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Pharmacological modulation of learning-induced plasticity in human auditory cortex

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Abstract. *Purpose:* Converging evidence from animals and humans indicate that the primary auditory cortex is continuously reshaped in an experience-dependent way. Reorganisation in primary auditory cortex can be observed at the level of receptive fields, topographic maps and brain activations measured with neuroimaging methods. Several neuromodulatory systems were shown to contribute to such an experience-dependent reorganization.
Methods: This paper reviews evidence addressing the cholinergic, noradrenergic, dopaminergic and serotonergic modulation of learning-, experience-, and injury-induced plasticity in the auditory cortex.
Results: Regarding learning-induced plasticity in the auditory cortex most studies have investigated the role of the cholinergic system and shown that ACh is essential for this form of rapid plasticity. Nevertheless there is also evidence that the catecholamines dopamine and noradrenaline might contribute to learning- and experience-induced changes in the auditory cortex.
Conclusions: I suggest, that the available experimental data on cholinergic and noradrenergic modulation of plasticity offers a promising basis for potential pharmacological interventions to aid recovery of aural functions.

Keywords: Plasticity, psychopharmacology, auditory cortex, drug, experience

1. Introduction

Several studies have highlighted the importance of neuromodulators, especially the cholinergic system, in regulating learning-induced plasticity in the auditory cortex. This review will summarize research on pharmacological modulation of plasticity in humans and animals. The main focus is on neurochemical mechanisms of rapidly induced plasticity in associative learning situations, but evidence from studies on training-induced plasticity as well as findings on recovery of function after injury are also considered. Since the number of studies is small that specifically address pharmacological modulation of plasticity in the auditory cortex, I will also consider evidence showing neurochemical modulation of plasticity outside the auditory cortex, assuming that similar neurochemical mechanisms may be responsible for promoting plasticity in other primary sensory and motor cortices.

An important issue when addressing the pharmacological modulation of plasticity is its clinical application. The use of pharmacological interventions for promoting cognitive or motor functions after brain injury has recently received some attention (Parton et al., 2005). One of the most promising approaches has been the administration of amphetamines for recovery of motor and language functions after stroke (Martinsson and Eksborg, 2004). Even though in the auditory system, evidence from basic research in animals and humans offers a promising basis for potential pharmacological interventions, there are currently no clinical applications of this knowledge. One preliminary study however suggests that amphetamine might be useful for improving aural rehabilitation and increasing neural ac-

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tivity in the auditory cortex after cochlear implantation (Tobey et al., 2005).

2. Plasticity in the auditory cortex

The processing of auditory information depends not only on the physical properties of stimuli but also on prior experience and learning. Response properties of single neurons and neuron populations are continuously reshaped in an experience-dependent way throughout life to meet changing behavioural needs. Plasticity refers to such an experience-related structural and/or functional neuronal reorganization. Different techniques have been used to gauge plastic changes in animals and humans. These include the analysis of receptive fields in single cells, topographic cortical maps, brain activations measured in metabolic studies and lately brain activity measured with neuroimaging methods in humans (Bakin and Weinberger, 1990; Recanzone et al., 1993; Thiel et al., 2002b).

Plasticity encompasses a variety of different concepts, ranging from plastic changes that are induced rapidly up to modifications observed only at longer time scales. I will refer to rapidly induced plasticity in associative learning situations as learning-induced plasticity. Plasticity observed in perceptual learning situations, which involves repeated training over several days and weeks will be referred to as training-induced plasticity. Finally injury-induced plasticity relates to reorganization evident after damage to the periphery or central nervous system.

