



ELSEVIER

Cognitive Brain Research 14 (2002) 187–198

COGNITIVE
BRAIN
RESEARCH

www.elsevier.com/locate/bres

Research report

The timing and laminar profile of converging inputs to multisensory areas of the macaque neocortex

Charles E. Schroeder^{a,b,c,*}, John J. Foxe^{a,b,d}

^a*Cognitive Neuroscience and Schizophrenia Program, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd., Bldg. 37, Orangeburg, NY 10962, USA*

^b*Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA*

^c*Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA*

^d*Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA*

Abstract

Two fundamental requirements for multisensory integration are convergence of unisensory (e.g. visual and auditory) inputs and temporal alignment of the neural responses to convergent inputs. We investigated the anatomic mechanisms of multisensory convergence by examining three areas in which convergence occurs, posterior auditory association cortex, superior temporal polysensory area (STP) and ventral intraparietal sulcus area (VIP). The first of these was recently shown to be a site of multisensory convergence and the latter two are more well known as ‘classic’ multisensory regions. In each case, we focused on defining the laminar profile of response to the unisensory inputs. This information is useful because two major types of connection, feedforward and feedback, have characteristic differences in laminar termination patterns, which manifest physiologically. In the same multisensory convergence areas we also examined the timing of the unisensory inputs using the same standardized stimuli across all recordings. Our findings indicate that: (1) like somatosensory input [J. Neurophysiol., 85 (2001) 1322], visual input is available at very early stages of auditory processing, (2) convergence occurs through feedback, as well as feedforward anatomical projections and (3) input timing may be an asset, as well as a constraint in multisensory processing. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Multisensory; Temporal coincidence; Feedback; Current source density; ERP

1. Introduction

Multisensory integration is essential for the production of the seamless, unified representation of the world that we experience subjectively. This integration requires the anatomical convergence of unisensory inputs onto single neurons or ensembles of interconnected neurons [46], and some degree of temporal alignment of the unisensory inputs [54]. A detailed explication of the brain mechanisms of multisensory processing has been conducted in the carnivore superior colliculus (reviewed by Stein and Meredith [54]), and substantial progress has also been made at the neocortical level, most notably in monkeys [1,2,8,15,16,19,20,24,25,27,36–38,52] and more recently in humans [4,5,7,10,12,21,30].

Despite these advances, large questions remain about the anatomical substrates of multisensory convergence in

primates. We know, for example, that several ‘classic’ multisensory regions, including the superior temporal polysensory area, or STP [53], and the intraparietal (IP) sulcus [52] do receive converging ascending (feedforward) sensory inputs. However, several cortical areas at low levels in their respective sensory processing hierarchies have been shown or suggested to be sites of multisensory convergence, including auditory association cortex [7,45] and the human MT+ complex [4,5], and these areas have not been shown to receive the appropriate feedforward convergence of sensory inputs. In fact, the lack of the clear anatomical substrate for multisensory convergence has led to the speculation that convergence in these ‘unisensory’ areas occurs through combination of feedforward and feedback inputs [6]. Similarly large questions remain about the temporal parameters of the converging sensory inputs. We know that there is a temporal window for integration of neural responses to stimulus inputs from different modalities, as well as for our perception of multisensory inputs as ‘fused’ (i.e. relating to the same object (reviewed by Stein and Meredith [55])). However, the timing of

*Corresponding author. Tel.: +1-845-398-6539; fax: +1-845-398-6545.

E-mail address: schrod@nki.rfmh.org (C.E. Schroeder).

sensory inputs to neocortex has received very little attention, beyond a few studies of response latencies in the visual system [14,32,44,47]. Virtually nothing is known about the timing of convergent multisensory inputs in different cortical structures, and the picture becomes much more complex when the combination of feedforward and feedback input is invoked.

In the present study, we investigated the laminar profile and the timing of sensory inputs in several of the primate neocortical areas in which multisensory convergence occurs. The laminar profile of sensory activation is of interest because it can help to distinguish between feedforward and feedback inputs, due to their differing laminar termination patterns [45,47]. We investigated posterior auditory association cortex, which our recent studies show to be a multisensory region [45], and compared the timing and laminar profile of auditory, somatosensory and visual responses in this region to those of corresponding responses in more ‘classic’ multisensory regions including the superior temporal polysensory (STP) area, and lateral and ventral intraparietal (IP) Areas. Our findings indicate that: (1) like somatosensory input [45], visual input is available at very early stages of auditory processing, (2) convergence occurs through feedback, as well as feedforward anatomical projections and (3) input timing may be an asset, as well as a constraint in multisensory processing.

2. Materials and methods

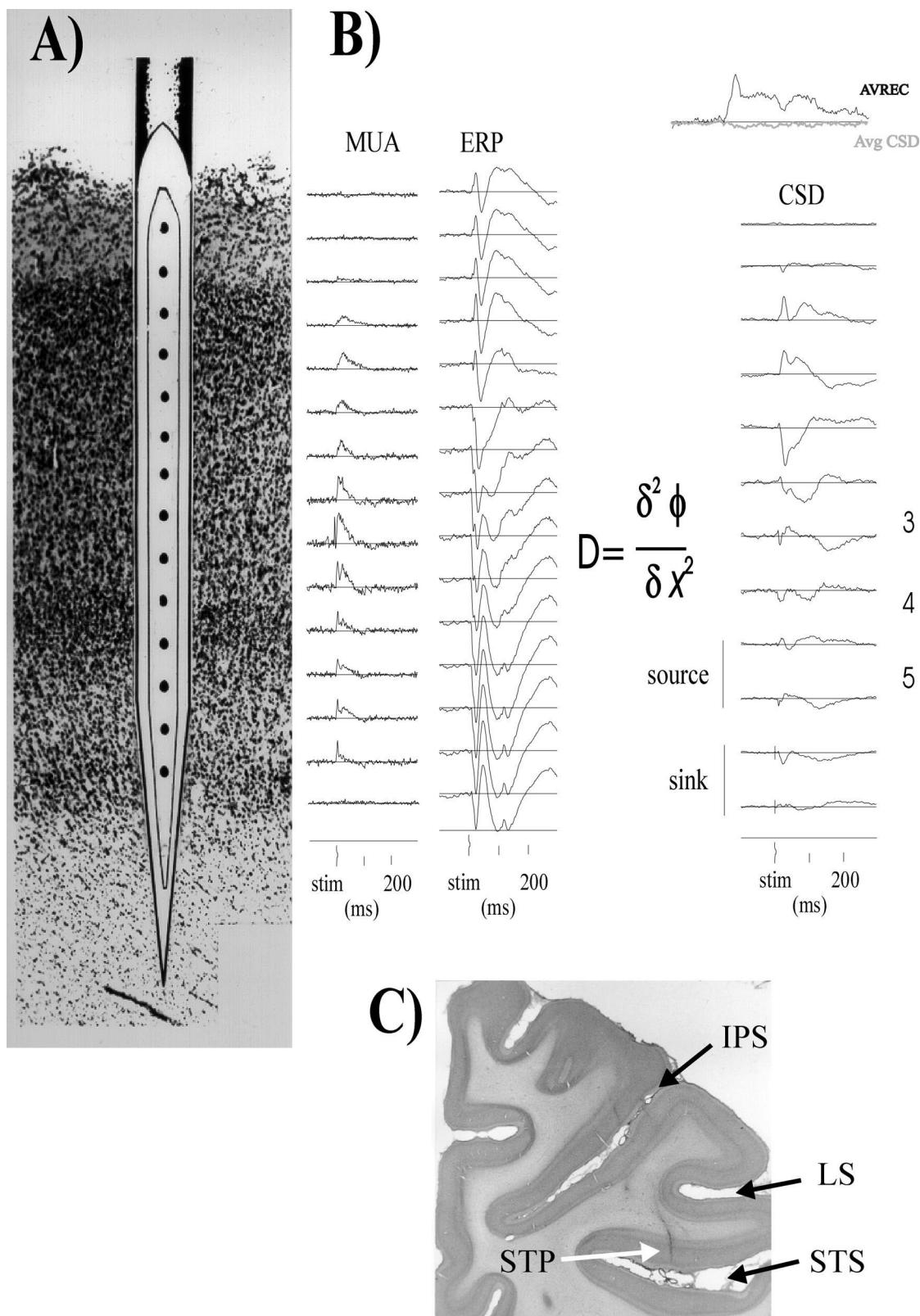
Five male macaques (*M. fascicularis*) weighing between 5 and 8 kg were subjects in this study. Each also served in one or more additional auditory visual or somatosensory studies. Preparation of subjects for chronic awake recording was performed using aseptic techniques, under general anesthesia (sodium pentobarbital 25.0 mg/kg), as described previously [47]. Throughout surgery, the rectal temperature and respiration rate were continuously monitored and maintained within physiological limits. Perioperative care included the use of systemic analgesics, local and systemic antibiotics and parenteral fluid replacement. The monkey was positioned in a stereotaxic instru-

