Feedback that confirms reward expectation triggers auditory cortex activity

Reward activates auditory cortex

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Abstract

Associative learning studies have shown that the anticipation of reward and punishment shape the representation of sensory stimuli which is further modulated by dopamine. Less is known about whether and how reward delivery activates sensory cortices and the role of dopamine at that time point of learning. We used an appetitive instrumental learning task where participants had to learn that a specific class of frequency modulated tones predicts a monetary reward, following fast and correct responses in a succeeding reaction time task. This fMRI data was previously analyzed regarding the effect of reward anticipation, but here we focus on neural activity to the reward outcome relative to the reward expectation and tested whether such activation in the reward reception phase is modulated by L-dopa. We analyzed neural responses at the time point of reward outcome under three different conditions i) when a reward was expected and received ii) when a reward was expected but not received and iii) when a reward was not expected and not received. Neural activity in auditory cortex was enhanced during feedback delivery when either an expected reward was received or when the expectation of obtaining no reward was correct. This differential neural activity in auditory cortex was only seen in subjects who learned the reward association and not under dopaminergic modulation. Our data provide evidence that auditory cortices are active at the time point of reward outcome. However, responses are not dependent on the reward itself, but on whether the outcome confirmed the subject’s expectations.

Keywords

Reward delivery, auditory cortex, neuroimaging, instrumental learning
Introduction

Prior evidence suggests that the expectation of reward and punishment shapes the representation of stimuli in sensory cortices (David et al. 2012). Animal data indicate that reward expectation can influence neural activity in sensory cortices (Shuler and Bear 2006; Pantoja et al. 2007; Brosch et al. 2011). In primary visual cortex, Shuler and Bear (2006) discovered neurons that predicted the timing of water reward delivery. In primary somatosensory cortex, Pantoja and colleagues (2007) found stimulus-related neural responses that correlated with reward delivery in a tactile discrimination task. These stimulus related activities were only present when the task was well learned, suggesting that neural activity in sensory cortex is strongly modulated by reward contingency in association with learning. Brosch et al. (2011) studied primates performing an auditory categorization task and found that neural activity in auditory cortex not only reflected reward expectancy but was directly related to the reward itself in a size-dependent manner. Responses in auditory cortex were also observed in trials with prediction errors, i.e. when a mismatch between expected and received rewards occurred. These findings demonstrate that the auditory cortex receives reward feedback which can be used for adaptation to specific task requirements.

Scheich et al. (2011) further underline the role of auditory cortex in deducing the task specific meaning of sound by learning and suggest that even primary auditory cortex is influenced in a multimodal manner by other sensory stimuli, reward and punishment. This evidence is supported by human fMRI and MEG studies showing an increased representation of auditory stimuli which signal a reward or punishment (Thiel et al. 2002a, 2002b; Kluge et al. 2011; Puschmann et al. 2012). Whereas Thiel
et al. (2002a,b) showed that the representation of auditory stimuli is modulated by classical aversive conditioning and the cholinergic neurotransmitter system. Puschmann et al. (2012) showed that the representation of auditory stimuli can also be increased by instrumental appetitive conditioning. However, this effect was only seen in subjects who learned the reward association. Using the same paradigm and a pharmacological fMRI approach where half of the participants received 100 mg of the dopamine precursor L-dopa, Weis et al. (2012) provide further evidence for a dopaminergic modulation of neural responses in auditory cortex during reward anticipation. Hence, there is ample of evidence that cholinergic and dopaminergic neurotransmitter systems modulate the representation of auditory stimuli. Both studies concentrate on the time point of reward anticipation, however, since the paradigm consists of two different parts, in this current work we analyzed the data of the two previous studies (Puschmann et al. 2012, Weis et al. 2012) focusing on the reward delivery phase instead of reward anticipation.

