might be possible that the anterior and posterior DMPFC encode valence in reciprocal fashion. Reciprocal emotion-related modulations have been found earlier in the lateral and medial prefrontal cortex [Northoff et al., 2004]. Another reason for the opposite U-shapedness could stem from the different tasks. The present study had a non-emotional judgment task, whereas in the previous study the task was to evaluate whether the presented stimuli were positive or negative. Hence our previous results regarding DMPFC could be flavored by the cognitive evaluation of the emotional realm, whereas the current results might reflect more purely the automatic emotional processing, since emotion was not consciously attended to. Also different stimulus modalities, i.e. auditory in the present and visual in the previous study, could explain the different results.

Lewis et al. [2007] reported U-shaped correlations in the right lateral orbitofrontal cortex and anterior and subgenual cingulate cortices, and Viinikainen et al. [2010] (in addition to DMPFC) in the bilateral DLPFC and insula. None of these areas revealed U-shaped correlations in the current study. In addition to different stimulus modality, this could be partly due to big differences in stimulus presentation times, since our auditory stimuli (6 sec sound clips) were much longer than the stimuli used in previous studies. Our results are also in contrast with earlier parametric PET valence study with music stimuli in which the correlations between valence and rCBF activity were positively linear in the right orbitofrontal and medial subcallosal cingulate cortex and inversely linear in the right hippocampal gyrus and posterior cingulate cortex [Blood et al., 1999]. This may be due to the differences in stimuli (music vs. natural sounds) and measurement modality. However, Mitterschiffthaler et al. [2007] have shown that happy and sad musical pieces activate the bilateral superior temporal gyrus (STG) compared to neutral musical pieces, consistently with our results.

Negative and Positive Valence

Paton et al. [2006] have demonstrated neurons in the primate amygdala that respond specifically to either positive or negative value of visual stimulus. If negative va-

lence correlates positively with BOLD signal and positive valence positively in the same region, the result across the whole valence scale would be a U-shaped response curve. It is hence possible that the observed U-shaped valence dependency is in fact a result of separate processing mechanisms for negative valence and positive valence, possibly in adjacent neuronal subregions. In our experiment, negative and positive valences were evaluated separately for each stimulus. In principle, this allowed us to seek for separate mechanisms for them in the brain. However, negative valence and positive valence showed very strong correlations with each other and also with bipolar valence in the evaluations of our subjects. Thus, based on these evaluations, it is not possible to make independent inferences, and we cannot say anything conclusive about the involvement of separate negative and positive valence processing mechanisms. However, also earlier neuroimaging results give support that such mechanisms exist [Grabenhorst et al., 2007; Lewis et al., 2007; Viinikainen et al., 2010].

Alternative Explanation to Quadratic Valence Dependency

An alternative explanation for the U-shaped responses on valence may be that the activated brain regions processed stimulus salience, which increases to both negative and positive ends of the valence continuum. Salience refers to the capability of stimuli to draw attentional resources, either because of their relevance to behavior in a given context (e.g., for achieving biological drives and psychological needs) or because of their novelty [cf. Downar et al., 2002; Liberzon et al., 2003; Vuilleumier, 2005]. Although high absolute (positive or negative) valence is typically associated with high salience, this is not necessarily so. For example, the musical stimuli used in the present experiment were of high valence (i.e., pleasant) but may not have been highly salient. Disentangling the effects of valence and salience is not trivial.

Said et al. [2009] found a U-shaped response with respect to face trustworthiness in the bilateral amygdala and Winston et al. [2007] and Liang et al. [2010] reported a U-shaped response as function of face attractiveness in the right amygdala. These results have been proposed to emanate from general salience processing; the extremes of the scales are more biologically relevant and, thus, induce greater activation. In similar vein, salience could account for our responses, e.g., in the amygdala, but in particular, we consider that the auditory cortex could be influenced by salience, as is the case with the visual cortex [Lang et al., 1998; Taylor et al., 2005]. Increased salience means increased attention [Vuilleumier, 2005], and attention has been found to enhance activity in the auditory cortex [Grady et al., 1997; Jäncke et al., 1999]. STG has been stated to respond to the stimulus salience in neutral behavioral context [Downar et al., 2002]. In an earlier PET

study by Liberzon et al. [2003], salience was interpreted to be the explanation for the sublenticular extended amygdala and visual cortex activations to positive and aversive visual stimuli, and also the DMPFC showed activations to these stimuli when compared to baseline. These results are very much analogous to those of our experiment in the auditory domain.

Granger Causalities and Seed VOI Correlations

A group of neurons in amygdala of alert macaque monkeys respond to tones [Nishijo et al., 1988]. Yuki [2002] found a weak input from the lateral basal nucleus of amygdala to the primary auditory cortex of macaque monkeys (area TC), but stronger connections from the lateral, lateral basal, and accessory basal nuclei of amygdala to the superior temporal association cortex (area TA). The rostral TA showed dense and intermediate TA moderate projections to the lateral nucleus of amygdala. Different nuclei in amygdala are also interconnected. Thus, there appears to be bidirectional connections between amygdala and auditory cortex, yet connections from amygdala to cortex appear to be more widespread and complex. We did not find significant Granger causalities between amygdala and auditory cortex in our data. However, significant correlations between the amygdala and auditory cortex time series were found. These findings could mean that the connections during sound valence perception are bidirectional. However, amygdala might have a role in boosting auditory cortex activity, as has been suggested to happen in the visual domain [Vuilleumier et al., 2004]. Armony et al. [1998] found that only rats with intact amygdala were able to sustain long-latency responses in the auditory cortex to fear-conditioned stimulus and suggest that direct connections from amygdala to auditory cortex are a possible explanation.

Preliminary meta-analysis of Barrett et al. [2007] shows that the bilateral amygdala and DMPFC are the most commonly activated areas in emotion studies, and their co-activation has been established meta-analytically [Kober et al., 2008]. Our study makes no exception. However, the DMPFC activity was not significantly correlated with that in the amygdala or auditory cortex. This suggests that the DMPFC has a different role in valence processing, and, is perhaps activated irrespective of stimulus modality [Foshati et al., 2003; Heinzl et al., 2005; Viinikainen et al., 2010].

All significant activations found in the present study showed U-shaped relationship with valence. This gives a reason to believe that the time series behavior in most of these regions is also similar. Support for this view was obtained from the correlation analysis using bilateral auditory cortex and amygdala as seed regions. Multiple regions showed correlation to each area, respectively. An interesting node that showed correlations to the seed regions is thalamus, which was long ago described as the

coordinating center for emotional reactions [Cannon, 1931]. Significant correlations between the brain regions (see Table V) might be a manifestation of a common network influenced by emotional valence of sounds.

CONCLUSIONS

We found a U-shaped dependency of emotional valence of auditory stimulus and BOLD signal strength in several brain regions, being especially strong bilaterally in the auditory cortex, amygdala, and DMPFC. Taking into account earlier research, this suggests that the same system involving amygdala and auditory cortex processes valence of non-verbal emotional vocalizations [Fecteau et al., 2007; Sander and Scheich, 2001], speech prosody [Ethofer et al., 2006; Wiethoff et al., 2009], and other emotionally evocative sounds. Interestingly, our results show that even sensory auditory cortex and auditory thalamus are not immune to emotional processing. More research is required to differentiate the roles of salience and valence in processing of emotional auditory as well as other types of sensory stimuli.

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