Learning-induced plasticity in human audition: Objects, time, and space

Article *in* Hearing research · January 2011

DOI: 10.1016/j.heares.2010.03.086 · Source: PubMed

Lucas Spierer
Université de Fribourg
64 PUBLICATIONS **1,222** CITATIONS
SEE PROFILE

Fosco Bernasconi
École Polytechnique Fédérale de Lausanne
31 PUBLICATIONS **455** CITATIONS
SEE PROFILE

Jeremy Grivel
Lausanne University Hospital
27 PUBLICATIONS **398** CITATIONS
SEE PROFILE

Stephanie Clarke
Lausanne University Hospital
177 PUBLICATIONS **6,891** CITATIONS
SEE PROFILE

Hearing Research 271 (2011) 88–102

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research paper

Learning-induced plasticity in human audition: Objects, time, and space

Lucas Spierer [a,1], Marzia De Lucia [b,c,1], Fosco Bernasconi [a], Jeremy Grivel [d], Nathalie M.-P. Bourquin [a], Stephanie Clarke [a], Micah M. Murray [a,b,c,e,*]

[a] *Neuropsychology and Neurorehabilitation Service, Department of Clinical Neuroscience, Vaudois University Hospital Center and University of Lausanne, Switzerland*
[b] *Electroencephalography Brain Mapping Core, Center for Biomedical Imaging, Vaudois University Hospital Center and University of Lausanne, Switzerland*
[c] *Radiology Department, Vaudois University Hospital Center and University of Lausanne, Switzerland*
[d] *Community psychiatry Service, Vaudois University Hospital Center and University of Lausanne, Lausanne, Switzerland*
[e] *Department of Hearing and Speech Sciences, Vanderbilt University, Nashville, TN, USA*

ARTICLE INFO

Article history:
Received 23 December 2009
Received in revised form
16 February 2010
Accepted 3 March 2010
Available online 27 April 2010

ABSTRACT

The human auditory system is comprised of specialized but interacting anatomic and functional pathways encoding object, spatial, and temporal information. We review how learning-induced plasticity manifests along these pathways and to what extent there are common mechanisms subserving such plasticity. A first series of experiments establishes a temporal hierarchy along which sounds of objects are discriminated along basic to fine-grained categorical boundaries and learned representations. A widespread network of temporal and (pre)frontal brain regions contributes to object discrimination via recursive processing. Learning-induced plasticity typically manifested as repetition suppression within a common set of brain regions. A second series considered how the temporal sequence of sound sources is represented. We show that lateralized responsiveness during the initial encoding phase of pairs of auditory spatial stimuli is critical for their accurate ordered perception. Finally, we consider how spatial representations are formed and modified through training-induced learning. A population-based model of spatial processing is supported wherein temporal and parietal structures interact in the encoding of relative and absolute spatial information over the initial ~300 ms post-stimulus onset. Collectively, these data provide insights into the functional organization of human audition and open directions for new developments in targeted diagnostic and neurorehabilitation strategies.

1. Introduction

Sounds convey information about what they signify/identify as well as about where they are located in space. This information is furthermore conveyed dynamically. Evidence based on anatomy, (neuro)psychology, and brain imaging suggest that these functions are likely mediated by specialized brain networks. The structural organization of auditory areas has been investigated both in humans (e.g. Rivier and Clarke, 1997; Morosan et al., 2001; Wallace et al., 2002) and non-human primates (e.g. Kaas and Hackett, 2000) using anatomical, cytoarchitectonic, and immunohistochemical methods. These data support a parallel and largely hierarchical organization wherein at least two interconnected pathways originate in the primary or "core" auditory cortex (and perhaps also subcortically; Rauschecker et al., 1997; Kraus and Nicol, 2005). One of these pathways projects from primary auditory cortex caudally along the superior temporal cortex to parietal cortices as well as dorsal subdivisions of frontal and prefrontal cortices. A second pathway projects from primary auditory cortex rostrally along the superior temporal cortex into ventral subdivisions of frontal and prefrontal cortices (e.g. Hackett et al., 1999; Romanski et al., 1999; Kaas and Hackett, 2000).

Auditory recognition and spatial functions appear to graft onto these anatomical pathways, and the 'what' and 'where' nomenclature previously described for the visual system has been employed (Ungerleider and Mishkin, 1982). However, distinctions between the auditory and visual systems should be noted (e.g. Werner-Reiss and Groh, 2008). Anterior portions of lateral belt areas in non-human preferentially respond to conspecific

---

Abbreviations: AEP, auditory evoked potential; BA, Brodmann's Area; fMRI, functional magnetic resonance imaging; IID, inter-aural intensity difference; ITD, inter-aural temporal difference; MMN, mismatch negativity; PSR, posterior sylvian regions; STDP, spike timing dependent plasticity; TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; TOJ, temporal order judgment.

[*] Corresponding author. CHUV, Radiodiagnostic, BH08.078, Rue du Bugnon 46, 1011 Lausanne Switzerland.

E-mail address: micah.murray@chuv.ch (M.M. Murray).

[1] These authors contributed equally to this work.

0378-5955/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.heares.2010.03.086

vocalizations independent of their azimuthal position, whereas caudal portions demonstrate preferentiality to the spatial position of sound sources independent of vocalization (e.g. Tian et al., 2001; see also Rauschecker et al., 1997; Lomber and Malhotra, 2008; Bizley et al., 2009). Data from humans generally supports a similar distinction (Clarke et al., 1998, 2000, 2002; Alain et al., 2001, 2009; Maeder et al., 2001; Warren and Griffiths, 2003; Arnott et al., 2004; De Santis et al., 2007), with some notable exceptions (e.g. Zatorre et al., 1999; Weeks et al., 1999; Middlebrooks, 2002). Others have supported a more nuanced model wherein the dorsal pathway is instead functionally organized around action representations rather than spatial processing per se (e.g. Zatorre et al., 2002; Hickok and Poeppel, 2007). More recently, it has been proposed that a third functional (and perhaps left-hemisphere lateralized) pathway, specialized for temporal processing of auditory information, may also exist (e.g. Zatorre et al., 2002; Zaehle et al., 2009; see also Spierer et al., 2009a).

Another important consideration for the functional organization and putative plasticity within the auditory system is the propagation of neural responses. Such temporal information constrains when stimulus driven brain activity can contribute to sensory and/or cognitive phenomena, including plasticity. Robust local field activity within the human primary auditory cortices at approximately 15–20 ms post-stimulus onset in response to rudimentary stimuli, including clicks and tone bursts, has been recorded intracranially (e.g. Liegeois-Chauvel et al., 1994). Additional studies measuring postsynaptic potentials in humans have demonstrated widespread auditory-driven cortical activity within the initial 50–100 ms post-stimulus onset in regions including parietal and frontal cortices in response to rudimentary stimuli (clicks, pips, and noise bursts) (e.g. Giard et al., 2000; Inui et al., 2006; De Santis et al., 2007; Spierer et al., 2008a), complex environmental sounds (Murray et al., 2006; De Lucia et al., 2009a; also Romanski and Goldman-Rakic, 2002 for data in monkeys), and speech (Besle et al., 2008). Others suggest there to be responses in visual cortices, including primary visual cortex, at early latencies in response to rudimentary sounds (tones and noise bursts) in the case of multisensory interactions (e.g. Giard and Peronnet, 1999; Molholm et al., 2002; Romei et al., 2007, 2009).

Given this rapid and diffuse propagation of auditory responses, plastic effects within the auditory system that are observed to onset relatively early in time post-stimulus presentation in humans need not be, and likely are not, restricted to low-level cortices. Likewise, effects that are observed within low-level auditory cortices need not be limited to purely sensory-driven, feedforward modulations. Instead, the effects can also follow from feedback modulations as well as phase-resetting of ongoing activity; to name but a couple of the myriad alternatives for candidate mechanisms. Identifying, characterizing and mapping these effects will hopefully become a focus of increased research and has certainly been one motivation for our concentration on the use of non-invasive electrophysiologic measures in humans. Here we review some of our efforts in these domains that principally, though not exclusively, involved the use of electrical neuroimaging analyses of auditory evoked potentials (AEPs). Electrical neuroimaging refers to a set of analyses of scalp-recorded electroencephalographic data that permit the differentiation of modulations in response strength, topography, and latency within and between experimental conditions or populations (reviewed in Murray et al., 2008a). These analyses often also curtail the application of source estimation methods (reviewed in Michel et al., 2004). One of the main benefits of electrical neuroimaging is its ability to provide statistically-based and neurophysiologically interpretable results, which in turn facilitates translational research across imaging methods and/or species, thereby allowing for stronger models of sensory and cognitive processes.

This review focuses on the identification of spatio-temporal brain mechanisms in humans that subserve learning-induced plasticity during the processing of sounds of environmental objects, the temporal sequence of rudimentary stimuli, and the spatial position of sounds. Throughout this text, we use several different qualifiers of the term "plasticity". As will be clear below, we are far from having a full understanding of precisely what in objet, temporal, and spatial processing is rendered plastic (though our data do provide some insights). Instead, we sought to use terminology that is descriptive of the task or experimental setting in which the plasticity effects are obtained. In discussing the plasticity with sounds of environmental objects we use the moniker "repetition-induced plasticity" to refer to the fact that repeated exposure to the objects is sufficient to engender plasticity in performance and neural activity. In discussing the plasticity in temporal and spatial processing of sounds, we use the moniker "training-induced plasticity" to refer to the fact that the effects were all subsequent to a session of targeted practice on an explicit discrimination task.

2. Object discrimination and learning-induced plasticity

Recognizing relevant sounds is an essential survival skill. We recognize people, objects or animals by (among other things) the sounds they produce. Moreover, this recognition often takes place in noisy contexts and in the absence of visual or other sensory information (see Murray and Spierer, 2009 for a consideration of the impact of auditory object discrimination on multisensory processes). How we process and discriminate sounds is currently the focus of a fertile field of research that aims at identifying which brain networks are specialized in different aspects of sound processing as well as unfolding the temporal stages that can lead to a coherent perceptual representation. Detailing such spatio-temporal dynamics is an essential first step in determining which processes and types of object representations can in turn be subject to learning-induced plasticity. Similarly, by providing insights on how different categories of sounds of objects are represented one can generate models for the kinds of impairments and potential extent of rehabilitation in auditory object recognition one might anticipate after focal brain damage. In the following we review recent findings focusing on categorical discrimination of sounds and repetition-induced plasticity of sound representations.

2.1. Categorical discrimination

Human listeners can readily determine and discriminate between semantic categories of environmental sounds. This ability has been widely investigated in neuropsychological patients (Warrington and Shallice, 1984; Silveri et al., 1997) and more recently in healthy participants with neuroimaging methods (Lewis et al., 2005; Murray et al., 2006; Engel et al., 2009). This body of work provides evidence for the existence of specialized networks for particular categories of environmental sounds within the putative 'what' pathway, including superior and middle temporal cortices bilaterally and extending into motor-related cortices of the so-called mirror neuron system (e.g. Rizzolatti et al., 2002). Indeed, functional magnetic resonance imaging (fMRI) results showed that correctly categorizing animal vocalizations activated middle portions of the left and right superior temporal gyri, whereas tool sounds preferentially elicited a response within a wide left-lateralized network largely overlapping with the mirror system (Lewis et al., 2005). To determine the speed and likely neurophysiologic mechanism mediating basic-level semantic categorization we applied electrical neuroimaging analyses to AEPs in response to acoustically and psychophysically controlled sounds.