2.1. Learning-induced plasticity in animals

Learning-induced plasticity within the auditory cortex is often studied in aversive conditioning paradigms (Edeline, 1999; Weinberger, 2004). In aversive conditioning a previously neutral stimulus, such as a tone (conditioned stimulus; CS), acquires significance through its prediction of a future aversive event, such as an electric shock (unconditioned stimulus; US). Learning-induced plasticity in such associative learning paradigms has been documented with a variety of different methods and species. Several studies have demonstrated that frequency responsive receptive fields in the primary auditory cortex are retuned during aversive conditioning (Bakin and Weinberger, 1990; Weinberger et al., 1993; Edeline et al., 1993). Most studies reported a shift of the receptive fields towards the frequency of the CS with reduced responses to the previously best frequency (Bakin and Weinberger, 1990; see however Ohl and Scheich, 2005). The learning-induced changes are acquired rapidly after only a few pairings of the tone and footshock and have an enduring effect on the receptive fields of auditory cortical neurons (Weinberger et al., 1993; Edeline et al., 1993). Frequency receptive fields in primary auditory cortex were also shown to be rapidly modified in other learning paradigms such as habituation learning, instrumental avoidance learning and frequency discrimination learning (Condon and Weinberger, 1991; Edeline and Weinberger, 1993; Bakin et al., 1996). A complementary approach is to study learning-induced plasticity by investigating changes in cerebral metabolism (Gonzalez-Lima and Scheich, 1986; Poremba et al., 1998) or tonotopic maps (Rutkowski and Weinberger, 2005). These studies provide evidence for an increased spatial representation of conditioned stimuli in the auditory cortex. An elegant study by Rutkowski et al. (2005) further suggests that the extent of the area tuned to the CS frequency is related to the behavioural importance of the sound.

2.2. Learning-induced plasticity in humans

Several neuroimaging studies, using eye-blink and aversive conditioning paradigms, have shown learning-induced changes in regional cerebral blood flow (rCBF) or blood-oxygen-level dependent (BOLD) signal in the human auditory cortex (Molchan et al., 1994; Schreurs et al., 1997; Morris et al., 1998; Thiel et al., 2002a; Thiel et al., 2002b). Molchan et al. (1994) and Schreurs et al. (1997) provided evidence for increased rCBF in primary auditory cortex when comparing the paired presentation of a tone and an air puff in an eye blink conditioning paradigm with explicitly unpaired presentations of the tone and air puff. This suggests increased neural activity in the auditory cortex during associative learning. Using functional magnetic resonance imaging (fMRI) and a differential aversive conditioning paradigm we found evidence for an increase in BOLD signal in the auditory cortex for a tone which was paired with an aversive event as compared to a tone, which was not paired with the aversive event. That is, auditory stimuli with an acquired relevance induce greater neural activity in the auditory cortex than stimuli without relevance.

Overall, the findings demonstrate that blood-flow based techniques such as positron emission tomography (PET) or fMRI are able to gauge learning-induced changes in associative learning paradigms and provide

valuable evidence regarding mechanisms of plasticity in the human brain. It should be however emphasised that despite some striking similarities between learning-induced receptive field or map plasticity in animals and plasticity seen with neuroimaging methods in humans, there are differences in the underlying techniques to measure plasticity (e.g. neuronal responses vs. haemodynamic responses), and experimental protocols (i.e. animal studies mostly compare receptive fields before and after conditioning has taken place while neuroimaging studies often assess learning-induced changes during conditioning). Nevertheless, the fact that both measures of plasticity are sensitive to cholinergic manipulations (see below) suggests at least some commonality.

2.3. Training- and injury-induced plasticity

Changes in the cortical representation of auditory stimuli have also been found with behavioural training or after injury (Irvine et al., 2001). In the auditory cortex of owl monkeys Recanzone et al. (1993) have shown a reorganization of frequency representation following several weeks of frequency discrimination training which correlated with performance. However, in cats improvements in frequency discrimination were not accompanied by changes in tonotopic maps (Brown et al., 2004). Several studies in human volunteers have reported plastic changes in auditory cortex activity after successful frequency discrimination training or a pitch memory task (Cansino and Williamson, 1997; Menning et al., 2000; Jancke et al., 2001; Gaab et al., 2006). Note, that both, decreases and increases in the measured signal were found and it has been shown that depending on the training task used, an increased or reduced representation is found in the auditory cortex (Guenther et al., 2004). Several other studies, not mentioned in further detail here, have investigated consequences of auditory experience in relation to learning speech sounds (e.g. Callan et al., 2003) or plasticity in musicians (Pantev et al., 2003). However, in contrast to learning-induced plasticity observed in associative learning situations, auditory experiences associated with behavioural training require at least several hours of practice to develop and tonotopic reorganizations are not always observed.

