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Subthreshold auditory inputs to extrastriate visual neurons are responsive to parametric changes in stimulus quality: Sensory-specific versus non-specific coding

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Abstract

A new subthreshold form of multisensory processing has been recently identified that results from the convergence of suprathreshold excitatory inputs from one modality with subthreshold inputs from another. Because of the subthreshold nature of the second modality, descriptive measures of sensory features such as receptive field properties or location are not directly apparent as they are for traditional bimodal neurons. This raises the question of whether or not subthreshold signals actually convey sensory-specific receptive field information as seen in their bimodal counterparts, or if they represent non-specific effects such as arousal. The present experiment addressed this issue in visually-responsive neurons from the cat posterolateral lateral suprasylvian cortex (PLLS). Single-unit electrophysiological techniques were used to record neuronal responses to visual, auditory and combined visual-auditory stimuli while the intensity of stimulation in the subthreshold auditory modality was systematically altered. The results showed that subthreshold multisensory neurons were sensitive to changes in auditory stimulus intensity. These receptive field sensitivities are similar to those observed in bimodal neurons and thereby represent sensory-specific, not arousal-related responses. In addition, these results provide further support for the notion that multisensory processing occurs along a dynamic continuum of neuronal convergence patterns from bimodal to purely sensory-specific.

Keywords

Crossmodal; Multisensory; Modulation; Bimodal; Arousal; Non-specific sensory activation

1. Introduction

Until very recently, the only neuronal model of multisensory processing was that of the bimodal neuron. These multisensory neurons are recognized by their discharges in response to independent presentation of stimuli from more than one modality (e.g., respond to visual alone and to auditory alone, etc.). Being relatively easy to identify by this simple yet definitive property, bimodal neurons have been observed in organisms with nervous systems across phylogeny and throughout the neuroaxis (see Stein and Meredith, 1993 for review). Such

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apparent prevalence naturally underscored their robustness as a model of multisensory processing. Furthermore, because of the suprathreshold nature of their response, it has been easy to establish direct correlations between their firing rates and their response preferences. Consequently, not only could each of a bimodal neuron's receptive fields be mapped, but each of their specific response preferences could also be examined and quantified, such as response threshold, visual direction selectivity, auditory binaural character, or tactile spatial summation, to name but a few.

As described recently (Allman and Meredith, 2007; Dehner et al., 2004), a new form of multisensory neuron has been identified. This neuron vigorously responds to stimulation from only one modality, but this response can be significantly modified by inputs from another modality which appears ineffective when presented alone. Because of these physiological properties, this form of multisensory neuron has been designated as “subthreshold,” although other authors also use the term “modulated/modulatory” to describe the same effect (Driver and Noesselt, 2008). Subthreshold multisensory neurons have been described in the cat anterior ectosylvian (AES; Dehner et al., 2004; Meredith, 2002; Meredith et al., 2006) and posterolateral lateral suprasylvian (PLLS; Allman and Meredith, 2007) cortices, although this form of multisensory processing also appears in figures in several other reports (Barraclough et al., 2005; Bizley et al., 2007; Newman and Hartline, 1981; Sugihara et al., 2006). In the case of the PLLS, subthreshold multisensory neurons discharged in response to visual, but not auditory, stimulation, but when visual and auditory cues were combined, the response was significantly facilitated (Allman and Meredith, 2007). However, given that the auditory input in this case was subthreshold, it was not apparent if the auditory-induced effects were spatially delimited or if they were sensitive to parametric changes in stimulation quality. In other words, it has not been determined if subthreshold inputs to multisensory neurons encode information that is sensitive to the physical qualities of the stimuli they represent. If not, then subthreshold inputs may represent non-specific effects of sensory stimulation, such as arousal. If so, then these basic similarities among subthreshold and suprathreshold multisensory processing indicate that subthreshold signals may simply represent scaled-down versions of their suprathreshold counterparts. The present experiment addressed this question using quantitative electrophysiological recording and stimulation methods in which the physical properties of the subthreshold stimulation modality were systematically altered.