ment, the skin and fascia overlying the calvarium were resected and appropriate portions of the skull were removed. To provide electrode access to the brain, groups of 80–100 stainless steel tubes (18 gauge), glued together in a parallel matrix, were sealed with surgical grade silastic and implanted over the cortex of interest, in contact with the intact dura. Individual epidural guide tubes were positioned overlying central and frontal sites to serve as fixed ground and reference electrodes. The matrices, monitors and plexiglass bars with sockets (to permit painless head restraint) were secured to the skull with stainless steel screws embedded in dental acrylic. Two weeks recovery time were allowed prior to the beginning of data collection. Data were collected with the monkey comfortably seated in a primate chair in an electrically shielded, sound attenuated chamber. All procedures were approved by the Institutional Animal Care and Use Committee of the Nathan Kline Institute, and conformed to the Principles of Laboratory Animal Care (NIH Publ. #86-23, rev. 1985).

Data were collected bilaterally from somatosensory visually-responsive sites in the lateral and ventral regions of the intraparietal (IP) sulcus (e.g. Ref. [8]), from auditory belt/parabelt cortical regions posterior to A1 (e.g. Ref. [22]), and from regions of the upper bank of the superior temporal sulcus, corresponding to the superior temporal polysensory area (e.g. Ref. [2]). Laminar current source density (CSD) and multiunit activity profiles were obtained by recording with a linear array multicontact electrode, positioned so as to straddle the cortex from the pial surface to the white matter (see Fig. 1). CSD analysis is an index of the laminar profile of transmembrane current flow, the first order response to synaptic activation of neural tissue, while multiunit activity reflects the related action potential patterns within the local neuronal population [47]. For quantification, CSD profiles were collapsed into a single waveform, reflecting the average across layers (AVREC—see Fig. 1), and grand mean responses were computed across penetrations and across subjects (Fig. 7).

Auditory stimuli were delivered at 65 dB (SPL) either binaurally or monaurally through Sennheisser HD565 headphones coupled with 50 cc tubes placed against the

Fig. 1. (A, B) Laminar activity profiles consisting of multiunit activity (MUA) patterns, event related field potentials (ERPs) and the derived current source density (CSD) pattern. Responses were evoked by 65 dB binaural clicks. Profiles were sampled from all laminae simultaneously using a linear array multielectrode with intercontact spacings of 150 μm . At the left is a schematic illustration of the recording multielectrode positioned and scaled with respect to the laminae of auditory cortex. Each tracing (ERP, MUA, CSD) represents an average of 100 stimulus-evoked responses. Those on the left represent the averaged responses to binaural 65 dB clicks. The CSD reflects local postsynaptic potential (PSP) patterns and MUA reflects the concomitant action potential patterns. In the CSD profile downward deflections (dark shaded) signify net extra cellular current sinks (representing inward transmembrane currents) and upward deflections (stippled) indicate net extra cellular current sources (representing outward currents); sinks and sources are associated with local depolarization and hyperpolarization in local neuronal ensembles, respectively. At the bottom of the CSD profile are two expanded waveforms. One is the average rectified current flow or AVREC pattern (black tracing) obtained by averaging together the absolute value of the CSD across all sites in the laminar profile. The AVREC waveform is a simplification of the CSD used for quantification and comparison. The other is the averaged CSD pattern (gray), which is computed as a check on the adequacy of the CSD implementation; when proper conditions are met and the current flow distribution is sampled adequately, this waveform should approach zero over its length. MUA patterns are obtained by full-wave rectification and averaging of the high frequency activity at each electrode contact (upward deflection represents excitation). Each MUA trace is in effect a multiunit histogram. Scale bar (lower right)=1.4 mv/mm^2 for CSD, 0.1 mv/mm^2 for AVREC and 1.6 μV for MUA. (C) Coronal brain section illustrating the histological reconstruction of recording sites; shown are a number of penetration tracks through the intraparietal sulcus (IPS) and the superior temporal sulcus (STS).



external auditory canal [45]. A combination of stimuli consisting of 100- μ s clicks, 100-ms pure tones and band-passed noise (5 ms on/off ramps) was used to characterize best frequency and produce optimal stimulation at each recording site. Quantified (averaged) responses to best frequency tones and clicks were obtained at each recording site. Somatosensory (hand) responses were quantified using electrical stimulation of peripheral nerves from the hand. For this, 100- μ s square-wave (constant current) electrical pulses delivered with gold cup EEG electrodes to the skin over the median nerve in the forearm contralateral to the recording site [49,50]; 80 dB white noise was used to mask any co-incident auditory stimulation. For visual stimulation, light flashes 10 μ s in duration and 7.8×10^5 lux intensity, were generated by a Grass PS-2 photostimulator and presented at 2/s from a diffuser subtending 20° visual angle, directly in front of the animal [51,52]. As for somatosensory stimulation, white noise was used to mask the click of the lamp discharge and extraneous noise.

Electrolytic lesions were made during certain of the later penetrations to aid in reconstructing the locations of physiological recordings with respect to the boundaries and laminae of cortical regions of interest. These lesions were made by passing 5–10 μ A of anodal current through one electrode contact for 10–15 s. Post-mortem, electrode penetrations were reconstructed histologically to confirm locations of recording sites [45,47]. Alternate sections were stained for Nissl substance, and other products. Potassium ferricyanide was helpful in outlining electrode tracks and electrolytic marking lesions. Acetylcholine esterase (AchE) [31] and parvalbumin (PV) [18,22] helped determine the borders between cortical areas, such as those between A1 and surrounding regions [18,45].

3. Results

3.1. Manifestations of feedforward and feedback convergence in auditory association cortex

Fig. 2 displays a direct replication of earlier findings from our laboratory [45]. The laminar profile of auditory response in posterior auditory association cortex has the pattern predicted by the anatomy of feedforward input: initial response centered on lamina 4, followed by responses in the extragranular laminae. Feedforward auditory input to the region in question, caudomedial (CM) auditory cortex, is well established [18,22].

In the same location, the overall timing and the laminar activation sequence for a convergent somatosensory input are nearly identical to the timing and sequence of the auditory input. This suggests that the somatosensory input, like the auditory input is conveyed by a feedforward projection. The source of the somatosensory input is unclear at this time, because the anatomical interface between the auditory and somatosensory areas of the

lateral sulcus region is not clearly delineated.¹ Findings obtained with the same laminar activity analysis techniques also point to a ‘feedback-mediated’ visual input into auditory cortex (Fig. 2). This form of visual–auditory convergence has been observed to date in three monkeys, in all cases, in posterior auditory association cortices. Thus far, visual–auditory and somato–auditory convergence regions appear to be in non-overlapping zones, although we have observed one example of trimodal (visual/auditory/somatosensory) convergence in posterior auditory cortex. As was shown above (Fig. 1), auditory inputs have the characteristics of a feedforward anatomical projection: i.e. with initial activation centered on lamina 4. This is typical throughout the core and belt regions of auditory cortex (Fig. 3) [45].

The visual input profile, in contrast, has a bilaminar pattern, with initial responses beginning simultaneously in the supra- and infragranular laminae. This is the physiological pattern predicted by the anatomy of feedback projections [9,40]. Another point of contrast between the co-located auditory and visual response profiles concerns response timing. Visual response latency (~50 ms) is considerably longer than the auditory response latency (~11 ms). The large timing difference between convergent visual and auditory inputs to a single location contrasts with the lack of any corresponding timing difference between convergent somatosensory and auditory inputs to single auditory cortical locations (Fig. 1). With proper analysis and interpretation, these latency data can help to identify input sources and possibly also to predict the characteristics of multisensory interactions. This issue is treated in a subsequent section.

