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Experience-dependent modulation of tonotopic neural responses in human auditory cortex

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Experience-dependent plasticity of receptive fields in the auditory cortex has been demonstrated by electrophysiological experiments in animals. In the present study we used PET neuroimaging to measure regional brain activity in volunteer human subjects during discriminatory classical conditioning of high (8000 Hz) or low (200 Hz) frequency tones by an aversive 100 dB white noise burst. Conditioning-related, frequency-specific modulation of tonotopic neural responses in the auditory cortex was observed. The modulated regions of the auditory cortex positively covaried with activity in the amygdala, basal forebrain and orbitofrontal cortex, and showed context-specific functional interactions with the medial geniculate nucleus. These results accord with animal single-unit data and support neurobiological models of auditory conditioning and value-dependent neural selection.

Keywords: experience-dependent plasticity; classical conditioning; tonotopic auditory cortex; medial geniculate nucleus; amygdala; nucleus basalis of Meynert

1. INTRODUCTION

Plasticity of cortical organization, a prominent feature of early 'critical periods' of cerebral development (Hubel & Wiesel 1970; Fox 1992), also occurs in the adult mammalian brain. Significant changes in afferent input (Merzenich *et al.* 1983, 1984; Pons *et al.* 1991; Elbert *et al.* 1995) and more subtle manipulations involving perceptual learning (Weinberger & Diamond 1987; Recanzone *et al.* 1993; Scheich *et al.* 1993) have been shown to produce plastic changes in the receptive fields of sensory cortical cells. The neural mechanisms underlying learning-related plasticity of the sensory cortex have been extensively investigated in animal electrophysiological studies, which have examined how tonotopic auditory responses are affected by classical conditioning (Ashe *et al.* 1989; McKenna *et al.* 1989; Metherate & Weinberger 1990; Metherate & Ashe 1991; Edeline & Weinberger 1992). These single-unit data implicate afferents from the medial geniculate nucleus (MGN) of the thalamus, amygdala and basal nucleus of Meynert in the conditioning-related plasticity observed in the animal auditory cortex (Weinberger 1995).

Previous functional neuroimaging studies employing eye-blink conditioning of tones have reported experience-dependent changes in the activity of the human auditory cortex (Molchan *et al.* 1994; Schreurs *et al.* 1997). There are no previous reports, however, of frequency-specific, learning-related changes in human auditory cortex activity comparable to those seen in animal studies (Edeline & Weinberger 1993). In the present study, we used positron emission tomography (PET) to measure neural responses in volunteer human subjects following discriminatory aversive conditioning of high- and low-frequency tones. Frequency-specific modulation of responses in the auditory cortex, and functional interactions with MGN, amygdala and the basal forebrain were predicted on the basis of models derived from animal single-unit data (Weinberger 1995). As the study paradigm involved the deliberate manipulation of reinforcement contingencies, the activation of brain regions implicated in stimulus-reinforcement associations, such as orbitofrontal cortex, was also expected (Thorpe *et al.* 1983; Rolls 1995).

2. METHODS

(a) *Subjects*

A total of six right-handed male subjects (mean age 27.7 years) took part in the study which was approved by the local hospital ethics committee and the UK Administration of Radioactive Substances Advisory Committee. All subjects were unmedicated and had no previous history of psychiatric or neurological illness.

(b) *PET scan acquisition and analysis*

Scans of the distribution of $H_2{}^{15}O$ were obtained by using a Siemens–CPS ECAT EXACT HR+ PET Scanner operated in high sensitivity 3D mode. Subjects received a total of 350 Mbq of $H_2{}^{15}O$ over 20 s through a forearm cannula for each of the 12 scans, and activity was measured during a 90 s time-window. The PET images had a 6.4 mm transaxial and 5.7 mm axial resolution (full width at half-maximum), and activity was sampled with $2 \times 2 \times 2\,mm^3$ voxels. The data were analysed with statistical parametric mapping (SPM96, Wellcome Department of Cognitive Neurology, London; `http://www.fil.ion.ucl.ac.uk/spm`) implemented in Matlab (Mathworks, Sherborn, Massachusetts). Structural MRIs from each subject were co-registered to the PET data following realignment of the PET time-series. All the scans

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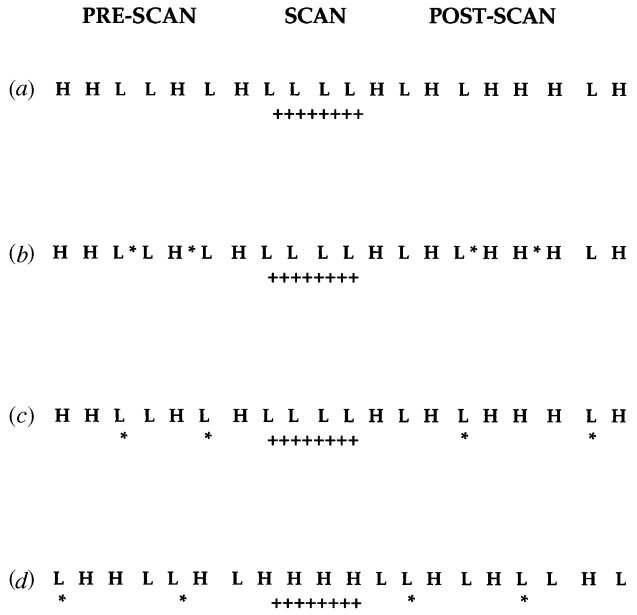

Figure 1. Diagrammatic representation of pseudorandom stimulus sequences. (*a*) A non-conditioning sequence during which no noises are played. (*b*) An unpaired sequence, identical to (*a*), except that four noise bursts are played midway between tones. (*c*) A conditioning sequence, identical to (*a*) and (*b*) except that the four noise bursts occur immediately following low-frequency tones. In (*c*) the tone frequency paired with the noise (CS+) is played in the 90 s scanning window. In (*d*), a conditioning sequence similar to (*c*), the tone frequency explicitly unpaired with noise (CS−) is presented during scanning. Noises never occur in any of the scanning windows. H represents high-frequency tones; L represents low-frequency tones; *represents noise burst; +++ represents scanning window.