2. Results

A total of 4 recording penetrations traversed the lateral bank of the lateral suprasylvian sulcus that contains PLLS, as confirmed by reconstruction of the recording tracks (shown in Figure 1) and correlation with reported receptive field progressions across the region (Palmer et al., 1978). Similar to our previous findings in this area (Allman and Meredith, 2007), qualitative sensory testing revealed unimodal auditory neurons near the lip of the PLLS sulcus (presumably in Area DZ; Stecker et al., 2005), unimodal visual neurons deeper within the bank toward the fundus, and bimodal (auditory-visual) neurons wedged between the two groups. For this investigation, the auditory and bimodal neurons were not studied further, but a total of 127 visual neurons were tested quantitatively for the presence of subthreshold auditory influences.

Stimulation intensity effects

A total of 127 PLLS neurons were tested for their responses to separate and combined presentations of visual and auditory stimuli in which the auditory cues occurred at three different intensities (66, 75 or 81dB SPL). Of these neurons, 35% ($n=45/127$) had their visual response significantly facilitated by a concurrent auditory stimulus that was ineffective when presented alone. A representative example of the results of such tests is shown in Figure 2,

where the response of a subthreshold multisensory neuron to a visual stimulus was slightly increased when combined with the lowest intensity auditory stimulus (VA66 dB). However, the visual response was significantly facilitated when presented in combination with auditory stimuli at the intermediate (VA75 dB) and loudest (VA81 dB) intensities.

A similar incremental effect was seen at the population level, as displayed in Figure 3. Here, the response of each subthreshold multisensory neuron to the visual stimulus alone was plotted against its response to the combined stimuli for each of the three different auditory intensity conditions. For the population of subthreshold multisensory neurons ($n=45$) presented the different visual/auditory-intensity combinations, the slopes of the lines fit to the scatter plots increased progressively with the intensity of the auditory stimulus (VA66dB slope=1.19, $r^2=0.95$; VA75dB slope=1.22, $r^2=0.90$; VA81dB slope=1.26, $r^2=0.95$). Note, also, that for each intensity condition, all of the data points plotted above the line of unity. Ultimately, the average response of the population of subthreshold multisensory neurons was calculated for the different auditory intensities, as depicted in Figure 4. For the population, when the lowest intensity auditory stimulus was combined (VA66dB), there was an average increase of 2.4 spikes/trial representing a statistically significant 25% increase over that elicited by the visual stimulus alone. The intermediate intensity auditory stimulus combination (VA75dB) yielded an average increase of 3.0 spikes/trial over that evoked by the visual stimulus alone, representing a statistically significant 31% increase. For the same population, the loudest auditory stimulus combination (VA81dB) yielded the largest average increase in spikes/trial (3.1), representing a significant 32% increment over that produced by the visual stimulus alone as well as a significant increase above that elicited by the lowest auditory intensity stimulus combination (VA66dB versus VA81dB). Collectively, both the single neuron and population results indicate that progressive, not all-or-nothing, changes in subthreshold responses occur as a result of parametric changes in stimulation intensity.

3. Discussion

These results show that the subthreshold multisensory processing in PLLS neurons appears to be based on a receptive field structure and its properties. All subthreshold auditory effects were generated with stimuli presented in the contralateral auditory field, which is consistent with known binaural inputs to auditory cortex (Brugge and Merzenich, 1973; Imig and Adrian, 1977; Middlebrooks et al., 1980). Furthermore, progressive increases in auditory stimulus intensity resulted in concomitant response changes, which is also a common response feature observable in many auditory cortices. In fact, numerous parametric studies of stimulus feature processing have been conducted in each of the sensory systems, as well as for bimodal multisensory neurons (Meredith and Stein, 1986; Perrault et al., 2005). These investigations showed that multisensory neurons directly alter their discharge rates in relation to systematic increases (or decreases) in stimulus effectiveness. Similarly, multisensory neurons that show receptive field properties such as direction selectivity, velocity tuning, spatial summation, etc., preserve these same properties when in the presence of multisensory stimulation (Stein et al., 1993). This same, general sensory principle was obeyed by subthreshold multisensory PLLS neurons of the present study which showed increases in response facilitation corresponding to increases in auditory stimulation intensity.

Due to the temporal configuration of stimuli used in the present experiment, these data indicate that subthreshold auditory influences on visual processing can occur in relation to stimuli that occur up to 15-17 meters distant to the animal. The potential to code increases in stimulus intensity also contributes to the functional basis for another of the principles of multisensory integration identified as the property of “inverse effectiveness.” Identified in bimodal neurons, but also observed in areas of primate sensory cortex (Kayser et al., 2005; 2007), this phenomenon describes the negative relationship between the effectiveness of the stimulation

with the proportion of multisensory integration produced (Meredith and Stein, 1986). However, this inverse effect was not directly addressed in the present study, since the effectiveness of the visual stimulation was not modulated here.

