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How Dopamine Shapes Representations in Auditory Cortex

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Abstract. The neural representation of sound in the auditory cortex is not invariably predetermined by its acoustical properties, but it is constantly reshaped while the listener acquires new experiences. Such plastic changes are a prerequisite for lifelong learning and allow some degree of rehabilitation after brain injuries. Several neurotransmitter systems modulate these plastic changes. In this paper, we focus on how the neurotransmitter dopamine modulates learning-related plasticity in auditory cortex, and how animal and human research can complement each other in providing an experimental approach that has relevance for studying mechanisms of recovery of function.

Keywords. dopamine, auditory, learning, plasticity, neuroimaging.

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Introduction

Adaptation to a changing environment is a prerequisite for lifelong learning and recovery after damage to the central nervous system. Over one hundred years ago, the psychologist William James suggested that "organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity" (James, 1890). Nowadays, neuroscientific methods, which range from single cell recordings of receptive fields in animals to the assessment of hemodynamic changes by means of functional imaging in humans, allow to investigate the neurobiological basis of such plasticity. In auditory cortex learning-related changes have been demonstrated in a variety of associative learning paradigms in animals and men (for reviews see Schreiner & Polley, 2014; Thiel, 2007; Weinberger, 2007). In this paper we provide an overview of how the neurotransmitter dopamine modulates such learning-related plasticity, and how animal and human research can complement each other in providing an experimental approach that has relevance to studying mechanisms of recovery and treatment effects in patients with injuries.

Learning-related plasticity in auditory cortex: animal and human evidence

The neural representation of sound in the auditory cortex is not always predetermined by its acoustical properties, but it is constantly reshaped while the listener acquires new experiences (Froemke & Jones, 2011; Pienkowski & Eggermont, 2011). If a sound gains behavioral relevance in the actual environment, neuronal receptive fields in auditory cortex can adjust rapidly, resulting in increased neuronal responses to this specific sound (Bakin, South, & Weinberger, 1996; Edeline, Pham, & Weinberger, 1993). The fact that this re-tuning may improve both the detection and the recognition of relevant stimuli has been suggested (Froemke et al., 2013). Such plastic changes are a prerequisite for lifelong learning and allow some degree of rehabilitation after brain injuries (Albert & Kesselring, 2012; May, 2011). In the auditory system neuronal plasticity can be observed in different time scales. Professional musicians, who have experienced an extensive lifelong auditory training, show profound structural changes in auditory sensory areas, affecting both the size and the cortical organization (Meyer, Elmer, & Jancke, 2012; Schneider et al., 2002). Following the insertion of a cochlear implant, the auditory cortex of a formerly deaf patient is reshaped by the newly available auditory input, resulting in an extensive restoration of sensory abilities only a few months after implantation (Fallon, Irvine, & Shepherd, 2008; Kral & Sharma, 2012; Moore & Shannon, 2009). In addition to these progressively developing structural changes, the auditory cortex also shows more rapidly evolving forms of functional plasticity, which modulate the actual representation of stimuli in auditory cortex (Ohl & Scheich, 2005; Scheich et al., 2011; Spierer et al., 2011). Experimental data suggest that the latter type of plasticity may play a role in adjusting the auditory system to current needs by facilitating the cortical processing of behavioral relevant stimuli (Bao, Chang, Woods, & Merzenich, 2004; Froemke et al., 2013; Liu & Schreiner, 2007).

The formation of changes in auditory cortex activity is often observed in associative learning paradigms in animals, in which subjects have to learn to relate a specific sound to some kind of reward or punishment (Blake, Heiser, Caywood, & Merzenich, 2006; Blake, Strata, Churchland, & Merzenich, 2002; Condon & Weinberger, 1991; Diamond & Weinberger, 1986; Ohl, Scheich, & Freeman, 2001). In such experiments, learning the significance of a sound is frequently associated with a re-tuning of neuronal receptive fields, resulting in an increased cortical representation of the relevant stimulus (Bieszczad & Weinberger, 2010; Polley, Steinberg, & Merzenich, 2006; Weinberger, 2007). This re-tuning can occur rapidly within only a few stimulus presentations and has been shown to consolidate after the experiment (Edeline et al., 1993; Galvan & Weinberger, 2002). Hence, changes in receptive fields can persist up to several days in the absence of further training (Weinberger, Javid, & Lepan, 1993). The effect can, however, be neutralized rapidly if the stimulus is repeatedly presented in a neutral context; thus, it loses its relevance (Diamond & Weinberger, 1986).