In a first study, we compared responses to sounds of living and man-made objects (Fig. 1a; Murray et al., 2006). Differential processing of these categories of complex environmental sounds began within 70 ms post-stimulus onset through modulations in response strength within posterior middle temporal regions of the right hemisphere (Brodmann's Areas (BA) 21/22), though a wider bilateral network of temporal and (pre)frontal regions was observed at this latency in response to both categories (cf. Fig. 4 in Murray et al., 2006). Over this time period there was no evidence for modulations in response topography and by extension no evidence for a change in the configuration of active brain generators. As categorization processes continued in time, distinct configurations of brain networks were active in response to sounds of living and man-made objects. Specifically, our analyses revealed a latency shift over the 155–257 ms post-stimulus period between sets of networks involving bilateral sources within the posterior portion of the superior and middle temporal cortices as well as pre-motor cortices. Responses to sounds of man-made objects exhibited an earlier shift between generator configurations than those to sounds of living objects. A final analysis in this study compared responses elicited by the same sounds when they served as distracters versus when they served as targets in order to ascertain the upper temporal limit for the initiation of categorical brain processes while also controlling for any undetected differences in low-level acoustic features. Such task-related modulations were evident at 100 ms post-stimulus onset and provide an indication of when sufficient

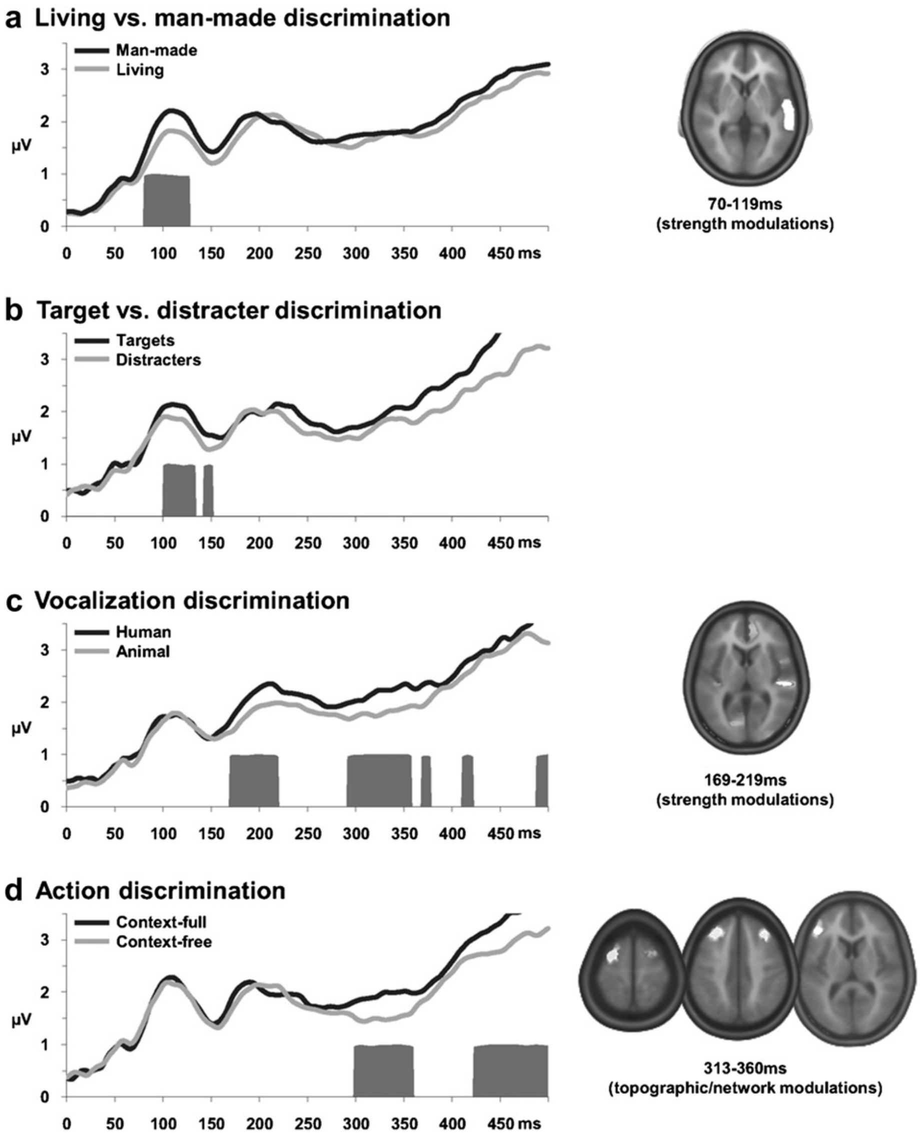


Fig. 1. Global field power (GFP) waveforms in response to different categories of sounds of environmental objects as well as loci of significant effects in source estimations. In each panel are shown group average waveforms as well as the results of millisecond-by-millisecond paired *t*-tests ($1 - p$-value shown). Only effects meeting the $p < 0.05$ criterion for at least 10 consecutive data points are shown. Often effects persisted for longer durations than this criterion. Where applicable, source estimation findings are also displayed. All data shown were recorded from the same individuals who completed a living vs. man-made oddball detection paradigm (see Murray et al., 2006 for details). Results across these panels provide an indication of the temporal hierarchy mediating the discrimination of sounds of environmental objects. (a) Comparison of responses to sounds of man-made and living environmental objects. Effects began at 70 ms and were localized to the right middle temporal cortex (modified from Murray et al., 2006). (b) Comparison of responses when sounds served as targets vs. when they served as distracters within the living vs. man-made oddball detection paradigm. Differences provide an upper limit on the brain discrimination of these categories. Effects began at 100 ms (modified from Murray et al., 2006). (c) Comparison of responses to non-verbal human vocalizations and animal vocalizations. Effects began at ~170 ms and were localized to the right superior temporal sulcus and superior temporal gyrrus (modified from De Lucia et al., submitted for publication). (d) Comparison of responses to sounds of man-made environmental objects that were the consequence of context-full or context-free actions. Effects began at ~300 ms and were localized to premotor and inferior (pre)frontal regions (modified from De Lucia et al., 2009a).

cerebral processing of the sounds has transpired to permit categorical discrimination (Fig. 1b). Of interest, however, is the fact that reaction times on the categorization task were on average ~900 ms. There would thus appear to be at least a partial dissociation between brain and behavioral indices of categorization processes raising the possibility that learning and plasticity might differentially affect these indices (see Section 2.2 below). In addition, the delay between the latency of cortical and behavioral categorization indices raises questions of what processes are intervening and how such may in turn be subject to learning and/or plasticity. An obvious candidate for these intervening processes is more fine-grained categorical processing and semantic analyses, even if not explicitly required by task demands. We have to date considered two examples: the discrimination of human from animal vocalizations and the discrimination of sounds with and without associated socio-functional action representations. Importantly, the effects we obtain with these other situations are obtained despite participants performing an orthogonal task. As such, this paradigmatic approach likely reveals intrinsic 'tuning' properties of the auditory system in humans.

2.1.1. Vocalization discrimination

The ability to discriminate conspecific vocalizations within the more general category of sounds of living objects is essential for communication and interactions, not only because it is at the basis of language but also because it carries information about the speaker's identity and intentions. In humans, deficits in voice recognition can be reliably dissociated from both speech and environmental sound recognition; a syndrome termed phonagnosia (e.g. Assal et al., 1981). Circumscribed brain regions exhibiting differential responses to human voices have been identified within the middle and anterior superior temporal sulcus (reviewed in Belin, 2006). Evidence from intracranial recordings in monkeys also supports the role of superior temporal structures in vocalization processing, though the precise spatial distribution within and beyond the temporal lobes and extent of hemispheric specialization remain disputed (Poremba et al., 2004; Petkov et al., 2008; Remedios et al., 2009). For example, differential responses to classes of vocalizations have been observed in left ventral prefrontal cortices (Fecteau et al., 2005; Cohen et al., 2007).

Information on the spatio-temporal dynamics of these processes can address such discrepancies by resolving which region(s) exhibit vocalization-sensitive responses and in which sequence. To date, a limited set of studies have examined vocalization discrimination. However, the precise latency and underlying basis for effects remains ambiguous. Levy et al. (2001) reported there to be a 'Voice-Specific-Response' (VSR), peaking at 320 ms post-stimulus onset that was more pronounced for voices than for musical instruments. Subsequent studies, however, disagree as to whether this effect depends on active listening and/or categorization (Levy et al., 2003; Gunji et al., 2003). Similarly problematic in these previous works is that the principal contrast was between semantic categories of living and man-made objects, which as discussed above, has been shown to engage distinct brain networks (Lewis et al., 2005; Murray et al., 2006; Altmann et al., 2007; Staeren et al., 2009). More recently, Charest et al. (2009) compared AEPs in response to human vocalizations (both speech and non-speech) with those in response to either environmental sounds or bird songs. While they observed human voice-related AEP waveform modulations beginning at 164 ms, this effect was primarily driven by the human speech sounds, making it difficult to specifically ascribe these effects to vocalization processing.

In order to identify a voice-sensitive electrophysiological response and its precise mechanisms, latency, and location; we applied electrical neuroimaging analyses to AEPs in response to acoustically- and psychophysically-controlled human and animal non-verbal vocalizations (De Lucia et al., submitted for publication). Three time periods of differential responses were identified (Fig. 1c); the earliest of which was over the 169–219 ms post-stimulus period and followed from strength modulations in the absence of topographic differences. Source estimations identified statistical effects within the right STS (BA22) and extending into the STG (BA41), though we would emphasize that absolute differences in source strength were more widely distributed and encompassed additional functional regions (e.g. within the frontal cortex). Parsimony thus argues for common (or at least a statistically indistinguishable) network of brain regions varying in its strength as a function of vocalization type.

More generally, our results argue against the conventional notion of functional selectivity as a mechanism mediating vocalization discrimination. The electrical neuroimaging analyses allowed us to demonstrate that the initial stages of vocalization discrimination are based on modulations in response strength of a common brain network. Second, the latency of our effects allowed us to situate voice discrimination along a more general timeline of auditory object discrimination (Fig. 1). There was no evidence that conspecific vocalizations are subject to facilitated processing over other types of objects, because the initial differential responses occurred ~70–100 ms after discrimination along more basic levels. It is nonetheless noteworthy that the latency of the earliest vocalization discrimination is nearly synchronous with effects identified for face discrimination (Bentin et al., 2007). Voice and face processes likely unfold in parallel to mutually inform one another (Schroeder et al., 2008; Ghazanfar, 2009). Finally, we compared responses across a wider variety of sound object categories and showed that at no point were those to human vocalizations stronger than to all other categories (rather the converse at some latencies). Stronger responses would be required to endorse the viewpoint that human vocalizations are subject to selective processing.

Our results support a paradigm shift in the conceptualization of conspecific voice discrimination not only with regard to the time course attributed to these processes, but more generally to the notion of whether specific brain regions or rather distributed brain networks mediate functional sensitivity. Future investigations will likely focus on the interplay between this widespread pattern of activation and plasticity phenomena. In everyday life we commonly learn how to recognize the voice of a new acquaintance (and other related identity information). However, the fragility of this ability is evident not only in our capacity to forget voices, but also in the clinical observation that voice recognition can be selectivity impaired in brain-lesioned patients. Understanding at which stage of vocalization processing these phenomena take place promises to impact on our understanding of vocalization-related deficits and their rehabilitation.

2.1.2. The role of action representations in categorical discrimination

Recent research indicates there to be strong links between recognizing an object and the actions associated with that object (e.g. Rizzolatti et al., 2002). Through learning and plasticity, such object representations are thought to engender distinct neuronal response patterns or networks. In the case of sounds, these networks can include (amongst elsewhere) premotor and (pre) frontal cortices often, but not exclusively, attributed to the so-called audio-visual mirror neuron system (e.g. Kohler et al., 2002; Keysers et al., 2003; Hauk et al., 2006). One possibility is that learnt action representations are operating in concert with and perhaps also guiding object recognition processes. We therefore determined the spatio-temporal dynamics wherein object and action-related effects transpire and situated one with respect to the other both in time and in terms of localization.

However, the kind(s) of actions driving differential activity within the auditory mirror system (and elsewhere) have yet to be specified. A complication for generating a synthesis in terms of the necessary conditions for observing response modulations within the human auditory mirror neuron system is that action-related differences between stimuli are often confounded by semantic differences. For example, response differences between the sound of paper being ripped and a non-speech vocalization may either reflect action-related processes, man-made vs. living categorization, or a more fine-grained discrimination of the vocalization. We circumvented this confound by comparing AEPs to different subtypes of sounds of man-made environmental objects that each had an associated action (De Lucia et al., 2009a). Specifically, we considered two psychophysically-validated sub-groups of sounds of actions: those conveying a specific social and/or functional context often cuing listeners to act in response (e.g. a ringing telephone) and those sounds not forcibly linked to a specific context and not cuing a responsive action (e.g. notes on a piano). We use the terms 'context-related' and 'context-free', respectively, as shorthand to refer to this distinction.

Beginning ~300 ms post-stimulus onset responses to context-related sounds significantly differed from context-free sounds both in the strength and topography of the electric field at the scalp (Fig. 1d). Action representations appear to differentially affect object discrimination only at relatively late stages. Additionally, such topographic differences indicate that sounds of different action sub-types engage distinct configurations of intracranial generators. Activity within premotor and inferior (pre)frontal regions (BA6, BA8, and BA45/46/47) was significantly stronger in response to sounds of actions that typically cue an action on the part the listener. This localization is consistent with the role of these areas in the audio-visual mirror neuron system. It is essential to note that the regions identified in this study are also involved during earlier stages of auditory object processing. These earlier stages include, but are not limited to, living vs. man-made categorical discrimination. In this regard, it does not appear to be the case that regions of the mirror neuron system are only or selectively active over a specific time period or in response to one and only one category of environmental sound.