While these studies compellingly demonstrate that sensory cortices develop increased responses to stimuli that gain behavioral relevance due to prediction of reward or punishment only few studies addressed the question whether reward delivery may activate sensory cortices. Previous studies by Pleger and colleagues (2008) showed that the somatosensory cortex is activated at the time of reward delivery in the absence of concurrent somatosensory input. This study showed for the first time in humans, that rewards do not only influence classical reward-related regions, but also processing in early sensory cortices. A subsequent study demonstrated that the behavioral and neural effects were enhanced by L-dopa and attenuated by haloperidol (Pleger et al. 2009) suggesting that the dopaminergic system may also modulate reward-related activity in sensory cortices. Similar results
for the visual cortex were provided by Weil et al. (2010) who found in a visual
discrimination task that a financial reward increased neural activity in striatum and
orbitofrontal cortex as well as in visual areas. Again, the activity in visual areas
appeared at the time point of reward delivery when no visual stimulus was present. In
line with the results of Pleger et al. (2008), the delivery of reward at the end of the
trial lead to improved performance and enhanced neural activity in visual cortex in the
subsequent trial suggesting some kind of “teaching signal” propagated via feedback
connections from reward-related areas to sensory cortex.

In contrast to the visual and somatosensory system only few studies focused on
reward-related activity in human auditory cortex. Further, there is currently no human
data investigating neural activity in sensory cortex when an expected reward is not
received. To fill this gap, we here reanalyzed the datasets of Puschmann et al. (2012)
and Weis et al. (2012) with focus on the time point of reward delivery instead of the
time point of reward anticipation. While our previous studies have shown increased
auditory cortex activity when an auditory stimulus indicates a later reward, the
present analysis was performed to investigate whether the reward, which is
presented in the absence of any auditory stimulation, reactivates auditory cortex as
reported for other modalities and whether such reactivation is modulated by
dopaminergic stimulation.

Participants had to learn that a specific category of frequency modulated (FM) tones
predicts a monetary reward when fast and correct responses were made in a
succeeding reaction time task. An event-related fMRI design allowed us to temporally
distinguish BOLD responses associated with auditory discrimination and reward
anticipation at the beginning of each trial from those attributed to the subsequent
non-auditory rewarding feedback. We focused our analysis on neural responses during the receipt of feedback under three conditions i) when a reward was expected and received (CS+ trial), ii) when a reward was expected but not received due to slow and incorrect responses in potentially rewarded trials (CS+ trial) and iii) when a reward was not expected and not received (CS- trial). We hypothesized that reward delivery and reward omission would modulate neural activity in auditory cortex and reward-related dopaminergic brain regions.

Since we found effects of dopaminergic modulation within the left auditory cortex during reward anticipation in our previous study (Weis et al. 2012), we expected that dopaminergic stimulation would also influence reward-related activations in auditory cortex.
Methods

Subjects
All 105 participants were scanned with the same paradigm and fMRI data acquisition techniques including either a standard fMRI protocol or a double blind pharmacological fMRI protocol. All participants were right-handed as indexed by a handedness inventory (Oldfield 1971), had no history of neurological or psychiatric disease and were not on any kind of medication (except for contraceptives). The study was conducted in accordance with the Declaration of Helsinki (World Medical Association 2008) and the experiments were approved by the ethics committee of the University of Magdeburg.

39 healthy, right handed, normal hearing volunteers (18 female, 21 male, age range: 18-31 years, mean age: 24 years) participated in the standard fMRI protocol. Five subjects were excluded from all further analyses due to severe head movements during fMRI scanning. 66 healthy, right handed, normal hearing volunteers (20 female, 46 male, age range: 25-42 years, mean age: 28 years) participated in the pharmacological fMRI protocol receiving either 100 mg of L-dopa (Madopar LT®) or placebo (solution containing glucose dissolved in water) 30 minutes before starting the fMRI measurement in a double blind between group design (see Weis et al. 2012 for more details). A clinical evaluation was first carried out to ensure that subjects had no conditions contraindicative for L-dopa administration. The age range was restricted to above 25 years of age according to the patient information sheet. Participants were asked to avoid excessive alcohol intake on the evening before the test session and to refrain from eating, smoking and drinking coffee for two hours prior to the experiment. Four subjects were excluded from all further analyses due to
non-compliance with task instructions; five subjects due to severe head movement during fMRI scanning. Two further subjects were excluded after analysis of blood samples due to non-detectable L-dopa levels.

