Superior Colliculus Neurons Use Distinct Operational Modes in the Integration of Multisensory Stimuli

Thomas J. Perrault, Jr., J. William Vaughan, Barry E. Stein, and Mark T. Wallace
Department of Neurobiology and Anatomy, Wake Forest University School of Medicine, Winston-Salem, North Carolina

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Perrault, Thomas J. Jr., J. William Vaughan, Barry E. Stein, and Mark T. Wallace. Superior colliculus neurons use distinct operational modes in the integration of multisensory stimuli. J Neurophysiol 93: 2575–2586, 2005. First published January 5, 2005; doi:10.1152/jn.00926.2004. Many neurons in the superior colliculus (SC) integrate sensory information from multiple modalities, giving rise to significant response enhancements. Although enhanced multisensory responses have been shown to depend on the spatial and temporal relationships of the stimuli as well as on their relative effectiveness, these factors alone do not appear sufficient to account for the substantial heterogeneity in the magnitude of the multisensory products that have been observed. Toward this end, the present experiments have revealed that there are substantial differences in the operations used by different multisensory SC neurons to integrate their cross-modal inputs, suggesting that intrinsic differences in these neurons may also play an important deterministic role in multisensory integration. In addition, the integrative operation employed by a given neuron was found to be well correlated with the neuron’s dynamic range. In total, four categories of SC neurons were identified based on how their multisensory responses changed relative to the predicted addition of the two unisensory inputs as stimulus effectiveness was altered. Despite the presence of these categories, a general rule was that the most robust multisensory enhancements were seen with combinations of the least effective unisensory stimuli. Together, these results provide a better quantitative picture of the integrative operations performed by multisensory SC neurons and suggest mechanistic differences in the way in which these neurons synthesize cross-modal information.

INTRODUCTION

Neurons in the superior colliculus (SC) are able to alter their sensitivity to external events by integrating inputs that they derive from different sensory channels. Many neurons in the SC receive combinations of visual, auditory, and somatosensory inputs, and their multisensory responses differ significantly from those evoked by any of their unisensory inputs (Bell et al. 2001; Binns and Salt 1996; Frens and Van Opstal 1998; Jiang et al. 2001; King and Palmer 1985; Meredith and Stein 1986a; Peck 1996; Perrault et al. 2003; Populin and Yin 2002; Wallace et al. 1996). The ability to integrate sensory information in this way is of substantial value in facilitating the role of the SC in controlling orientation behaviors (Stein et al. 1989).

Previous work has shown that multisensory interactions in SC neurons (and in multisensory neurons in other brain structures) (see Brett-Green et al. 2003; Calvert et al. 2001; Chudler et al. 1995; Duhamel et al. 1998; Fuster et al. 2000; Wallace et al. 1992, 2004) are critically dependent on the spatial and temporal relationships of the cross-modal stimuli that are presented as well as on their physical characteristics. For example, when presented with cross-modal stimuli in close spatial and temporal proximity, an SC neuron typically exhibits a significantly enhanced response, whereas when those same stimuli are displaced from one another in space and/or time, that neuron either fails to integrate them (i.e., they are dealt with as 2 separate events) or the integration results in a depressed response (Jiang and Stein 2003; Kadunce et al. 1997, 2001; Meredith et al. 1987; Meredith and Stein 1986a, b, 1996). Additionally, the magnitude of the response enhancement has been found to be greatest when the individual components of the multisensory stimulus are weakly effective when presented on their own (Meredith and Stein 1986a). As these stimuli become increasingly more effective, the magnitude of the response enhancement declines.

Collectively, these spatial, temporal, and inverse effectiveness principles of multisensory integration provide an important predictive framework for understanding how stimulus characteristics shape multisensory interactions in SC neurons. Furthermore, these principles have also been helpful in predicting the effects of various multisensory stimulus combinations on overt behaviors (Cornel et al. 2002; Diederich et al. 2003; Frens et al. 1995; Hughes et al. 1994, 1998; Jiang et al. 2002; Stein et al. 1989; Wilkinson et al. 1996). However, despite their utility, these principles are not sufficient to completely explain the wide range of multisensory interactions that can be observed in SC neurons. For example, whereas some neurons exhibit multisensory response enhancements several times greater than would be predicted based on the sum of their individual unisensory responses, others show maximum enhancements that are less than a simple addition of these responses. Such variability suggests that there are additional factors contributing to the multisensory product. One plausible possibility is that there are inherent differences in the capacity of different SC neurons to integrate their cross-modal inputs (Nozawa et al. 1994; Perrault et al. 2003; Quessy et al. 2000).

Given the importance of the magnitude of the unisensory response for the multisensory product (i.e., inverse effectiveness), we posited that one factor that may play an important role in multisensory interactions is a neuron’s dynamic range—the range of responses over which it codes stimulus changes. The present study examined the importance of this factor among visual-auditory SC neurons by systematically manipulating the effectiveness of the visual and auditory stimuli over
a neuron’s complete dynamic range and examining the consequences of such changes on the multisensory product. The data indicate that the underlying computational operation governing a multisensory response differs substantially among neurons with different dynamic ranges. Portions of this work have been published in abstract form (Perrault et al. 2000).