Similar changes in tonotopic representations in primary auditory cortex are also seen after restricted cochlear lesions in animals (see Irvine et al., 2000). The changes are evident as expanded representations of frequencies represented at loci in the unaffected part of the cochlea. In humans, one neuroimaging study investigated the effects of high frequency hearing loss and was able to demonstrate cortical map reorganization in the auditory cortex (Dietrich et al., 2001). In contrast to training-induced reorganization there is however only limited evidence for perceptual consequences of a deprivation-induced reorganization.

3. Neurochemical modulation of plasticity in auditory cortex

3.1. The cholinergic system

Basal forebrain cholinergic neurons send projections to the entire cortical mantle, including the primary auditory cortex (Kamke et al., 2005). A considerable amount of data indicate the importance of the cholinergic basal forebrain in modulating responses of cortical neurons. Evidence for long lasting changes in neuronal reactivity due to iontophoretical application of acetylcholine (ACh) was shown by Krnjevic and Phillis (1963a) in anaesthetised animals. Several other animal studies confirmed this modulatory role of basal forebrain ACh upon responses to visual (Sato et al., 1987), auditory (Metherate and Ashe, 1991) or somatosensory (Tremblay et al., 1990) stimulation. The cholinergic modulation of neuronal responsiveness in auditory and visual cortex is blocked by the administration of atropine, suggesting an effect mediated through muscarinic cholinergic receptors (Sato et al., 1987; Metherate and Ashe, 1991). While the majority of responses are facilitated by ACh, a suppression of firing rate has also been found (Sato et al., 1987; Tremblay et al., 1990; Metherate and Ashe, 1991). The direction of cortical response modulation can vary depending, for example, on the strength of basal forebrain stimulation, the cortical layer of ACh application or the type of neuron investigated (Metherate and Ashe, 1991; Xiang et al., 1998; Kimura et al., 1999).

It is widely reported that increases in cortical ACh release occur when animals are presented with behaviourally relevant, aversive stimuli (Acquas et al., 1996; Thiel et al., 2000). With regard to learning-induced plasticity, a striking observation is that auditory cortex receptive field and map plasticity can not only be induced by pairing a tone with an aversive event but also by pairing the tone with electrical stimulation of the nucleus basalis (Hars et al., 1993; Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998; Miasnikov et al., 2001) or an iontophoretic administration

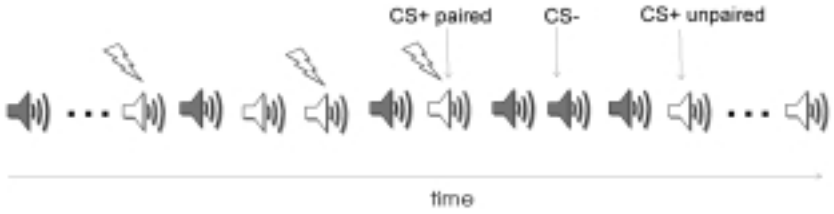

Fig. 1. Schematic illustration of the aversive conditioning approach used in the fMRI studies.