3.2. Feedforward input convergence in classic multisensory cortices: STP and IP sulcal areas

Laminar profile recordings in area STP reflect feedforward convergence of visual, auditory and somatosensory inputs in this brain region. Fig. 4 illustrates this point for an STP recording site in which all three modalities converge. In this site, the different modalities of inputs appear to have different response gains, with that of the visual input being the greatest and that of the auditory input being the weakest. There are also clear differences in the temporal parameters of response, including the prominent differences in both response duration and onset latency. In our sample of data from 18 penetrations in four animals, it is not always possible to resolve the precise laminar activation sequence, however, the large difference between feedforward (lamina 4—centered) and feedback (lamina 4—excluding) is generally apparent. As in this representative case, initial input from each modality targets

¹This uncertainty parallels that which we expressed (above) concerning the question of auditory inputs into the early stages of extrastriate visual cortex.

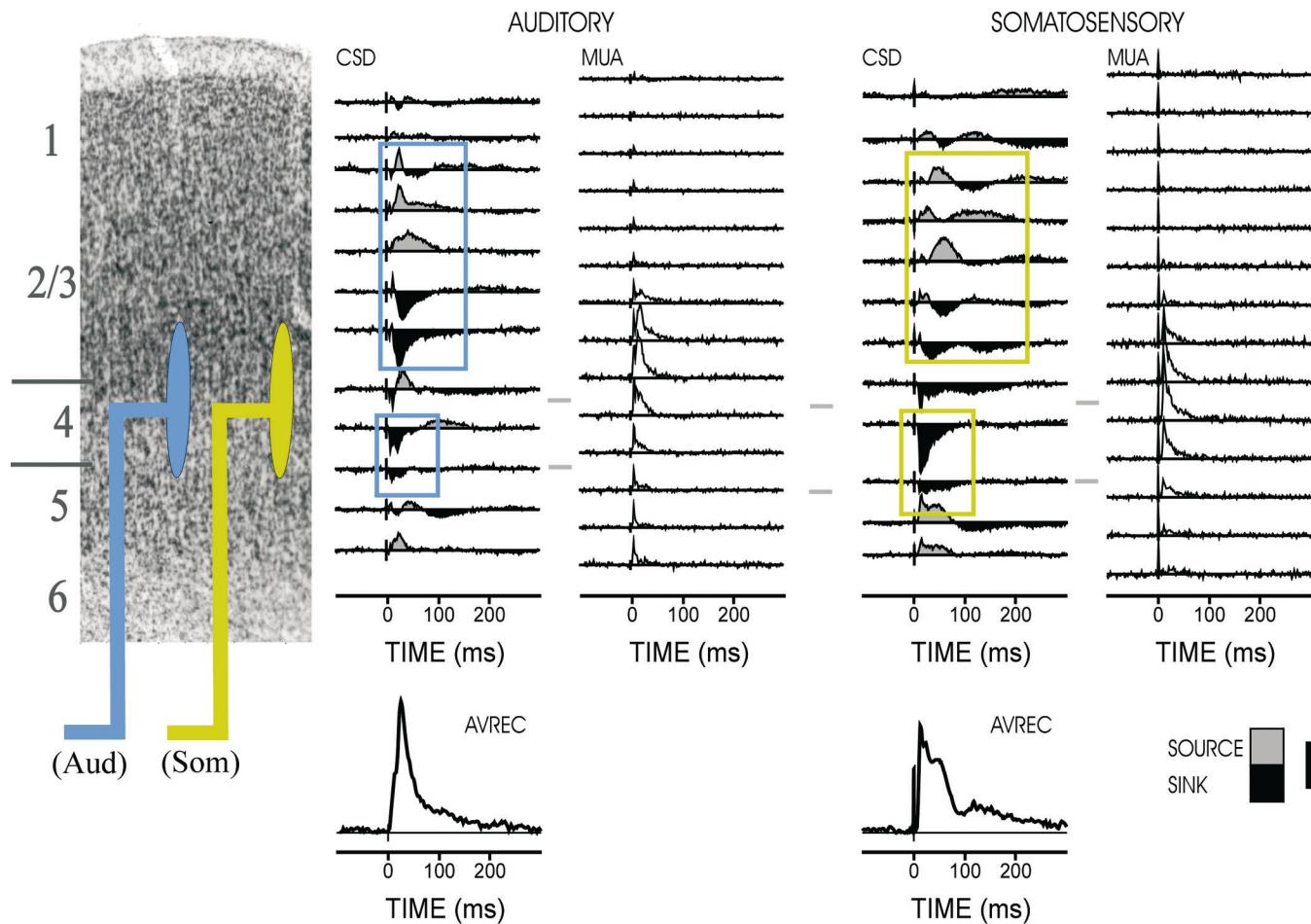


Fig. 2. Laminar CSD and MUA profiles evoked by auditory (left) and somatosensory stimuli (right) and recorded from one site in auditory association cortex, posteromedial to A1 cortex. Profiles were sampled from all laminae simultaneously using a linear array multielectrode with intercontact spacings of 150 μm . Each tracing CSD and MUA represents an average of 100 stimulus-evoked responses. Those on the left represent the averaged responses to binaural 65 dB clicks. Those on the right were elicited by electrical stimulation (2–3 mA, 100 μs square pulse) of the contralateral median nerve at the wrist. AVERC patterns computed for each of the CSD profiles are shown at the bottom. The boxes circumscribe CSD configurations that reflect the initial excitatory response at the depth of lamina 4 (lower boxes), and the subsequent excitation of the pyramidal cell ensembles in laminae 2/3 (upper boxes). Scale bar (lower right)=1.4 mv/mm 2 for CSD, 0.1 mv/mm 2 for AVERC and 1.6 μV for MUA. At the extreme left is a diagram depicting the laminar pattern of termination for feedforward inputs from auditory (blue) and somatosensory (olive) systems.

the middle laminae of the cortex, approximating a feedforward input pattern. Fig. 5 illustrates responses from a site of visual somatosensory (hand input) convergence in the ventral-lateral bank of the intraparietal sulcus, near the fundus of the sulcus, probably corresponding to VIP [8]. In this site we could not detect any auditory input, but there were clear visual and somatosensory (hand) inputs. To date, we have collected laminar activation profiles from visual-somatosensory convergence sites, the ventral and lateral areas of the IP sulcus during 14 multielectrode penetrations in two monkeys. In less than one half of these cases (six passes) did the electrode array penetrate at an angle that would allow a valid implementation of a 1-dimensional CSD analysis (see Ref. [47] for a discussion of this point). Because of this, we do not have confidence that we have resolved the ‘typical’ laminar activation profile in any one of the IP sulcus regions. Moreover, we

have not yet reconstructed enough marking lesions of appropriate size and position to accurately assign features of the laminar activation profile to specific cortical layers. What we can say is that, based on the laminar patterns of MUA, and on our smaller sample of laminar CSD profiles, we do not see convincing evidence that either the visual or the somatosensory input is conveyed by a feedback projection. Obviously, further research on this issue is required.