Complementing these findings, previous neuroimaging work in humans also revealed the rapid formation of learning-related changes in auditory cortex activity (Kluge et al., 2011; Morris, Friston, & Dolan, 1998; Thiel, Bentley, & Dolan, 2002; Thiel, Friston, & Dolan, 2002; van Wassenhove & Nagarajan, 2007). In line with animal data that show increased representations of the behaviorally relevant sound in auditory cortex, functional magnetic resonance imaging (fMRI) data in humans show increased BOLD responses to sounds, which have been paired with an electric shock to the foot in a classical conditioning experiment (Thiel, Bentley, et al., 2002; Thiel, Friston, et al., 2002). On the other hand, some studies have reported decreased auditory cortex activity following stimulus discrimination training (Brechmann & Scheich, 2005; Jancke, Gaab, Wustenberg, Scheich, & Heinze, 2001). Although the majority of animal studies report increased responses, there are a few experiments also showing decreased responses to relevant sounds after learning (Ohl & Scheich, 1996, 1997). It has been suggested that these discrepancies reflect the use of experimental paradigms with differing complexity, requiring different cortical representations of the relevant sound (Scheich et al., 2011).

The cholinergic system and the learning-related auditory cortex plasticity

Research in both animals and humans has provided compelling evidence suggesting that the cholinergic neurotransmitter system plays a crucial role in promoting the formation of learning-related changes in cortical representation of sounds (Weinberger, 2004). Pairing a tone presentation with direct electrical stimulation of the nucleus basalis, a region containing high concentrations of cholinergic projection neurons, induces changes in auditory cortex receptive fields, which result in increased neuronal responses to the paired stimulus (Bakin & Weinberger, 1996; Kilgard & Merzenich, 1998; Kilgard, Vazquez, Engineer, & Pandya, 2007). This effect can be abolished by administering atropine, a cholinergic antagonist which blocks muscarinic acetylcholine receptors (Miasnikov, McLin, & Weinberger, 2001). In humans, the cholinergic modulation in auditory cortex has been investigated by Thiel and colleagues (2002a; 2002b) with pharmacological fMRI in an aversive classical conditioning experiment in which one of two different pure tones was repeatedly paired with an electric shock to the foot. In a placebo condition, this procedure resulted in enhanced auditory cortex responses to the conditioned stimulus, the so called CS+, whereas responses to the neutral stimulus, the so called CS-, which was never paired with the shock, were not affected. However, if participants received scopolamine, a muscarinic antagonist, before the experiment, no conditioning-related changes in BOLD responses could be observed (Thiel et al., 2002b). This suggests that blockade of cholinergic neurotransmission reduces learning-related plasticity in human auditory cortex, which would be in line with the animal findings. Similarly, the administration of physostigmine, a cholinesterase inhibitor that enhances cholinergic activity, before the conditioning phase resulted in no differences in BOLD signal between the conditioned and the neutral tone (Thiel et al., 2002a). Under physostigmine, however, responses to both stimuli were enhanced after conditioning as compared to the pre-conditioning phase, indicating that boosting the cholinergic system results in changes not only for conditioned but also for neutral sounds (Thiel, 2007).