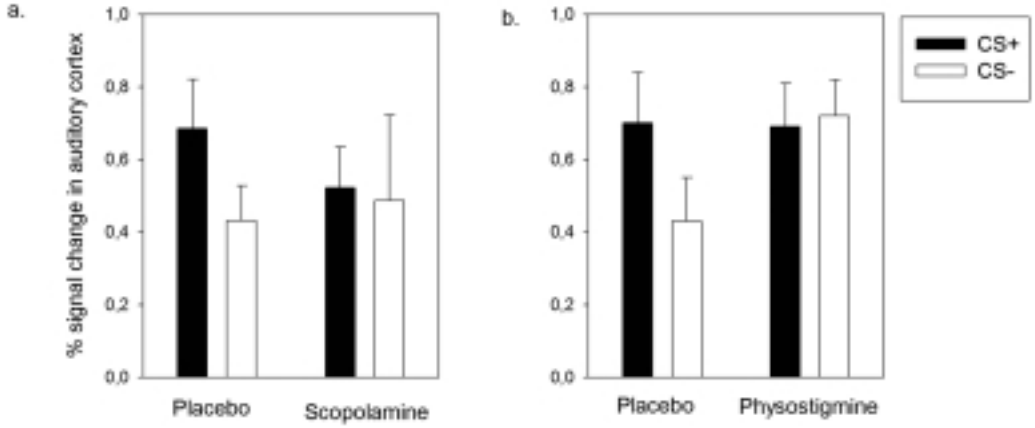

Fig. 2. Plots of percent signal change (mean and S.E.M.) of two voxels in the auditory cortex illustrating cholinergic modulation of learning-induced BOLD activity (for full data see [68; 69]) a. Effects of cholinergic blockade with scopolamine in a right auditory cortex voxel showing a significant group by conditioning interaction ($x = 57$, $y = -15$, $z = 6$) b. Effects of cholinergic enhancement with physostigmine. Activity in a left auditory cortex voxel showing a group by conditioning interaction in the follow up study ($x = -63$, $y = -18$, $z = 9$). Note that in comparison with placebo, scopolamine reduced activations to the CS+ whereas physostigmine increased activations to the CS−. Reprinted from Neurobiology of Learning and Memory, 80, Thiel, Cholinergic modulation of learning and memory in the human brain as detected with functional neuroimaging, 234–244, Copyright (2003), with permission from Elsevier".

of ACh (Metherate and Weinberger, 1989). A study by McLin et al. (2002) further underlines that stimulation of the cholinergic basal forebrain not only induces frequency specific neuronal plasticity but also elicits cardiac and respiratory responses to the frequency of the tone, indicating the induction of behavioural associative memory. The plasticity induced by pairing nucleus basalis stimulation with a tone is blocked by systemic or cortical atropine which suggests that activation of muscarinic ACh receptors is crucial to this form of learning-induced plasticity (Bakin and Weinberger, 1996; Miasnikov et al., 2001).

In order to investigate the role of the cholinergic system in learning-induced plasticity in humans we performed two fMRI studies involving a cholinergic drug challenge (Thiel et al., 2002a; Thiel et al., 2002b). Learning-induced auditory plasticity was studied in a differential conditioning paradigm. We used two tones of different frequency as CS (400 Hz or 1600 Hz). One of these tones was paired with an electric shock to the left leg (CS+) whereas the other was never paired with a shock (CS−). A partial reinforcement schedule was used in which only one half of the CS+ stimuli were paired with the aversive event (CS+ paired) and the other half were not (CS+ unpaired). This enabled the comparison of BOLD activity to the CS+ in the absence of the shock with activations to the CS− (see Fig. 1). In other words, two auditory stimuli are compared, one with acquired significance and one without. Learning-induced plasticity in this context is defined as a higher BOLD signal to the unpaired CS+ as compared to the CS−.

In our first study subjects were given in a between group design either placebo or 0.4 mg of the muscarinic antagonist scopolamine intravenously to block cholinergic function (Thiel et al., 2002b). A reaction time measure indicated behavioural learning in the placebo but not the scopolamine group. In the placebo group, learning-induced enhancement of the BOLD response in the auditory cortex was evident to the CS+ but not to the respective CS−. Under scopolamine, the enhancement of BOLD activity to the CS+ was

blocked, suggesting that cholinergic muscarinic receptors are involved in these learning-induced responses (see Fig. 2a). The findings provide *in vivo* evidence that learning-induced plasticity in human auditory cortex is attenuated by blockade of cholinergic neurotransmission.

Since a cholinergic blockade was found to impair learning-induced plasticity we aimed to further investigate the clinically more relevant question whether an increase in cholinergic function would increase plasticity. We used the same differential conditioning paradigm and between group design as above but the cholineesterase inhibitor physostigmine to boost cholinergic function (Thiel et al., 2002a). Data in the placebo group showed again an enhanced BOLD response to the CS+ as compared to the CS− in the auditory cortex, indicating learning-induced changes. In contrast to our hypothesis however, the physostigmine group did not show any differential activation to the CS+ vs. CS−. This absence of learning-induced plastic changes was however different from that seen previously with scopolamine. While scopolamine prevented the increased neural activation to the CS+ but did not interfere with activity to the CS−, physostigmine increased activations to the CS− without interfering with the CS+ (see Fig. 2b). We therefore suggest that in healthy human volunteers, cholinergic blockade reduces neuronal processing of relevant stimuli, whereas cholinergic stimulation increases processing of irrelevant stimuli. Both mechanisms reduce learning-induced plasticity in the auditory cortex. The effects of physostigmine could reflect that cholinergic stimulation in *healthy* volunteers may overstimulate an otherwise perfectly balanced cholinergic system.