2.2. *Learning-induced plasticity in object representations*

The studies reviewed above describe the time course of the categorization of environmental sounds either at a relatively coarse or more fine-grained level. It is similarly important to ascertain the conditions under which and the mechanisms by which object representations can be rendered plastic via learning or repeated exposure. One well-studied example of modifications in object representations is repetition priming, which refers to performance enhancement on implicit memory tests following repeated exposure to stimuli (e.g. Tulving and Schacter, 1990). Two classes of repetition priming have been described (Schacter et al., 2004). Perceptual priming is linked to the physical features of the stimulus, such that changes to these features across initial and repeated stimulus exposures reduces and in some cases eliminates the behavioral facilitation. Conceptual or semantic priming occurs despite such changes and is instead linked to the underlying referent object itself. While both classes of priming have been documented using visual object as well as both visual and acoustic linguistic stimuli, it remains controversial as to whether semantic priming can be elicited with sounds of environmental objects (Stuart and Jones, 1995; Chiu, 2000).

Mechanistically, repetition priming is often paralleled by reduced brain responses for repeated versus initial stimulus presentations. This is commonly referred to as repetition suppression (e.g. Desimone, 1996). With regard to auditory stimuli, neuroimaging investigations have almost exclusively utilized linguistic stimuli and have obtained priming-related effects within extrastriate visual and prefrontal cortices (Buckner et al., 2000; Badgaiyan et al., 2001). The predominant interpretation is that such extrastriate visual regions mediate priming irrespective of the sensory modality and also despite changes in the surface features of the stimuli (Badgaiyan et al., 2001). The implication is that common regions and mechanisms are involved in both perceptual and semantic priming of auditory and visual stimuli (Schacter et al., 2004). More recently, it has been shown that auditory cortices of the temporal lobe are involved in perceptual priming of sounds of environmental objects (Bergerbest et al., 2004), suggesting that priming sounds of environmental objects might instead recruit distinct networks from what has been previously observed with either linguistic auditory or visual object stimuli. Specifically, repetition-induced plasticity in representations of sounds of environmental objects would appear to recruit temporal lobe structures traditionally associated with auditory functions.

Work by our group first focused on determining the time course and probable mechanism of perceptual repetition priming of sounds of environmental objects (Murray et al., 2008b). We were particularly interested in determining whether repetition suppression is contemporaneous with or subsequent to the initial categorical discrimination of sounds of environmental objects. Our experimental conditions included initial and repeated presentations of acoustically identical stimuli from the above living vs. man-made categorization task (Murray et al., 2006). This study did not differentially examine perceptual and semantic contributions to repetition priming (though we return to this below). Behaviorally, repetition priming effects were observed as a significant speeding of reaction times (Fig. 2). This effect was robust to long intervening periods between initial and repeated stimulus presentations. In our case, the average interval between the initial and repeated presentation of target sounds was approximately 7 min. Plus, when we included block of the experiment as a factor in our analyses, there was still only a main effect of initial vs. repeated exposure. Electrophysiologically, we observed a suppression of the strength of responses to repeated sound presentations over the 156–215 ms post-stimulus period (Fig. 2). Additional analyses indicated that repetition suppression of equivalent magnitude was observed during both the first and the final blocks of trials of the experiment. These collective results suggest that repetition priming effects 'reset' between blocks.

We are currently investigating the impact of high numbers of stimulus repetitions on mechanisms of repetition-induced plasticity in order to determine whether priming effects with sounds of objects saturate as they do with visual stimuli (Hauptmann and Karni, 2002). We compared AEPs to initial and repeated stimulus repetitions from the first of 25 experimental blocks with the same conditions from the last of 25 experimental blocks, thereby generating a 2×2 within subject design (Bourquin et al., in preparation). Repetition suppression effects differed between these experimental blocks. The first block exhibited effects identical to those reported by Murray et al. (2008b) within left middle temporal cortices, whereas the last block exhibited effects that now also included modulations within right temporo-parietal regions. Mechanisms of plasticity related to object representations can themselves vary as a function of the exposure to the items.

We additionally sorted responses to living and man-made objects in the Murray et al. (2008b) study, in order to determine if stimulus repetition differentially affected one or the other category

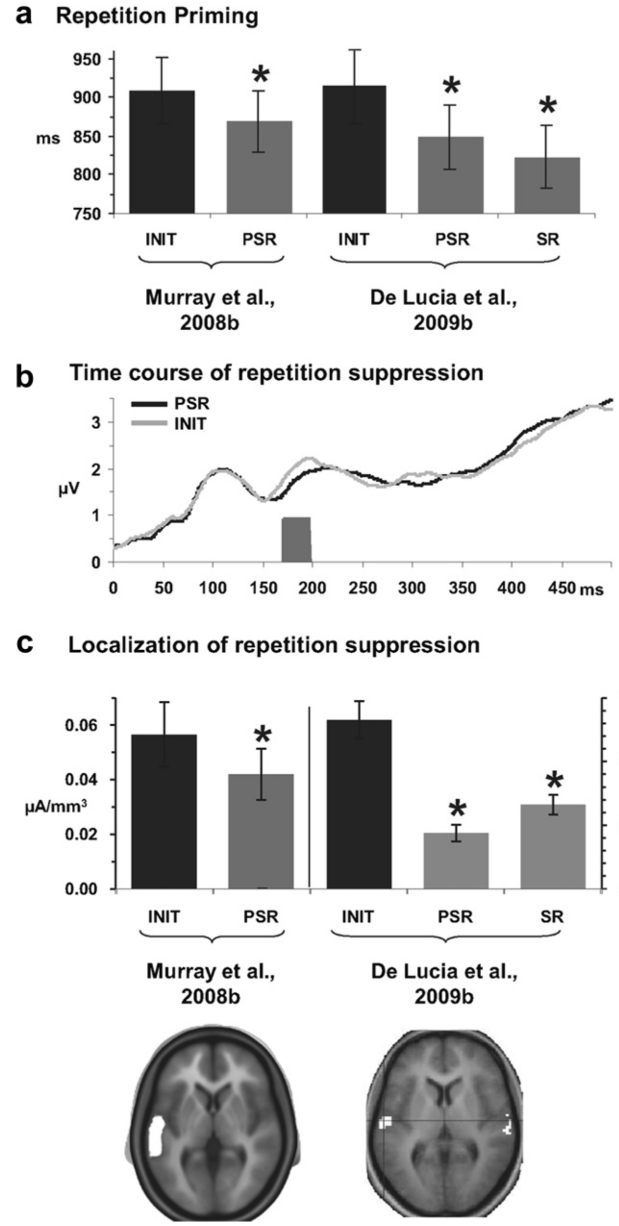


Fig. 2. Effects of auditory object repetition on behavior and brain activity. Throughout this figure INIT refers to the initial presentation of a stimulus, PSR to physical and semantic repetitions of a stimulus (i.e. the same exemplar), and SR to semantic repetitions (i.e. a different exemplar). Asterisks indicate significant differences with respect to the INIT condition. a. Mean reaction times (s.e.m. indicated) during the completion of a living vs. man-made categorization task. The left side displays data from Murray et al. (2008b), and the right side from De Lucia et al. (2009b). Both studies demonstrate there to be repetition priming (i.e. facilitated reaction times to repeated stimuli). The data from De Lucia et al. (2009b) show that priming does not depend on repeating the identical acoustic features of the stimuli. (b) Global Field Power (GFP) waveforms in response to INIT and PSR conditions in Murray et al. (2008b). These data show that repetition suppression occurs starting at ~170 ms post-stimulus onset, which is considerably after the initial categorization of the sounds (see Fig. 1). (c) Results of source estimations of AEP data (left side) and fMRI analyses (right side) both demonstrate there to be significantly weaker responses to repeated stimulus presentations within Brodmann's Area 22. The bar graph plots scalar values of source estimations in the case of AEP data and beta values in the case of fMRI data from the node/voxel with the maximal difference.

of sounds. There was no evidence for differences in repetition suppression as a function of sound category. Finally, estimated sources for these effects of plasticity were localized to the left middle temporal gyrus and superior temporal sulcus (BA22), which have been implicated in associating sounds with their abstract representations and actions (Fig. 2). Repetition suppression effects with sounds of objects are subsequent to and occur in different brain regions from what has been previously identified as the earliest discrimination of the same auditory object categories.

To address the relative contributions of acoustic and semantic features more directly, we then conducted an event-related fMRI study where we repeated either identical or different exemplars of the initially presented object (De Lucia et al., 2009b). We reasoned that identical exemplars share both physical and semantic features, whereas different exemplars share only semantic features. Reaction times were significantly faster for repeated than initial presentations both when an identical exemplar was used and when different exemplars of the same referent object were used (Fig. 2). There was no evidence that the magnitude of the reaction time facilitation differed between perceptual and semantic priming. Nor was there a correlation between the magnitude of one and that of the other (cf. Fig. 1 in De Lucia et al., 2009b). Repetitions of acoustic and/or semantic features produced equivalent suppression of hemodynamic responses within overlapping brain regions that included not only auditory association cortices but also premotor, prefrontal, and cingulate cortices. In this regard, there was no evidence of either a distinct mechanism or network of brain regions mediating semantic priming. In contrast to Bergerbest et al. (2004), there was no evidence for a systematic relationship between behavioral and neurophysiologic measures of priming in any of our studies. However, their use of a blocked design makes any correlation somewhat suspect due to uncontrolled modulations in attention and arousal. Additional studies will be necessary to determine if, when, and where there is a direct causal relationship between neurophysiologic and behavioral manifestations of repetition priming within the auditory modality. Such notwithstanding, our collective AEP and fMRI results suggest that repetition priming with sounds of environmental objects involves at least minimal access to semantic attributes.

2.2.1. *Mechanisms supporting repetition suppression as a form of learning-induced plasticity*

Our results support repetition suppression as an archetypical mechanism, extending observations within extrastriate visual cortices with visual and linguistic stimuli to the auditory system with sounds of environmental objects. Grill-Spector et al. (2006) overviewed three putative neural mechanisms that could mediate repetition suppression: fatigue, sharpening, and facilitation. Fatigue models propose there to be a proportionally equivalent reduction in neural responsiveness across initial and repeated presentations without any modulation in either their pattern or temporal profile, such that all neurons responsive to a given object, including those most selective, exhibit repetition suppression. Sharpening models propose that repetition leads to a reduction in the number of neurons responsive to a stimulus, with effects predominantly impacting those neurons least selective for a given object. Facilitation models propose there to be a latency shift in response profiles following repeated exposure. Each of these models would propose there to be a reorganization (either in the spatial distribution or timing) of neural activity and of neural representations, such that the spatio-temporal profile of activity in response to a given stimulus/object changes across initial and repeated presentations.

Our electrical neuroimaging analyses indicate that repetition suppression following repeated exposure to sounds of objects occurs via a modulation in the strength of responses within statistically indistinguishable brain networks. In addition, both the source estimation of AEPs in Murray et al. (2008b) and the event-related fMRI results in De Lucia et al. (2009b) independently support a mechanism whereas a common network of brain regions within left middle temporal cortices modulates its strength of responsiveness. In the case of the AEP findings, there was no evidence of latency shifts across initial and repeated exposures, arguing against predictions based on facilitation. Additional studies will be required to resolve between fatigue and sharpening models of repetition suppression.

Repetition suppression may be considered another example of cortical plasticity that may reflect a similar underlying comparison mechanism as the auditory mismatch negativity (MMN). The auditory MMN is a differential brain response between infrequently presented (also termed rare or deviant) stimuli within a stimulus series (e.g., Näätänen et al., 2005, 2007). The MMN is considered to be an index of the current stimulus' access to and comparison with a perceptual or memory trace for the consistencies in the stimulus series. The MMN can be elicited on the one hand by changes in low-level acoustic features and on the other hand by alterations in more complex stimulus features, semantic attributes, and arbitrary patterns (e.g., Näätänen et al., 2007). The MMN to such changes in features typically manifests as a signal increase, rather than suppression, and cannot be fully explained by adaptation or habituation of sensory components (e.g. Näätänen et al., 2005 for discussion; though see Ulanovsky et al., 2003; May and Tiitinen, 2009 for alternative accounts). Javitt et al. (1996) dissociated sensory responses and MMN generation in several ways. First, their multi-laminar recordings in primary auditory cortex of awake macaques showed that sensory responses were concentrated in granular cell layers, whereas MMN generation was focused in supra-granular layers. Second, application of the *N*-methyl-D-aspartate antagonist phencyclidine blocked generation of the MMN, while leaving sensory responses intact. More generally, the robust clinical observation of impaired MMN generation in patients with schizophrenia despite intact sensory responses provides a further line of evidence for the dissociation of these processes (e.g. Javitt, 2009; also Lavoie et al., 2008). More recently, it has been proposed that both the MMN and repetition suppression may both follow from cortical responses being based on predictive coding of stimuli (Friston, 2005; Garrido et al., 2009). Establishing a more direct neurophysiologic link between mechanisms of repetition suppression and MMN generation will require additional experimentation and modeling that will undoubtedly provide insights concerning auditory sensory processing, memory formation/retrieval, and decision-making.

3. Temporal discrimination and learning-induced plasticity

An accurate registration of the relative timing between the occurrence of auditory events on a sub-second time scale is required for establishing coherent representations based on the ongoing flow of auditory information. In turn, such temporal processing is believed to be involved in several high-level cognitive functions. Support for this perspective comes from evidence that temporal processing impairments are implicated in a range of neurological and psychiatric conditions (e.g. Mauk and Buonomano, 2004).