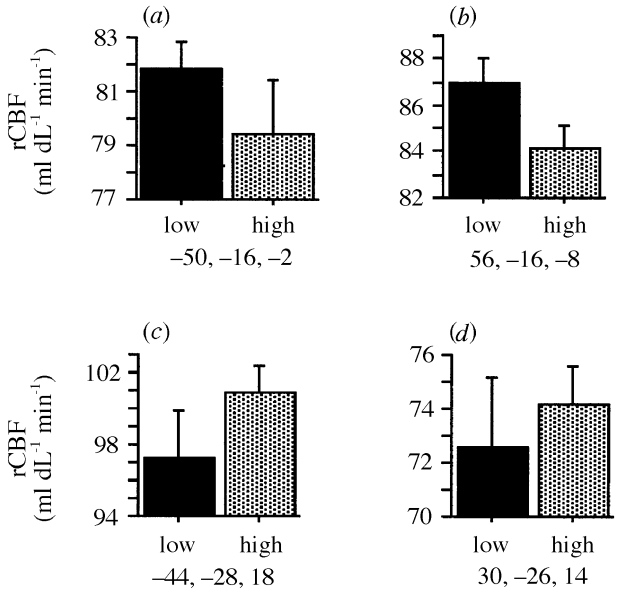

Figure 2. Graphical displays of the mean rCBF values (in ml dl^{-1} min^{-1}) at the voxels in auditory cortex which show maximal selectivity for frequency. Bars represent two standard errors. Low = 200 Hz; high = 8000 Hz. (*x*, *y*, *z*) coordinates of the voxels are shown below each graph, where *x*, *y* and *z* refer to orthogonal planes (sagittal, coronal and transverse, respectively) centered on the anterior commissure. (*a*) Low-frequency selective left auditory cortex: Z-score = 3.02, $p = 0.001$; (*b*) low-frequency selective right auditory cortex: Z-score = 2.28, $p = 0.011$; (*c*) high-frequency selective left auditory cortex: Z-score = 2.62, $p = 0.004$; (*d*) high-frequency selective right auditory cortex: Z-score = 1.98, $p = 0.024$.

were then transformed into a standard stereotactic space (Talairach & Tournoux 1988; Friston *et al.* 1995*a*,*b*). The scans were smoothed by using a Gaussian filter set at 12 mm full-width at half-maximum. The rCBF measurements were adjusted to a global mean of 50 ml dl^{-1} min^{-1}.

A blocked (by subject) ANCOVA model was fitted to the data at each voxel, with a condition effect for each of the conditioning contingencies, and global CBF as a confounding covariate. Predetermined contrasts of the condition effects at each voxel were assessed by using a *t*-statistic, giving a statistical parametric map (SPM) for each contrast. Uncorrected *p*-values were used for brain regions predicted to show differential activity in a particular contrast. To assess the significance of activations in unpredicted regions, a Bonferroni correction of the *p*-values was used, as each contrast involved numerous comparisons (at every brain voxel). To identify brain regions which positively covaried in activity with conditioning-modulated regions of auditory cortex, rCBF values for the maximal foci ($x = -50$, $y = -26$, $z = 10$ and $x = -50$, $y = -16$, $z = -2$ in the left auditory cortex) were used as covariates of interest in a separate regression analysis implemented in SPM96. To test for the presence of learning-related changes in the contribution of the MGN to auditory cortex activity, the rCBF values at the maximal focus in MGN ($x = -12$, $y = -26$, $z = -2$) were grouped into two separate conditioning and non-conditioning covariates. By using the condition blocks and the overall global flow as confounds, regressions were calculated at every voxel in the brain for both covariates of interest, and differences in the gradients of the pairs of regression lines directly tested at each voxel. The resulting SPM(t) demonstrates the presence of significant psychophysiological interactions (Friston *et al.* 1997), i.e. context-specific changes in the contribution of MGN to other brain regions. The general methods employed by SPM are described in detail by Friston *et al.* (1995*a*,*b*).

Table 1. *Regions of transverse temporal gyrus which show decreased responses to the conditioning of* (*a*) *high-frequency tones and* (*b*) *low-frequency tones*

(The areas were identified by contrasting non-conditioned and CS+ scans for tones of the same frequency. The coordinates, Z-scores and uncorrected *p*-values of the maximal voxels are shown.)

	coordinates (*x*, *y*, *z*)	Z-score	*p*-value
(*a*) *high-frequency conditioning*			
L. transverse temporal gyrus	−50, −26, 10	3.50	<0.001
R. transverse temporal gyrus	32, −30, 12	1.4	n.s.
(*b*) *low-frequency conditioning*			
L. transverse temporal gyrus	−50, −16, −2	3.38	<0.001
R. transverse temporal gyrus	54, −20, 0	2.50	0.006