The group size remaining in the analysis was 89 subjects in total, \( n = 34 \) (18 male, 16 female, mean age = \( 24 \pm 1 \) years) for no drug (standard fMRI protocol), \( n = 28 \) for placebo (20 male, 8 female, mean age = \( 28 \pm 1 \) years), and \( n = 27 \) for L-dopa (18 male, 9 female, mean age = \( 29 \pm 1 \) years).

Task

We used an instrumental learning paradigm, where participants had to learn the association of a specific category of FM tones with the chance to gain a monetary reward in a subsequent reaction time task (Knutson et al. 2000). At the beginning of each trial, an FM tone was presented which indicated whether the upcoming trial was potentially rewarded with 50 cent (CS+ trials) or not (CS- trials) (see Figure 1). The FM tones differed with respect to five stimulus features each with two different levels (for further details see below): direction, duration, loudness, frequency range, and modulation rate. Participants were informed that one category of these FM tones predicts a reward chance, but had to find out the relevant feature by trial and error. The relevant reward-prediction feature was duration (400 ms vs. 800 ms). Whether the short or long duration FM tones predicted the reward was randomized across subjects. The number of short and long duration FM tones (i.e. CS+ and CS- trials) was the same. To assess the individual learning rate, participants had to indicate via button press after each tone if they expected a reward in the upcoming trial or not. They had to press the left button with the index finger if they expected a reward and the right button with the middle finger if they did not expect a reward.
Note that the rewards were obtained for fast responses in a following number comparison task. Here, participants had to indicate by button press if the number (1, 4, 6 or 9) presented on the screen for 100 ms, was smaller or larger than five, either with the index finger for ‘smaller’ or with the middle finger for ‘larger’. Based on an individual reaction time threshold which was piloted before the experiment (see below), fast and correct responses in CS+ trials were financially rewarded (Pappata et al. 2002; Wittmann et al. 2005; Knutson et al. 2000). The reward was indicated by a 50-Euro-Cent coin displayed on the screen at the end of each trial 1.5 seconds after onset of the number presentation. In CS- trials no reward was given independent of the subject’s answer, which was signaled by a neutral feedback (grey square). The same feedback was also given for slow or incorrect answers in CS+ trials. A temporal jitter was used between the FM tone and the number comparison task in steps of 1.5 seconds ranging from 4.5 to 12.0 seconds. The inter-trial-interval ranged from 3.0 to 12.0 seconds also in steps of 1.5 seconds. A fixation cross was presented in the middle of the screen during all delays and during presentation of the FM tones. The total experiment comprised 160 trials in 42 minutes. Participants received payment of the amount of gained reward at the end of the experiment.

(Insert Figure 1 around here)

To obtain an individual reaction time threshold for fast responses, participants performed the number comparison tasks prior to entering the MRI scanner. As during scanning, they had to indicate via button press whether the presented number was smaller or larger than five. The 80 % value of reaction time in 80 trials was calculated and taken as a starting threshold for gaining a potential reward in the following
paradigm during fMRI measurement. This reaction time threshold was 405 ± 11 ms in
the standard fMRI protocol, and 560 ± 10 ms for the pharmacological fMRI study
(T(1,84) = 9.29, \( p < 0.001 \)). However, there was no difference between the L-dopa
(560 ± 94 ms) and placebo (559 ± 64 ms) group (T(1,53) = 0.08, \( p = 0.9 \)). All
experimental control software was programmed in MATLAB (The MathWorks, Inc.,
Natick, MA, USA) using Cogent 2000.