The dopaminergic system and learning-related auditory cortex plasticity

Even though the majority of pharmacological approaches focused on the cholinergic system, there is also some evidence indicating that noradrenaline and dopamine may affect the development of functional changes in auditory cortex. Manunta and Edeline (1997, 1998, 1999) demonstrated that the application of noradrenaline can lead to a decrease of both evoked and spontaneous activity of auditory cortex neurons. Furthermore, pairing a tone with the administration of noradrenaline changes neuronal frequency tuning curves in auditory cortex resulting in decreased responses to the paired stimulus (Manunta & Edeline, 2004). First evidence indicating a dopaminergic influence on learning-dependent plasticity came from a study by Stark and Scheich (1997), who used in vivo microdialysis in gerbils to study dopaminergic activity in auditory cortex during electric shock avoidance training. During the experiment animals learned to avoid an electric shock to the foot by changing the compartment of a shuttle box in response to an auditory target stimulus. Their data showed an increased concentration of homovanillic acid, a metabolite of dopamine, during initial learning but not during later re-training phases. Based on this observation, the authors suggested that dopamine may be important for the initial formation of an association between a tone and a behavioral response, but not during later re-training of this association. Moreover, several studies show that pairing a tone with a direct electric microstimulation of the ventral tegmental area, a midbrain region containing a high concentration of dopaminergic projection neurons, results in an increased spatial representation of this stimulus in primary auditory cortex (Bao, Chan, & Merzenich, 2001; Hui et al., 2009; Kisley & Gerstein, 2001). No changes in the representation of the paired stimulus were observed when dopaminergic D1 and D2 receptor antagonists were administered to the animals before the initiation of the pairing procedure (Bao et al., 2001).

Pharmacological functional magnetic resonance imaging (fMRI) studies in humans investigating the role of dopamine in learning-related auditory plasticity

In order to investigate whether the dopaminergic neurotransmitter system modulates learning-related plasticity in human auditory cortex, we performed two fMRI studies using an auditory operant appetitive conditioning paradigm since it is known that dopamine plays a major role in reward learning (Puschmann, Brechmann, & Thiel, 2013; Weis, Puschmann, Brechmann, & Thiel, 2012). In the paradigm, participants had to learn to associate a specific category of auditory input with the chance to gain a monetary reward in a subsequent reaction time task. Previous work using such tasks, in which a reward was associated with a visual or auditory cue, found increased neural activity in dopaminergic brain areas not only during the reward delivery but also during reward anticipation, when the reward-predicting stimulus was presented (Knutson, Fong, Adams, Varner, & Hommer, 2001; Schultz, Dayan, & Montague, 1997; Wittmann et al., 2005). Several animal studies investigating dopaminergic midbrain activity during associative learning tasks showed that before the animals learned a given stimulus-reward association, dopaminergic neurons responded during reward delivery (Ljungberg, Apicella, & Schultz, 1992; Schultz, Apicella, & Ljungberg, 1993). After learning, however, dopaminergic activity was observed in response to the reward-predicting stimulus but no longer during reward delivery. Based on these findings, we hypothesized that in our experiment, learning the relevance of the auditory cue should result in increased dopaminergic responses to this cue, which might then, in turn, lead to learning-induced changes in the auditory cortex representation of this stimulus.

The operant conditioning paradigm is depicted in Figure 1. In each trial, participants had to indicate via key press whether a number presented on a screen was larger or smaller than five. In half of the trials (CS+ trials), fast and accurate responses resulted in a reward of 50 Euro cent, whereas wrong or slow responses led to neutral feedback. In the other half (CS- trials), however, participants always received neutral feedback, independent of their response. To indicate which trials were potentially rewarded, a frequency modulated (FM) tone was presented at the beginning of each trial. The FM tones differed in several sound features, including frequency range, loudness, modulation rate, modulation direction, and duration. Participants were instructed that a specific class of sounds predicted a reward chance in the upcoming trial, but they had to learn the relationship between tone and reward by trial and error during fMRI measurements. We used the sound duration as the reward-predicting cue. For half of the subjects, long FM tones (800 ms) indicated a reward chance; for the other half, short FM tones (400 ms) were associated with the potential monetary reward in the reaction time task. After each tone, participants had to state their reward expectation for the upcoming trial via a key press, allowing us to gauge their individual learning progress. To slow down the progress of learning during the experiment, the reaction time threshold leading to a reward in the reaction time task was adjusted individually so that participants received only about 80% of the potential reward. Consequently, most participants did not identify the correct association between tone and reward