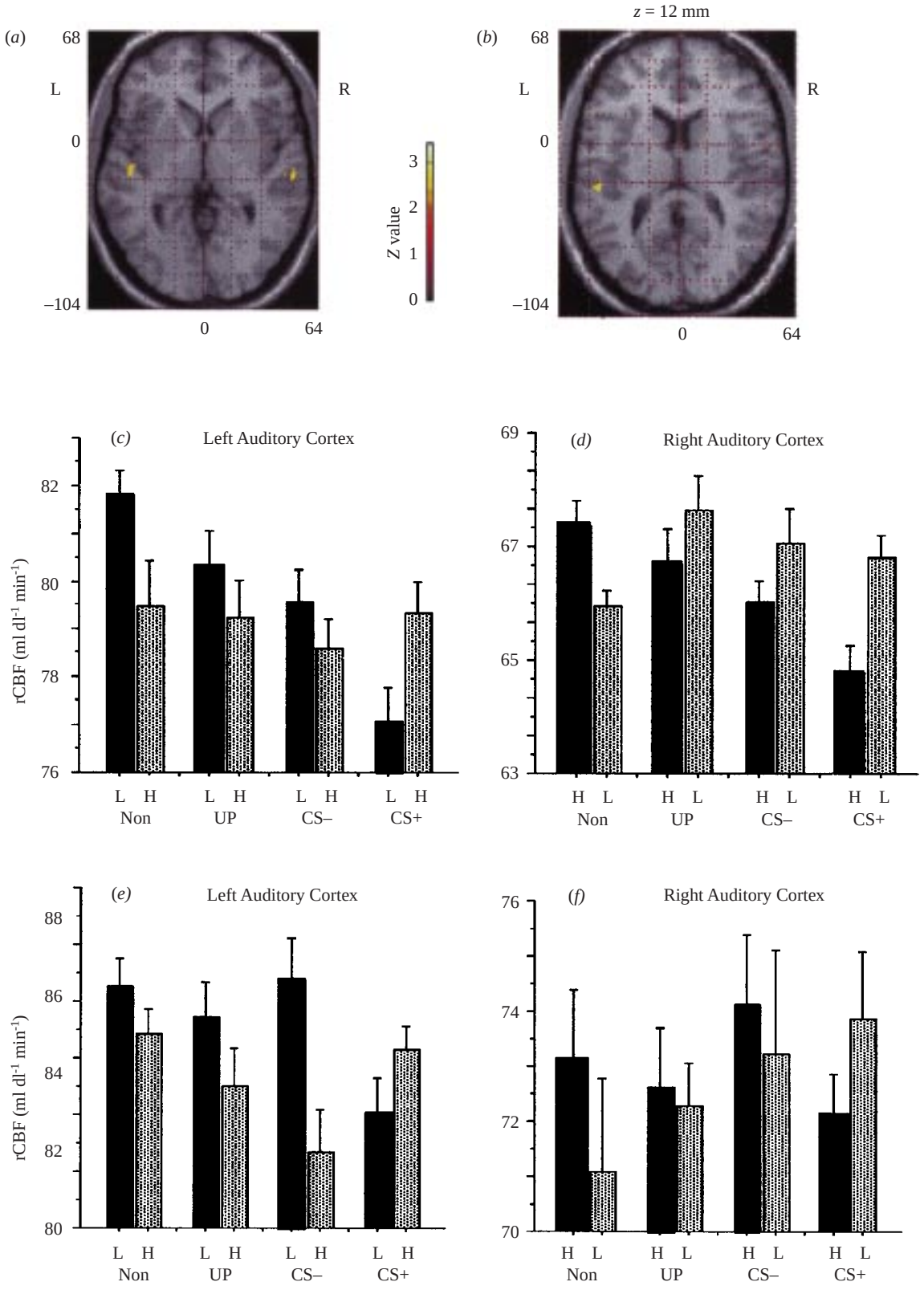

Figure 3. Experience-dependent modulation of response in auditory cortex. (*a*) An SPM, displaying bilateral regions of auditory cortex, in which the response to low-frequency tones is decreased by low-frequency conditioning. (*c*) and (*d*) Graphical displays of mean rCBF values (in ml dl^{-1} min^{-1}) for the maximal voxels displayed in (*a*) (left auditory cortex, $x=-50, y=-16, z=-2$; right auditory cortex, $x=54, y=20, z=0$). (*b*) An SPM showing a region of left auditory cortex in which the response to high frequency tones is reduced by high-frequency conditioning. (*e*) and (*f*)Graphical displays of mean rCBF values (in ml dl^{-1} min^{-1}) for the maximal voxel in (*b*) ($x=-50, y=-26, z=-10$) and the maximal voxel for a corresponding region in right auditory cortex ($x=54, y=20, z=0$), which showed a similar pattern of responses with high-frequency conditioning but failed to reach significance in this contrast. In both (*a*) and (*b*), contrasts of non-conditioning and CS+ scans are shown on transverse slices of a canonical MRI image with a threshold of $p=0.01$. In (*c*)–(*f*) the bars represent two standard errors. L=low-frequency tones; H=high-frequency tones; Non=non-conditioned scans; UP=scans in which both tone frequencies were unpaired with noise; CS+=scans in which the tone frequency associated with noise was presented; CS−=scans in which the tone frequency explicitly not associated with noise was presented.

(c) *Experimental design*

Subjects were presented with 12 sequences of auditory stimuli, each consisting of ten high-frequency (8000 Hz) and ten low-frequency (200 Hz) pure tones presented in a pseudorandom order. The tones, presented via earphones, had a duration of 4 s, an intensity level of 70 dB, and an average inter-stimulus interval of 20 s (range 15–25 s). We employed three different types of sequence.