Investigations of temporal processing generally involve two types of relative timing tasks. Synchrony detection tasks require participants to detect whether two sounds occur at the same time. Temporal order judgment (TOJ) tasks require the discrimination of which of two sounds occurs first. The processing of the order of stimuli's occurrence is required when proper stimulus representation depends on its intrinsic or relative position within a sequence. This is the case, for instance, in speech comprehension where the order of phonemes determines word meaning (Hirsh, 1959). Despite relative-timing paradigms being extensively applied over the last decades, our understanding of the underlying neural basis remains largely inferential as most studies involved only psychophysics.

3.1. Hemispheric specialization and inter-hemispheric interactions in temporal processing

Lesion studies reveal that patients with damage to the left temporo-parietal cortices exhibit impaired TOJ performance (e.g. Wittmann et al., 2004). These results are in line with previous evidence for left hemisphere dominance for the processing of auditory temporal features (e.g. Zatorre et al., 2002; Zaehle et al., 2009). Anatomical data similarly support a degree of hemispheric specialization. A larger number of cells, as well as greater connectivity and more heavily myelinated neurons have been observed within left more than right supratemporal structures, which has been interpreted as facilitating conditions for fast neural transmission (e.g. Anderson et al., 1999). Collectively, these results support that the temporal stamping required for accurate stimuli ordering depends on left hemispheric structures, putatively due to their anatomo-functional advantages for fast temporal processing.

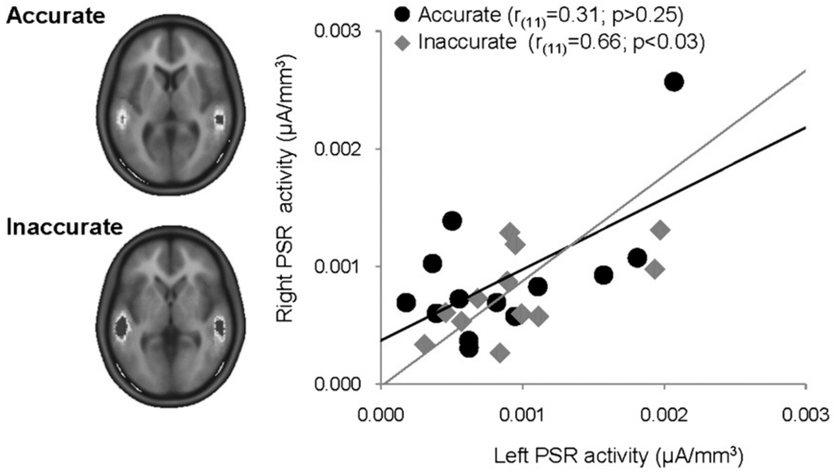
By comparing AEPs in response to accurate and inaccurate TOJ performance, we identified when during the course of stimulus processing a temporal 'stamp' is established to guide TOJ perception (Bernasconi et al., 2010a; Fig. 3a). Response modulations between accurate and inaccurate TOJ manifested over the 33–77 ms post-stimulus period and were the result of changes in the topography of the electric field at the scalp (and by extension in the underlying configuration of intracranial sources). Consistent with the hypothesis for a left hemispheric dominance in TOJ, source estimations performed over this time period revealed a modulation of left, but not right, superior temporal activity as a function of performance accuracy, as well as a significant correlation between left, but not right, superior temporal cortex and behavioral sensitivity.

Our results further revealed that over the 33–77 ms interval, the activity between left and right superior temporal cortices was correlated when performance was inaccurate but not when it was accurate, suggesting that the extent of functional connectivity, or coupling, between posterior temporal homotopic areas impacts TOJ accuracy. This result suggests that in a near-threshold context, accurate TOJ can be achieved within the left superior temporal cortex only when temporal processing occurring within this region is functionally released from the interfering influence of right hemisphere. Activity within right hemisphere structures could have interfered with temporal integration mechanisms occurring in the contralateral (i.e. left) homotopic region. In agreement with the likely importance of inter-hemispheric interactions in auditory functions, Westerhausen et al. (2009) used diffusion tensor imaging to show that variability in fiber tracks interconnecting the superior temporal lobes correlated with performance on an auditory discrimination task.

Several studies indicate that mechanisms supporting temporal discrimination are highly interactive with those mediating attention (Eagleman, 2008). Consequently, right hemispheric structures might likewise play a role in TOJ performance. However, it is controversial as to whether attention impacts the amplitude (McDonald et al., 2005) and/or timing (Vibell et al., 2007) of brain activity during temporal processing. These studies advanced that temporal order perception could depend on gating and/or latency mechanisms, respectively reflected by increases in response amplitude and/or decreases in the processing latency to attended versus unattended stimuli (see Vibell et al., 2007 for discussion).

Support for the involvement of gating mechanisms in TOJ comes from studies showing that the manipulation of exogenous attentional cues induced shifts in the point of subjective simultaneity

a **Inter-hemispheric coupling and TOJ accuracy**
(topographic modulations @ 39-77ms)



b **Inter-hemispheric coupling and training-induced TOJ proficiency**
(topographic modulations @ 43-76ms)

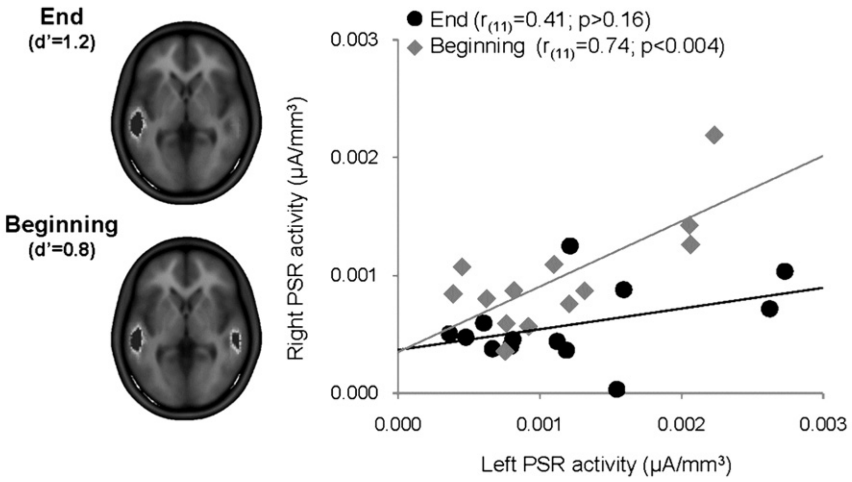


Fig. 3. Patterns of inter-hemispheric coupling during TOJ performance and acquisition of proficiency. (a) Source estimations during the 39–77 ms post-stimulus period when topographic AEP modulations were observed between trials resulting in accurate vs. inaccurate TOJ performance are displayed. Prominent sources were observed within posterior sylvian regions bilaterally, though the degree of bilateral responses varied between accurate and inaccurate trials. The cluster plot shows that responses between the hemispheres were significantly coupled on inaccurate trials and decoupled on accurate trials. (b) Source estimations during the 43–76 ms post-stimulus period when topographic AEP modulations were observed between trials at the end vs. beginning of a TOJ training session. Performance sensitivity (*d*′) significantly improved, and prominent sources were again observed within posterior sylvian regions bilaterally. Again the extent of bilateral activation differed as a function of training. At the beginning of training when performance was poor, responses between the hemispheres were significantly coupled. At the end of training when performance was improved, responses between the hemispheres were de-coupled.

accompanied by a gain in the amplitude of early visual evoked potentials (e.g. Luck et al., 2000). Gating would likely rely on an active inhibitory network, designed to reduce the flow of redundant sensory information associated with sensory overload (Kisley et al., 2004). As accurate TOJs require unbiased perception of the first and/or second sound of the pair, they cannot be achieved if the processing of each of the two sounds interferes with each other. An adequate gating of the first sound would therefore facilitate TOJ by inhibiting the response to the second sound. Auditory gating mechanisms typically manifest around 50 ms post stimulus onset (e.g. Pelizzone et al., 1987), which is a time period corresponding to the latency of the effects we have observed (Bernasconi et al., 2010a). However, we would exclude that a pure gating mechanism explains our results, because we found that accurate TOJ was associated with a reduction of left superior temporal activity, rather than in an increase in response strength to the first sound as would be expected according to the gating hypothesis. Additionally, pure gating mechanisms would have likely manifested as a modulation in global field power in the absence of topographic modulations. Rather, we observed topographic modulations in the absence of modulations in global field power. That is, the mechanism operating to influence TOJ accuracy appears to rely on changes in the configuration of active brain regions rather than simply changes in their level of activity.

The prior-entry hypothesis is more consistent with our results. It proposes that TOJ depends on the processing speed of sensory stimuli that in turn determines their order of arrival into consciousness (Titchener, 1908); though the precise neurophysiologic mechanism for such remains controversial. The general threshold model (Ulrich, 1987) postulates that TOJ might depend on the arrival time of the sensory information at a hypothetical "temporal comparator"; the arrival time depending on parameters including transduction time or transmission latencies of the information from the receptor to a comparator (Pöppel, 1988; Stelmach and Herdman, 1991). In an electrophysiologic study using a cross-modal visuo-tactile TOJ task, Vibell et al. (2007) provide support for the prior-entry hypothesis by showing that attention shifts the latency of visual evoked potentials, consistent with a speeding-up of sensory processing. Our pattern of results in Bernasconi et al. 2010a likewise supports prior-entry as a putative mechanism for temporal order perception. The topographic modulation could result from a rapid latency shift across conditions. That is, accurate TOJ might result in a faster transition from one active configuration of brain areas to another, which in turn might appear as a topographic difference in the electric field as the scalp. Differences in the prioritization of stimulus processing might therefore account for our effects. In this sense, inputs from right superior temporal cortices might have perturbed the processing latency, rather than or in addition to, the temporal stamping mechanisms occurring within left superior temporal cortices. Greater interference from right to left superior temporal areas could in turn have resulted from the higher level of functional coupling we found the inaccurate than accurate condition.

3.2. *Learning-induced plasticity in temporal processing*

To date, only a few studies have addressed behavioral plasticity of temporal representations, and none directly addressed its neural underpinnings. Some psychophysical studies document improvements in TOJ performance with experience (e.g. Hirsh, 1959), but only a few report empirical data directly supporting training-induced improvements (e.g. Mossbridge et al., 2006, 2008).

We recently identified the spatio-temporal brain correlates of training-induced improvements in auditory TOJ (Bernasconi et al., 2010b). Thirty minutes of training significantly improved TOJ performance. AEPs recorded at the beginning vs. the end of training revealed that over the 43–76 ms post-stimulus time period responses to trials when TOJ performance was accurate differed topographically as a function of training blocks (Fig. 3b). This is evidence for the engagement of distinct configurations of brain networks at the beginning vs. at the end of the training session. Source estimations in turn revealed that TOJ improvement was associated with a change in the lateralization pattern of brain responses from a bilateral pattern within posterior sylvian regions (PSR) at the beginning of training to a left-lateralized pattern at the end of training. Moreover, activity within the left but not right PSR correlated with discrimination performance (Fig. 3b). These results are in strong agreement with previous evidence of a left temporo-parietal dominance for TOJ (Davis et al., 2009; Wittmann et al., 2004) and more generally for the involvement of left supratemporal plane in the processing of auditory temporal features (Zatorre et al., 2002; Zaehle et al., 2009; Foxton et al., 2009). Collectively, these results support that the temporal stamping required for accurate stimuli ordering depends on left PSR structures, putatively due to their anatomo-functional advantages for fast temporal processing.

The plastic changes underlying TOJ improvement in Bernasconi et al. (2010b) impacted right PSR responses and their interaction with left PSR, but not directly the activity within the left PSR. We interpreted these results as indicating that the TOJ improvement was mediated by a release of task-relevant representations comprised within the left PSR from temporally imprecise and interfering activity and/or inputs from the right PSR. Left and right PSR activity indeed correlated at the beginning but not at the end of the training session. One neurophysiologic model for such plasticity and improvements in TOJ performance is based on reductions in synaptic latency mediated by spike timing dependent plasticity (STDP; reviewed in Buonomano and Merzenich, 1998; Weinberger, 2004).

STDP models assume that the temporal association between pre- and post-synaptic activation occurring with repeated exposure to stimuli in turn modifies synaptic strength and reduces response latencies (Song et al., 2000). In this way, the timing of the activated neural circuitry would be sharpened and the ordering of input facilitated (e.g. Legenstein et al., 2005). According to STDP, neural circuits with sharp response latencies would in turn respond synchronously to stimulus onsets and would consequently see their activity preserved or reinforced, whereas responses within regions with less synchronous response patterns would diminish. Due to the anatomo-functional advantage of the left PSR for fast temporal processing reviewed above, repeated exposure to the sound pairs would be reinforced by STDP, whereas less sharply tuned regions, including right PSR would see their responses reduced. Finally, the initial functional connection between left and right hemispheres would be predicted to be suppressed due to the general differences in levels of synchronicity. STDP (or a similar mechanism) could therefore account for both the decrease in right superior temporal sulcus response and the decoupling between left and right PSR, in turn sharpening the left posterior superior temporal sulcus response and facilitating the processing of temporal order.