3.3. Interaction/integration in multisensory convergence regions

An important point to make about multisensory convergence regions is that with the relatively cursory stimulation methods we have used, the evidence of interaction between the converging inputs is extremely variable. Fig. 6 illus-

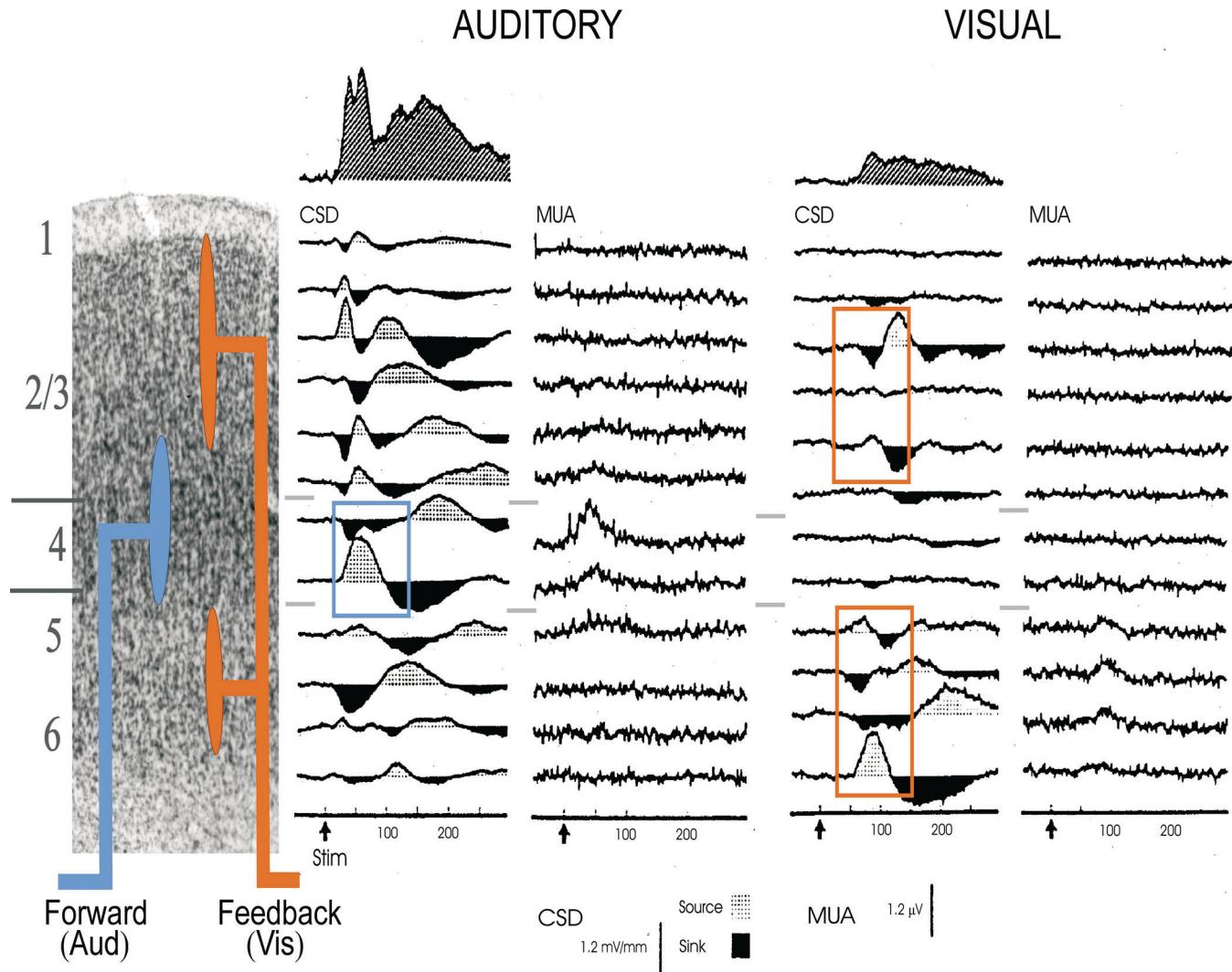


Fig. 3. Laminar CSD and MUA profiles evoked by auditory (left) and visual stimuli (right) and recorded from one site in auditory association cortex, poster lateral to A1 cortex. Intercontact spacing on the multielectrode was 150 μm . Each tracing represents an average of 100 stimulus-evoked responses. Those on the left represent the averaged responses to binaural 65 dB clicks. Those on the right were elicited by intense binocular light flashes (10 μs duration, 7.8×10^5 lux intensity). The boxes circumscribe CSD configurations that reflect the initial excitatory response at the depth of lamina 4 (blue—auditory profile), as opposed to, above and below lamina 4 (red—visual profile). At the extreme left is a diagram depicting the laminar pattern of termination for feedforward inputs from auditory (blue) and feedback visual (red) systems.

brates the testing method and one outcome, moderate multisensory enhancement.

To test for interaction, we sample responses to each unisensory input and then the response to combined input. If the response to the combined input equals the summed responses to the unisensory inputs, the effect is termed ‘additive’. If the combined response either exceeds or undercuts the additive response, the effect is termed ‘supra-additive’ or ‘sub-additive’. In Fig. 6 the ‘condensed’ (AVREV) CSD response to visual stimulation alone reveals a robust initial response with an onset latency of ~26 ms. The visual MUA response at the maximum point in the laminar profile is also robust and has a slight later onset latency. The (AVREV) CSD response to

somatosensory stimulation alone reveals a small initial response with an onset latency of ~12 ms, and the somatosensory MUA response measured at the same laminar location as the visual MUA response is flat. The combination of a small CSD response with a flat MUA response most likely reflects subthreshold excitation.² When the visual and somatosensory stimuli are given together there is clear supra-additive interaction, in that, for both the CSD and MUA measures, response amplitude is clearly increased beyond the point of simple additivity.

²Use of this term does not distinguish between the possibilities that subthreshold excitation reflects weak excitatory input without concurrent inhibition, versus a combination of the two.

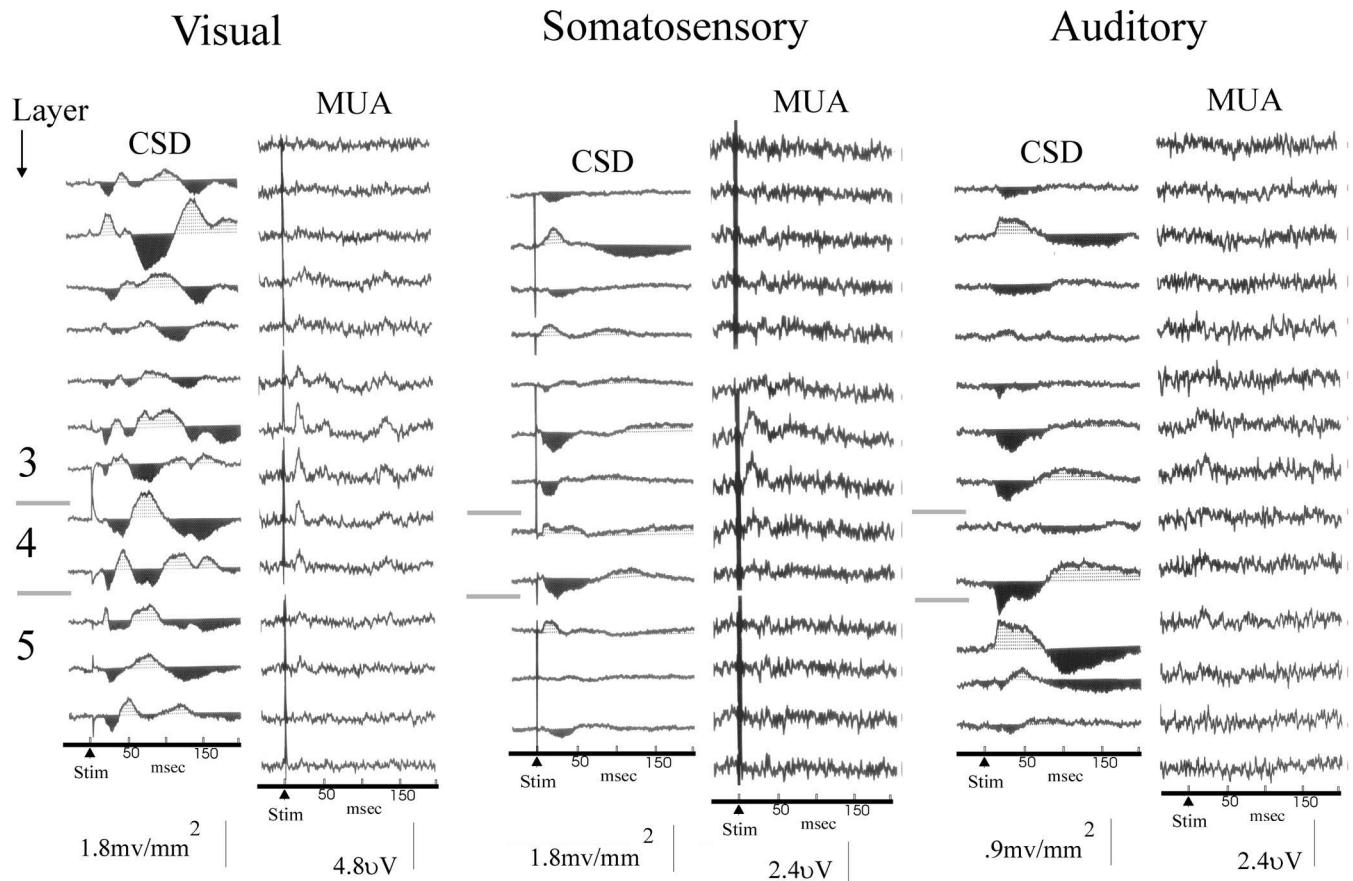


Fig. 4. Laminar CSD and MUA profiles evoked by visual (left), somatosensory (middle) and auditory (right) stimuli, recorded from one site in the superior temporal polysensory area (STP), on the upper bank of the posterior superior temporal sulcus (STS). Stimuli and conventions are like those in Figs. 2 and 3.