1. Non-conditioning sequence, during which only the pure tones were played (see figure 1*a*).
2. Unpaired sequence, in which four 100 dB white noise bursts (1 s duration) were played midway between tones through the same earphones. The noises in this condition occurred with equal frequency between low–high, high–low, high–high, and low–low consecutive tone pairs, to ensure no differential conditioning to one frequency (see figure 1*b*).
3. Conditioning sequence, in which four 100 dB white noise bursts were played immediately after the offset of tones of one frequency to produce discriminatory classical conditioning in a 4:10 partial reinforcement schedule (figure 1*c*,*d*). The tone frequency paired with noise represented the positively conditioned stimulus (CS+); the tone frequency explicitly unpaired with noise was the CS−. In three subjects the CS+ was always the low tone; in the other three subjects the high tone was the CS+.

The stimuli were presented in blocks of three non-conditioning (N), three unpaired (U) and six conditioning sequences (C), which were counterbalanced across the six subjects (i.e. CNU, CUN, NCU, NUC, UCN, UNC) to control for non-specific order and time effects. In three of the conditioning sequences, the CS+ tone frequency was presented during the scanning window (figure 1*c*); in the other three conditioning sequences the tone frequency explicitly unpaired with the noise (CS−) was played (figure 1*d*). CS+ and CS− sequences were presented alternately within the block. Whenever a conditioning block preceded unpaired or non-conditioning blocks, a habituation sequence, consisting of 15 high and 15 low tones in pseudorandom order, without any noises, was interposed to extinguish conditioned responses.

In the 90 s PET scanning window, four tones of the same frequency were presented consecutively at 15 s intervals without any noises, i.e. all pairings of tones and noise, and all unpaired noises, occurred before or after scanning (figure 1). The onset time of the scan was varied between 80, 160 or 240 s after the start of the sequence for each subject, to ensure an even temporal distribution of noises across the unpaired and conditioning sequences. Subjects were not aware of the variable scan onset time.

(d) *Behavioural measurements*

Throughout the experiment, subjects' skin conductance responses (SCRs) were monitored to index autonomic conditioning. SCRs were measured with galvanic skin response equipment by using Ag–AgCl electrodes attached to the palmar surface of the middle phalanges of the index and middle fingers of the right hand. Readings of skin conductance (in micro-Siemens; μS) were stored digitally on computer. All SCRs were square root transformed to attain statistical normality (Levey 1980). By using the SCR in the 4 s period before presentation as a baseline, the maximal SCR deflection in the period 0.5–4 s following a tone presentation was assigned as the value for the SCR to that tone. The mean SCRs for the CS+ and CS− tones were calculated and the differences tested using a paired *t*-test.

During all three types of sequence, subjects did the same frequency-discrimination task, pressing left or right response buttons to indicate whether the tone was high or low. Subjects were informed that noises would be played during the experiment, but were told that this was irrelevant to the explicit (frequency-discrimination) task. They were not informed of the significance of the noise stimuli to the experimental design. All subjects were debriefed after scanning.

3. RESULTS

(a) *Behavioural responses*

All subjects demonstrated differential conditioned SCRs. The mean SCR for CS+ tones, 0.384 μS (s.e. = 0.015) was significantly ($p < 0.001$) greater than the CS− mean, 0.343 μS (s.e. = 0.009). Differential SCRs were not observed for the corresponding tones in the non-conditioned or unpaired sequences. All subjects reported awareness of the conditioning contingency, and stated that the CS+ presentation became a predictor of the noise burst. All subjects performed at ceiling (greater than 95% of responses correct) on the explicit frequency-discrimination task.

(b) *Differential responses to non-conditioned tone frequencies*

Differential neural responses to the two tone frequencies (200 Hz and 8000 Hz) were determined by contrasting the scans for the high- and low-frequency tones in the non-conditioning sequences. Discrete regions of the bilateral transverse temporal gyrus (auditory cortex) showed significant frequency-selective responses (see figure 2). Other brain regions, not predicted *a priori*, also showed differential responses to high and low frequencies, but none reached a corrected level of significance.

(c) *Differential responses to conditioned and non-conditioned tones*

The previously identified frequency-selective regions of auditory cortex (figure 2) showed frequency-specific decreases in response during conditioning sequences (table 1). SPMs displaying these modulated regions of transverse temporal gyrus, together with the mean rCBF values at the maximal voxels for each of the experimental conditions are shown in figure 3. Responses to low tones in the previously identified low-frequency selective region of auditory cortex were decreased by the association of low tones and noise (figure 3*a*,*c*,*d*). Responses to high tones in this region were not decreased by conditioning. As a consequence of this plasticity of response, reversals of frequency selectivity were recorded in the auditory cortex during conditioning. In the low-frequency right auditory cortex, reversals of selectivity also occurred in the unpaired and CS− conditions, although the greatest change was seen in the CS+ condition (see figure 3*d*). Similar responses were observed in the high-frequency selective regions of auditory cortex (figure 3*e*,*f*). Conditioning-related decreases in the high-frequency region of right auditory cortex failed to reach significance, but the plot of rCBF values (figure 3*f*) reveals a similar pattern of response to that measured in corresponding areas.

Table 2. *Regions with enhanced responses to (a) all CS+ tones compared with all CS− and (b) all CS− compared with all CS+*

(The coordinates, Z-score and uncorrected p-value of the maximal voxel is shown.)

	coordinates (x, y, z)	Z-score	p-value
(*a*) *CS+ versus CS−*			
R. orbitofrontal cortex	2, 44, −30	2.60	0.005
(*b*) *CS− versus CS+*			
L. orbitofrontal cortex	−32, 12, −8	3.76	<0.001
R. transverse temporal gyrus	56, −26, 12	3.60	<0.001
L. medial geniculate nucleus	−12, −26, 2	3.50	<0.001
L. transverse temporal gyrus	−44, −16, 6	2.90	0.002
basal forebrain	−10, −10, −2	2.55	0.005

In the contrast of all conditioning (CS+ and CS−) with all non-conditioning scans there was significantly ($p<0.001$) increased activity in a region of left inferoposterior thalamus (maximal voxel, $x=-22$, $y=-28$, $z=-4$) that included the MGN and pulvinar. Increased responses in other regions, not predicted *a priori*, were not significant when corrected for numerous comparisons.