The general time course of the effects we have observed provides some insights on the likely basis upon which temporal processing and temporal discrimination are performed. Temporal stamping mechanisms and plastic changes accompanying behavioral improvements revealed in our studies (Bernasconi et al., 2010b, submitted) would appear to occur at similarly early processing stages and prior to stimulus feature integration. Prior studies of spatial processing have only observed effects at latencies beyond approximately 100 ms post-stimulus onset (e.g. De Santis et al., 2007; Spierer et al., 2008a, b; Murray and Spierer, 2009).

4. Spatial discrimination and learning-induced plasticity

4.1. *An overview of auditory spatial processing*

While there is general consensus that accurate spatial processing of sounds relies on cortical activity (Jenkins and Masterton, 1982; Heffner and Heffner, 1990; King et al., 2007), the precise manner in which spatial positions are represented and accurate discrimination achieved remain unresolved, particularly in humans. Spatiotopic representations have been identified in subcortical but not cortical structures in animals (e.g. Palmer and King, 1982; Woods et al., 2006). At the cortical level, recent investigations suggest that sub-populations of location-sensitive cortical neurons over-sample and respond preferentially to the more lateral regions of either the ipsilateral or contralateral hemispace while also exhibiting their steepest tuning curves for positions that straddle the midline (Stecker et al., 2005). Based on these findings, Stecker and colleagues proposed an opponent-channel theory of spatial coding wherein two sub-populations, or "spatial channels", represent locations according to the slopes of their response area and by graded changes in response rate. Such observations speak in favor a model of spatial representations based on the patterned activity of population responses. Inaccurate encoding of spatial positions could result from the activity of less specific neurons (Ghose, 2004; Ohl and Scheich, 2005), from noise-related responses (Rainer et al., 2004), or from inaccurate perceptual templates (Li et al., 2004).

In humans, mechanisms of auditory spatial discrimination have commonly been assessed using the MMN (e.g. Deouell et al., 2006, 2007; Spierer et al., 2008b; also Salminen et al., 2009). These studies showed that MMN amplitude correlated positively with deviations in azimuthal eccentricity and with subjects' discrimination accuracy. Spatial comparisons underlying change detection have been proposed to rely on a separate memory trace that encodes regularity in the auditory environment ("memory-trace model"; Näätänen et al., 2005) and which is thought to be localized in the posterior superior temporal gyrus (Deouell et al., 2006) and/or regions along the putative spatial or "where" dorsal–lateral processing stream (Deouell et al., 2006, 2007).

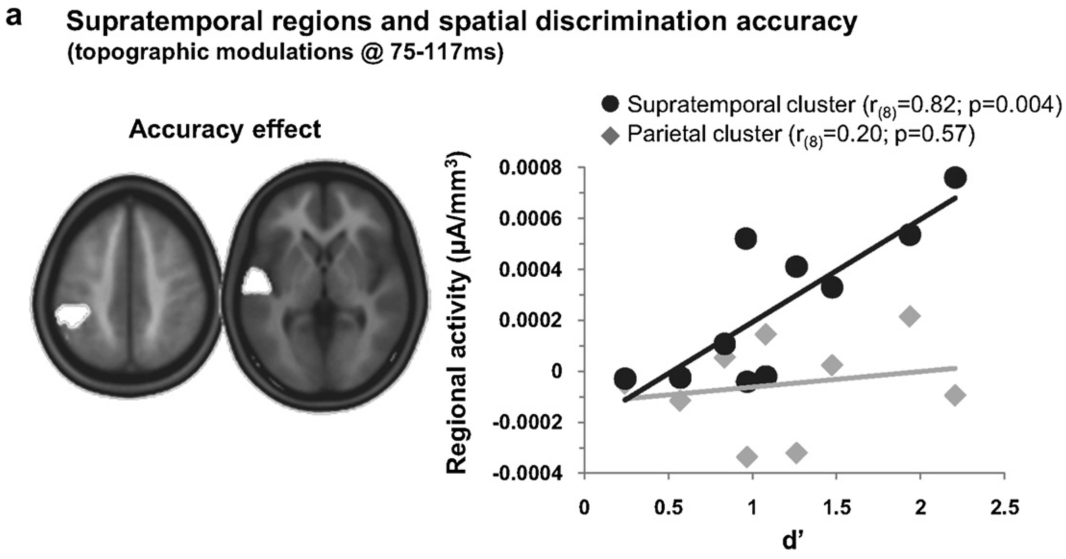
We recently provided evidence for the critical role of supratemporal regions in spatial encoding accuracy by demonstrating that responses to physically identical acoustic stimuli differed topographically according to subsequent performance accuracy on a spatial discrimination task at approximately 100 ms post-stimulus onset, indicative of changes in the configuration of the underlying intracranial sources preceding correct vs. incorrect spatial discriminations (Fig. 4a; see also Spierer et al., 2008a; as well as Ohl and Scheich, 2005; Ohl et al., 2001 for similar findings in animal models). Analyses of distributed source estimations revealed largely similar sets of activated regions for both conditions, with stronger activity within the contralateral (left) supratemporal plane and inferior parietal lobule preceding correct vs. incorrect discriminations (Spierer et al., 2008a). A positive correlation was found between discrimination sensitivity (d') and the strength of sources within the posterior supratemporal plane (BA41). No such correlation was observed within parietal cortices or elsewhere. Consistent with a model based on population-based encoding of spatial positions, we hypothesized that the activity within the supratemporal plane was stronger when the spatial position of the stimulus is more reliably encoded due to a larger differential response between neural populations constituting each opponent channel. On trials leading to incorrect performance, responses within the supratemporal plane would be smaller because of inaccurate and/or imprecise encoding of spatial information. Supporting this proposition are data from Deouell et al. (2007), who demonstrated that responses within the planum temporale (as well as anterior regions along the superior temporal gyrus) to different (supra-threshold; i.e. 15°) spatial lateralizations increased as the number of stimulated positions increased within a block of trials.

The determinant role of supratemporal cortices in spatial encoding accuracy provides insights on the relative function of regions involved in auditory spatial processing. First, our effects at 75–117 ms were lateralized to the left (contralateral) superior temporal plane. This finding is in agreement with previous evidence demonstrating the prominent role of the contralateral hemisphere in the processing of interaural temporal information (Krumbholz et al., 2005, 2007; see also Zatorre and Penhune, 2001 for support for a left-hemisphere dominance in spatial discrimination), at least at early latencies post-stimulus onset. While these "early" effects are left-lateralized, it is likely the case that bilateral networks are involved during subsequent time periods (e.g. Tardif et al., 2006). Electrophysiological recordings in the supratemporal plane of non-human primates suggest that the posterior part of the supratemporal gyrus comprises an early representation of sound sources (Rauschecker, 1998; Recanzone et al., 2000; Woods et al., 2006). In humans, MMN studies also suggest that these representations as well as spatial comparison mechanisms underlying change detection may reside within the planum temporale (Tata and Ward, 2005; Sonnadara et al., 2006; Deouell et al., 2006, 2007; Salminen et al., 2009). By contrast, our data would instead suggest that more lateral regions of the superior temporal plane play a particularly important role in spatial functions at early latencies (see also Tardif et al., 2006), which are also anterior to regions of the planum temporale implicated in the above-mentioned prior studies (see also Zatorre and Penhune, 2001 for similar conclusions based on neuropsychological findings). Further investigations are required to disentangle the role of specific areas within the superior temporal regions in spatial processing.

Aside from superior temporal cortices, there is also evidence in both humans and non-human primates for a prominent role of parietal structures in spatial localization processes (e.g. Griffiths et al., 1996; Mazzoni et al., 1996; Stricanne et al., 1996; Weeks et al., 1999; Ducommun et al., 2002; Zatorre et al., 2002; Deouell et al., 2006, 2007; Tardif et al., 2006; De Santis et al., 2007; Spierer et al., 2008b). Neuropsychological studies of spatial functions have likewise shown that temporal and/or parietal lobe lesions lead to impairments in sound localization (e.g. Ruff et al., 1981; Bisiach et al., 1984; Pinek et al., 1989; Vallar et al., 1995; Griffiths et al., 1997; Tanaka et al., 1999; Bellmann et al., 2001; Clarke et al., 2000, 2002; Zatorre and Penhune, 2001; Zimmer et al., 2003). However, it is likewise the case that temporal and parietal regions are differentially involved depending on whether the spatial task requires absolute or relative localization.

Following the initial analysis of auditory spatial information within the supratemporal plane, higher-order processing of auditory spatial information has been proposed to occur along the parieto-frontal 'where' stream (Alain et al., 2001; Maeder et al., 2001; Ducommun et al., 2002; Arnott et al., 2004; Tardif et al., 2006; De Santis et al., 2007). However, we would emphasize that data concerning the temporal dynamics of activity in these regions shows them to be responsive at early latencies, making it important to distinguish between temporal hierarchies and processing hierarchies. Data from non-human primates suggest that the posterior parietal cortex rather than the supratemporal plane is involved in high-level spatial processes (Rauschecker, 1998). A positron emission tomography study in humans also demonstrated the absence of activity in the supratemporal plane on an absolute localization task (Weeks et al., 1999). Consistently, Lewald et al. (2002, 2004a, b) reported that focal repetitive transcranial magnetic stimulation of the posterior parietal cortex induced a systematic shift in the perceived lateralization of a sound source position, whereas the acuity of position discrimination remained unaffected.

Several lines of evidence suggest that along the above-described processing hierarchy of auditory spatial information, initial stages involve temporal regions contralateral to the stimulation while right parietal hemisphere dominates for higher-order spatial processes. Lesion data indeed reveal no differences between deficits associated with right and left temporal lesions (Sanchez-Longo and Forster, 1958; Efron et al., 1983), while studies including patients with parietal lesions suggest a right hemispheric dominance (Ruff et al., 1981; Bisiach et al., 1984; Tanaka et al., 1999). Our own clinical data emphasize the role of the right hemisphere in the processing of binaural spatial cues (i.e. inter-aural intensity and time differences; IID and ITD, respectively) in a large-scale neuropsychological study including 25 right-hemisphere and 25 left-hemisphere brain damaged patients (Spierer et al., 2009b). Precise computation of contralateral spatial information involved the left hemisphere, while the right hemisphere was involved in the processing of the whole of auditory space. On the other hand, the building up of global auditory spatial representations relied on right temporo-parietal cortices. While numerous neuroimaging studies speak in favor of right hemispheric dominance for auditory spatial processing particularly at post-stimulus latencies >200 ms (Kaiser and Lutzenberger, 2001; Ducommun et al., 2002; Herrmann et al., 2002; Lewald et al., 2002; De Santis et al., 2007; Spierer et al., 2009c), initial processing stages would appear to involve more the contralateral than the ipsilateral hemisphere.



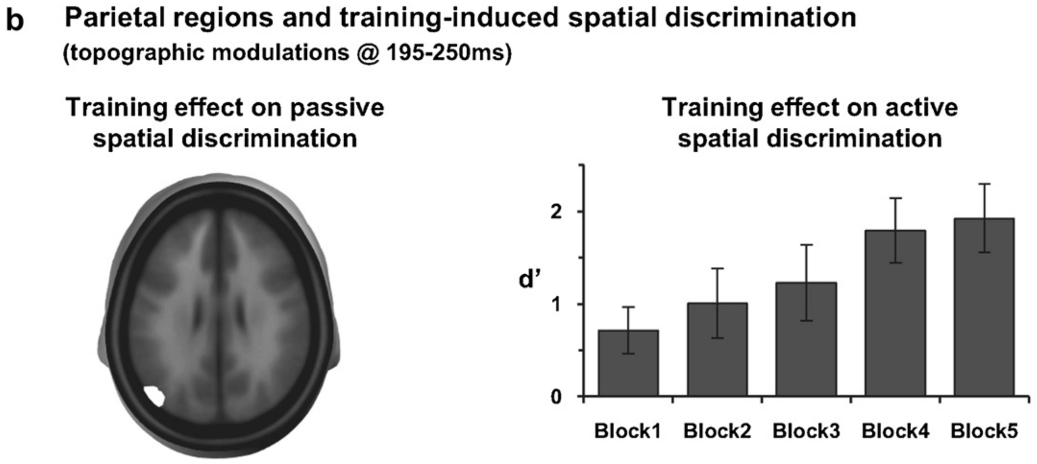


Fig. 4. The role of supratemporal and parietal cortices in spatial discrimination. (a) Source estimations during the 75–117 ms post-stimulus period when topographic AEP modulations were observed between trials resulting in accurate vs. inaccurate spatial discrimination performance are displayed. Significantly stronger source estimations were observed within supratemporal and parietal cortices within the left (contralateral) hemisphere. It was only differential activity within the supratemporal cortex that significantly correlated with performance sensitivity (d'). (b) Source estimations during the 195–250 ms post-stimulus period when topographic AEP modulations were observed between trials of passively presented sounds prior to or immediately following spatial discrimination training. Training led to significantly increased activity within left (contralateral) parietal cortices. Training also led to significant improvements in spatial discrimination sensitivity (d').