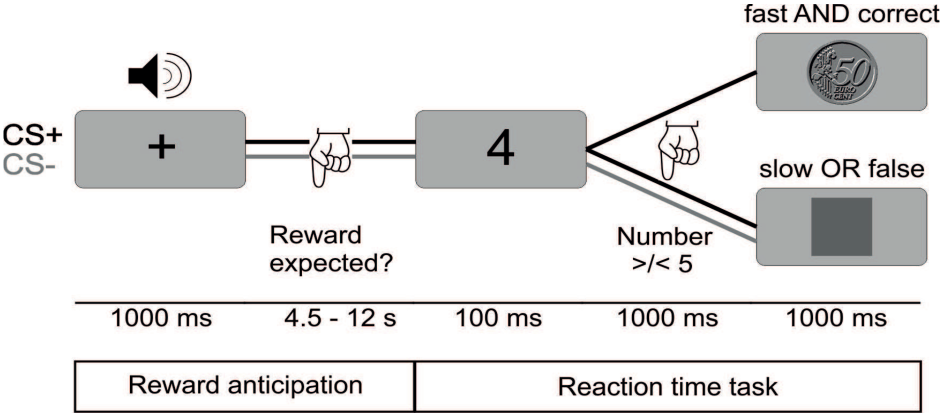

Figure 1. Appetitive operant conditioning paradigm: Each trial started with an FM tone. Participants were instructed that a specific category of tones (CS+) predicted a reward chance in the upcoming reaction time task and had to learn the correct categorization scheme by trial and error. To gauge the participants' learning progress they had to indicate after each tone whether they expected a reward in the upcoming trial or not. Subsequently, participants had to indicate whether a number presented on a screen was smaller or larger than five. In CS+ trials, fast and correct responses were rewarded with fifty Euro cent. Slow or false responses resulted in a neutral feedback. In the other half of trials (CS-), responses always led to neutral feedback. Figure from (Weis et al., 2012).

instantaneously at the beginning of the experiment, but only after an initial phase of trial and error.

To investigate if learning-related plasticity occurs in appetitive conditioning paradigms in humans, we analyzed BOLD activity during reward anticipation and compared the signal to FM tones in CS+ trials with BOLD activity to FM tones in CS- trials. This differential activity was analyzed separately for participants who learnt the correct stimulus-reward association and in non-learners, who did not show any learning behavior in the course of the experiment. We were particularly interested in whether learning-induced changes occurred exclusively in learners, and whether such changes in auditory cortex activity are paralleled by similar effects in parts of the dopaminergic system, which would provide a first indication for a dopaminergic influence on learning-related plasticity in human auditory cortex.

We studied thirty-nine participants with the above task in an fMRI setting (Puschmann et al., 2013). Sixteen participants learned the correct association between the presented FM tones and the chance to gain a monetary reward. On the average, the learning performance of this group was at chance level during the first quarter of the experiment and reached ceiling level (i.e., over 90% of FM tones were assigned correctly) in the last quarter of the experiment (see Figure 2). Comparing reaction times between the unlearned (i.e., the first quarter) and learned (i.e., fourth quarter) phases of the experiment, we observed a significant decrease in reaction times in potentially rewarded trials after learning. At the same time, this group showed a significant learning-dependent difference in BOLD responses to the reward-predicting (CS+) and neutral sounds (CS-) in the left auditory cortex (see Figure 3A). At the end of the experiment, BOLD responses to reward-predicting stimuli were significantly increased as compared to neutral tones, demonstrating learning-dependent changes. In contrast, no differences between categories were observed at the beginning of the experiment. Our functional imaging data also showed a learning-related difference in BOLD responses in large parts of the dopaminergic neurotransmitter system, in particular within the dopaminergic midbrain (ventral tegmental area/substantia nigra) and the nucleus accumbens (see Figure 3B and C). No significant changes, either on the behavioral level or regarding BOLD responses, were observed in the group of non-learners (*n*=9), who showed no learning progress and stayed at chance level during all parts of the experiment. A third group of subjects (*n*=10), who showed some