Stimuli

Each stimulus dimension (frequency range, modulation rate, loudness, direction and
duration) consisted of two principle levels. There was a low and a high frequency
band, each containing five onset frequencies separated by half-tone steps (500 Hz,
530 Hz, 561 Hz, 595 Hz, 630 Hz / 1630 Hz, 1732 Hz, 1826 Hz, 1915 Hz, 2000 Hz).
Frequencies varied either with 0.25 octaves/second or 0.5 octaves/second. Sound
level was individually adjusted under scanner noise for both louder and quieter
sounds differing approximately by 10 phon. Sound duration was either 400 ms (short)
or 800 ms (long). The modulation direction was either rising or falling. In total, the
combination of all possible values of the five dimensions resulted in 160 different
stimuli; with eighty of them predicting a potential reward (all short or all long FM
tones).

fMRI data acquisition

FMRI data acquisition was performed on a 3 T Siemens MAGNETOM Trio MRI
scanner (Siemens AG, Erlangen, Germany) with an eight-channel head array. Key-
presses were recorded using a MR-compatible response keypad (LUMITouch,
Photon Control Inc., Burnaby, BC, CDN). Acoustic stimuli were delivered by MR
compatible headphones (MR confon OPTIME 1, MR confon GmbH, Magdeburg, Germany).

During functional measurements 1680 T₂*-weighted gradient echo planar imaging (EPI) volumes (time of repetition (TR) = 1.5 ms, time of echo (TE) = 30 ms, flip angle α = 80°, field of view (FoV) = 192 x 192 mm², voxel-size = 3.0 x 3.0 x 3.0 mm³) were obtained within one session. Volumes consisted of 24 interleaved slices (gap of 0.3 mm) ranging from the anterior cingulate cortex dorsally to the inferior colliculus in the brain stem. After the experimental task a high-resolution T₁-weighted structural volume was obtained from each subject.

Behavioral data analysis

To assess whether participants learned the tone reward association we analyzed individual learning rates. The expectation of reward was indicated by the subjects after presentation of the FM tone and reflects whether the tone-reward association was learnt. For each subject, we determined the individual learning curve using the cumulative sum of correct responses as function of experimental trial according to (Gallistel et al. 2004). The final sum of the correct responses was compared across groups by means of a Kruskal-Wallis test. In a second step we grouped subjects into learners and nonlearners. Learners were defined as those subjects who reached about 90% correct responses at least within the last 40 trials. Using such criterion, 17 subjects in the L-dopa group, 12 in the placebo group and 19 in the no drug study were classified as learners. Subjects who never exceed 65 % correct responses during the whole paradigm were classified as nonlearners. This resulted in 8 subjects in the L-dopa group, 8 in the placebo group and 12 subjects in the no drug study within the group of nonlearners. We had to exclude 13 participants since their
performance could neither be classified as learner nor nonlearner (L-dopa: 2, placebo: 8, no drug: 3). Figure 2 depicts the mean of the individual learning curves (smoothed on individual level with a sliding average of ± 15 trials around each data point) for learners and nonlearners in each of the three groups.

fmRI data analysis

All MRI data were processed and analyzed using SPM8 (FIL, Wellcome Trust Centre for Neuroimaging, UCL, London, UK). To correct for head motion the functional time series were spatially realigned and unwarped. The structural T₁-weighted volume was registered to a mean functional image and segmented in order to obtain spatial normalization parameters. Using these parameters functional and structural images were normalized to the Montreal Neurological Institute (MNI) template brain. Finally, normalized functional volumes were smoothed with a three-dimensional Gaussian kernel of 4 mm full-width-half-maximum.

Effects of receipt of reward

The single-subject model contained six regressors. The first two regressors modeled the BOLD responses to CS+ and CS- tones, respectively, whereas the last four regressors modeled the feedback phase. For CS+ trials with correct reward expectations, one regressor accounted for receipt of reward after fast and correct responses (named “reward expected & received” in further analysis), another one for neutral feedback after slow responses (“reward expected & not received”). For CS- trials, we used one regressor modeling neutral feedback after correct reward expectations (“reward not expected & not received”). All other event types (i.e. CS+ or CS- trials with wrong reward expectations or trials with no button press in the reaction time task) were pooled into one additional error regressor due to the low
amount of total errors. Time series in each voxel were high-pass filtered to 1/128 Hz
and modeled for temporal autocorrelation across scans with an AR(1) process. Note,
that the data on reward anticipation has been published elsewhere (Puschmann et al.
2012; Weis et al. 2012).

