Review

Auditory spatio-temporal brain dynamics and their consequences for multisensory interactions in humans

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ABSTRACT

Recent multisensory research has emphasized the occurrence of early, low-level interactions in humans. As such, it is proving increasingly necessary to also consider the kinds of information likely extracted from the unisensory signals that are available at the time and location of these interaction effects. This review addresses current evidence regarding how the spatio-temporal brain dynamics of auditory information processing likely curtails the information content of multisensory interactions observable in humans at a given latency and within a given brain region. First, we consider the time course of signal propagation as a limitation on when auditory information (of any kind) can impact the responsiveness of a given brain region. Next, we overview the dual pathway model for the treatment of auditory spatial and object information ranging from rudimentary to complex environmental stimuli. These dual pathways are considered an intrinsic feature of auditory information processing, which are not only partially distinct in their associated brain networks, but also (and perhaps more importantly) manifest only after several tens of milliseconds of cortical signal processing. This architecture of auditory functioning would thus pose a constraint on when and in which brain regions specific spatial and object information are available for multisensory interactions. We then separately consider evidence regarding mechanisms and dynamics of spatial and object processing with a particular emphasis on when discriminations along either dimension are likely performed by specific brain regions. We conclude by discussing open issues and directions for future research.

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1. Introduction

It is increasingly acknowledged that multisensory interactions are a fundamental component of human brain organization, such that multisensory phenomena can be observed both early in time after a stimulus is presented and also within lower-tier levels of cortical anatomic hierarchies, including primary cortices. Anatomic tracing studies have revealed direct projections to visual areas V1 and V2 from primary (Falchier et al., 2002) as well as association areas (Falchier et al., 2002; Rockland and Ojima, 2003; Cappe and Barone, 2005) of macaque auditory cortex. Others have not only observed similar patterns of projections from somatosensory (Fu et al., 2003; Hackett et al., 2007) and visual systems (Schroeder and Foxe, 2002) that terminate in belt and parabelt auditory association areas, but also describe the laminar activation profile of

multisensory convergence in these auditory regions as consistent with feedforward inputs (Schroeder et al., 2001, 2003; Schroeder and Foxe, 2002). More recent evidence highlights the role of thalamic structures, in particular the pulvinar, as a potential substrate and/or relay for multisensory interactions (Cappe et al., 2009). Thus, in non-human primates, the initial stages of sensory processing can already have access to information from other sensory modalities.

In strong agreement are the repeated observations in humans of non-linear neural response interactions within the initial 100 ms post-stimulus onset (Giard and Peronnet, 1999; Foxe et al., 2000; Molholm et al., 2002; Lutkenhoner et al., 2002; Fort et al., 2002a,b; Gobbele et al., 2003; see also Murray et al., 2004, 2005a; Gonzalez Andino et al., 2005) and/or within brain regions traditionally held to be 'unisensory' in their function (e.g. Macaluso et al., 2002; Calvert, 2001; Foxe et al., 2002; Murray et al., 2004, 2005a,b; Martuzzi et al., 2007; Meylan and Murray, 2007; see also Ghazanfar et al., 2005; Kayser et al., 2005, 2007 for recent functional evidence from non-human primates). Such findings have on the one hand led to a revised model of the organization of

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sensory integration (Wallace et al., 2004) and on the other hand to a reconsideration of unisensory processing. That is, unisensory functions are likely not conducted in isolation, but rather can be influenced by (and perhaps also subject to) ongoing responses driven by stimulation of other sensory modalities (and vice versa).

Despite such evidence, the specific kinds of information either shared and/or integrated between the senses remain largely unknown, particularly in humans. This is in part because the overwhelming majority of the abovementioned studies that examined the latency of effects involved the presentation of rudimentary stimuli (i.e. flashes, tones, vibrations, etc.), rather than ethologically relevant complex stimuli, though this is now increasingly the case. In this review, we consider how the spatio-temporal dynamics of unisensory auditory processes might constrain and provide testable hypotheses for the kinds of information available for multisensory interactions at a given post-stimulus latency or in a particular cortical region. In particular, we focus on spatial and discrimination processes of rudimentary and complex environmental sounds of objects.[1]

2. Auditory response propagation

One important consideration in multisensory research is the propagation of neural responses throughout cortical (and subcortical) regions. Such temporal information constrains *when* stimulus-driven brain activity can contribute to multisensory phenomena. In the case of audition, human intracranial recordings have documented robust local field activity within the primary auditory cortices at ~15–20 ms post-stimulus onset in response to rudimentary stimuli, including clicks and tone bursts (e.g. Liegeois-Chauvel et al., 1994; Howard et al., 2000; Godey et al., 2001; Brugge et al., 2003). 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; Molholm et al., 2006; De Santis et al., 2007a; Spierer et al., 2007a), complex environmental sounds (Murray et al., 2006), and speech (Besle et al., 2008). Others suggest there to be responses in visual cortices 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). Such rapid and widespread activity is indeed consistent with predictions based on anatomical studies in humans (Rivier and Clarke, 1997; Tardif and Clarke, 2001) as well as non-human primates (e.g. Romanski et al., 1999a,b; Kaas and Hackett, 2000) that place superior and middle temporal regions ~2–3 synapses from primary fields and frontal regions ~2–4 synapses from primary fields (cf. Fig. 1 of Kaas and Hackett, 2000). This is also evident in studies that have stimulated one region while recording from another, which can in turn be used to provide a sense of conversion from synaptic distance to temporal delay. For example, Howard et al. (2000) stimulated and recorded from Heschl's gyrus (considered the locale of the primary auditory cortices in humans) and a posterior lateral superior temporal region, which are believe to be reciprocally interconnected (e.g. Rivier and Clarke, 1997), in addition to each likely receiving direct thalamic inputs. Howard et al. (2000) showed there to be evoked potential responses in the posterior lateral superior temporal region just 2.5–3.0 ms after electrical stimulation of Heschl's gyrus.