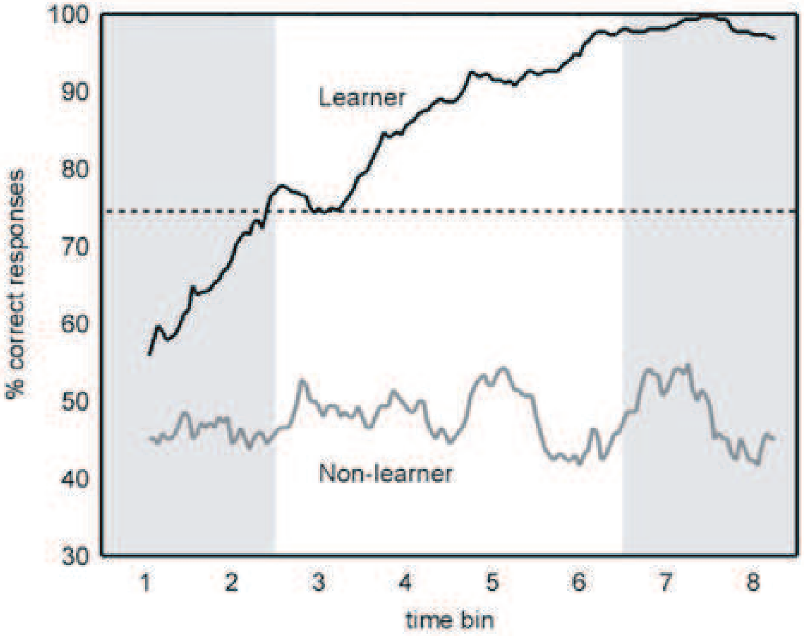

Figure 2. Learning curves in the appetitive operant conditioning paradigm. Data is derived from the volunteers' indication in the reward anticipation phase. Dotted line indicates the lower border of above-chance-performance. Learners were defined as those participants, showing a clear increase in the percentage of correct responses over time and reaching a stable plateau of at least 90 % correct responses within the first 6 time bins. Non-learners were defined as those participants never reaching at least a level of 66.4 % correct responses. Figure from (Puschmann et al., 2013) with permission of Wiley Periodicals. © 2012 Wiley Periodicals, Inc.

learning behavior but did not reach a high categorization performance, was not analyzed in the experiment.

While similar effects in auditory cortex and dopaminergic midbrain regions suggest that dopamine may contribute to learning-related plasticity, causality can only be demonstrated with pharmacological approaches. We, therefore, performed a second study where we combined fMRI with a pharmacological challenge (Weis et al., 2012). The dopaminergic precursor L-dopa (100 mg; *n*=27) or placebo (*n*=28) were administered to human volunteers before they performed the appetitive operant conditioning paradigm described above. Behaviorally, we found no difference in learning curves under L-dopa and placebo suggesting that dopamine did not affect learning the stimulus-reward association. Dopaminergic stimulation had however an impact on the speed of responding, especially in unrewarded trials, which were significantly slowed down over the course of the experiment. Differences in BOLD activity between reward-predicting (CS+) and neutral sounds (CS-) were found in the nucleus accumbens, dopaminergic midbrain regions, and left insula (see Figure 4A). In contrast to our expectations and results of the first study, we found no evidence for learning-related changes, i.e. higher responses to CS+ as compared to CS- sounds, in auditory cortex which may have been due to the faster learning in this second study (see Weis et al 2012 for further discussion). Dopaminergic stimulation, as compared to placebo, increased BOLD activity in left auditory cortex; Broca's area and anterior cingulate cortex (see Figure 4B). Note that this increase occurred for both reward predicting (CS+) and neutral (CS-) FM tones. The left sided increase in neural activity is in line with findings of Brechmann and Scheich (2005) who showed an involvement of the left auditory cortex, when participants had to categorize FM tones according to their duration. Thus, the dopaminergic modulation of activity in auditory cortex occurred in a region involved