The influence of the cholinergic system on training-induced auditory plasticity has not been investigated. Training-induced plasticity has however often been studied in the motor system, where it has been shown that changes in functional topography are observed after training voluntary movements (Nudo et al., 1996). Two studies support a cholinergic role in training-induced motor plasticity. First, the muscarinic antagonist scopolamine is able to attenuate training-induced motor plasticity in humans (Sawaki et al., 2002). Second, animal evidence suggests that lesions of the cholinergic basal forebrain abolish training-induced map expansions in the primary motor cortex (Conner et al., 2005).

With regard to injury-induced plasticity, nucleus basalis lesions were found to block topographic reorganizations after peripheral injury in the somatosensory cortex (Juliano et al., 1991). These findings are in contrast with recent evidence by Kamke et al. (2005) in the auditory cortex that suggests that cholinergic input is not required for lesion-induced plasticity. It is currently open whether the observed discrepancies are due to difference between cortical systems or rather differences in experimental design between the studies (see Kilgard, 2005 for further discussion).

3.2. The noradrenergic system

Noradrenergic neurons are located in the pontine and medullary reticular formation. The main source of the central noradrenergic innervation is the locus ceruleus, which provides widespread projections to the entire brain (Drouin and Tassin, 2002). With regard to plasticity in the auditory system, the work of Edeline and colleagues suggests that the iontophoretic application of noradrenaline primarily decreases evoked responses in the auditory cortex of anaesthetised rats (Manunta and Edeline, 1997; Manunta and Edeline, 1998). Further, pairing a particular tone frequency with a noradrenaline application changed frequency tuning curves in the auditory cortex, suggesting that noradrenaline modulates learning-induced plasticity. The effect was dependent on alpha noradrenergic receptors and was in most cases evident as a response decrease (Manunta and Edeline, 2004).

There is ample evidence for a noradrenergic role in training-induced and injury-dependent plasticity in the motor system. In healthy humans it has been shown that amphetamine can facilitate plasticity induced by motor training (Butefisch et al., 2002; Tegenthoff et al., 2004) and language learning (Breitenstein et al., 2004). Further, a single dose of the noradrenaline reuptake inhibitor reboxetine improves motor skill acquisition and excitability in the motor cortex of healthy volunteers (Plewnia et al., 2004). These findings underline the importance of noradrenergic neurotransmission for training-induced plasticity, at least in the motor cortex.

Regarding potential clinical applications, the combination of amphetamines with behavioural training is currently one of the most promising pharmacological approaches in stroke recovery (Boyeson and Feeney, 1990).[1] Amphetamine acts on a variety of neurotransmitter systems including the dopaminergic, noradrenergic and serotonergic system but it has been suggested

[1] Note, however, that due to the small number of studies and open safety-issues the routine use of amphetamines is currently not indicated for the treatment of stroke.

that the noradrenergic action is crucial for the recovery-promoting effects after injury (Boyeson and Feeney, 1990; see however Breitenstein et al., 2006). In animals it was shown that a single dose of amphetamine can promote motor recovery after motor cortex ablation (Feeney et al., 1982). Recovery-promoting effects of amphetamine were also observed after lesions of the visual and sensorimotor cortices (Feeney and Hovda, 1985; Schmanke and Barth, 1997). These findings indicate that pharmacological interventions may show similar effects in different sensory and motor cortices and that beneficial effects of amphetamine might also be seen after damage to the auditory cortex. Indeed, a preliminary study by Tobey et al. (2005) in eight patients with cochlear implants provides first evidence that the additional use of d-amphetamine in aural rehabilitation facilitates speech tracking scores and neural activity in the auditory cortex in adult cochlear implant users. The study therefore suggests that a noradrenergic/dopaminergic intervention may be useful for promoting recovery of function in the auditory system.

3.3. The dopaminergic system

The dopaminergic input to the cortex originates in the ventral tegmental area (Moore and Bloom, 1978). Iontophoretic application of dopamine to cells in the cerebral cortex results mostly in a depression of neuronal activity (Krnjevic and Phillis, 1963b). With regard to learning-induced plasticity, *in vivo* microdialysis provides evidence for increased dopaminergic activity in the primary auditory cortex during learning of tone-shock associations (Stark and Scheich, 1997). Further, it has been shown that pairing a particular tone frequency with stimulation of the ventral tegmental area shifts frequency response curves and increases the spatial representation of the respective frequency area in the primary auditory cortex. Since the effects were blocked by D1 and D2 receptor antagonists, the findings suggest that the neurotransmitter dopamine enables learning-induced plasticity in the auditory cortex (Kisley and Gerstein, 2001; Bao et al., 2001).