Given this speed and diffuseness of auditory response propagation, multisensory effects involving auditory stimuli and observed to onset relatively early in time post-stimulus presentation (e.g. ~50 ms for both auditory–visual and auditory–somatosensory interactions between rudimentary stimuli) in humans need not be (and likely are not) restricted to low-level cortices, though multiple phases of interactions that continue to be observed for several hundreds of milliseconds have also been documented (e.g. Molholm et al., 2002). 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 (e.g. Schroeder and Foxe, 2002; Lakatos et al., 2007). Identifying, characterizing and mapping these effects will hopefully become a focus of increased research.

An additional consideration is that the above timing of auditory cortical responses would make it theoretically possible for auditory-driven responses to reach primary visual cortices prior to the arrival of visually-driven thalamo-cortical responses, which have been shown to onset in humans approximately 40–50 ms post-stimulus presentation (see e.g. Foxe and Simpson, 2002; Foxe et al., 2008 for examples of studies using event-related potentials or Schroeder et al., 1998 for an example of local field potential recordings in monkeys). Studies combining psychophysical measures with the application of single-pulse TMS provide some insights on this issue (Romei et al., 2007, submitted for publication; see also Ramos-Estebanez et al., 2007 for the case of somatosensory-driven effects in visual cortices). In these studies, phosphene perceptions induced by sub-threshold single TMS pulses over the occipital pole were enhanced by either auditory (Romei et al., 2007, submitted for publication) or somatosensory (Ramos-Estebanez et al., 2007) stimulation that preceded TMS stimulation by as little as 40 ms. Additional results show that reaction times to external auditory stimuli can be facilitated by single-pulse TMS applied over the occipital pole 60–90 ms after sound onset (Romei et al., 2007). Such results demonstrate the perceptual relevance of early-latency multisensory interactions within low-level visual cortices.

3. The dual pathway model

Sounds convey information both about what they signify/identify as well as about where they are located in space. Anatomical, neuropsychological, psychophysical, hemodynamic neuroimaging, and electrophysiological evidence suggest that these functions are likely mediated by specialized brain networks. The structural organization of auditory areas has been investigated both in humans (Rivier and Clarke, 1997; Clarke and Rivier, 1998; Morosan et al., 2001; Tardif and Clarke, 2001; Wallace et al., 2002; Chiry et al., 2003) and non-human primates (e.g. Kosaki et al., 1997; Kaas and Hackett, 2000) using anatomical, cytoarchitectonic, and immunohistochemical methods. These data support a parallel and hierarchical organization wherein (at least) two interconnected pathways originate in the primary (also termed "core") auditory cortex (and perhaps also subcortically; Rauschecker et al., 1997; Kraus and Nicol, 2005). One pathway projects from primary auditory cortex caudally along the superior temporal cortex and into 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., 1999a,b; Kaas and Hackett, 2000 for review).

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[1] We do not consider here the cases of either speech or other dynamic/moving stimuli in this review, though both are important lines of research (e.g. Senkowski et al., 2007; Maier et al., 2008; Cappe et al., 2009). One challenge with such varieties of stimuli is determining when the 'informative' portions of such dynamic stimuli are presented in either modality. In the case of speech, for example, the visual information of a particular articulation precedes the corresponding auditory information (see e.g. Munhall et al., 1996; van Wassenhove et al., 2005 for discussion).

Sound recognition and localization functions appear to map onto the abovementioned rostral–ventral and caudal–dorsal pathways, which has resulted in the use of the 'what' and 'where' pathway distinction previously described for the visual system (Ungerleider and Mishkin, 1982). While not the focus of the present review, we would be remiss to not mention that important distinctions between the auditory and visual systems have been noted. On the one hand, while the visual system encodes space retinotopically, the prevailing model of spatial functions in the auditory system emphasizes the role of population encoding (e.g. Werner-Reiss and Groh, 2008). On the other hand, while the primary visual cortex is a single anatomical structure, the primary auditory cortex can be subdivided into at least three sub-regions (e.g. Kaas and Hackett, 2000; Rivier and Clarke, 1997). Such notwithstanding, electrophysiological recordings from lateral belt areas in non-human primates indicate that anterior portions preferentially responded to specific vocalizations independent of their azimuthal position, caudal portions demonstrated such preferentiality to position independent of the specific vocalization (e.g. Tian et al., 2001; see also Rauschecker et al., 1997; Recanzone et al., 2000; Lomber and Malhotra, 2008; Bizley et al., 2009). It is worth mentioning, however, that this dichotomy was not absolute; subgroups of neurons in both regions demonstrated selectivity to both position and vocalization features (Tian et al., 2001). When coupled with the fact that the latency of the preferential responses was not reported (as well as with the limited spatial sampling of intracranial recordings), it becomes possible for these effects to be the consequence of selective processes elsewhere and/or earlier in time. This is further exacerbated by the fact that these effects were obtained in an anesthetized preparation in whom top-town, attention, and task-related effects are masked.

Data from humans generally supports a similar distinction between auditory 'what' and 'where' functional pathways (Clarke et al., 1998, 2000, 2002; Alain et al., 2001, 2009; Maeder et al., 2001; Warren and Griffiths, 2003; Arnott et al., 2004; Ahveninen et al., 2006; Viceic et al., 2006; De Santis et al., 2007a), with some notable exceptions (e.g. Zatorre et al., 1994, 1999; Weeks et al., 1999; Middlebrooks, 2002; Hall, 2003). 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). Such notwithstanding and of particular relevance to the subject of this review, there has been little consensus regarding the spatio-temporal dynamics of differential processing along these pathways and the impact of selective attention. Those studies using a delayed match-to-sample (DMS) task with noise bursts or tones obtained spatial vs. recognition differences either 300 ms following onset of the first stimulus of the pair (Alain et al., 2001) or 80–110 ms following onset of the second stimulus of the pair (Anourova et al., 2001). Using a target detection task with meaningful sounds presented at any of seven different simulated locations, Herrmann et al. (2002) estimated equivalent current dipole (ECD) locations from MEG recordings 120–160 ms post-stimulus onset. They found that ECD coordinates within the right hemisphere, but not the left, were more lateral in response to blocks of trials requiring location discrimination than to those requiring semantic discrimination. This was the opposite of Anourova et al. (2001), who observed that ECD coordinates were more medial for location discrimination than for pitch discrimination. Still others have restricted their analyses to the mismatch negativity derivation without directly comparing responses with spatial and pitch information (e.g. Schroger and Wolff, 1997; Ozaki et al., 2004; Näätänen et al., 2005 for review) or have focused instead on the conjunctive processing of pitch and location (e.g. Takegata et al., 2001) or