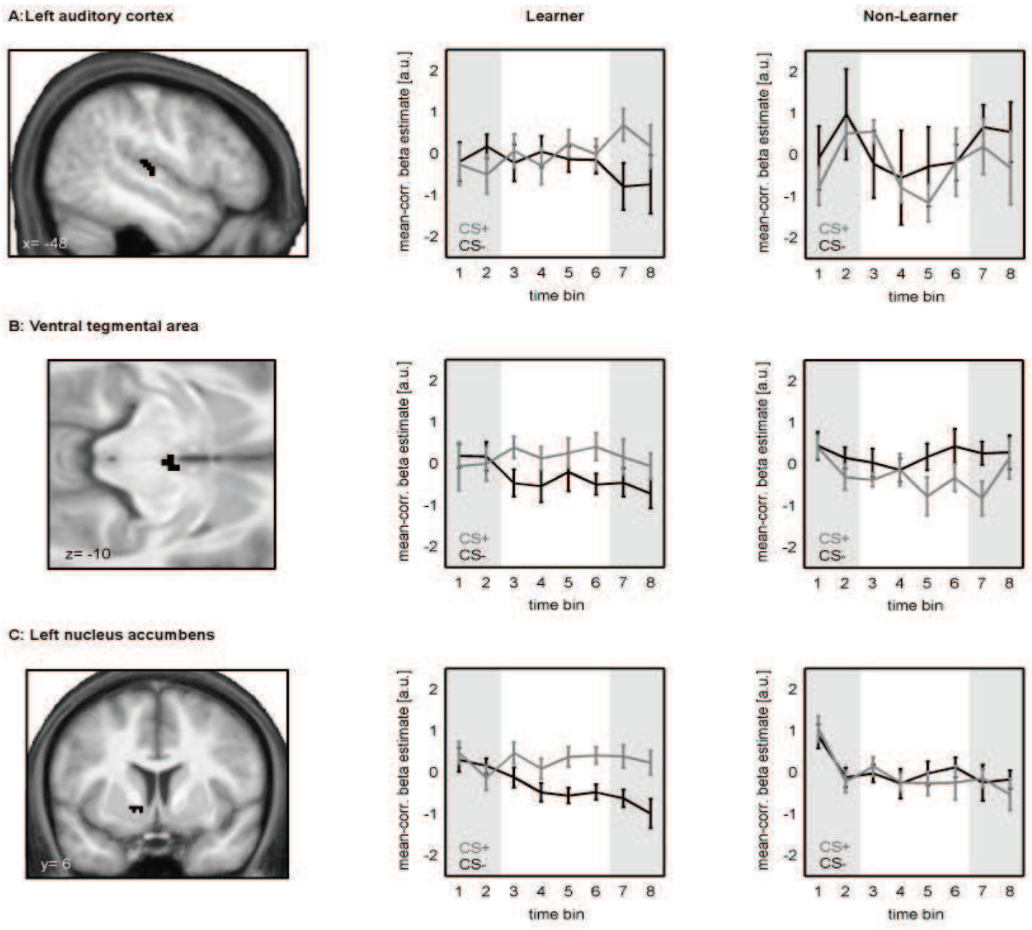

Figure 3. BOLD activity during the reward anticipation phase. Left Side: Regions showing a conditioning by time interaction, i.e. increases to the reward-predicting CS+ as compared to the neutral CS- FM tone over the course of the experiment. Right side: Average time-courses of the signal within the brain regions in the learner and non-learner group. Figure from (Puschmann et al., 2013) with permission of Wiley Periodicals. © 2012 Wiley Periodicals, Inc.

in categorizing the specific reward-predicting feature (i.e. duration) of the auditory stimuli. Furthermore, neural activity in this brain region correlated with L-dopa plasma levels and learning rate. Hence, dopaminergic stimulation may be beneficial to increase neural activity in auditory cortex in a stimulus-unspecific way. Note that no effects of dopaminergic stimulation were found at the time point where the reward was delivered, even though a reactivation of auditory cortex was present at this time (Weis, Brechmann, Puschmann, & Thiel, 2013).