Non-specific cortical activation?

An alternate interpretation for subthreshold multisensory processing in cortex might be that these inputs represent non-spiking effects that result from changes in arousal. It is well-known that sensory information can also reach cortex through what is regarded as 'non-specific' pathways, designated as the ascending reticular activating system (for review, see Gottesmann, 1999; Lin, 2000). Originating in the mesencephalic and medullary reticular formation, these areas receive convergent somatic, visceral, auditory, vestibular and visual information (Blair and Thompson, 1995; Heym et al., 1982; Rasmussen et al., 1986) and project to the 'nonspecific regions' of the thalamus, including the midline and intralaminar thalamic nuclei (Fuller, 1975; Krout et al., 2002; Lin, 2000; Steriade and Glenn, 1992). Collectively, these thalamic nuclei have broad projections to diencephalic and telencephalic regions, including primary sensory and association cortices (Van der Werf et al., 2002). Activation of this system, either in the brainstem (Munk et al., 1996; Wu et al., 2007) or thalamus (MacDonald et al., 1998) has long been known to affect cortex through desynchronization of ongoing oscillatory behavior of its principal neurons (e.g., Munk et al., 1996). Cortical desynchronization, which is characterized by a low-amplitude fast EEG in the 20-60 Hz range, is critical for fast, efficient execution of cortical processing but does not alter the specificity of cortical responses to sensory stimuli (Steriade, 1996). Furthermore, although cortical desynchronization can far outlast the duration of the initiation stimulus, sensory stimulation is adequate, but not necessary, for cortical desynchronization. Curiously, in contrast to the hundreds of anatomical and behavioral studies of the ascending reticular activating system, there is scant physiological data regarding the specific sensory properties required to trigger the system.

A corollary of the cortical arousal system is the brainstem startle reflex, in which intense and/or novel auditory, tactile, vestibular or visual stimulation evoke strong, bilateral co-contraction of flexor muscles (for review, see Koch, 1998; Yeomans and Frankland, 1995; Yeomans et al., 2002). The neural basis for the startle reflex resides in neurons in the nucleus reticularis pontis caudalis, which are known to receive short latency tactile, acoustic and vestibular input (Yeomans et al., 2002) that, in turn, project directly to vast numbers of brainstem and spinal cord motor neurons (for review, see Yeomans and Frankland, 1995). Neurons in this pontine reticular nucleus exhibit consistently high auditory response thresholds (>80dB SPL) as well as response habituation to repeated stimuli (Wu et al., 1988). Somatosensory activation frequently required forceful stimulation and receptive fields were often bilateral (Seigel and Tomaszewski, 1983). Thus, stimulus adequacy for startle responses apparently only requires meeting an all-or-nothing threshold.

Sensory specific cortical activation

Given these features of 'non-specific,' alerting/arousal phenomena, it is evident that the present results are **NOT** consistent with them. Not only are the subthreshold multisensory effects reliably elicited by repeated (e.g., are not novel), low intensity stimuli (e.g., below 80 dB SPL requirement for startle), the responses are parametrically related to changes in auditory stimulation intensity. Furthermore, preliminary tests using auditory stimuli at different spatial locations indicate that subthreshold effects are elicited by stimuli presented in a limited (contralateral) region of sensory space. In addition, the temporal effects of subthreshold stimulation appear to be much shorter than the duration of cortical desynchronization, since subthreshold influences were not maintained through the subsequent visual-only trials that sometimes occurred only 3-7 seconds later. Ultimately, the subthreshold auditory effects were not observed in every neuron. Thus, rather than a generally distributed product observed over

all susceptible neurons—as that which results from cortical arousal—auditory inputs to PLLS neurons appear to specifically target some neurons but not others.

Collectively, the present results and their implications indicate that subthreshold auditory influences observed in visual PLLS neurons are sensory in nature and undoubtedly contribute to the role of the retinotopically-organized region (Palmer et al., 1978) in visual motion processing (Rauschecker et al., 1987). These observations are also consistent with the receptive field-based sensory processing that occurs in bimodal multisensory neurons. This possibility is important for its implications for the general principles of multisensory architecture. On the one hand, it certainly is possible that there are myriads of pools of different forms of multisensory neuron, each dedicated to a particular processing task. Alternatively, there may be a single pattern of multisensory convergence that is stretched over a continuum from completely bimodal neurons at one end, to purely sensory-specific ('unimodal') at the other. Such a continuum for multisensory convergence is consistent with the range of sensory-specific ('unimodal'), subthreshold multisensory, and bimodal neurons observed in the PLLS.