Moreover, in both the CSD and MUA responses, there is a shortening of the response latency relative to the visual alone condition, suggesting that the subthreshold somatosensory facilitation of the visual response is occurring at the level of the PSP in local neurons.

3.4. Temporal parameters of multisensory convergence

When auditory and somatosensory stimuli are presented at less than 1 m from the head (i.e. within arm's reach), the response in the multisensory convergence region of auditory association cortex is rapid and approximately simultaneous for these input modalities. Visual–auditory convergence in auditory cortex, however, contrasts greatly with this pattern of effects. That is, for stimuli presented within arm's reach, there is a large delay for visual relative to auditory responses. In order to gain an overall impression of the temporal patterns of visual–auditory, visual–somatosensory and somato–auditory convergence across different neocortical areas, we have assembled a set of grand mean activation patterns for separate sensory inputs that converge in three of the brain regions we have studied

(Fig. 7). The waveforms shown in Fig. 7 are based on a condensed (AVREC) representation of the laminar CSD profile, obtained by taking the absolute value of the CSD at each point in the laminar profile and averaging across the points in the profile, for each point in time. The single penetration AVREC waveforms are then averaged across penetrations and subjects for a given area.

Several aspects of the temporal pattern of multisensory convergence for peripersonal space, visual, auditory and somatosensory are evident in the summary figure. Firstly, somatosensory input, when present in any structure, is as early as, or earlier than, either auditory or visual input to the same region. Secondly, while auditory input to auditory cortex is on average, much earlier than visual input, in STP, auditory and visual inputs are approximately coincident. Finally, consistent with a dominant magnocellular input into the response onset in dorsal stream visual areas, response latencies in STP and IP are very short (~25–27 ms), actually close to the mean response latency in lamina 4C of area V1 [47], while the visual input into auditory association cortex has a latency of about twice this value; the latter being an extremely long latency for this type of visual stimulation in an awake monkey. The interpretive

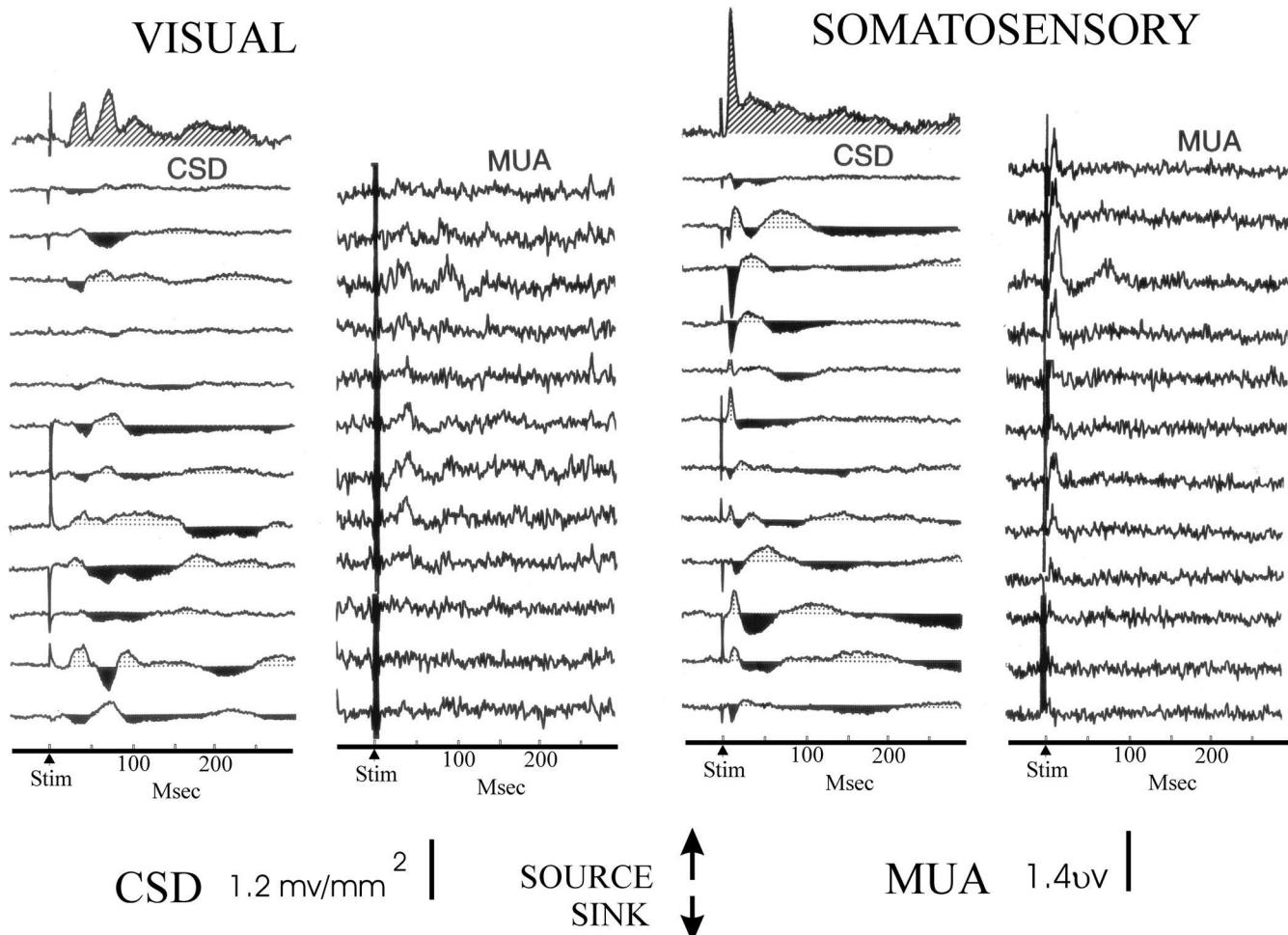


Fig. 5. Laminar CSD and MUA profiles evoked by visual (left) and somatosensory (right) stimuli, recorded from one site in the ventral-lateral part of the intraparietal sulcus (IPS), near the fundus of the sulcus. Laminar locations of the features of the physiologic profiles are not depicted as these are uncertain. Stimuli and conventions are otherwise like those in Figs. 2–4.

details and implications of these timing relationships will be discussed below.

4. Discussion

As discussed at the outset, both STP and IP sulcus regions are classic areas of multisensory convergence receiving feedforward projections from two or more sensory modalities. More recently, we have recognized that posterior auditory association cortex receives converging auditory, somatosensory and visual inputs (present results; [45]). Thus far, there appears to be a segregation of the region into auditory–somatosensory and auditory–visual convergence zones, although the precise mapping has not yet been established. Preliminary findings [11] suggest a bias of the cutaneous somatosensory representation toward the head and hand surfaces. No such information has been developed for the visual input. The sources of the somatosensory and visual inputs into this early stage of the

auditory processing hierarchy are unclear at this time.³ However, it is likely that CM auditory cortex corresponds to one of the somatosensory representations in the same region, defined by earlier unit mapping studies that did not test for auditory responsiveness. For example, somato-recipient CM may correspond to ventral somatosensory area (VS) as defined by Krubitzer et al. [23]. This being the case, the input could be provided by nearby areas S2 and/or PV. If CM/VS corresponds to the retro-insular (RI) region [39], possible additional sources of feedforward input include areas 3b, 1, 2 and 5 [3]. Preliminary results of tracer studies [11] support areas 5 and 7 as potential sources of somatosensory and visual input to posterior auditory association cortex. There is also a possibility that visual input is relayed to this region along with a vestibular input, through projections from visual area MST [17].