4.2. Learning-induced plasticity in spatial processing

We recently detailed the spatio-temporal mechanisms whereby subjects learn to discriminate the position of sequentially presented pairs of sounds lateralized with ITDs (Spierer et al., 2008b). Before training, when subjects were unable to discriminate reliably between the two spatial positions, there was no evidence of neural response differences. Rather, responses to both positions engaged indistinguishable parieto-temporal networks bilaterally. After 40 min of discrimination training, responses to the spatial positions now differed in their electric field topography and by extension the configuration of the underlying brain generators. Source estimations localized these changes to the left inferior parietal cortices, contralateral to the hemispace of the stimulus (Fig. 4b). These effects of training were restricted to the trained positions but did not depend on the specific order in which stimuli at these positions were presented. Nor did they depend on whether this order matched that used during training. This pattern is consistent with mechanisms involving the refinement of spatial representations and/or coding for the trained locations. The establishment of spatial anchors or mnemonic templates would have restrained the transfer of the effect of training to sound pairs involving one of the two trained positions. Similarly, if the training had yielded to a general improvement in discriminating ITD cues, discrimination performance would have also improved for untrained positions. There was no evidence that this was occurring. It thus appears that training induced modulation of the encoding of the absolute positions of the stimuli.

Several types of neurophysiological modifications could have occurred with training, including alterations in the quantity of neurons recruited to respond to stimulation of a particular spatial location, in the synchrony of such neural responses, and in the spatial tuning of neural populations (e.g. Ohl and Scheich, 2005). Effects in our study were limited to topographic changes in the response to the more lateral and less frequently presented of the two simulated positions, with no evidence of modifications in response strength. Such results run counter to what would have been predicted by modification in neuronal recruitment or response synchrony as it would likely not have specifically affected just one of the stimulated positions. Similarly, responses to both positions would be affected in the case of a general attention or arousal mechanism or a general learning-induced change in spatial coding. Furthermore, these mechanisms would likely have resulted in a change in the strength of responses, rather than the configuration of underlying brain generators. Instead, our results are consistent with the refinement of neuronal spatial tuning at a population level. Previous studies have shown that pitch training was accompanied by an increase in neuronal selectivity and decrease of the corresponding cortical representation (Edeline and Weinberger, 1993; Recanzone et al., 1993). In our study, training selectively changed the topography of the electric field and decreased the activity of sources within left inferior parietal cortices (cf. Fig. 5 in Spierer et al., 2008b). A putative neural mechanism may involve inhibitory processes in generating plasticity via the exclusion of the activity of less specific neurons (Ghose, 2004; Ohl and Scheich, 2005) or noise-related responses (Rainer et al., 2004). Li et al. (2004) further extended this notion in terms of refining a perceptual template, wherein those neurons that respond most strongly might not convey the greatest amount of information regarding a learned discrimination. Rather, greater differential responses to the spatial positions may instead occur in neurons exhibiting weaker response magnitude. In this case, the inhibition of such strongly responding neurons would produce a more informative response profile (Ghose, 2004).

On the whole, our results lend additional support to the concept of auditory spatial representations based on population coding. Together with the finding that this effect occurred at a relatively late processing stage (around 250 ms), our findings would support a multiphase spatial processing hierarchy that includes the transformation of spatial representations both along relative and absolute dimensions as well as along egocentric and allocentric frames of reference.

5. Conclusions

Current models of the organization of the auditory system posit that the processing of semantic, temporal or spatial auditory information relies on partially segregated processing streams. The studies we reviewed above indicate that in addition to their anatomo-functional heterogeneity, distinct neurophysiological mechanisms subserve training-induced plastic changes within each of these pathways.

Auditory object-related plasticity has been investigated by several experimental paradigms involving repetition priming. Based on our electrical neuroimaging and fMRI studies, we provided evidence that repetition-induced plasticity involves strength modulations within a common network of brain regions principally within the temporal lobe both when the initial and repeated stimuli are identical exemplars as well as when they are physically different but refer to a common referent object (and are thus semantically related). These findings challenge existing models wherein priming is mediated by extrastriate visual regions and prefrontal cortices, irrespective of their surface features and in both visual and auditory modalities. With respect to the timing of these effects, we have shown that perceptual priming took place over the 156–215 ms post-stimulus period and therefore subsequent to basic-level living vs. man-made categorical discrimination. This finding provides additional support to the notion that perceptual priming can indeed imply access to some semantic features of the auditory stimulus even when exposed to repetition of identical sounds. Ongoing investigations are targeting mechanisms of learning to recognize individual sounds, such as when a sound is initially unrecognizable but is subsequently categorized upon its repetition or further rendered identifiable at a finer semantic scale.

Learning-induced plasticity in temporal representations were first evident around 60 ms post-stimulus onset and involved modifications both in the lateralization pattern from bilateral to left posterior sylvian regions and in the functional coupling between the hemispheres. The latency of our effect is consistent with modifications during the initial stages of auditory processing, rather than changes in higher-level functions or representations of the sound sources. Future investigations will focus on isolating processes of temporal discrimination by introducing paradigmatic changes such that the first and second sounds differ in other acoustic features aside from their spatial location. Such will provide insights on the extent to which temporal processing (and learning thereof) is independent of the acoustic features defining the temporal separation between events.

Neuroplastic changes in auditory spatial representations or the ability to accurately discriminate spatial representations occurred over several time periods throughout the 70–250 ms post-stimulus interval. In all instances, however, modulations manifested as changes in the topography of the electric field at the scalp and by extension the configuration of intracranial sources. This indicates that spatial representations at a population level are subject to plasticity, which is consistent within current models of spatial encoding of sounds. While we have emphasized population-level modulations, it is likely also the case that effects are occurring at a finer spatial (and mechanistic) scale that what is currently possible with non-invasive techniques in humans. In addition to general spatial encoding, we also demonstrated that relative and absolute spatial representations of sound sources can be differentiated both in time and in terms of the principal brain regions implicated, including hemispheric dominance. Relative locations appear to be differentiated within supratemporal regions at earlier latencies than absolute locations within parietal structures. However, the reader should note that there is also clear evidence for the (near) simultaneous responsiveness of these regions to sounds in general. As such, we by no means wish to give the impression that parietal and supratemporal structures are responding in a strictly serial manner. Still, differential involvement and encoding of relative and absolute spatial positions would appear to manifest at over multiple periods and brain regions. Additionally, the right hemisphere would appear to contain a representation of the whole of auditory space, whereas the representation in the left hemisphere would appear to be largely restricted to the contralateral space. Determining how these subvarieties of spatial representations are rendered plastic will be an important direction for future research.

Acknowledgements

This work has been supported by grants from the Swiss National Science Foundation (K-33K1_122518/1 to MDL; 3100AO-103895 to SC; 3100AO-118419 to MMM), a grant from the Pierre Mercier Foundation for Science (to LS and JG), and an inter-disciplinary grant from the Faculty of Biology and Medicine of the Centre Hospitalier Universitaire Vaudois and University of Lausanne (to LS and JG). Analyses of EEG data were performed using the Cartool software (http://brainmapping.unige.ch/cartool.htm) which is developed by Denis Brunet from the Functional Brain Mapping Laboratory, Geneva, Switzerland, and is supported by the EEG Brain Mapping Core of the Center for Biomedical Imaging (CIBM) of Geneva and Lausanne. MRI and fMRI data acquisition were supported by the Center for Biomedical Imaging (http://www.cibm.ch), The University of Lausanne; The Swiss Federal Institute of Technology, Lausanne; The University of Geneva; The University Hospital Center, Lausanne; The University Hospital of Geneva; and the Leenaards and the Jeantet Foundations.

References

Alain, C., Arnott, S.R., Hevenor, S., Graham, S., Grady, C.L., 2001. “What” and “where” in the human auditory system. Proc. Natl. Acad. Sci. USA 98, 12301–12306.

Alain, C., McDonald, K.L., Kovacevic, N., McIntosh, A.R., 2009. Spatiotemporal analysis of auditory “what” and “where” working memory. Cereb. Cortex 19, 305–314.

Altmann, C.F., Doehrmann, O., Kaiser, J., 2007. Selectivity for animal vocalizations in the human auditory cortex. Cereb. Cortex 17, 2601–2608.

Anderson, B., Southern, B.D., Powers, R.E., 1999. Anatomic asymmetries of the posterior superior temporal lobes: a postmortem study. Neuropsychiatry Neuropsychol Behav Neurol 12, 247–254.

Arnott, S.R., Binns, M.A., Grady, C.L., Alain, C., 2004. Assessing the auditory dual-pathway model in humans. Neuroimage 22, 401–408.

Assal, G., Aubert, C., Buttet, J., 1981. [Cerebral asymmetry and voice recognition (author’s transl)]. Rev. Neurol. (Paris) 137, 255–268.

Badgaiyan, R.D., Schacter, D.L., Alpert, N.M., 2001. Priming within and across modalities: exploring the nature of rCBF increases and decreases. Neuroimage 13, 272–282.

Belin, P., 2006. Voice processing in human and non-human primates. Philos. Trans. R. Soc. Lond. B Biol. Sci. 361, 2091–2107.

Bellmann, A., Meuli, R., Clarke, S., 2001. Two types of auditory neglect. Brain 124, 676–687.

Bentin, S., Taylor, M.J., Rousselet, G.A., Itier, R.J., Caldara, R., Schyns, P.G., Jacques, C., Rossion, B., 2007. Controlling interstimulus perceptual variance does not abolish N170 face sensitivity. Nat. Neurosci. 10, 801–802.

Bergerbest, D., Ghahremani, D.G., Gabrieli, J.D., 2004. Neural correlates of auditory repetition priming: reduced fMRI activation in the auditory cortex. J. Cogn. Neurosci. 16, 966–977.

Besle, J., Fischer, C., Bidet-Caulet, A., Lecaignard, F., Bertrand, O., Giard, M.H., 2008. Visual activation and audiovisual interactions in the auditory cortex during speech perception: intracranial recordings in humans. J. Neurosci. 28, 14301–14310.

Bernasconi, F., Grivel, J., Murray, M.M., Spierer, L., 2010a. Interhemispheric coupling between the posterior sylvian regions impacts successful auditory temporal order judgment. Neuropsychologia, in press.

Bernasconi, F., Grivel, J., Murray, M.M., Spierer, L., 2010b. Plastic brain mechanisms for attaining auditory temporal order judgment proficiency. Neuroimage 50, 1271–1279.

Bisiach, E., Cornacchia, L., Sterzi, R., Vallar, G., 1984. Disorders of perceived auditory lateralization after lesions of the right hemisphere. Brain 107, 37–52.

Bizley, J.K., Walker, K.M., Silverman, B.W., King, A.J., Schnupp, J.W., 2009. Interdependent encoding of pitch, timbre, and spatial location in auditory cortex. J. Neurosci. 29, 2064–2075.

Bourquin, N., Spierer, L., Murray, M.M., Clarke, S. Distinct neural networks keep track of often versus recently heard sound objects, in preparation.

Buckner, R.L., Koutstaal, W., Schacter, D.L., Rosen, B.R., 2000. Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming. Brain 123, 620–640.

Buonomano, D.V., Merzenich, M.M., 1998. Net interaction between different forms of short-term synaptic plasticity and slow-IPSPs in the hippocampus and auditory cortex. J. Neurophysiol. 80, 1765–1774.

Charest, I., Pernet, C.R., Rousselet, G.A., Quinones, I., Latinus, M., Fillion-Bilodeau, S., et al., 2009. Electrophysiological evidence for an early processing of human voices. BMC Neurosci. 10, 127.

Chiu, C.Y., 2000. Specificity of auditory implicit and explicit memory: is perceptual priming for environmental sounds exemplar specific? Mem. Cognit. 28, 1126–1139.

Clarke, S., Adriani, M., Bellmann, A., 1998. Distinct short-term memory systems for sound content and sound localization. Neuroreport 9, 3433–3437.

Clarke, S., Bellmann Thiran, A., Maeder, P., Adriani, M., Vernet, O., Regli, L., et al., 2002. What and where in human audition: selective deficits following focal hemispheric lesions. Exp. Brain Res. 147, 8–15.

Clarke, S., Bellmann, A., Meuli, R.A., Assal, G., Steck, A.J., 2000. Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. Neuropsychologia 38, 797–807.