Clinical Relevance

Understanding the mechanisms of neuroplasticity is of clinical relevance for the recovery of sensory and motor function. Previous studies in humans already indicated that administration of the dopamine precursor L-dopa facilitates novel word learning, improves motor cortex plasticity in healthy human subjects and motor recovery after stroke (Knecht et al., 2004; Monte-Silva, Liebetanz, Grundey, Paulus,

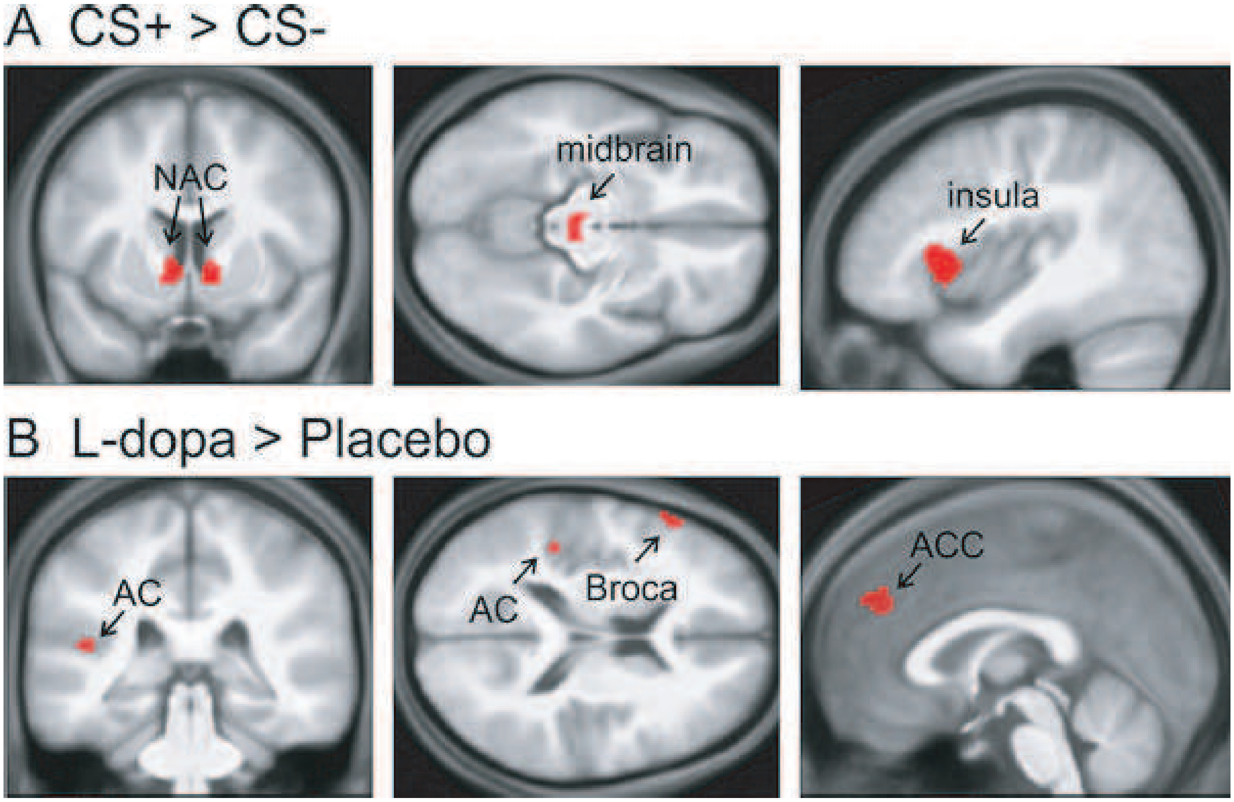

Figure 4. BOLD activity during the reward anticipation phase in the pharmacological fMRI study. A. Differences in BOLD activity to the reward-predictig CS+ as compared to the neutral CS- FM tone (main effect of conditioning) B. Differences in BOLD activity to L-dopa as compared to placebo (main effect of drug). Abbreviations: NAC- nucleus accumbens, AC- auditory cortex, ACC-anterior cingulate cortex. Figure from (Weis et al., 2012).

& Nitsche, 2010; Scheidtmann, 2004). With respect to auditory rehabilitation, data in a few subjects who received a cochlear implant and amphetamine together with aural rehabilitation therapy showed increased speech tracking skills and auditory cortex activity in these amphetamine treated subjects (Tobey et al., 2005). Given our own human data (Puschmann et al., 2013; Weis et al., 2012) and the available animal evidence (Stark and Scheich 1997, Bao et al. 2001), future clinical studies should further investigate the role of dopaminergic stimulation in auditory rehabilitation.

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