Single subject contrasts coding for neural activity increases during different reward
conditions were entered into a full-factorial ANOVA design for further analysis. The
following factors were included in the ANOVA model: group (L-dopa / placebo / no
drug), learning status (learner / nonlearner) and reward condition (“reward expected
& received” / “reward not expected & not received” / “reward expected & not
received”). Within this full-factorial ANOVA model, we calculated F-contrasts for all
main effects and interactions. Results of this and all other analyses are reported as
statistically significant at a threshold of $p < 0.05$, corrected for whole brain with family-
wise errors (FWE) and a minimum cluster size $k = 40$ or at $p < 0.05$ corrected for
auditory cortex as a region of interest as in our previous study (Weis et al. 2012). To
further visualize significant effects in auditory cortex and striatum during reward
delivery, we extracted average beta values as a function of reward condition, group
and learning status in a sphere of radius of 6 mm around the activation peak maxima.
Additionally, we calculated the time course of the BOLD response within those
regions, as function of reward condition, relative to the two important time points
within the paradigm (i) reward anticipation (sound presentation) and (ii) reward
delivery (feedback presentation).
Results

Behavioral data
Overall, subjects learnt the task quickly and had a high number of correct reward expectations. There were no significant differences in accuracy between the three groups “no drug”, “L-dopa”, and “placebo” ($\chi^2(1,2) = 3.52, p = 0.1$, Kruskal-Wallis test). Figure 2 illustrates the learning curves for learners and nonlearners in each group. Note that learning curves in the pharmacological study were numerically steeper for both placebo and L-dopa as compared to the no drug condition. Similarly, there was no significant difference in the amount of reward received in the pharmacological study for the L-dopa compared to the placebo group (L-dopa: $31 \pm 0.8 \, \text{€}$, placebo: $31.8 \pm 0.5 \, \text{€}$, $T(1,53) = -0.84, p = 0.4$). However, subjects in the no drug condition received significantly less reward (no drug study: $27.2 \pm 1.2 \, \text{€}$, pharmacological study: $31.4 \pm 0.5 \, \text{€}$, $T(1,84) = 3.59, p > 0.001$).

Functional MRI data
We found a significant main effect of reward condition and a reward condition x learning status interaction. All other main effects and interactions were not significant. A main effect of reward condition was seen in reward related dopaminergic areas such as substantia nigra / ventral tegmental area, the left and right striatum and the pallidum (see Figure 3B and Table 1). The mean time course plots of the BOLD response during the phase of reward delivery (i.e. feedback, 4B right side) illustrates that this main effect was due to significantly higher neural activity when a reward was expected and received in CS+ trials as compared to the situation when no reward
was delivered. There was no difference between neural activity when a reward was expectedly (CS- trials) or unexpectedly (CS+ trials) not received. This result clearly shows that the striatum was only activated when a reward was received. Note that striatal BOLD activity during the reward phase was higher than during the reward anticipation phase (i.e. sound, 4B left side). Differences in neural activity as a function of reward condition were also seen in anterior and middle cingulate cortex as well as in the ventral stream of the visual pathway including bilateral middle, inferior occipital and fusiform gyrus. As for the striatum, this main effect of reward condition was due to enhanced BOLD activity when a reward was received.

A modulation of neural activity as a function of reward condition was also found within the left and right auditory cortex (Figure 3A). The mean time course plots of the BOLD response (i.e. feedback, 4A right side) illustrate that the main effect in auditory cortex was due to significantly higher neural activity in the case of correct expectation of a reward in CS+ trials and correct expectation of no reward in CS- trials. In other words, neural activity in auditory cortex reflects correct expectations independent from the delivery of reward. Note that neural activity in auditory cortex during the reward phase was half the size of neural activity during the reward anticipation phase when the sound was present (sound, 4A left side).