Cohen, Y.E., Theunissen, F., Russ, B.E., Gill, P., 2007. Acoustic features of rhesus vocalizations and their representation in the ventrolateral prefrontal cortex. J. Neurophysiol. 97, 1470–1484.

Davis, B., Christie, J., Rorden, C., 2009. Temporal order judgments activate temporal parietal junction. J. Neurosci. 29, 3182–3188.

De Lucia, M., Camen, C., Clarke, S., Murray, M.M., 2009a. The role of actions in auditory object discrimination. Neuroimage 48, 475–485.

De Lucia, M., Cocchi, L., Martuzzi, R., Meuli, R.A., Clarke, S., Murray, M.M., 2009b. Perceptual and semantic contributions to repetition priming of environmental sounds. Cereb Cortex.

De Lucia, M., Clarke, S., Murray, M.M., A temporal hierarchy for conspecific vocalization discrimination in humans, submitted for publication.

De Santis, L., Clarke, S., Murray, M.M., 2007. Automatic and intrinsic auditory “what” and “where” processing in humans revealed by electrical neuroimaging. Cereb. Cortex 17, 9–17.

Deouell, L.Y., Heller, A.S., Malach, R., D’Esposito, M., Knight, R.T., 2007. Cerebral responses to change in spatial location of unattended sounds. Neuron 55, 985–996.

Deouell, L.Y., Parnes, A., Pickard, N., Knight, R.T., 2006. Spatial location is accurately tracked by human auditory sensory memory: evidence from the mismatch negativity. Eur. J. Neurosci. 24, 1488–1494.

Desimone, R., 1996. Neural mechanisms for visual memory and their role in attention. Proc. Natl. Acad. Sci. USA 93, 13494–13499.

Ducommun, C.Y., Murray, M.M., Thut, G., Bellmann, A., Viaud-Delmon, I., Clarke, S., et al., 2002. Segregated processing of auditory motion and auditory location: an ERP mapping study. Neuroimage 16, 76–88.

Eagleman, D.M., 2008. Human time perception and its illusions. Curr. Opin. Neurobiol. 18, 131–136.

Edeline, J.M., Weinberger, N.M., 1993. Receptive field plasticity in the auditory cortex during frequency discrimination training: selective retuning independent of task difficulty. Behav. Neurosci. 107, 82–103.

Efron, R., Koss, B., Yund, E.W., 1983. Central auditory processing. IV. Ear dominance–spatial and temporal complexity. Brain Lang. 19, 264–282.

Engel, L.R., Frum, C., Puce, A., Walker, N.A., Lewis, J.W., 2009. Different categories of living and non-living sound-sources activate distinct cortical networks. Neuroimage 47, 1778–1791.

Fecteau, S., Armony, J.L., Joanette, Y., Belin, P., 2005. Sensitivity to voice in human prefrontal cortex. J. Neurophysiol. 94, 2251–2254.

Foxton, J.M., Weisz, N., Bauchet-Lecaignard, F., Delpuech, C., Bertrand, O., 2009. The neural bases underlying pitch processing difficulties. Neuroimage 45, 1305–1313.

Friston, K., 2005. A theory of cortical responses. Philos. Trans. R. Soc. Lond. B Biol. Sci. 360, 815–836.

Garrido, M.I., Kilner, J.M., Kiebel, S.J., Stephan, K.E., Baldeweg, T., Friston, K.J., 2009. Repetition suppression and plasticity in the human brain. Neuroimage 48, 269–279.

Ghazanfar, A.A., 2009. The multisensory roles for auditory cortex in primate vocal communication. Hear. Res. 258, 113–120.

Ghose, G.M., 2004. Learning in mammalian sensory cortex. Curr. Opin. Neurobiol. 14, 513–518.

Giard, M.H., Peronnet, F., 1999. Auditory-visual integration during multimodal object recognition in humans: a behavioral and electrophysiological study. J. Cogn. Neurosci. 11, 473–490.

Giard, M.H., Fort, A., Mouchetant-Rostaing, Y., Pernier, J., 2000. Neurophysiological mechanisms of auditory selective attention in humans. Front. Biosci. 5, D84–D94.

Griffiths, T.D., Rees, A., Witton, C., Cross, P.M., Shakir, R.A., Green, G.G., 1997. Spatial and temporal auditory processing deficits following right hemisphere infarction. A psychophysical study. Brain 120, 785–794.

Griffiths, T.D., Rees, A., Witton, C., Shakir, R.A., Henning, G.B., Green, G.G., 1996. Evidence for a sound movement area in the human cerebral cortex. Nature 383, 425–427.

Grill-Spector, K., Henson, R.N., Martin, A., 2006. Repetition and the brain, neural models of stimulus-specific effects. Trends Cogn. Sci. 10, 14–23.

Gunji, A., Koyama, S., Ishii, R., Levy, D., Okamoto, H., Kakigi, R., et al., 2003. Magnetoencephalographic study of the cortical activity elicited by human voice. Neurosci. Lett. 348, 13–16.

Hackett, T.A., Stepniewska, I., Kaas, J.H., 1999. Callosal connections of the parabelt auditory cortex in macaque monkeys. Eur. J. Neurosci. 11, 856–866.

Hauk, O., Shtyrov, Y., Pulvermuller, F., 2006. The sound of actions as reflected by mismatch negativity: rapid activation of cortical sensory-motor networks by sounds associated with finger and tongue movements. Eur. J. Neurosci. 23, 811–821.

Hauptmann, B., Karni, A., 2002. From primed to learn: the saturation of repetition priming and the induction of long-term memory. Brain Res. Cogn. Brain Res. 13, 313–322.

Heffner, H.E., Heffner, R.S., 1990. Effect of bilateral auditory cortex lesions on sound localization in Japanese macaques. J. Neurophysiol. 64, 915–931.

Herrmann, C.S., Senkowski, D., Maess, B., Friederici, A.D., 2002. Spatial versus object feature processing in human auditory cortex: a magnetoencephalographic study. Neurosci. Lett. 334, 37–40.

Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nat. Rev. Neurosci. 8, 393–402.

Hirsh, I.J., 1959. Auditory perception of temporal order. J. Acoust. Soc. Am. 31, 759–767.

Inui, K., Okamoto, H., Miki, K., Gunji, A., Kakigi, R., 2006. Serial and parallel processing in the human auditory cortex: a magnetoencephalographic study. Cereb. Cortex 16, 18–30.

Javitt, D.C., Steinschneider, M., Schroeder, C.E., Arezzo, J.C., 1996. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc. Natl. Acad. Sci. USA 93, 11962–11967.

Javitt, D.C., 2009. Sensory processing in schizophrenia: neither simple nor intact. Schizophr Bull. 35, 1059–1064.

Jenkins, W.M., Masterton, R.B., 1982. Sound localization: effects of unilateral lesions in central auditory system. J. Neurophysiol. 47, 987–1016.

Kaas, J.H., Hackett, T.A., 2000. Subdivisions of auditory cortex and processing streams in primates. Proc. Natl. Acad. Sci. USA 97, 11793–11799.

Kaiser, J., Lutzenberger, W., 2001. Location changes enhance hemispheric asymmetry of magnetic fields evoked by lateralized sounds in humans. Neurosci. Lett. 314, 17–20.

Keysers, C., Kohler, E., Umilta, M.A., Nanetti, L., Fogassi, L., Gallese, V., 2003. Audiovisual mirror neurons and action recognition. Exp. Brain Res. 153, 628–636.

King, A.J., Bajo, V.M., Bizley, J.K., Campbell, R.A., Nodal, F.R., Schulz, A.L., et al., 2007. Physiological and behavioral studies of spatial coding in the auditory cortex. Hear. Res. 229, 106–115.

Kisley, M.A., Noecker, T.L., Guinther, P.M., 2004. Comparison of sensory gating to mismatch negativity and self-reported perceptual phenomena in healthy adults. Psychophysiology 41, 604–612.

Kohler, E., Keysers, C., Umilta, M.A., Fogassi, L., Gallese, V., Rizzolatti, G., 2002. Hearing sounds, understanding actions: action representation in mirror neurons. Science 297, 846–848.

Kraus, N., Nicol, T., 2005. Brainstem origins for cortical 'what' and 'where' pathways in the auditory system. Trends Neurosci. 28, 176–181.

Krumbholz, K., Hewson-Stoate, N., Schönwiesner, M., 2007. Cortical response to auditory motion suggests an asymmetry in the reliance on inter-hemispheric connections between the left and right auditory cortices. J. Neurophysiol. 97, 1649–1655.

Krumbholz, K., Schonwiesner, M., von Cramon, D.Y., Rubsamen, R., Shah, N.J., Zilles, K., et al., 2005. Representation of interaural temporal information from left and right auditory space in the human planum temporale and inferior parietal lobe. Cereb. Cortex 15, 317–324.

Lavoie, S., Murray, M.M., Deppen, P., Knyazeva, M.G., Berk, M., Boulat, O., Bovet, P., Bush, A.I., Conus, P., Copolov, D., Fornari, E., Meuli, R., Solida, A., Vianin, P., Cuénod, M., Buclin, T., Do, K.Q., 2008. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 33, 2187–2199.

Legenstein, R., Naeger, C., Maass, W., 2005. What can a neuron learn with spike-timing-dependent plasticity? Neural Comput. 17, 2337–2382.

Levy, D.A., Granot, R., Bentin, S., 2001. Processing specificity for human voice stimuli: electrophysiological evidence. Neuroreport 12, 2653–2657.

Levy, D.A., Granot, R., Bentin, S., 2003. Neural sensitivity to human voices: ERP evidence of task and attentional influences. Psychophysiology 40, 291–305.

Lewald, J., Foltys, H., Topper, R., 2002. Role of the posterior parietal cortex in spatial hearing. J. Neurosci. 22, RC207.

Lewald, J., Meister, I.G., Weidemann, J., Topper, R., 2004a. Involvement of the superior temporal cortex and the occipital cortex in spatial hearing: evidence from repetitive transcranial magnetic stimulation. J. Cogn. Neurosci. 16, 828–838.

Lewald, J., Wienemann, M., Boroojerdi, B., 2004b. Shift in sound localization induced by rTMS of the posterior parietal lobe. Neuropsychologia 42, 1598–1607.

Lewis, J.W., Brefczynski, J.A., Phinney, R.E., Janik, J.J., DeYoe, E.A., 2005. Distinct cortical pathways for processing tool versus animal sounds. J. Neurosci. 25, 5148–5158.

Li, R.W., Levi, D.M., Klein, S.A., 2004. Perceptual learning improves efficiency by re-tuning the decision 'template' for position discrimination. Nat. Neurosci. 7, 178–183.

Liegeois-Chauvel, C., Musolino, A., Badier, J.M., Marquis, P., Chauvel, P., 1994. Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. Electroencephalogr. Clin. Neurophysiol. 92, 204–214.

Lomber, S.G., Malhotra, S., 2008. Double dissociation of 'what' and 'where' processing in auditory cortex. Nat. Neurosci. 11, 609–616.

Luck, S.J., Woodman, G.F., Vogel, E.K., 2000. Event-related potential studies of attention. Trends Cogn. Sci. 4, 432–440.

Maeder, P.P., Meuli, R.A., Adriani, M., Bellmann, A., Fornari, E., Thiran, J.P., et al., 2001. Distinct pathways involved in sound recognition and localization: a human fMRI study. Neuroimage 14, 802–816.

Mauk, M.D., Buonomano, D.V., 2004. The neural basis of temporal processing. Ann. Rev. Neurosci. 27, 307–340.

May, P.J., Tiitinen, H., 2009. Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. Psychophysiology. doi:10.1111/j.1469-8986.2009.00856.x.

Mazzoni, P., Bracewell, R.M., Barash, S., Andersen, R.A., 1996. Spatially tuned auditory responses in area LIP of macaques performing delayed memory saccades to acoustic targets. J. Neurophysiol. 75, 1233–1241.

McDonald, J.J., Teder-Salejarvi, W.A., Di Russo, F., Hillyard, S.A., 2005. Neural basis of auditory-induced shifts in visual time-order perception. Nat. Neurosci. 8, 1197–1202.

Michel, C.M., Murray, M.M., Lantz, G., Gonzalez, S., Spinelli, L., Grave de Peralta, R., 2004. EEG source imaging. Clin. Neurophysiol. 115, 2195–2222.

Middlebrooks, J.C., 2002. Auditory space processing: here, there or everywhere? Nat. Neurosci 5, 824–826.

Molholm, S., Ritter, W., Murray, M.M., Javitt, D.C., Schroeder, C.E., Foxe, J.J., 2002. Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. Brain Res. Cogn. Brain Res. 14, 115–128.

Morosan, P., Rademacher, J., Schleicher, A., Amunts, K., Schormann, T., Zilles, K., 2001. Human primary auditory cortex: cytoarchitectonic subdivisions and mapping into a spatial reference system. Neuroimage 13, 684–701.