(d) *Differential responses to CS+ and CS− tones*

All CS+ scans (i.e. both high and low frequency) were contrasted with all CS− scans to determine neural responses related to discriminatory conditioning. Only one region, in right orbitofrontal cortex (maximal voxel, $x=2$, $y=44$, $z=-30$, $p=0.005$), showed increased responses to CS+ tones relative to CS−. In contrast, a significantly greater response to CS− tones relative to CS+ was seen in auditory cortex and several other regions predicted *a priori* to show differential responses in auditory conditioning (see table 2). Activations in the left MGN and right auditory cortex are displayed in figure 4. Other unpredicted areas with differential responses to CS+ and CS− tones failed to reach a corrected level of significance.

(e) *Regression analyses*

On the basis of an animal model of the mechanisms underlying experience-dependent receptive field plasticity (Weinberger 1995), it can be predicted that neural structures such as the MGN, amygdala and basal forebrain will demonstrate functional interactions with the auditory cortex. Brain regions which positively covaried in activity with the conditioning-related regions of the left auditory cortex (maximal foci, $x=-50$, $y=-26$, $z=10$ and $x=-50$, $y=-16$, $z=-2$) were identified by a regression analysis (see § 2). The bilateral involvement of the amygdala in this analysis is illustrated in figure 5. Other significant brain regions are detailed in table 3. Unpredicted brain areas identified in the analysis (including the left anterior insula and anterior cingulate displayed in figure 5) failed to reach a corrected level of significance.

A regression analysis based on the activity in the maximally activated voxel in the left MGN ($x=-12$, $y=-26$, $z=-2$) was done to detect the presence of context-specific interactions (see § 2; Friston *et al.* 1997). In essence, this analysis tests for changes in the covariation of MGN activity with other brain regions during conditioning and non-conditioning sequences. As predicted, the MGN ($x=-12$, $y=-26$, $z=-2$) showed a significant ($p<0.001$) context-specific interaction with the auditory cortex ($x=-50$, $y=-12$, $z=-4$) (see figure 6). Other unpredicted regions identified in this analysis failed to reach a corrected level of significance.

4. DISCUSSION

The relative location of the frequency-selective neural responses in transverse temporal gyrus (see figure 2) is consistent with the tonotopic organization of monkey auditory cortex (Morel *et al.* 1993) and with data from previous neuroimaging experiments in humans (Pantev *et al.* 1996; Lantos *et al.* 1997). A marked lateralization of responses to the left hemisphere (see figure 2, table 1) was evident, which has been observed in other neuroimaging studies by using binaural tone presentations (Molchan *et al.* 1994; Lantos *et al.* 1997). The significance of this lateralization is unclear: in the present study it may be related to the explicit frequency-discrimination task done by the subjects.

According to a probabilistic map derived from a large series of magnetic resonance scans (Penhune *et al.* 1996), the maximal foci associated with the high and low tones in the present study (see figure 2 and table 1) lie several millimetres outside the boundary of primary auditory cortex, with the two frequencies at opposing ends of the map. However, in the contrast of all CS− tones with all CS+ tones (table 2*b*), the maximal voxel in left transverse temporal gyrus lies within the central 75–100% boundary of the map. This spatial distribution accords with the tonotopic organization of auditory cortex, as responses to pure low (200 Hz) or high (8000 Hz) frequencies will tend to be more peripheral and widely separated than activity related to both frequencies (as in the all CS+ and all CS− conditions). Therefore, although the involvement of surrounding auditory cortical areas cannot be excluded by the present PET data, with their limited spatial resolution, the observed neural activity is consistent with the activation and modulation of primary auditory cortex.

The pattern of neural responses observed across the different conditions (see figure 3) provides compelling evidence for experience-dependent, frequency-specific modulation of auditory cortex activity. As noises were never presented in the scanning window, identical physical stimuli (pure tones) were presented during the scans for each condition. As scan order was counterbalanced within and across subjects, the differences in neural activity between conditions must therefore reflect the changing association between tones and noise (i.e. CS+ tone predicts the noise in conditioning sequences, but not in non-conditioning sequences). These human neuroimaging results accord with animal single-unit data, which are discussed in detail in the next paragraph.

Experience-dependent receptive-field plasticity has been demonstrated in the auditory cortex of the guinea-pig (Edeline & Weinberger 1993), the Mongolian gerbil (Scheich *et al.* 1993), and the owl monkey (Recanzone *et*