³This uncertainty parallels that which we expressed (above) concerning the question of auditory inputs into the early stages of extrastriate visual cortex.

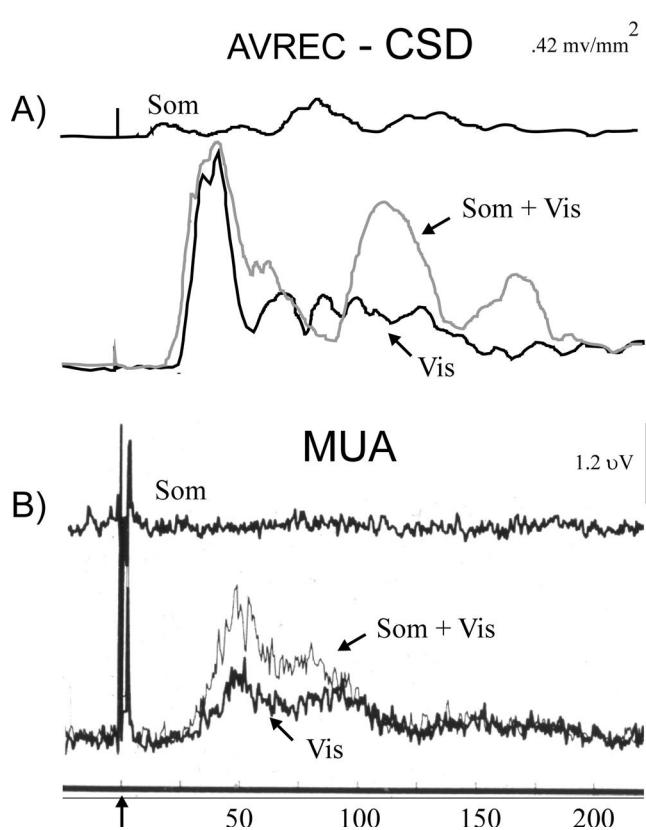


Fig. 6. Illustration of multisensory interaction in cortical area VIP. (A) AVREC representations of CSD responses to somatosensory stimulation alone (top), visual stimulation alone (bottom, black) and combined visual/somatosensory stimulation. (B) MUA responses in the same three stimulation conditions, recorded from a mid cortical depth at which the maximal unisensory MUA response was observed.

Recording of laminar response profiles with linear array multielectrodes is an established means of defining the functional correlates of lamina 4-dominated, feedforward inputs in visual [13,14,29,46–49,51,58], somatosensory [34,49,50] and auditory [45,56,57] cortices. A more limited set of data have demonstrated the functional correlates of feedback (lamina 4-excluding) inputs in the visual system [28,29]. Such recordings in areas of multisensory convergence [45], provide an opportunity to investigate the functional correlates of these input patterns. Our essential findings are that: (1) in auditory cortex, both somatosensory and auditory inputs have a feedforward pattern (Fig. 2), while visual inputs to the region have a feedback pattern (Fig. 3). (2) In STP, all three modalities of input appear to have a feedforward input pattern. (3) In the IP sulcal regions, visual and somatosensory inputs do not show obvious evidence of feedback input patterns, although given our very limited sampling to date, firm conclusions about the exclusive or major patterns of input convergence are not possible.

The functional evidence of the involvement of a feedback circuit in auditory–visual convergence is important as

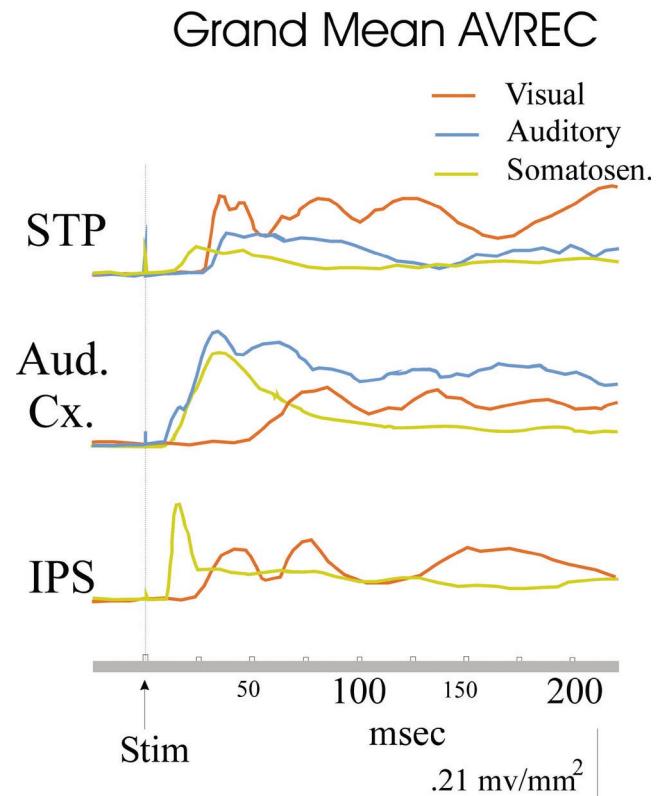


Fig. 7. Grand mean AVREC waveforms illustrating the onset timing and temporal pattern of CSD responses to standard form unisensory visual, auditory and somatosensory stimulation in three regions receiving multisensory convergence of inputs. These waveforms were obtained by averaging together single case waveforms (like those in Figs. 1–3), across penetrations and across subjects.

it outlines a phenomenon that has been the subject of widespread speculation by researchers in multisensory processing. Concerning structural substrates, there are several circuits that could produce feedback multisensory convergence in auditory cortex. These circuits include one in which the origin of the visual feedback input is STP [33,54], and another in which the origin is prefrontal cortex [42,43]. Such ‘suborning’ of activity in unisensory cortex by feedback-mediated input from another sensory modality is an intriguing mechanism for multisensory convergence. Just as feedback circuits have been invoked in the case of auditory input into early visual processing, one could account for early visual–auditory interactions in auditory processing [7,12,30] by positing that auditory inputs progress up their processing hierarchy until the point at which they converge with visual input (e.g. STP or PFC), and then are conveyed by feedback projections to the putative ‘unisensory’ auditory areas. Our findings on visual–auditory convergence in auditory cortex (Fig. 3) outline a physiological response pattern that conforms to this explanation, although somato–auditory convergence in posterior auditory cortex appears to utilize feed forward

mechanisms. In view of the multiple possible feedback routes for multisensory convergence in auditory cortex, or, for that matter any sensory area, it is in some respects remarkable that there is enough sensory segregation to promote unimodal sensory representation at early cortical processing stages. Obviously, under normal circumstances, there is a strong bias in favor of specific patterns of unimodal representation and processing in lower order cortical areas. However, the striking findings in the congenitally deaf human [26], along with the earlier work on developmental sensory re-wiring in ferrets [41,59], indicate that there is great potential for altering this bias during development.

Two points about the temporal parameters of activity in converging multisensory pathways merit emphasis. Firstly, in view of the large latency advantage of one modality over another observed in several of the comparisons, we need to consider the possibility that latency advantage confers a processing advantage. For example, an early-arriving input may have preferential access to local cellular excitability and thus, be in a position to modulate or even dominate (inhibit or enhance) the processing of a later-arriving input. Alternatively, the later-arriving input may be enhanced by modulation of local excitability promoted by an earlier-arriving input. The supra-additive effects of somatosensory–visual interaction may illustrate the latter type of effect. However, these somatosensory responses were elicited by electrical stimulation of median nerve, and these latencies slightly underestimate the latency of a response to stimulation of the volar hand surface [50]. Also, the relative timing of somatosensory, visual and auditory components of a multisensory stimulus (e.g. an object held in the hand, looked at and listened to) would vary considerably depending on whether it is active or inert, that is whether it moves actively, or must be turned with the hand. Thus, while neural processing of somatosensory inputs might be faster than that of other, particularly visual inputs, the significance of this factor, relative to the complex temporal dynamics of the physical stimuli, is unclear. All of these considerations serve to underscore the point that the closer attention should be paid to the impact of timing in multisensory, as well as unisensory processing.