Results of the reward condition x learning status interaction suggest that the findings in auditory cortex were dependent on learning status (see Figure 5). We extracted
mean beta values as a function of reward condition, learning status and group (Figure 6A) to illustrate the interaction and to confirm that results are similar for all three groups (placebo, L-dopa, no drug). The results suggest that only those participants who learned the reward association showed increased neural activity in auditory cortex in the case of a correct expectation.

(Insert Figure 5 around here)

(Insert Figure 6 around here)

Other regions showing a similar learning-dependent effect were in the right insula and the anterior cingulate cortex as well as in the left and right angular gyrus and the precuneus (Table 2, Figure 5). Neural activity in the striatum was not found to be modulated by learning status (Figure 6B). This effect was similar in all groups (placebo, L-dopa, no drug).

(Insert Table 2 around here)
**Discussion**

We aimed to investigate whether reward delivery in an auditory instrumental learning task activates auditory cortex at the time point of the receipt of reward and whether reward-related activations in auditory cortex are modulated by dopamine. Our results show that neural activity in auditory cortex is enhanced when either an expected reward is obtained or when the expectation of obtaining no reward was correct as compared to unexpectedly not receiving a reward. Importantly, this pattern was only seen in volunteers who learned the reward association. In contrast, neural activity in dopaminergic brain regions was only enhanced upon receipt of a reward, and independent from learning the reward association. We found no evidence for a dopaminergic modulation at the time point of the receipt of reward.

**Effects of reward delivery in auditory cortex**

Our data demonstrate on the one hand increased neural activity in left and right auditory cortex at the time point of reward delivery, although there is no auditory stimulation at this time. This finding is in line with monkey evidence in auditory cortex and extends human evidence from somatosensory and visual cortices which were shown to be activated in rewarded trials compared to unrewarded trials in sensory discrimination tasks (Brosch et al. 2005, 2011; Pleger et al. 2008, 2009; Weil et al. 2010). Brosch et al. (2011) recorded neuronal activity in auditory cortex of two monkeys while performing an auditory discrimination task. Correct responses were rewarded with the size of reward depending on performance in the previous trial. Increases in firing rate were observed for large as well as small rewards and decreases were found when no reward was obtained after an incorrect response. However in the latter case neuronal activity increased afterwards. Note however that in that study, monkeys were always able to receive a reward for correct performance.
In contrast, participants in our study were aware that they did not receive a reward in 50% of the trials (CS-) and that the reward was dependent on fast reaction times in the number comparison task. In spite of conceptual differences between our study and the study by Brosch et al. (2011), the basic common finding of both approaches is, however, that the auditory cortex is responsive to non-auditory feedback signaling the correctness of the previous behavioral choice within the trial.

The high amount of CS- trials and unrewarded CS+ trials enabled us to further dissociate reward delivery from confirmation of an expectation. Our data provide new evidence that the increase of activity at the point of reward delivery is rather linked to the confirmation of an expectation than to the receipt of reward per se. To our best knowledge this study is thus the first in humans to indicate that sensory cortices do not only reflect reward delivery but also correct expectations of reward outcome – irrespective of receipt of reward. Note, however, that in our paradigm, both situations provide valuable feedback to establish a successful behavioral strategy i.e. selecting the correct acoustic feature (stimulus duration) and attributing the correct motor behavior (pressing one button for short tones and the other for long tones). Hence, the absence of a reward in CS- trials indicates correct prior classification of the stimulus and contributes in a similar way to learning as the receipt of a reward in CS+ trials. In contrast, in the above mentioned studies (Pleger et al. 2008, 2009; Weil et al. 2010), subjects had to solve a sensory discrimination in a two-alternative forced choice task and received a reward for correct judgments only.