Even though most of the evidence on recovery-promoting actions of amphetamine suggests that the main action is dependent on noradrenergic neurotransmission, some data also speaks in favour of a dopaminergic role. First, the recovery-promoting actions of amphetamine can be blocked by the dopaminergic antagonist haloperidol (Feeney et al., 1982). Second, there is evidence in humans for increased recovery of motor functions after l-dopa administration (Scheidtmann et al., 2001). Even though l-dopa is the precursor of both, dopamine and noradrenaline, only a small fraction of l-dopa is converted into noradrenaline, suggesting that recovery-promoting effects of l-dopa may primarily be due to the dopaminergic action of the drug (Breitenstein et al., 2006).

3.4. The serotonergic system

The serotonergic innervation of the cortex originates from the brain stems raphe nuclei (Azmitia and Segal, 1978). Iontophoretic application of serotonin (5-HT) was shown to induce both, inhibition and excitation of cortical neurons (Krnjevic and Phillis, 1963b). With regard to learning-induced plasticity in the auditory cortex *in vivo* microdialysis data suggest however that 5-HT is rather related to the stress induced by the aversive stimulus in conditioning paradigms than to associative learning (Stark and Scheich, 1997). Even though this would speak against a critical role of 5-HT in learning-induced plasticity, there is at least evidence for a serotonergic modulation of training-dependent plasticity in the motor cortex (Pleger et al., 2004). This finding in healthy volunteers is in line with clinical evidence showing that stimulation of serotonergic function increases functional recovery from motor deficits after stroke (Pariente et al., 2001). Further research is needed to investigate in more detail the potential role of serotonin in plasticity in the auditory cortex.

4. Conclusions

I have summarised evidence that drugs targeting different neurotransmitter systems are able to modulate learning- and experience-induced plasticity and recovery of function. Regarding learning-induced plasticity in the auditory cortex most studies have investigated the role of the cholinergic system and shown that ACh is essential for this form of rapid plasticity. Nevertheless there is also evidence that the catecholamines dopamine and noradrenaline might contribute to learning- and experience-induced changes in the auditory cortex and to aural rehabilitation after cochlear implantation.

Several questions however deserve further attention: It is currently unknown, whether different neuromodulatory systems subserve similar, overlapping functions in promoting plasticity or whether their action can be differentiated. For example, even though pairing a tone with electrical stimulation of brain areas containing either cholinergic or dopaminergic neurons both increase

the spatial representation of the respective tone in the primary auditory cortex, other measures, such as the representation of adjacent frequencies or the effects in the secondary auditory cortex were shown to differentiate between a "dopaminergic" VTA and "cholinergic" nucleus basalis stimulation (Bao et al., 2001). A second question that will need to be investigated in further detail is whether different forms of plasticity are amenable to the same neurochemical modulation. If different forms of plasticity are not manifestations of the same cellular processes it will be unlikely that one neuromodulator equally influences all forms of plasticity. Indeed for the cholinergic system it has recently been shown that despite its role in learning-induced plasticity, cholinergic function is not necessary for lesion-induced plasticity (Kamke et al. 2005). Furthermore it would be valuable to know, whether similar neurochemical mechanisms operate in different primary sensory and motor cortices. If this was the case, many of the findings on training-induced plasticity and recovery of function obtained for example in the motor system might also be applied to the auditory system.

Finally, it will be necessary to show that the neurochemical modulation of plasticity found in animals can also be observed in the human brain and that results obtained with rather simple auditory stimuli also apply to more complex stimuli. Recently the combination of psychopharmacology and functional neuroimaging (also known as pharmacological MRI) has been used increasingly to investigate the pharmacological modulation of brain activity (Honey and Bullmore, 2004). A similar approach using MEG will add valuable information on drug action with high temporal resolution (Kahkonen, 2006). Such approaches in combination with suitable paradigms for investigating auditory plasticity will enable researchers to study the neurochemical modulation of neural activity in the human auditory cortex and provide an experimental approach that has relevance to studying mechanisms of recovery and treatment effects in patients with injury.

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