on differences between non-spatial auditory features such as pitch, intensity, and duration (e.g. Giard et al., 1995; Levanen et al., 1996).

Work from our group has addressed the spatio-temporal organization of auditory functions by comparing event-related potentials in response to acoustically identical rudimentary stimuli (band-pass filtered tones) under two contexts; one wherein the pitch varied and the other wherein the lateralization varied (induced using inter-aural time differences; ITD) (De Santis et al., 2007a). The development of this type of paradigm was meant to facilitate application in various clinical and developmental populations as well as in animal species for translational research. In addition, this paradigm allowed us to contrast responses to acoustically identical stimuli that simply varied across blocks in terms of the feature that was likely to modulate. We were particularly interested in determining not only when differential effects of spatial and pitch processing onset, but also whether any such effects followed from activity within truly distinct networks or rather from the degree of activity within a common set of brain regions. Beginning 100 ms post-stimulus onset, our electrical neuroimaging analyses (reviewed in Murray et al., 2008a) revealed that the electric field topography significantly differed between conditions, indicative of the recruitment of distinct intracranial generators. A distributed linear inverse solution and statistical analysis thereof revealed activations within superior temporal cortex and prefrontal cortex bilaterally that were common for both 'what' and 'where' conditions, as well as regions within the right temporo-parietal cortices that were selective for the 'where' condition. That these effects occurred during passive listening and while participants attended to the visual modality (i.e. to a muted film) supports the proposition that segregated 'what' and 'where' processing is an organizing principle in the auditory system that is not the simple result of attentional modulations that differentially affect recognition and spatial functions.[2] While effects were obtained with rudimentary stimuli and a passive listening paradigm, others have nearly simultaneously demonstrated there to be dissociable effects of selective attention on spatial and recognition functions with speech stimuli (phonemes) beginning ~100 ms post-stimulus onset that are likewise dissociable with regard to the regions in which the effects occur (Ahveninen et al., 2006). These collective results would therefore suggest that differential 'what' and 'where' processing onsets at a similar latency irrespective of whether the stimuli were rudimentary or more complex, whether the participants passively or actively listened, and whether they performed a discrimination of either the location or identity of the stimuli. However, more recently Alain et al. (2009) have proposed that top-down influences from attention and task-demands as well as the general differentiation of spatial and recognition information only manifest from roughly 200 ms post-stimulus onset onwards. These authors further claimed that this latency is indicative of the time required to extract identity and spatial information from environmental sounds; a claim which our own and others' data summarized in this review would sharply refute (see Sections 4 and 5, below).

With regard to multisensory interactions, these data would suggest that non-linear effects observed during the initial 50–100 ms post-stimulus either between audition and vision (e.g. Giard and Peronnet, 1999; Molholm et al., 2002) or between audition and touch (Foxe et al., 2000; Murray et al., 2005a,b; Gonzalez Andino et al., 2005; Sperdin et al., 2009) may not reflect integration

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[2] It is also worthwhile to mention that this what/where distinction is not absolute. Rather, there is evidence for interactions between these pathways (Tardif et al., 2008). Moreover, there is also evidence that what and where functional pathways may be further divisible, such that different binaural spatial cues may recruit separate, but interacting, brain networks (Tardif et al., 2006; Spierer et al., 2009), or that different subclasses of acoustic objects may be differentially routed (see Section 5, below).

involving specific auditory features. The reasoning is the following. The abovementioned studies provide evidence that the earliest discrimination of pitch and position contained within the same acoustic signals manifests at ~100 ms post-stimulus onset. A similar conclusion can likewise be garnered from studies using the mismatch negativity (MMN) as their dependent measure (e.g. Näätänen et al., 2007 for a recent review). In such studies, the MMN typically manifests at latencies >100 ms post-stimulus onset and is elicited by deviant stimuli defined (at a rudimentary level) by their pitch, duration, or location. By contrast, there is no evidence that the human auditory system differentially processes these features at earlier latencies, including latencies when nonlinear interactions involving sounds have been observed (i.e. 50–100 ms). By extension, then, these early non-linear effects would appear to be insensitive to variations in these acoustic features. In agreement, effects of auditory–visual spatial alignment on event-related potential indices of multisensory interactions have only been reported at latencies later than 100 ms (Teder-Sälejärvi et al., 2005). This is by no means to suggest that early non-linear effects will be unaffected by the stimulus tuning properties of individual neurons (to the extent that such can be reliably detected with scalp-recorded activity) or populations of neurons. For example, auditory–somatosensory interactions beginning at ~50 ms post-stimulus onset are modulated by whether the ipsilateral or contralateral hand was stimulated (Murray et al., 2005a; see also Fu et al., 2003 for evidence in non-human primates). More generally, identifying the necessary circumstances for inducing facilitative interactions can in turn provide insights into the likely organization of inputs onto structures (i.e. populations of neurons in the case of non-invasive studies in humans) contributing to multisensory integration (cf. Zampini et al., 2007; Tajadura-Jiménez et al., 2009).