A second point of temporal patterning that is evident in Fig. 7 concerns the overall pattern of timing offset between the inputs converging from different modalities, across different multisensory areas. In short, the pattern of auditory–visual latency offset across cortical regions is consistent with the proposition that the different regions may be set-up to optimize audiovisual integration at different ranges of distance from the observer. To expand on this point, note first that for an audiovisual stimulus at less than 1 m, the degree of synchrony between convergent visual and auditory inputs varies markedly across different structures. For example, our findings in posterior auditory cortex (Fig. 7) suggest that auditory input is very fast (~10

ms) while visual input is relatively slow (~50 ms). Thus, given an audiovisual stimulus at a typical conversational distance, auditory and visual inputs would be asynchronous and unable to support the precise temporal ordering necessary for audiovisual speech perception. However, with the relatively slow speed of sound (~1100 ft/s) relative to that of light, the relative timing of inputs in such a location would be appropriate for synchronization of inputs generated by audiovisual stimuli at a distance of ~40 feet from the observer. In STP on the other hand, response latency for auditory input from a sound source at 1 m (~25 ms latency) is comparable to that of a visual input from the same source (~23 ms—Fig. 10), so that the inputs are in synchrony. Note that for audiovisual sources located at greater distances (e.g. ~40 ft) from the observer, inputs into STP would become asynchronous, when auditory and visual inputs into posterior auditory cortex begin to synchronize. Based on the timing relationship between auditory and visual inputs, posterior auditory cortex and STP may contain complementary representations of near ‘peripersonal’ and far ‘extra personal’ space. Regarding this possibility, two caveats are in order. The first is that while these simple unisensory response latency estimates set a lower boundary on the timing of auditory–visual interactions in each brain region, for audiovisual stimuli located at different distances from the observer, they do not specify the time point at which a significant interaction occurs. This issue will require additional experimentation. The second caveat is that the findings in macaque monkeys have implications for understanding the temporal pattern of brain activation in humans, but multisensory interaction latencies, like unisensory response onset latencies, are likely to differ between monkeys and humans. Additional experiments will be required to firm up the comparison of monkey and human findings.

In current models of brain organization, there appears to be a hierarchical progression from the processing of simple to more complex aspects of unimodal stimuli within each sensory system [3,9,35]. The phenomenon of early multisensory convergence in supposedly ‘unisensory’ areas such as auditory association cortex, has interesting implications for the hierarchical model of brain organization. Firstly, this finding challenges the common view that multisensory convergence and integration are deferred until relatively late in processing. Secondly, the fact that early multisensory convergence can occur through feedback as well as feedforward circuits highlights the potential higher order functions of low-level sensory cortices. On one hand, it is likely that the recruitment of low level sensory areas into a brain circuit underlying the conscious experience of a stimulus is partially attributable to feedback-dependent processes that occur relatively late in post stimulus time [28,29,46]. Thus, the evolving concept of the sensory processing hierarchy should incorporate a temporal as well as an anatomical dimension [46]. On the other hand, it is clear that multisensory input is also available

through feedforward circuits at the onset of processing in low-level sensory areas such as CM auditory cortex. Findings of this sort may eventually cause us to change how we think about low level sensory processing.

Acknowledgements

Sincere appreciation to T. McGinnis, Deirdre Foxe and Noelle O'Connell for their valuable technical and conceptual assistance. This work was supported in part by grants from the National Institute of Mental Health (MH61989-CES, MH60358-CES, MH63434-JJF).

References

- [1] L.A. Benevento, J. Fallon, B.J. Davis, M. Rezak, Auditory–visual interaction in single cells in the cortex of the superior temporal sulcus and the orbital frontal cortex of the macaque monkey, *Exp. Neurol.* 57 (1977) 849–872.
- [2] C. Bruce, R. Desimone, C.G. Gross, Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque, *J. Neurophysiol.* 46 (1981) 369–384.
- [3] H. Burton, R. Sinclair, *Somatosensory Cortex and Tactile Perceptions*. Pain and Touch, Academic Press, 1996, Chapter 3.
- [4] G.A. Calvert, P. Hansen, S.D. Iversen, M.J. Brammer, Detection of audio–visual integration sites in humans by application of electrophysiological criteria to the bold effect, *Neuroimage* 14 (2001) 428–438.
- [5] G.A. Calvert, R. Campbell, M.J. Brammer, Evidence from functional magnetic resonance imaging of cross-modal binding in human heteromodal cortex, *Curr. Biol.* 10 (2000) 649–657.
- [6] G.A. Calvert, M. Brammer, E.T. Bullmore, R. Campbell, S.D. Iversen, A.S. David, Response amplification in sensory-specific cortices during crossmodal binding, *Neuroreport* 10 (1999) 2619–2623.
- [7] G.A. Calvert, E.T. Bullmore, M.J. Brammer, R. Campbell, S.C. Williams, P.K. McGuire, P.W. Woodruff, S.D. Iversen, A.S. David, Activation of auditory cortex during silent lipreading, *Science* 276 (1997) 593–596.
- [8] J.R. Duhamel, C.L. Colby, M.E. Goldberg, Ventral intraparietal area of the macaque: convergent visual and somatic response properties, *J. Neurophysiol.* 79 (1998) 126–136.
- [9] D.J. Felleman, D.C. Van Essen, Distributed hierarchical processing in the primate cerebral cortex, *Cereb. Cortex* 1 (1991) 1–47.
- [10] J.J. Foxe, I.A. Morocz, M.M. Murray, B.A. Higgins, D.C. Javitt, C.E. Schroeder, Multisensory auditory–somatosensory interactions in early cortical processing revealed by high-density electrical mapping [In Process Citation], *Brain Res. Cogn. Brain Res.* 10 (2000) 77–83.
- [11] K.G. Fu, T. Johnston, A.S. Shah, L. Arnold, J. Smiley, T.A. Hackett, P.E. Garraghty, C.E. Schroeder, Characterization of somatosensory input to auditory association cortex in macaques, *Soc. Neurosci. Abs.* (2001) 390.
- [12] M. Giard, F. Peronet, Auditory–visual integration during multimodal object recognition in humans: a behavioral and electrophysiological study, *J. Cogn. Neurosci.* 11 (1999) 473–490.
- [13] S.J. Givre, J.C. Arezzo, C.E. Schroeder, Effects of wavelength on the timing and laminar distribution of illuminance-evoked activity in macaque V1, *Vis. Neurosci.* 12 (1995) 229–239.
- [14] S.J. Givre, C.E. Schroeder, J.C. Arezzo, Contribution of extrastriate area V4 to the surface-recorded flash VEP in the awake macaque, *Vision Res.* 34 (1994) 415–438.
- [15] M.S. Graziano, X.T. Hu, C.G. Gross, Visuospatial properties of ventral premotor cortex, *J. Neurophysiol.* 77 (1997) 2268–2292.
- [16] M.S. Graziano, G.S. Yap, C.G. Gross, Coding of visual space by premotor neurons, *Science* 266 (1994) 1054–1057.
- [17] W.O. Gulden, O.J. Grusser, Is there a vestibular cortex?, *Trends Neurosci.* 21 (1998) 254–259.
- [18] T.A. Hackett, I. Stepniewska, J.H. Kaas, Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys, *J. Comp. Neurol.* 394 (1998) 475–495.
- [19] K. Hikosaka, E. Iwai, H. Saito, K. Tanaka, Polysensory properties of neurons in the anterior bank of the caudal superior temporal sulcus of the macaque monkey, *J. Neurophysiol.* 60 (1988) 1615–1637.
- [20] J. Hyvarinen, Y. Shelepin, Distribution of visual and somatic functions in the parietal associative area 7 of the monkey, *Brain Res.* 169 (1979) 561–564.
- [21] V. Jousmaki, R. Hari, Parchment-skin illusion: sound-biased touch, *Curr. Biol.* 8 (1998) R190.
- [22] H. Kosaki, T. Hashikawa, J. He, E.G. Jones, Tonotopic organization of auditory cortical fields delineated by parvalbumin immunoreactivity in macaque monkeys, *J. Comp. Neurol.* 386 (1997) 304–316.
- [23] L. Krubitzer, J. Clarey, R. Tweedale, G. Elston, M. Calford, A re-definition of somatosensory areas in the lateral sulcus of macaque monkeys, *J. Neurosci.* 15 (1995) 3821–3839.
- [24] L. Leinonen, Functional properties of neurones in the parietal retroinsular cortex in awake monkey, *Acta Physiol. Scand.* 108 (1980) 381–384.
- [25] L. Leinonen, J. Hyvarinen, A.R. Sovijarvi, Functional properties of neurons in the temporo-parietal association cortex of awake monkey, *Exp. Brain Res.* 39 (1980) 203–215.
- [26] S. Levanen, V. Jousmaki, R. Hari, Vibration-induced auditory cortex activation in a congenitally deaf adult, *Curr. Biol.* 8 (1998) 869–872.
- [27] P. Mazzoni, R.M. Bracewell, S. Barash, R.A. Andersen, Spatially tuned auditory responses in area LIP of macaques performing delayed memory saccades to acoustic targets, *J. Neurophysiol.* 75 (1996) 1233–1241.
- [28] A.D. Mehta, C.E. Schroeder, Intermodal selective attention in monkeys II: physiologic mechanisms of modulation, *Cereb. Cortex* 10 (2000) 359–370.
- [29] A.D. Mehta, I. Ulbert, C.E. Schroeder, Intermodal selective attention in monkeys I: distribution and timing of effects across visual areas, *Cereb. Cortex* 10 (2000) 343–358.
- [30] S. Molholm, W. Ritter, M.M. Murray, D.C. Javitt, C.E. Schroeder, J.J. Foxe, Multisensory auditory–visual interactions during early sensory processing in humans: a high-density electrical mapping study, *Cogn. Brain Res.* (this issue).
- [31] A. Morel, P.E. Garraghty, J.H. Kaas, Tonotopic organization, architectonic fields, and connections of auditory cortex in macaque monkeys, *J. Comp. Neurol.* 335 (1993) 437–459.
- [32] L.G. Nowak, J. Bullier, The timing of information transfer in the visual system, *Cereb. Cortex* 12 (1993) 205–241.
- [33] D.N. Pandya, M. Hallett, S.K. Kmukherjee, Intra- and interhemispheric connections of the neocortical auditory system in the rhesus monkey, *Brain Res.* 14 (1969) 49–65.
- [34] N.N. Peterson, C.E. Schroeder, J.C. Arezzo, Neural generators of early cortical somatosensory evoked potentials in the awake monkey, *Electroencephalogr. Clin. Neurophysiol.* 96 (1995) 248–260.
- [35] J.P. Rauschecker, B. Tian, T. Pons, M. Mishkin, Serial and parallel processing in rhesus monkey auditory cortex, *J. Comp. Neurol.* 382 (1997) 89–103.
- [36] G. Rizzolatti, C. Scandolara, M. Gentilucci, R. Camarda, Response properties and behavioral modulation of ‘mouth’ neurons of the postarcuate cortex (area 6) in macaque monkeys, *Brain Res.* 225 (1981) 421–424.