4. Experimental Procedure

All procedures were performed in compliance with the Guide for Care and Use of Laboratory Animals (NIH publication 86-23), the National Research Council's Guidelines for Care and Use of Mammals in Neuroscience and Behavioral Research (2003), and the Institutional Animal Care and Use Committee at Virginia Commonwealth University. The surgical and experimental procedures were similar to those described previously for examining the PLLS cortex in cat (Allman and Meredith, 2007).

Surgical Procedures

Adult cats ($n=3$) were anesthetized with sodium pentobarbital (40 mg/kg with supplemental doses as necessary) and their heads placed in a stereotaxic frame. Under aseptic conditions, a craniotomy was performed to expose the PLLS cortex. Over the craniotomy, a stainless steel recording well was secured to the animal's head, using screws and dental acrylic, to provide access to the PLLS cortex during the recording experiment. The scalp was then sutured around the recording well. Routine postoperative care was provided for ~7 days, at which time the recording experiment was conducted.

Electrophysiological Recording Procedures

Recording sessions began by anesthetizing the animals (35 mg/kg Ketamine; 2 mg/kg Acepromazine) and securing the implanted recording well to a supporting bar. This allowed the head to be supported without obstructing the eyes or ears of the animal during the following sensory testing procedures. The animals were intubated through the mouth and maintained on a ventilator with expired carbon dioxide at ~4.5%. Heart rate and body temperature were monitored and a heating pad was used to maintain temperature at ~37°C. An intravenous line was placed in the saphenous vein for continuous administration of fluids and supplemental anesthetics (Ketamine 8 mg/kg/h; Acepromazine 0.5 mg/kg/h), and a muscle relaxant (Pancuronium bromide 0.3 mg/kg initial dose; 0.2 mg/kg/h supplement) was included to prevent spontaneous movements.

For extracellular recording, a glass-insulated tungsten electrode (tip exposure ~20 μm and impedance <1 M Ω) was inserted through the recording well into the PLLS cortex and advanced using a hydraulic microdrive. Neuronal activity was amplified, displayed on an oscilloscope and played on an audiomonitor. Electrode penetrations spanned from the lip of the PLLS sulcus, where the auditory Dorsal Zone (DZ) is found (Stecker et al. 2005), to the fundus of the PLLS cortex. Neurons were isolated regularly at 125 or 250 μm intervals along an electrode

penetration. Once a neuron was isolated, its sensory responses were characterized qualitatively at first, using manually presented stimuli. Auditory search stimuli were clicks, claps, whistles and hisses; visual search stimuli consisted of moving light or dark bars projected onto a translucent hemisphere (92 cm diameter) positioned in front of the animal.

To quantitatively examine the potential for subthreshold auditory inputs to influence visual responses, non-bimodal visually-responsive neurons were presented computer-triggered visual ('V,' moving light bar projected on translucent hemisphere using a galvanometer-driven mirror) and auditory stimuli ('A,' free-field, 100 ms duration, white noise, 10 ms shaped rise-fall gates from a hoop-mounted speaker (Tucker-Davis Technologies model ES1) 44 cm from the head), presented alone or in combination ('VA'). Visual stimulus movement direction, velocity and amplitude were independently controlled. For the combined VA conditions, the onset of the visual stimulus preceded the auditory stimulus by 50 ms to compensate for the latency differences between these two modalities. To assess whether systematic changes in the quality of the auditory stimulus would evoke parallel subthreshold response changes, auditory cues of different, preset intensity (SPL=66, 75 and 81dB) were presented alone or in combination with the standard, effective visual stimulus. Each separate (V, A66dB, A75dB, A81dB) or combined stimulus (VA66dB, VA 75dB, VA81dB) was repeated (25 times each) in a randomized fashion with 3-7 seconds between presentations. The visual stimulus was always presented within its receptive field and maintained the same stimulus qualities throughout. Auditory stimuli were presented in spatial register with the visual receptive field.