4. Spatial processing of sounds

4.1. Spatial coding via population responses

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 remains unresolved, particularly in humans. In animals, spatiotopic representations have been identified in subcortical structures (Palmer and King, 1982; Middlebrooks and Knudsen, 1984), but thus far no equivalent representation has been identified in cortex. Instead, recent single-unit recordings within core, rostral, and caudal auditory fields along the superior temporal plane in macaque monkeys indicate that these neurons are responsive to the full 360° of azimuth, though the extent of spatial sensitivity of individual neurons was more limited in caudal fields (Woods et al., 2006). There is instead growing consensus 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). According to Stecker and colleagues, the spatial position of a sound is encoded by differences in the activity of these two sub-populations. This proposition receives empirical support from recordings in three different fields of cat auditory cortex (primary auditory cortex, posterior auditory field, and dorsal zone; Stecker et al., 2005). Such observations speak in favor a model of spatial representations based on the patterned activity of population responses (Middlebrooks et al., 1994, 2002 Middlebrooks, 2003; Stecker et al., 2003; Stecker and Middlebrooks, 2003). Additional support for such a model stems from several observations including: spatial

discrimination abilities exceed the spatial tuning properties of single neurons; the timing of neuronal activity can convey information about the position of sounds (Stecker et al., 2005; King et al., 2007); and population-level neuronal activity is a better predictor of spatial discrimination performance than that of single neurons (Furukawa et al., 2000; Recanzone et al., 2000).

4.2. Implications of population-based spatial encoding on the 'spatial rule' of multisensory integration

The extent to which auditory spatial information is encoded at a population-level rather than by single neurons has direct implications for the manner in which spatially-related multisensory interactions involving sounds likely manifest. In this regard, it is pertinent to recall two aspects of the 'spatial rule' described most notably in the works of Stein, Meredith, and Wallace (reviewed in Stein and Meredith, 1993). The first is that this rule is based on the responsiveness (viz. action potentials) of *individual* neurons, rather than a population response (or other varieties of neural activity, such as local field potentials). The second is that this rule is also based on neuronal receptive field properties (i.e. the location of excitatory zones) rather than the spatial position of stimuli in the external world (cf. Fig. 10.8 in Stein and Meredith, 1993). As such, it is likely to be the case that multisensory interactions involving auditory spatial information are instead constrained by spatial representations at a population or regional level. To the extent that this is indeed the case, it would be inaccurate to consider the abovementioned spatial rule to be violated when multisensory interactions are observed despite wide spatial separation between stimuli (Murray et al., 2005a; see also Zampini et al., 2007; Tajadura-Jiménez et al., 2009). Rather, such evidence provides information about how a given auditory region likely represents spatial information, particularly when neuroimaging data are available.

4.3. Relative vs. absolute spatial processing

In addition to the issue of how spatial information is encoded, it is important to also consider which spatial information is encoded at a given post-stimulus latency and within a given brain region. In particular, there appears to be interplay between temporal and parietal structures in the encoding of relative and absolute spatial information that unfolds over the initial ~300 ms post-stimulus onset (Fig. 1).

Activity within temporal as well as parietal cortices has been shown to impact spatial localization accuracy (humans: Griffiths et al., 1998; Bushara et al., 1999; Weeks et al., 1999; Maeder et al., 2001; Ducommun et al., 2002; Zimmer and Macaluso, 2005; Deouell et al., 2006, 2007; Sonnadara et al., 2006; Tardif et al., 2006; De Santis et al., 2007a; Spierer et al., 2007a,b; non-human primates: Mazzoni et al., 1996; Stricanne et al., 1996; Schlack et al., 2005). Neuropsychological studies of spatial functions have also shown that temporal (e.g. Clarke et al., 2000; Zatorre and Penhune, 2001; Spierer et al., 2009; see also Lewald et al., 2004a,b for evidence based on rTMS) and/or parietal lobe lesions (Ruff et al., 1981; Bisiach et al., 1984; Pinek et al., 1989; Vallar et al., 1995; Griffiths et al., 1996, 1997; Tanaka et al., 1999; Bellmann et al., 2001; Clarke et al., 2002; Zimmer et al., 2003; Spierer et al., 2009) led to impairments in sound localization. However, none of these previous studies directly related the activity within these regions with encoding accuracy and discrimination performance. Rather, this literature would suggest that along the dorso-lateral auditory spatial processing stream (i.e. 'where' stream), temporal and parietal regions are differentially involved in the sound localization process as their importance depends on the spatial tasks subjects perform (absolute or relative localization). Electrophysiological recordings in non-human primates sug-
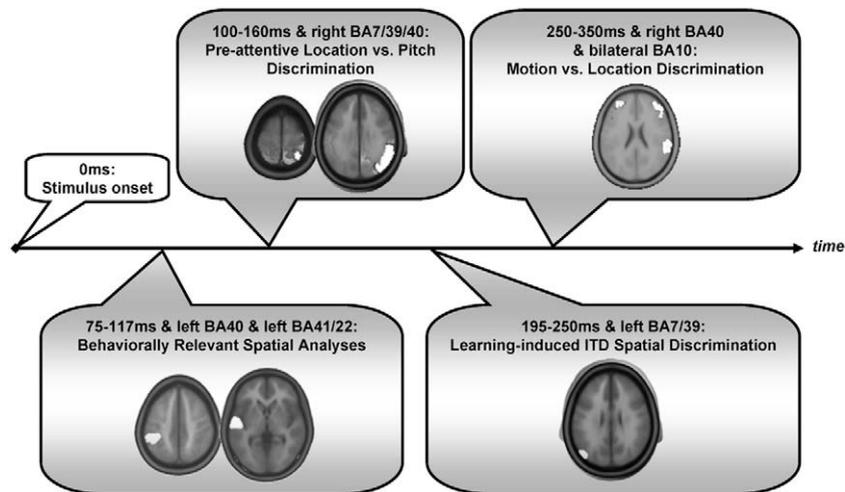
Fig. 1. Spatio-temporal dynamics of auditory spatial processes. This diagram summarizes the principal effects we have observed in our studies. For simplicity, we illustrate only the initial effects, though oftentimes subsequent effects were obtained.

gest that the posterior part of the supratemporal gyrus comprises an early representation of sound sources (Rauschecker, 1998; Kaas et al., 1999; Woods et al., 2006; Recanzone et al., 2000). 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), though the latency at which changes in location manifest are highly variable, ranging from ~100 to 250 ms (e.g. Sonnadara et al., 2006 for discussion).