Animal data by Pantoja et al. (2007) showed that neural activity in sensory cortex increased from stimulus presentation to reward outcome but only in trials were stimulus discrimination was important for receiving a reward compared to those trials
were animals received the reward independent of performance. This finding suggests that reward induced activation of sensory cortices is only observed when it is relevant for improving performance. In our task, reward delivery and reward omission (in the case of CS- trials) provided both important feedback for solving the FM tone categorization and hence led to increased auditory cortex activity. That auditory cortex activity at the time point of reward delivery may be important for learning is further strengthened by the finding that the effect was only found in subjects who learned the reward association. We thus conclude that when reward associations are learned, the auditory cortex responds whenever the outcome of a trial confirms the current strategy of solving the task. Note that neural activity in auditory cortex during reward outcome was not modulated by dopaminergic stimulation which is in contrast to the dopaminergic modulation during reward anticipation found in the same dataset previously (Weis et al. 2012).

**Effects of reward delivery in reward related brain regions**

Replicating many previous studies (Delgado et al. 2000; Elliott et al. 2000; Schultz 2000; Pleger et al. 2008), we found additional reward related neural activity in dopaminergic brain regions such as the left and right striatum and the midbrain. In contrast, to neural responses in auditory cortex, striatal neural activity was not significantly modulated by learning status.

Overall, the highest activity was seen for those trials in which a reward was received, compared to the other trials. Ventral striatal activity during reward delivery was also found in the sensory discrimination studies by Weil et al. (2010) and Pleger et al. (2008). Nevertheless, the result seems in contrast to other reward studies (e.g. Montague et al. 1996), showing that neural activity to the rewarding stimulus is
switched from reward delivery to reward predicting stimuli when participants learn the task. However, since here participants had to solve an instrumental learning task where a reward could only be obtained for fast and correct responses in CS+ trials, participants could not be sure to receive a reward at the end of the trial. Hence, the reward was not entirely predictable. It has been shown previously that striatal activations to rewards are still observed after learning when behavior-outcome contingencies are less predictable (Delgado et al. 2005). Note that, there were also numerically higher BOLD responses within the group of nonlearners when a reward was received in a CS+ trial which would support the idea that striatal activations to reward depend on predictability.

Reward-related activity was also present in the left and right insula and the anterior cingulate cortex which were suggested to form part of a saliency network (Menon and Uddin 2010; Menon 2011). The anterior cingulate cortex was also activated during rewarding feedback in a visual search paradigm where reward was shown to change visual saliency (Hickey et al. 2010). Neural activity in anterior cingulate cortex and left and right insula exhibited a reward condition x learning status interaction which suggests that in those regions, in contrast to the striatum, learning state plays a major role. Further reward-related increases in neural activity were present in the ventral stream of the visual pathway including the middle occipital gyrus, the inferior occipital gyrus and the fusiform gyrus which may be linked to processing the visually presented reward (50-Euro-Cent symbol).

Effect of dopaminergic modulation

As mentioned above, none of the regions showing a main effect of reward condition or reward condition by learning status interactions were sensitive to dopaminergic
modulation during the reward phase in our auditory appetitive instrumental learning task. This finding is in contrast to the study by Pleger et al. (2009) who compared L-dopa to placebo and haloperidol in a rewarded somatosensory discrimination task and showed that the behavioral and neural effects were enhanced under L-dopa and suppressed under haloperidol. However, the effects between L-dopa and placebo were small and most effects reported in that paper were due to differences between L-dopa and haloperidol. Note that our previous analysis of drug effects in the same data set during the reward anticipation phase yielded increased neural activity in left auditory cortex, Broca’s area and anterior cingulate cortex, which correlated with L-dopa plasma levels arguing against a general lack of sensitivity to detect drug effects in the current paradigm (Weis et al. 2012). Rather, we would like to suggest that L-dopa modulation is stronger in the reward anticipation than reward outcome phase which has also been reported previously (Guitart-Masip et al. 2012).