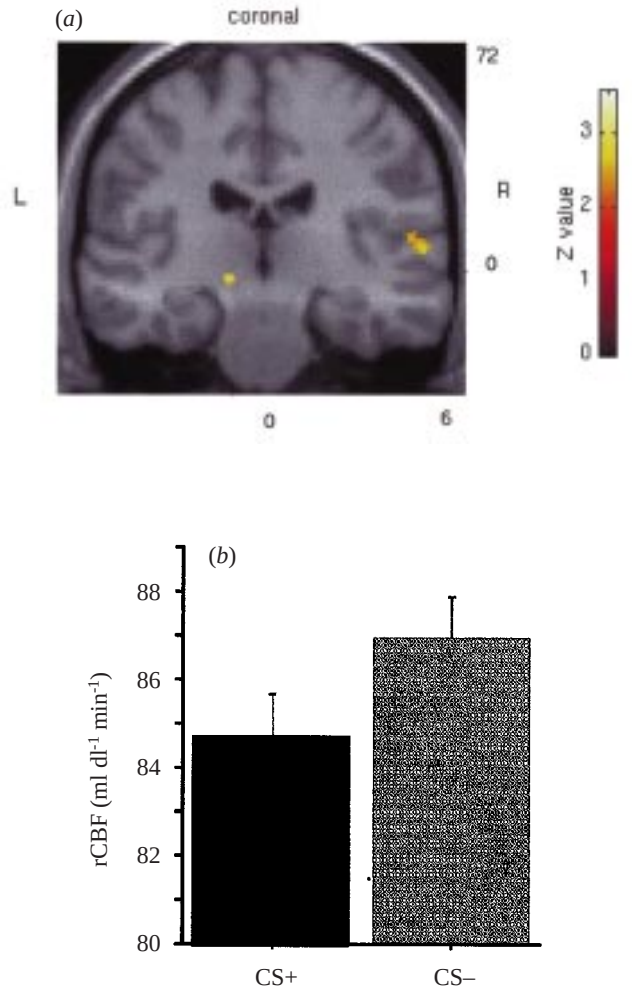

Figure 4. (*a*) An SPM showing greater activity in the region of the left MGN (maximal voxel $x=-12$, $y=-26$, $z=-2$) and right auditory cortex (maximal voxel $x=56$, $y=-26$, $z=12$) in the contrast of all CS− with all CS+ scans (threshold $p=0.01$). The PET data are displayed on a coronal slice ($y=-26$ mm) of a canonical MRI image. (*b*) A graphical display of the mean rCBF values (in ml dl^{-1} min^{-1}) for the maximal voxel in the left MGN ($x=-12$, $y=-26$, $z=-2$) in the CS+ and CS− conditions. The bars represent two standard errors.

Table 3. *Auditory cortex regression analysis*

(Regions with a positive regression of activity onto the voxels in left auditory cortex ($x=-50$, $y=-26$, $z=10$ and $x=-50$, $y=-16$, $z=-2$) which showed maximal conditioning-related changes of response (table 2). The rCBF values at these two voxels were used as covariates of interest and a conjunction analysis done in SPM96. The coordinates, Z-scores and uncorrected p-values of the maximal voxels are shown.)

	coordinates (x, y, z)	Z-score	p-value
R. orbitofrontal cortex	6, 52, −2	4.52	<0.001
L. amygdala	−22, −8, −12	4.31	<0.001
R. amygdala	30, −6, −18	3.61	<0.001
basal forebrain	8, −2, −12	3.74	<0.001
L. medial geniculate nucleus	−10, −26, −6	3.53	<0.001

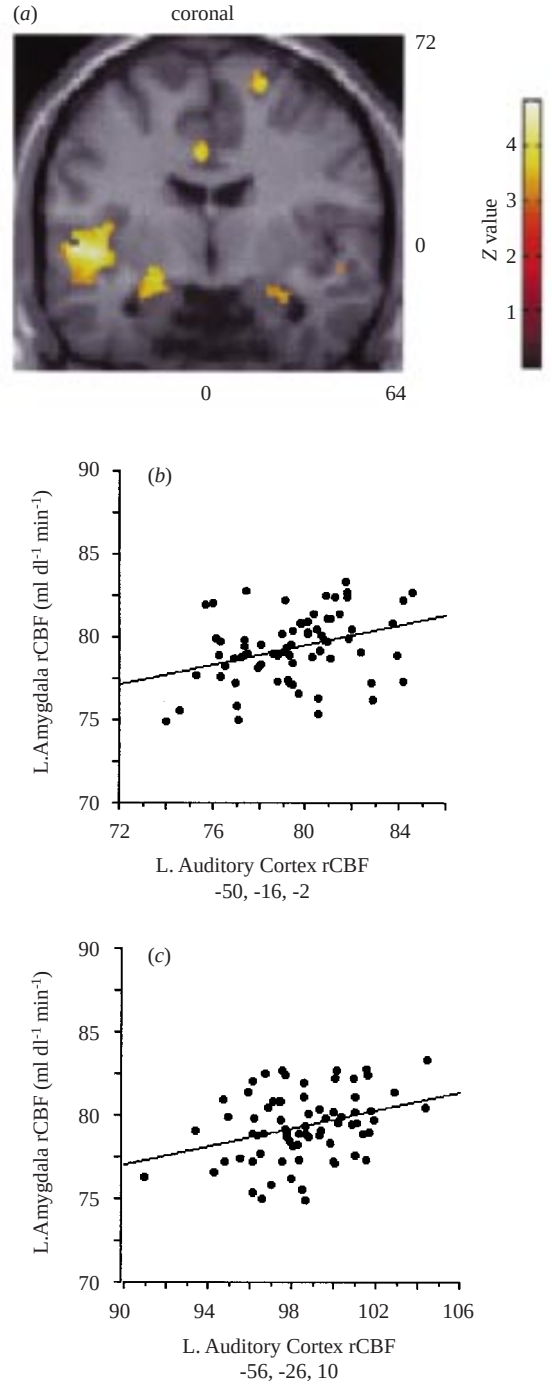

Figure 5. (*a*) An SPM displaying bilateral amygdala regions (maximal voxels $x=-22$, $y=-8$, $z=-12$, $p<0.001$, uncorrected, and $x=30$, $y=-6$, $z=-18$, $p=0.008$, uncorrected) which have a positive regression of activity onto the voxels in left auditory cortex which show maximal experience-dependent changes in high- ($x=-50$, $y=-26$, $z=10$ and low- ($x=-50$, $y=-16$, $z=-2$) frequency conditioning. The rCBF values (in ml dl^{-1} min^{-1}) at the two auditory cortex voxels were used as covariates of interest in an SPM96 conjunction analysis. Other regions shown (e.g. left anterior insula and anterior cingulate) were not predicted *a priori* and do not reach a corrected level of significance. The PET data (threshold $p=0.01$) are displayed on a coronal slice ($y=-8$ mm) of a canonical MRI image. (*b*) Bivariate regression plots of the rCBF values (in ml dl^{-1} min^{-1}) for the maximal voxel in the left amygdala ($x=-22$, $y=-8$, $z=-12$) onto the rCBF values for the two voxels in left auditory cortex ($x=-50$, $y=-26$, $z=10$ and $x=-50$, $y=-16$, $z=-2$).