4.3.1. The role of supratemporal structures

We recently confirmed 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 ~100 ms post-stimulus onset, indicative of changes in the configuration of the underlying intracranial sources preceding correct vs. incorrect spatial discriminations (Spierer et al., 2008; see also 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 (cf. Fig. 5 in Spierer et al., 2008). 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 with parietal cortices or elsewhere. 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.

Our electrical neuroimaging and neuropsychological data would suggest that more lateral regions of the supratemporal plane play a particularly important role in spatial functions within the initial 100 ms post-stimulus onset (see also Tardif et al., 2006

for an investigation of specific binaural cues and their interaction). It is worth mentioning that these supratemporal regions are also anterior to regions of the planum temporale implicated in the abovementioned prior studies (see also Zatorre and Penhune, 2001 for similar conclusions based on neuropsychological findings). While additional investigations will be necessary to further parse the functional roles (and timing) of regions within the superior temporal cortex, one possibility is that the lateral regions we have identified constitute an intermediate stage between responses in more medial (presumably primary cortices) and more posterior regions of the planum temporale (see Viceic et al., 2006).

4.3.2. The role of parietal structures

Following the initial analysis of auditory spatial information within the supratemporal plane, higher-order processing 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., 2007a,b). Data from non-human primates suggest that the posterior parietal cortex rather than the supratemporal plane is involved in high-level spatial processing (Rauschecker, 1998; Kaas et al., 1999). A PET 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 lateralization of perceived sound source position, whereas the acuity of position discrimination remained unaffected. A comparable shift in perceived sound lateralization can also be induced by repetitive TMS to the right occipital cortex (Lewald et al., 2004b), suggesting that the rTMS on the right posterior parietal cortex disrupts the integration of visual inputs and the transformation from auditory head-centered to visual eye-centered coordinates. Additional support for the role of parietal structures in the integration of auditory–visual coordinates comes from Collignon et al. (2008), who demonstrated that single-pulse TMS disrupts sound lateralization performance in a similar fashion, but earlier when applied to the occipital than to the posterior parietal cortex (50 ms vs. 150 ms post-stimulus onset).

Another line of evidence for the role of parietal structures in spatial analyses that involve absolute positions comes from our investigation of the spatio-temporal mechanisms whereby subjects learn to discriminate the position of sequentially presented pairs of sounds lateralized with inter-aural timing differences (ITDs). We demonstrated learning-induced modulations at

~200 ms post-stimulus onset within inferior parietal regions during a passive S1–S2 listening paradigm that was completed after participants had already achieved above-threshold sensitivity on a prior active discrimination task (Spierer et al., 2007a). Additionally, these effects were not explainable by generalization or the establishment of a spatial anchor or simple strengthening of representations of a given spatial position. Rather, these parietal effects likely followed from the engagement of a comparator mechanism, similar to that invoked to account for the MMN. More generally, our collective results would suggest that these modulations in parietal regions manifest only after the discrimination of the absolute positions of stimuli. Parietal regions would thus more likely comprise the transformation of spatial representations into coordinates and its consolidation of within egocentric and allocentric frames of reference (see also Karnath, 1997; Gentilucci et al., 1997; Mattingley et al., 1998; Bellmann et al., 2001), whereas temporal regions would be more involved in both absolute and relative localization as these two tasks require position encoding.

4.4. Hemispheric dominance for auditory spatial functions

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). We recently emphasized 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., 2009). Our results indicate that precise computation of contralateral spatial information occurs in the left hemisphere, while the right hemisphere is involved in the processing of the whole of auditory space. On the other hand, the building up of global auditory spatial representations relies 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, 2004; Herrmann et al., 2002; Lewald et al., 2002, Arnott, et al., 2004; De Santis et al., 2007a; Spierer et al., 2009), initial processing stages would appear to involve more the contralateral than the ipsilateral hemisphere.

4.5. General implications of auditory spatial processing on multisensory interactions

The results reviewed in this section highlight how (some) auditory spatial analyses unfold in time and space within the human cortex. First, we provided an overview of current models of spatial encoding of sounds in general, which are based on population-level responses rather than tuning profiles of individual neurons. The impact of this framework on multisensory interactions is significant on multiple levels. Spatial encoding mechanisms in the auditory system would appear to be highly distinct from that in the visual (retinotopic) or somatosensory (spatiotopic) system (see also Werner-Reiss and Groh, 2008).[3] As detailed above, different auditory spatial positions are likely encoded by the same cell ensem-

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[3] Such is not to discount the spatial maps that are observable within the superior colliculus. Rather, we here refer implicitly to the cortical representations of auditory spatial information.

bles that vary their response profiles. Consequently, multisensory interactions involving specific auditory spatial information are unlikely to be the product of rapid, feedforward, and sensory-driven input. Rather, at least minimal processing within the auditory system itself is likely required in order to establish relative and absolute spatial representations that would be affected by multisensory interactions. Likewise, because spatial information is likely represented by populations of neurons rather than by single cells, multisensory phenomena involving acoustic spatial features are unlikely to be directly analogous to effects observed at the single-cell level and used to generate the "spatial rule" (Stein and Meredith, 1993).