Mossbridge, J.A., Fitzgerald, M.B., O'Connor, E.S., Wright, B.A., 2006. Perceptual-learning evidence for separate processing of asynchrony and order tasks. J. Neurosci. 26, 12,708–12,716.

Mossbridge, J.A., Scissors, B.N., Wright, B.A., 2008. Learning and generalization on asynchrony and order tasks at sound offset: implications for underlying neural circuitry. Learn Mem. 15, 13–20.

Murray, M.M., Camen, C., Gonzalez Andino, S.L., Bovet, P., Clarke, S., 2006. Rapid brain discrimination of sounds of objects. J. Neurosci. 26, 1293–1302.

Murray, M.M., Brunet, D., Michel, C.M., 2008a. Topographic ERP analyses: a step-by-step tutorial review. Brain Topogr. 20, 249–264.

Murray, M.M., Camen, C., Spierer, L., Clarke, S., 2008b. Plasticity in representations of environmental sounds revealed by electrical neuroimaging. Neuroimage 39, 847–856.

Murray, M.M., Spierer, L., 2009. Auditory spatio-temporal brain dynamics and their consequences for multisensory interactions in humans. Hear Res. 258, 121–133.

Näätänen, R., Jacobsen, T., Winkler, I., 2005. Memory-based or afferent processes in mismatch negativity (MMN): a review of the evidence. Psychophysiology 42, 25–32.

Näätänen, R., Paavilainen, P., Rinne, T., Alho, K., 2007. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin. Neurophysiol. 118, 2544–2590.

Ohl, F.W., Scheich, H., Freeman, W.J., 2001. Change in pattern of ongoing cortical activity with auditory category learning. Nature 412, 733–736.

Ohl, F.W., Scheich, H., 2005. Learning-induced plasticity in animal and human auditory cortex. Curr. Opin. Neurobiol. 15, 470–477.

Palmer, A.R., King, A.J., 1982. The representation of auditory space in the mammalian superior colliculus. Nature 299, 248–249.

Pelizzone, M., Hari, R., Makela, J.P., Huttunen, J., Ahlfors, S., Hamalainen, M., 1987. Cortical origin of middle-latency auditory evoked responses in man. Neurosci. Lett. 82, 303–307.

Petkov, C.I., Kayser, C., Steudel, T., Whittingstall, K., Augath, M., Logothetis, N.K., 2008. A voice region in the monkey brain. Nat. Neurosci. 11, 367–374.

Pinek, B., Duhamel, J.R., Cave, C., Brouchon, M., 1989. Audio-spatial deficits in humans: differential effects associated with left versus right hemisphere parietal damage. Cortex 25, 175–186.

Pöppel, E., 1988. Mindworks. Time and Conscious Experience. Harcourt, Brace, Jovanovich, Boston.

Poremba, A., Malloy, M., Saunders, R.C., Carson, R.E., Herscovitch, P., Mishkin, M., 2004. Species-specific calls evoke asymmetric activity in the monkey's temporal poles. Nature 427, 448–451.

Rainer, G., Lee, H., Logothetis, N.K., 2004. The effect of learning on the function of monkey extrastriate visual cortex. PLoS Biol. 2, E44.

Rauschecker, J.P., Tian, B., Pons, T., Mishkin, M., 1997. Serial and parallel processing in rhesus monkey auditory cortex. J. Comp. Neurol. 382, 89–103.

Rauschecker, J.P., 1998. Cortical processing of complex sounds. Curr. Opin. Neurobiol. 8, 516–521.

Recanzone, G.H., Schreiner, C.E., Merzenich, M.M., 1993. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J. Neurosci. 13, 87–103.

Recanzone, G.H., Guard, D.C., Phan, M.L., Su, T.K., 2000. Correlation between the activity of single auditory cortical neurons and sound-localization behavior in the macaque monkey. J. Neurophysiol. 83, 2723–2739.

Remedios, R., Logothetis, N.K., Kayser, C., 2009. An auditory region in the primate insular cortex responding preferentially to vocal communication sounds. J. Neurosci. 29, 1034–1045.

Rivier, F., Clarke, S., 1997. Cytochrome oxidase, acetylcholinesterase, and NADPH-diaphorase staining in human supratemporal and insular cortex: evidence for multiple auditory areas. Neuroimage 6, 288–304.

Rizzolatti, G., Fogassi, L., Gallese, V., 2002. Motor and cognitive functions of the ventral premotor cortex. Curr. Opin. Neurobiol. 12, 149–154.

Romanski, L.M., Goldman-Rakic, P.S., 2002. An auditory domain in primate prefrontal cortex. Nat. Neurosci. 5, 15–16.

Romanski, L.M., Tian, B., Fritz, J.B., Mishkin, M., Goldman-Rakic, P.S., Rauschecker, J.P., 1999. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. Nat. Neurosci. 2, 1131–1136.

Romei, V., Murray, M.M., Merabet, L.B., Thut, G., 2007. Occipital transcranial magnetic stimulation has opposing effects on visual and auditory stimulus detection: implications for multisensory interactions. J. Neurosci. 27, 11465–11472.

Romei, V., Murray, M.M., Cappe, C., Thut, G., 2009. Auditory spatial deficits in the personal and extrapersonal frames of reference due to cortical lesions. Curr. Biol. 19, 1799–1805.

Ruff, R.M., Hersh, N.A., Pribram, K.H., 1981. Auditory spatial deficits in the personal and extrapersonal frames of reference due to cortical lesions. Neuropsychologia 19, 435–443.

Salminen, N.H., May, P.J., Alku, P., Tiitinen, H., 2009. A population rate code of auditory space in the human cortex. PLoS One 4, e7600.

Sanchez-Longo, L.P., Forster, F.M., 1958. Clinical significance of impairment of sound localization. Neurology 8, 119–125.

Schacter, D.L., Dobbins, I.G., Schnyer, D.M., 2004. Specificity of priming: a cognitive neuroscience perspective. Nat. Rev. Neurosci. 5, 853–862.

Schroeder, C.E., Lakatos, P., Kajikawa, Y., Partan, S., Puce, A., 2008. Neuronal oscillations and visual amplification of speech. Trends Cogn. Sci. 12, 106–113.

Silveri, M.C., Gainotti, G., Perani, D., Cappelletti, J.Y., Carbone, G., Fazio, F., 1997. Naming deficit for non-living items: neuropsychological and PET study. Neuropsychologia 35, 359–367.

Song, S., Miller, K.D., Abbott, L.F., 2000. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat. Neurosci. 3, 919–926.

Sonnadara, R.R., Alain, C., Trainor, L.J., 2006. Occasional changes in sound location enhance middle latency evoked responses. Brain Res. 1076, 187–192.

Spierer, L., Bernasconi, F., Grivel, J., 2009a. The temporoparietal junction as a part of the "when" pathway. J. Neurosci. 29, 8630–8632.

Spierer, L., Bellmann-Thiran, A., Maeder, P., Murray, M.M., Clarke, S., 2009b. Hemispheric competence for auditory spatial representation. Brain 132, 1953–1966.

Spierer, L., Bourquin, N.M.-P., Tardif, E., Murray, M.M., Clarke, S., 2009c. Right hemispheric dominance for echo suppression. Neuropsychologia 47, 465–472.

Spierer, L., Murray, M.M., Tardif, E., Clarke, S., 2008a. The path to success in auditory spatial discrimination: electrical neuroimaging responses within the supratemporal plane predict performance outcome. Neuroimage 41, 493–503.

Spierer, L., Tardif, E., Sperdin, H., Murray, M.M., Clarke, S., 2008b. Learning-induced plasticity in auditory spatial representations revealed by electrical neuroimaging. J. Neurosci. 27, 5474–5483.

Staeren, N., Renvall, H., De, M.F., Goebel, R., Formisano, E., 2009. Sound categories are represented as distributed patterns in the human auditory cortex. Curr. Biol. 19, 498–502.

Stecker, G.C., Harrington, I.A., Middlebrooks, J.C., 2005. Location coding by opponent neural populations in the auditory cortex. PLoS Biol. 3, e78.

Stelmach, L.B., Herdman, C.M., 1991. Directed attention and perception of temporal order. J. Exp. Psychol. Hum. Percept. Perform. 17, 539–550.

Stricanne, B., Andersen, R.A., Mazzoni, P., 1996. Eye-centered, head-centered, and intermediate coding of remembered sound locations in area LIP. J. Neurophysiol. 76, 2071–2076.

Stuart, G.P., Jones, D.M., 1995. Priming the identification of environmental sounds. Q. J. Exp. Psychol. A 48, 741–761.

Tanaka, H., Hachisuka, K., Ogata, H., 1999. Sound lateralisation in patients with left or right cerebral hemispheric lesions: relation with unilateral visuospatial neglect. J. Neurol. Neurosurg. Psychiatry 67, 481–486.

Tardif, E., Murray, M.M., Meylan, R., Spierer, L., Clarke, S., 2006. The spatio-temporal brain dynamics of processing and integrating sound localization cues in humans. Brain Res. 1092, 161–176.

Tata, M.S., Ward, L.M., 2005. Early phase of spatial mismatch negativity is localized to a posterior “where” auditory pathway. Exp. Brain Res. 167, 481–486.

Tian, B., Reser, D., Durham, A., Kustov, A., Rauschecker, J.P., 2001. Functional specialization in rhesus monkey auditory cortex. Science 292, 290–293.

Titchener, E.B., 1908. Lectures on the Elementary Psychology of Feeling and Attention. Macmillan, New York.

Tulving, E., Schacter, D.L., 1990. Priming and human memory systems. Science 247, 301–306.

Ulrich, R., 1987. Threshold models of temporal-order judgments evaluated by a ternary response task. Percept. Psychophys. 42, 224–239.

Ulanovsky, N., Las, L., Nelken, I., 2003. Processing of low-probability sounds by cortical neurons. Nat. Neurosci. 6, 391–398.

Ungerleider, L.G., Mishkin, M., 1982. Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. Behav. Brain Res. 6, 57–77.

Vallar, G., Guariglia, C., Nico, D., Bisiach, E., 1995. Spatial hemineglect in back space. Brain 118, 467–472.

Vibell, J., Klinge, C., Zampini, M., Spence, C., Nobre, A.C., 2007. Temporal order is coded temporally in the brain: early event-related potential latency shifts underlying prior entry in a cross-modal temporal order judgment task. J. Cogn. Neurosci. 19, 109–120.

Wallace, M.N., Johnston, P.W., Palmer, A.R., 2002. Histochemical identification of cortical areas in the auditory region of the human brain. Exp. Brain Res. 143, 499–508.

Warrington, E.K., Shallice, T., 1984. Category specific semantic impairments. Brain 107, 829–854.

Warren, J.D., Griffiths, T.D., 2003. Distinct mechanisms for processing spatial sequences and pitch sequences in the human auditory brain. J. Neurosci. 23, 5799–5804.

Weeks, R.A., Aziz-Sultan, A., Bushara, K.O., Tian, B., Wessinger, C.M., Dang, N., et al., 1999. A PET study of human auditory spatial processing. Neurosci. Lett. 262, 155–158.

Weinberger, N.M., 2004. Specific long-term memory traces in primary auditory cortex. Nat. Rev. Neurosci. 5, 279–290.

Werner-Reiss, U., Groh, J.M., 2008. A rate code for sound azimuth in monkey auditory cortex: implications for human neuroimaging studies. J. Neurosci. 28, 3747–3758.

Westerhausen, R., Grüner, R., Specht, K., Hugdahl, K., 2009. Functional relevance of interindividual differences in temporal lobe callosal pathways: a DTI tractography study. Cereb. Cortex 19, 1322–1339.

Wittmann, M., Burtscher, A., Fries, W., von Steinbüchel, N., 2004. Effects of brain-lesion size and location on temporal-order judgment. Neuroreport 15, 2401–2405.

Woods, T.M., Lopez, S.E., Long, J.H., Rahman, J.E., Recanzone, G.H., 2006. Effects of stimulus azimuth and intensity on the single-neuron activity in the auditory cortex of the alert macaque monkey. J. Neurophysiol. 96, 3323–3337.

Zaehle, T., Jancke, L., Herrmann, C.S., Meyer, M., 2009. Pre-attentive spectro-temporal feature processing in the human auditory system. Brain Topogr. 22, 97–108.

Zatorre, R.J., Mondor, T.A., Evans, A.C., 1999. Auditory attention to space and frequency activates similar cerebral systems. Neuroimage 10, 544–554.

Zatorre, R.J., Penhune, V.B., 2001. Spatial localization after excision of human auditory cortex. J. Neurosci. 21, 6321–6328.

Zatorre, R.J., Bouffard, M., Ahad, P., Belin, P., 2002. Where is ‘where’ in the human auditory cortex? Nat. Neurosci. 5, 905–909.

Zimmer, U., Lewald, J., Karnath, H.O., 2003. Disturbed sound lateralization in patients with spatial neglect. J. Cogn. Neurosci. 15, 694–703.