Data Analysis

For each data file collected, Spike2 software (Cambridge Electronic Design) was used to discriminate individual neurons using templates of the recorded action potentials. For each distinct waveform (i.e., single neuron), a peristimulus-time histogram was constructed for each stimulus condition. From the histogram, the response duration was determined and, for that response period, the mean spikes per trial and standard deviation were calculated. These results from individual neurons for each parametric intensity trial were tabulated and compared to assess whether stimulation-dependent response changes occurred.

Cross-modal effects were statistically evaluated at two levels. First, for each visual neuron tested, the mean spikes/trial from the visual condition was compared to the different combined visual-auditory conditions. Because these neurons showed no suprathreshold responses to auditory stimuli, and activity during acoustic stimulation resembled spontaneous levels, the mean spikes/trial for the auditory-alone condition was not a factor. When the response to any of the combined visual-auditory conditions was compared with that elicited by the visual-alone condition, those that showed a significant (paired 't'-test; $P < 0.05$) response change were classified as subthreshold multisensory responses (Allman and Meredith, 2007). In the second form of analysis, data from individual subthreshold multisensory neurons were grouped by treatment from which the population average (mean spikes/trial for) was calculated and compared using paired t-tests corrected for multiple pairwise comparisons (Bonferroni). In this manner, it was determined if the sample population of PLLS neurons were significantly influenced by auditory intensity and which condition was most effective at the population level.

Recording Site Reconstruction

The depth of each identified neuron within a penetration was noted and correlated with the results of the quantitative sensory tests. At the conclusion of each recording penetration a small electrolytic lesion (0.3 mA for 0.5 s) was made to facilitate histological reconstruction of the data. When the recording was finished, the animals received a barbiturate overdose and were perfused intracardially with saline followed by 10% formalin. The brains were then blocked stereotactically, removed and postfixed in 30% sucrose/formalin. Frozen sections (50 μ m) were

cut in the coronal plane through the recording sites, processed using standard histological procedures and counterstained. A projecting microscope was used to trace sections and reconstruct the recording penetrations.

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Figure 1.

Location of recording penetrations in posterolateral lateral suprasylvian (PLLS) visual area of the cat cortex. The schematic of the lateral view of cat cortex shows the anterior-posterior level corresponding to the 3 coronal sections (A-C). The coronal sections reveal the location of the PLLS area (shaded grey) and the 4 recording penetrations (grey lines). The thick, black arrows indicate the lateral suprasylvian sulcus.

Figure 2.

Changes in the intensity of auditory stimulation resulted in concomitant response changes for a representative subthreshold multisensory neuron. As indicated by the response rasters and histograms, this PLLS neuron showed a strong response to a visual stimulus ($V=9.8\pm4.5$ mean spikes/trial $\pm$ standard deviation), but not to the auditory stimulus presented alone (A81dB). When auditory stimuli of different preset intensities (66, 75 or 81dB) were presented in combination with the visual stimulus, the response was increased for each stimulus pair ($VA_{66dB}=11.4\pm3.9$; $VA_{75dB}=13.5\pm4.5$; $VA_{81dB}=13.0\pm4.8$) and was significantly facilitated (* * , $P<0.05$) at the louder intensities (VA_{75dB} , VA_{81dB}). The bar graph summarizes these incremental response changes correlated with progressive changes of intensity of the stimulus. Mean spontaneous activity = Sp.

Figure 3.

Responses of subthreshold multisensory neurons to combined stimuli (VA; y-axis) were consistently greater than the responses to the visual stimuli alone (V; x-axis); hence, they plotted above the line of unity (dashed). A separate plot is presented for each of the auditory stimulus intensity conditions, where it can be seen that the slope of the fitted lines (solid) increased progressively with increases in the intensity of the auditory stimulus (VA66dB slope=1.19; VA75dB slope=1.22; VA81dB slope=1.26).

Figure 4.

Average response levels (mean spikes/trial $\pm$ standard error of the mean) for the population of subthreshold multisensory neurons ($n=45$) to visual stimulation alone ($V=9.7\pm1.1$) were significantly (** , $P<0.05$) and incrementally facilitated by the presence of progressively louder auditory stimuli ($VA66dB=12.1\pm1.3$; $VA75dB=12.7\pm1.2$; $VA81dB=12.8\pm1.3$). Furthermore, not only did the loudest auditory combination ($VA81dB$) produce the strongest average response as well as the largest response change, it was also statistically greater (*† , $P<0.05$) than the combined response involving the lowest auditory stimulus ($VA81dB>VA66dB$).