In addition to general spatial encoding, this section also summarized results differentiating relative from absolute spatial representations of sound sources both in time and in terms of the principal brain regions implicated, including hemispheric dominance. Relative locations appear to be differentiated within supra-temporal 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 (see Section 2, above). 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. One implication of these data for multisensory phenomena is that depending on the latency and brain region, distinct varieties of spatial representations are likely available for integration with other sensory representations and are susceptible to impairments following brain damage (see e.g. Pavani et al., 2003; Spierer et al., 2007b for examples of multisensory neglect). Along these lines, it is interesting to note that effects of spatial attention on multisensory interactions appear unfold over several stages (Talsma and Woldorff, 2005). It may thus be the case that these different temporal stages reflect the integration of distinct spatial representations ranging from relative to absolute as well as varying in their reference frames. Detailing the extent to which this is the case will require continued research. Similarly, it will be of value for both basic and clinical research to determine the precise stage(s) as which multisensory interactions impact unisensory auditory spatial representations. For example, it may be possible to enhance learning effects and/or discrimination performance with complementary (and perhaps task-irrelevant) visual information (e.g. Tardif et al., 2008 for task-irrelevant interactions between near-threshold spatial and pitch information).

5. Recognition and discrimination of environmental sounds

As mentioned in Section 3, a sound object recognition network within the superior and middle temporal cortices that extends into the inferior (pre)frontal cortex has been proposed based on evidence from neuropsychology (e.g. Engelien et al., 1995; Vignolo, 1982, 2003; Fujii et al., 1990; Schnider et al., 1994; Clarke et al., 1996, 2000, 2002), animal electrophysiology (Romanski et al., 1999a,b; Tian et al., 2001; Cohen et al., 2006; Recanzone, 2008), hemodynamic brain imaging in humans (e.g. Belin et al., 2000; Maeder et al., 2001; Arnott et al., 2004; Bergerbest et al., 2004; Binder et al., 2004; Lewis et al., 2004, 2005; Rama et al., 2004; Zatorre et al., 2004; Engelien et al., 2006; Altmann et al., 2008; von Kriegstein et al., 2007; Doehrmann et al., 2008), and more recently hemodynamic imaging in non-human primates (Poremba et al., 2004; Petkov et al., 2008).

Despite such evidence concerning the brain regions involved in auditory object processing, there is comparatively sparse evidence regarding their temporal dynamics. Such information is essential for determining both when and during which processing steps different brain areas become active (Michel et al., 2004). In turn, this can assist in differentiating feedforward from feedback as well as sequential from parallel activity (Schroeder et al., 1998). Using electrical neuroimaging, we have identified the speed and locus of varieties of auditory object discriminations in order to construct a timeline of these processes (Fig. 2).

5.1. Categorical discrimination

We first examined the speed with which and likely neurophysiologic mechanism by which acoustically and psychophysically controlled sounds of living and man-made objects are initially discriminated (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 with posterior middle temporal regions of the right hemisphere (BA21/22), 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). Bilateral sources within the posterior portion of the superior and middle temporal cortices as well as premotor cortices were subsequently active (155–257 ms) in response to both categories of sounds, although with different durations. Additionally, by comparing AEPs elicited by the same sounds when they served as distracters vs. when they served as targets we determined the upper temporal limit for the initiation of categorical brain processes while also controlling for any undetected differences in low-level acoustic features (see Van-Rullen and Thorpe, 2001, for an application of this approach with visual stimuli). Such task-related modulations were evident at 100 ms, even though reaction times on this task were on average >900 ms, thereby partially dissociating brain and behavioral indices of categorization processes.

5.2. Repetition-induced plasticity

We next examined whether access to auditory object representations could be facilitated through repeated exposure (Murray et al., 2008b). Our results indicate that repetition suppression is subsequent to the above categorization and task-related effects, occurring at 156–215 ms post-stimulus onset, irrespective of whether the sounds were of living or man-made objects. These rep-

etition suppression effects were further localized to posterior middle temporal cortex and superior temporal sulcus of the left hemisphere, though sources over this period included bilateral temporal and (pre)frontal cortices as well as weaker sources within occipital and occipito-temporal cortices. The timing and localization of these repetition suppression effects would thus reflect plasticity in more associative-semantic, rather than purely perceptual functions, during the accessing of auditory object representations. An important conclusion that can be gleaned from our study as well as that by Bergerbest et al. (2004) is that repetition priming of auditory environmental objects involves distinct networks from those involved in repetition priming of auditory linguistic stimuli. Effects with auditory and visual linguistic stimuli during a word-stem completion task have been observed within extrastriate cortices irrespective of changes in the superficial physical features of the stimuli (Buckner et al., 2000; Badgaiyan et al., 2001). By contrast, our effects (and those of Bergerbest et al., 2004) were located within BA22, which likely represent intermediary hierarchical levels in auditory processing. These regions are highly interconnected both with surrounding auditory cortices, including feedback projections to belt and core regions, and also feedforward projections to additional temporal regions, including the temporal pole and superior temporal sulcus, as well as frontal cortices (Kaas and Hackett, 2000). The extent to which these cortical regions themselves contain object representations as well as projections to regions likely involved in associating objects with their meanings/actions (e.g. Lewis et al., 2005) as well as multisensory representations (e.g. Kohler et al., 2002; Beauchamp et al., 2004; Romanski, 2007) lends further support to the conceptualization of their role a 'computational hub' for auditory functions (Griffiths and Warren, 2002).