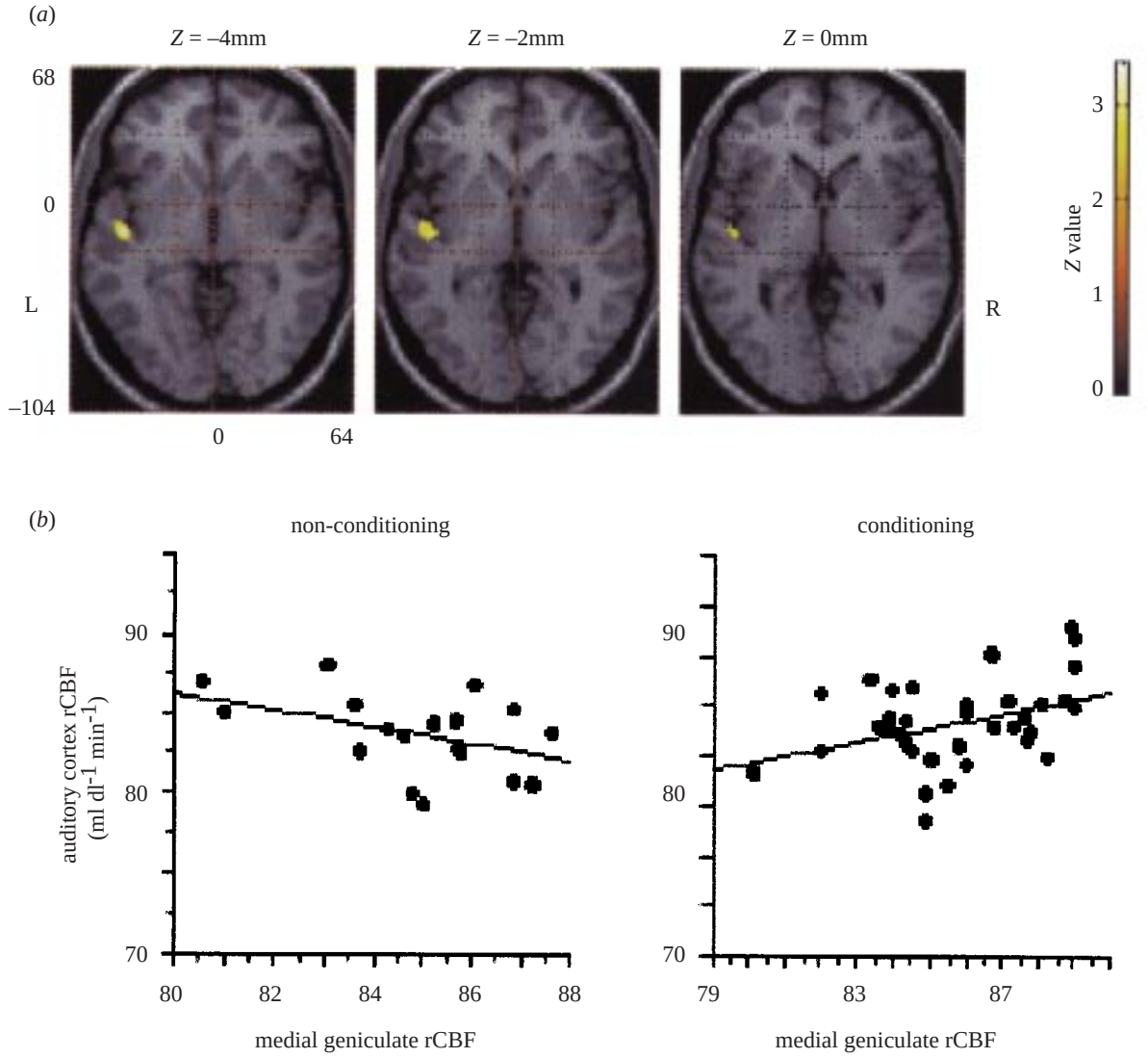

Figure 6. Context-specific interaction between medial geniculate nucleus and auditory cortex. (*a*) An SPM displaying a region of left auditory cortex having a significant context-specific interaction with the left medial geniculate nucleus (maximal voxel $x=-12$, $y=-26$, $z=-2$) in conditioning compared to non-conditioning scans. The analysis that produced the SPM is described in detail in § 2. A threshold of $p=0.01$ was used for the contrast. The PET data are displayed on serial transverse slices from a canonical MRI image. (*b*) Bivariate regression plots of rCBF values (in ml dl^{-1} min^{-1}) in the conditioning and non-conditioning scans between the maximal voxels in auditory cortex ($x=-50$, $y=-12$, $z=-4$) and medial geniculate nucleus ($x=-12$, $y=-26$, $z=-2$).

al. 1993). Immediately after two-tone discrimination learning in guinea-pigs, a small and narrowly tuned increase in the response of auditory cortex at the CS+ frequency occurs, together with decreased responses to a broad range of surrounding frequencies, presumably as a result of intrinsic lateral inhibition (Edeline & Weinberger 1993). The frequency-specific attenuation of response to the CS+ tones observed in the present study may, therefore, reflect the activity of these intrinsic inhibitory processes, because the smaller augmented responses will be masked as a result of the limited spatial resolution of PET. An alternative explanation is that a learned expectancy of the noise UCS in relation to the CS+ tone results in a generalized extrinsic inhibition of auditory cortex activity, which attenuates tonotopic responses to the CS+ tone. It is also possible that the decreased responses in auditory cortex to the CS+ tones reflect an extinction component of conditioning. Previous studies of auditory conditioning have reported decreases in auditory cortex activity during extinction (Molchan *et al.* 1994; Schreurs *et al.* 1997).