Conclusion

In summary, this study shows for the first time that the human auditory cortex responds to non-auditory feedback that signals the outcome of a learning trial. Strikingly, increased responses were observed whenever the outcome of a trial confirmed the subject’s expectations irrespective of reward. This differential activity was only seen in participants who learned the stimulus – reward association. Our findings thus support the view of a highly cognitive role of auditory cortex (Scheich et al. 2011). Whereas auditory cortex responses during reward anticipation have been found to be modulated by dopamine (Weis et al. 2012), this is not the case for responses during reward outcome.
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References


Figures

**Figure 1:** Paradigm. In the instrumental learning paradigm each trial started with an FM tone which differed in various features. In half of the trials participants had the chance to gain a monetary reward (CS+), whereas the other half of the trials always remained unrewarded (CS-). The main task for the participants was to find out by trial and error which feature of the FM tones predicts a reward. After each tone, they had to state their current reward expectancy for the upcoming trial via key press. To receive the reward, participants had to solve a simple reaction time task, in which they had to indicate whether a number shown on a screen was smaller or larger than five. If their answer in the number comparison task was fast and correct, they were rewarded with 50 Euro-Cent, if it was a CS+ trial. Slow and incorrect answers in CS+ trials resulted in no reward (indicated by a grey square). In the other half of the trials (CS-), participants were never rewarded, independent of the correctness and speed of their response.

**Figure 2:** Learning curves. Percent correct responses over number of trials averaged for all subjects in the different groups, but separated according to the learning status (solid line = learner, dashed line = nonlearner).

**Figure 3:** Main effect of reward condition. Brain areas showing differential responses as a function of reward condition (i.e. “reward expected & received”, “reward expected & not received” and “reward not expected & not received”). (A) Cortical regions: (1, 2) left and right auditory cortex, (6, 7) left and right insula, and (9, 10) left and right middle and inferior occipital and fusiform gyrus. (B) Subcortical regions: (3, 4) left and right striatum, (5) substantia nigra / ventral tegmental area, and (8) anterior
cingulate cortex. Activations are superimposed on the T1 template image available in SPM for cortical regions and on the mean of the individual subject T1 images for subcortical regions (p<0.05, FWE corrected, k > 40).

**Figure 4:** Time course of the BOLD response for reward anticipation and reward delivery within the left auditory cortex and striatum as a function of reward condition (“reward expected & received” (solid line), “reward not expected & not received” (dashed line) and “reward expected & not received” (dotted line)). This figure depicts the time course of the BOLD signal at two different time points within the experiment (left: reward anticipation phase when the sound was presented, right: reward phase when the feedback was presented). Note that the time courses are means over all groups, therefore, the L-dopa effect resulting from analyzing the reward anticipation reported in Weis et al. (2012) is not seen within this figure.

**Figure 5:** Interaction reward condition x learning status. Neural activity within the left (1) and right (2) auditory cortex (displayed at p < 0.001, masked with the auditory cortex) showing relation between reward condition and different learning states. Whole brain analysis revealed an effect in the anterior cingulate cortex (3) and left and right (4) insula as well as precuneus (5) (p < 0.05, FWE corrected, k > 40). All activations are superimposed on the mean T1 image of all participants.

**Figure 6:** Mean beta values in the left and right auditory cortex (A), left and right striatum (B) and anterior cingulate cortex (C) as a function of reward condition and learning status (right column = learner, left column = nonlearner). Increased neural activity occurs in auditory cortex whenever an expectation was correct – irrespective of whether a reward was received, only for those participants who learned the sound
– reward association. However, the striatal activity was increased only when a reward was received, but independent of the learning status. Note that results for the conditions have a similar pattern for all groups of subjects.
Table 1: Brain regions showing differential activity as a function of reward condition (i.e. main effect of reward in the full factorial ANOVA)

<table>
<thead>
<tr>
<th>Region</th>
<th>x</th>
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<th>z</th>
<th>Z</th>
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<tr>
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<td>8</td>
<td>-6</td>
<td>&gt;8</td>
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Table 2: Brain regions showing significant interaction between reward condition and learning status

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