5.3. Vocalization discrimination

Most recently, we have examined the spatio-temporal dynamics of vocalization discrimination by contrasting AEPs to human non-verbal vocalizations with those to animal vocalizations (De Lucia et al., in preparation). Our analyses revealed three time periods of differential responses. The first occurred over the 169–219 ms post-stimulus interval and followed from strength modulations of a common network with statistical differences within the right superior temporal sulcus and middle temporal gyrus (BA22); the localization of which is consistent with prior hemodynamic imaging (e.g. Belin et al., 2000). The second difference occurred over the 291–357 ms and also followed from strength modulations with statistical differences localized to the left precentral and inferior
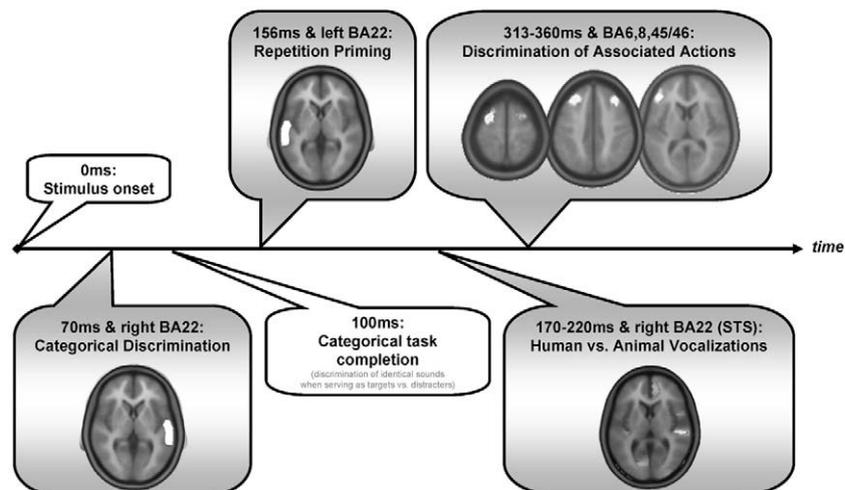

Fig. 2. Spatio-temporal dynamics of auditory object discrimination. This diagram summarizes the principal discrimination effects we have observed in our studies. For simplicity, we illustrate only the initial effects, though oftentimes subsequent effects were obtained.

frontal gyri (BA6/45). The timing of this effect replicates previous descriptions of a voice-selective response (Levy et al., 2001, 2003). The third effect occurred over the (389–667 ms), followed from strength and topographic modulations, and was localized to the left superior frontal gyrus (BA10). Several aspects of these results are worth noting. First, while we replicate the voice-selective response of Levy et al. (2001), our effects did not depend on participants' overt attention to voices, contrasting with subsequent observations by Levy et al. (2003). Second, the localization of our effects is consistent with prior hemodynamic imaging studies both for the initial effect within right STS (e.g. Belin et al., 2000) and also for the subsequent effect within the left inferior frontal gyrus (e.g. Fecteau et al., 2004; Cohen et al., 2006). Third, our earliest effect is substantially earlier than that previously described (Levy et al., 2001, 2003; Gunji et al., 2003). In fact, the latency of our earliest effect at 169–219 ms is highly compatible with models proposing that face and voice discrimination should take place along similar time scales (Belin et al., 2004).

5.4. The role of actions

Finally, we have begun investigating links between object and action representations (Murray et al., 2008c; De Lucia et al., submitted for publication). Recognition of visual, linguistic, and auditory stimuli can be influenced by associated actions (Gibson, 1979; Rizzolatti et al., 1996, Grezes et al. 2003; Barraclough et al., 2005; Pizzamiglio et al., 2005; Pulvermuller et al., 2005; Tettamanti et al., 2005; Lahav et al., 2007; Pazzaglia et al., 2008), and distinct neuronal response patterns or networks are observed for objects linked to actions. In the case of sounds, these networks can include premotor and (pre)frontal cortices often, but not exclusively, attributed to the so-called audio-visual mirror neuron system (Kohler et al., 2002; Keysers et al., 2003). More generally, such activations are consistent with current anatomical models of the auditory 'what' pathway (Rauschecker, 1998; Rauschecker and Tian, 2000) that includes projections to prefrontal and premotor regions (Romanski et al., 1999a,b; Kaas and Hackett, 2000). Functional imaging studies have indeed documented reliable activations within prefrontal cortices and elsewhere in response to environmental sounds and vocalizations (e.g. Lewis et al., 2005; Fecteau et al., 2005). One implication of this construct is that action representation is itself operating in concert with and perhaps guiding object recognition processes. However, the precise spatio-temporal relationship between object and action-related processes remains poorly understood, particularly with regard to sounds of environmental objects. The kind(s) of actions driving differential activity within the auditory mirror system have yet to be determined. One possibility can be derived from recent studies within macaque ventral (lateral) prefrontal cortices (vPFC). These neurons differentially responded to vocalizations referring to food discovery vs. other communicative situations, irrespective of the quality of the foods to which they referred (Cohen et al., 2006). These results suggest a dichotomy in the responsiveness within vPFC (and perhaps elsewhere) between sounds cuing listeners to act in response (e.g. partake in the discovered food) and those cuing perceptions (e.g. greetings) but not forcibly such responsive actions.

We identified the timing and neurophysiologic mechanism by which sounds of man-made environmental objects, all of which involve actions for their generation, are discriminated from one another (Murray et al., 2008c; De Lucia et al., submitted for publication). To determine the role of action representations in object discrimination, we focused on the impact of whether or not the sounds of actions typically cue the production of an action in response by the listener; a distinction we refer to as productive vs. perceptive. Electrical neuroimaging analyses revealed that AEPs to sounds of productive and perceptive actions first differed both

in their strength and topography beginning ∼300 ms post-stimulus onset, indicative of the recruitment of distinct configurations of brain networks. Source estimations identified regions within the premotor and inferior (pre)frontal cortices as responding significantly more strongly to sounds of productive than perceptive actions, consistent with the role of these areas in the audio-visual mirror neuron system. Action representations appear to differentially affect object discrimination only at relatively late stages. Such being said, it is essential to note that the regions identified in this study are also involved during these earlier stages of auditory object processing (cf. Figs. 4 and 5 in Murray et al., 2006). That is, it does not appear to be the case that regions of the mirror neuron system are only or selectively active over the 313–360 ms post-stimulus period. Rather, it appears that there is differential activity in these regions occurring first over this late time period.