- [37] G. Rizzolatti, C. Scandolara, M. Matelli, M. Gentilucci, Afferent properties of periarcuate neurons in macaque monkeys. I. Somatosensory responses, *Behav. Brain Res.* 2 (1981) 125–146.
- [38] G. Rizzolatti, C. Scandolara, M. Matelli, M. Gentilucci, Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses, *Behav. Brain Res.* 2 (1981) 147–163.
- [39] C.J. Robinson, H. Burton, Organization of somatosensory fields in areas 7b, retroinsula, postauditory, and granular insula of *M. fascicularis*, *J. Comp. Neurol.* 192 (1980) 69–92.
- [40] K.S. Rockland, D.N. Pandya, Laminar origins and terminations of cortical connections in the occipital lobe in the rhesus monkey, *Brain Res.* 179 (1979) 3–20.
- [41] A.W. Roe, S.L. Pallas, J.O. Hahm, M. Sur, A map of visual space induced in primary auditory cortex, *Science* 250 (1990) 818–820.
- [42] L.M. Romanski, B. Tian, J. Fritz, M. Mishkin, P.S. Goldman-Rakic, J.P. Rauschecker, Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex, *Nat. Neurosci.* 2 (2000) 1131–1136.
- [43] L.M. Romanski, J.F. Bates, P.S. Goldman-Rakic, Auditory belt and parabelt projections to the prefrontal cortex in the rhesus monkeys, *J. Comp. Neurol.* 403 (1999) 141–157.
- [44] M. Schmolesky, Y. Wang, D.P. Hanes, K.G. Thompson, S. Leutgeb, J.D. Schall, A.G. Leventhal, Signal timing across the macaque visual system, *J. Neurophysiol.* 79 (1998) 3272–3278.
- [45] C.E. Schroeder, R.W. Lindsley, C. Specht, A. Marcovici, J.F. Smiley, D.C. Javitt, Somatosensory input to auditory association cortex in the macaque monkey, *J. Neurophysiol.* 85 (2001) 1322–1327.
- [46] C.E. Schroeder, A.D. Mehta, J.J. Foxe, Determinants and mechanisms of attentional modulation of neural processing, *Front. Biosci.* 6 (2001) D672–684.
- [47] C.E. Schroeder, A.D. Mehta, S.J. Givre, A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque, *Cereb. Cortex* 8 (1998) 575–592.
- [48] C.E. Schroeder, D.C. Javitt, M. Steinschneider, A.D. Mehta, S.J. Givre, H.G. Vaughan Jr., J.C. Arezzo, *N*-methyl-d-aspartate enhancement of phasic responses in primate neocortex, *Exp. Brain Res.* 114 (1997) 271–278.
- [49] C.E. Schroeder, S. Seto, P.E. Garraghty, Emergence of radial nerve dominance in median nerve cortex after median nerve transection in an adult squirrel monkey, *J. Neurophysiol.* 77 (1997) 522–526.
- [50] C.E. Schroeder, S. Seto, J.C. Arezzo, P.E. Garraghty, Electrophysiologic evidence for overlapping dominant and latent inputs to somatosensory cortex in squirrel monkeys, *J. Neurophysiol.* 74 (1995) 722–732.
- [51] C.E. Schroeder, C.E. Tenke, S.J. Givre, J.C. Arezzo, H.G. Vaughan Jr., Striate cortical contribution to the surface-recorded pattern-reversal VEP in the alert monkey, *Vision Res.* 31 (1991) 1143–1157.
- [52] C.E. Schroeder, C.E. Tenke, S.J. Givre, J.C. Arezzo, H.G. Vaughan Jr., Laminar analysis of bicuculline-induced epileptiform activity in area 17 of the awake macaque, *Brain Res.* 7 (1990) 326–330.
- [53] B. Seltzer, D.N. Pandya, Converging visual and somatic sensory cortical input to the intraparietal sulcus of the rhesus monkey, *Brain Res.* 192 (1980) 339–351.
- [54] B. Seltzer, D.N. Pandya, Afferent cortical connections and archeitecture of the superior temporal sulcus and surrounding cortex in the rhesus monkey, *Brain Res.* 149 (1978) 1–24.
- [55] B.E. Stein, M.A. Meredith, in: *The Merging of the Senses*, MIT Press, Cambridge, MA, 1993, p. 224.
- [56] M. Steinschneider, D.H. Reser, Y.I. Fishman, C.E. Schroeder, J.C. Arezzo, Click train encoding in primary auditory cortex of the awake monkey: evidence for two mechanisms subserving pitch perception, *J. Acoust. Soc. Am.* 104 (1998) 2935–2955.
- [57] M. Steinschneider, C.E. Schroeder, J.C. Arezzo, H.G. Vaughan Jr., Speech-evoked activity in primary auditory cortex: effects of voice onset time, *Elecroencephalogr. Clin. Neurophysiol.* 92 (1994) 30–43.
- [58] M. Sur, S.L. Pallas, A.W. Roe, Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex, *Trends Neurosci.* 13 (1990) 227–233.
- [59] L. von Melchner, S.L. Pallas, M. Sur, Visual behaviour mediated by retinal projections directed to the auditory pathway, *Nature* 404 (2000) 871–876.