Plasticity of response to conditioned tone frequencies has also been observed in the MGN of the guinea-pig (Edeline & Weinberger 1991, 1992). In the present study, an increased response in the region of the MGN to CS− compared with CS+ tones was observed (maximal voxel, $x=-12$, $y=-26$, $z=-2$; figure 4), consistent with the suggestion that the MGN is an early site of auditory receptive-field plasticity (Edeline & Weinberger 1992). As the plastic receptive fields in MGN tend to be broadly tuned (Edeline & Weinberger 1992), there cannot be a simple one-to-one projection from the MGN to the narrowly tuned plastic reponses of the auditory cortex (Edeline & Weinberger 1993; Weinberger 1995). The context-specific

interaction identified in the present study (see figure 6) demonstrates how the MGN contribution to human auditory cortex can be influenced in a frequency-specific manner by learning. Similar conditioning-related interactions between MGN and auditory cortex have been observed in animals (McIntosh & Gonzalez-Lima 1995). There is evidence from animal studies employing exogenous application of cholinergic agents and stimulation of the nucleus basalis of Meynert (NBM) (Ashe *et al.* 1989; McKenna *et al.* 1989; Metherate & Weinberger 1990; Metherate & Ashe 1991; Hars *et al.* 1993) that this experience-dependent enhancement of MGN connectivity may involve the strengthening of synapses on the apical dendrites of layer IV pyramidal cells in the auditory cortex by the release of acetylcholine from basal forebrain projections (Weinberger 1995).

The observed covariation of activity between the amygdala, basal forebrain, MGN and auditory cortex (see table 3; figure 5) is consistent with the known anatomical and functional connections between these structures. Both MGN and auditory cortex send projections to the amygdala (LeDoux *et al.* 1984, 1985), which has been shown to mediate conditioned responses in both animals (Cohen 1974; LeDoux *et al.* 1984, 1988; Campeau & Davis 1995) and humans (Bechara *et al.* 1995; LaBar *et al.* 1995). The amygdala has strong connections with the NBM in the basal forebrain (Russchen *et al.* 1985), which lesion experiments in monkeys have implicated in the learning of stimulus-reinforcement associations (Roberts *et al.* 1992). The NBM itself sends widespread cholinergic projections to other brain regions, including the auditory cortex (Bigl *et al.* 1982; Mesulam *et al.* 1983).

Orbitofrontal cortex, which has strong connections to basal forebrain, amygdala, thalamus, and the temporal lobe (Jones & Powell 1970; Krettek & Price 1974, 1977; Seltzer & Pandya 1989), has been implicated in controlling responses in relation to changed stimulus-reinforcement contingencies (Jones & Mishkin 1972; Thorpe *et al.* 1983). The extinction phase of classical conditioning, during which the conditioned stimulus is presented without the unconditioned stimulus, represents such a change of contingency. Monkeys with orbitofrontal lesions and rodents with lesions to medial prefrontal cortex fail to extinguish unrewarded learned responses (Jones & Mishkin 1972; Morgan *et al.* 1993). In the present study, the CS+ tones were repeatedly presented without the noise during the scanning window, which therefore represents a change to an extinction phase. The enhanced response in right orbitofrontal cortex to CS+ versus CS− tones (table 3) may be related, therefore, to the changes in the reinforcement contingency introduced by the conditioning paradigm.

A previous human neuroimaging study of visual conditioning (Morris *et al.* 1997) has also demonstrated functional connections between thalamus, amygdala, basal forebrain, and orbitofrontal cortex. The similarity between the present study and that of Morris *et al.* (1997) in the network of brain regions identified suggests that the same neural mechanisms are involved in this form of learning across different sensory modalities. There are several differences between the two studies, however, in the pattern of responses observed, e.g. predominantly right-sided, enhanced responses for the conditioned visual stimuli in Morris *et al.* (1997), compared with the left-lateralized, inhibited responses to the auditory CS+s in the present study (table 1). These contrasting results may be related to (i) the different sensory modalities used for the conditioned stimuli in the two studies (i.e. visual versus auditory); (ii) the use of a CS and UCS with the same modality in the present study, but different in Morris *et al.* (1997); or (iii) the different conditioning protocols used in the two experiments (e.g. 100% reinforcement in Morris *et al.* (1997) versus 40% part reinforcement in the present study).

The present data provide evidence for frequency-specific, learning-related modulation of tonotopic responses in human auditory cortex, consistent with single-unit data in animals (Weinberger & Diamond 1987; Recanzone *et al.* 1993; Scheich *et al.* 1993). The identification of the amygdala, basal forebrain, and MGN as structures involved in these plastic changes accords with several neurobiological models of experience-dependent neural plasticity (Friston *et al.* 1994; Weinberger 1995). At a more general level, the study demonstrates that neuroimaging experiments can successfully address questions of functional integration and neural plasticity in the context of human learning.

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