5.5. Auditory object processing and its implications for multisensory interactions

This series of experiments demonstrate that the speed of auditory environmental object processing occurs within the same timeframe as that within the visual modality (Thorpe et al., 1996; Mouchetant-Rostaing et al., 2000; Michel et al., 2004), while also unfolding over several distinct time periods within the initial 300–400 ms post-stimulus onset. As in the case of visual object processing, access to semantic attributes of auditory objects thus occurs rapidly and via distributed activation of higher-level cortical regions. This timeframe carries implications for our understanding of multisensory integration of meaningful stimuli, which may be mechanistically distinct from integration of more rudimentary stimulus features (e.g. Laurienti et al., 2005; Lehmann and Murray, 2005). Recent evidence in the macaque has shown that multisensory integration of specific face and voice signals peaks at ∼85–95 ms within core and lateral belt cortices (Ghazanfar et al., 2005). The selectivity of these integration effects that these authors demonstrate suggests that categorization of voices occurred within this latency. However, the temporal dynamics of vocalization discrimination was not specifically assessed in this study or in others in which microelectrode recordings were made along the rostral and caudal portions of belt cortex in response to a variety of monkey calls at different azimuthal locations (Tian et al., 2001). Nonetheless, applying a "3:5" conversion ratio between latencies in macaques and humans (see Schroeder et al., 2008) would suggest that vocalization discrimination in humans should manifest around 150–160 ms post-stimulus; a latency consistent with out observations. Other findings of multisensory integration, albeit with corresponding delays, have been observed in human subjects in response to videos and sounds of syllabic vocalizations (Raij et al., 2000) as well as in response to images and animal vocalizations (Molholm et al., 2004; Yuval-Greenberg and Deouell, 2007; Schneider et al., 2008). The various latencies of our effects with auditory objects underscore those of the multisensory effects observed in these studies to suggest that unisensory and multisensory object processes might proceed in parallel, rather than serially. However, an important open question that is the focus of ongoing research in our group is whether the speed and/or mechanism of auditory object processing (e.g. categorical discrimination) can be facilitated by such processes in another sensory modality (Cappe and Murray, 2009; see e.g. Van Wassenhove et al., 2005 for the case of speech; Schneider et al., 2008 for the case of cross-modal priming of environmental objects).

6. Conclusions and outlook

This review has considered recent evidence regarding the spatio-temporal dynamics of auditory sensory-cognitive processes

within a multisensory framework. The current literature would suggest that there is a relatively substantial delay between when auditory responses can be recorded in human primary cortices (i.e. ∼20 ms post-stimulus onset as measured from intracranial evoked potentials) and when differential responsiveness to a given spatial or object feature first manifests (i.e. typically within the initial 100–150 ms post-stimulus onset; see Figs. 1 and 2). This delay is all the more striking when one also situates this timing alongside evidence for the rapid and parallel propagation of auditory signals throughout the brain (see Section 2). On the one hand, this temporal information can curtail interpretations that can perhaps be made regarding the functional significance of non-linear multisensory interactions observed between 50 and 100 ms post-stimulus onset. One possibility is that early effects are relatively 'unspecific' with regard to auditory spatial and object features (though we cannot unequivocally exclude the possibility that more specific effects are going undetected). For example, a series of ERP studies from the Giard laboratory showed there to be non-linear interactions as early as 40–50 ms post-stimulus over parieto-occipital scalp not only when discriminating between objects (Giard and Peronnet, 1999; see also Fort et al., 2002a), but also when performing a speeded detection task (Fort et al., 2002b). Moreover, there was no evidence for differential responses to the specific objects over the initial 200 ms post-stimulus onset. This pattern of results would suggest that these early non-linear interactions are insensitive to either the "object-ness" or the task demands. More recently, it has been shown that supra-additive non-linear interactions at 50 ms post-stimulus depend on attending to both sensory modalities with effects becoming sub-additive when attending to one, the other or neither modality (Talsma et al., 2007). By contrast, spatial attention modulated the magnitude (and to a lesser degree latency) of multisensory interactions from ∼100 ms post-stimulus onset onwards (Talsma and Woldorff, 2005). An important direction for continued research will be to more fully understand the interplay between attention and the integration of specific stimulus features (e.g. Röder and Büchel, 2009 for a recently commentary on this issue). It will also be important for future research to ascertain whether (and if so in what manner) early multisensory interactions are altering unisensory feature discrimination. While there is a large body of psychophysical research on this particular topic, corresponding neurophysiologic and neuroimaging data are presently scant. That is, early and low-level multisensory interactions involving acoustic information have now been documented by several independent laboratories. In our view, a critical next step is the determination of the functional utility of these interactions both in terms of performance (e.g. Sperdin et al., 2009 who demonstrate a link between early, low-level auditory somatosensory interactions and reaction time) and also in terms of perception.

While we have focused entirely here on auditory processing, it will likewise be important to have comparable evidence on the spatio-temporal dynamics of information processing within other senses. For example, we have begun investigating the functional organization of the somatosensory system (De Santis et al., 2007b; see also Reed et al., 2004; Reed et al., 2005; van Boven et al., 2005), with results supporting a similar what/where architecture as observed within the auditory and visual modalities. Technological improvements are likewise making it feasible to track the time course of olfactory (e.g. Boesveldt et al., 2007) and gustatory (Ohla et al., 2009) brain activity. These kinds of investigations will undoubtedly allow for a better understanding of the kinds of information available for and contributing to multisensory interactions at a given latency and within a given brain region. One possibility that is receiving increasing support is that multisensory interactions are themselves grafted on to functionally-specialized 'what' and 'where' pathways for processing identity and spatial information (e.g. Sestieri et al., 2006; Molholm et al., 2007; Chan

and Newell, 2008; Murray et al., 2009). To the extent that this is indeed the case, continued multisensory research will be undoubtedly useful for developing neurorehabilitation strategies (e.g. Ball and Haight, 2005; King, 2009), improving learning/teaching protocols (e.g. Murray et al., 2004, 2005b; Shams and Seitz, 2008), and diagnosing neurological and psychiatric illnesses (e.g. Iarocci and McDonald, 2006; Ross et al., 2007; Wallace, 2009).

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