METHODS

All procedures were carried out in accordance with the National Institutes of Health guidelines for animal research and were in compliance with an approved protocol at the Wake Forest University School of Medicine, which is accredited by the American Association for the Accreditation of Laboratory Animal Care. All experiments were performed in three adult cats weighing 2.5–5.0 kg. Animals were prescreened for normal vision and hearing prior to inclusion in the study.

Implantation procedure

Prior to electrophysiological recording, a recording well/head-holding device was implanted in the skull (McHaife and Stein 1983). Animals were rendered tractable with an intramuscular injection of ketamine HCl (20 mg/kg) and acepromazine maleate (0.2–0.4 mg/kg). Anesthesia was induced and maintained with isoflurane (1–4%) after endotracheal intubation. During surgery, hydration was maintained with intravenous infusion of lactated Ringer solution (4–8 ml/h) via the saphenous vein. This was followed by postsurgical subcutaneous administration of lactated Ringer (30 ml/kg). During surgery, expiratory CO2 was monitored and maintained between 3.5 and 4.5%. Body temperature was monitored with a rectal probe and maintained at 37–38°C by means of a thermostatically regulated heating pad. Sterile artificial tears were placed in the eyes to prevent corneal drying during the duration of the procedure. To ensure adequate levels of anesthesia, the electroencephalogram (EEG) was recorded by means of a silver wire attached to a bone screw overlying frontoparietal cortex. A high-amplitude, synchronous EEG, indicative of a deeply anesthetized state, was maintained for the duration of the surgery. Once anesthetized, the animal was placed in a stereotaxic frame, and a craniotomy exposed the cortex overlying the SC. A high-amplitude, synchronous EEG, indicative of a deeply anesthetized state, was maintained for the duration of the surgery. Once anesthetized, the animal was placed in a stereotaxic frame, and a craniotomy exposed the cortex overlying the SC. A stainless steel chamber that provides access to the SC as well as holds sterile saline was affixed to the skull using stainless steel bone screws and orthopedic bone cement. The margin of the wound was trimmed to form a clean interface with the implant. Analgesics (butorphanol 0.1–0.4 mg/kg or ketoprofen 1–2 mg/kg) were given as needed during surgery. Once anesthetized (0.5% proparacaine hydrochloride ophthalmic solution), the animal was intubated and the head-holder was attached to a mounting plate to stabilize the head without wounds or pressure points. A cannula was placed in the saphenous vein for the continuous delivery of anesthetic (ketamine: 4–8 mg · kg⁻¹ · h⁻¹), paralytic (pancuronium bromide: 0.2 mg · kg⁻¹ · h⁻¹), and fluids (lactated Ringer: 4–8 ml/h). Paralysis and artificial respiration are necessary because eye movements can produce significant displacement of visual receptive fields. Maintenance of adequate levels of anesthesia was done by monitoring multiple vital signs, including expiratory CO2, heart rate, and EEG.

For purposes of receptive field mapping, the pupils were dilated with 1% atropine sulfate and corrective contact lenses were placed on the anesthetized (0.5% proparacaine hydrochloride ophthalmic solution) corneas to adjust for retinoscopically determined refractive errors. The corneas to adjust for retinoscopically determined refractive errors. The optic discs were rear-projected and focused onto a 91-cm-diameter translucent hemisphere placed 45 cm from the eyes. Receptive field maps acquired from multiple sessions in the same and different animals could then be registered by aligning the position of the optic disc. After each recording session (1–3/wk), paralysis and anesthesia were reversed, and on return of normal respiration and locomotion, the animal was returned to its home cage. Experiments generally lasted between 8 and 12 h.

Neuronal isolation and recording

Parylene-insulated tungsten microelectrodes (tip diameter: 1–3 µm, impedance: 1–3 MΩ at 1 kHz) were positioned via an X-Y translational stage and lowered to the dorsal surface of the SC (identified by characteristic visual activity) by means of a manually driven micro-manipulator. Once at the SC surface, the electrode was advanced into stratum opticum (the transitional layer between the superficial and deep SC) by means of a hydraulic microdrive. From here, the electrode was advanced in 10-µm steps while presenting visual and auditory search stimuli as in previous studies (Meredith and Stein 1986a; Wallace et al. 1993). Single units were isolated (criterion signal: noise = 3:1) and digitized by means of a window discriminator (FHC). Neural activity was amplified and monitored, and data were collected using a customized suite of software that employs the 1401 Plus data acquisition system (Cambridge Electronic Design). In the current study, only visual-auditory multisensory neurons were examined.

Sensory stimuli

Although stationary light flashes were the primary visual stimulus (because of the fixed temporal nature of the stimulus), moving visual stimuli were used as well. Stationary visual stimuli consisted of the 50- to 100-ms illumination of a light-emitting diode (LED; 660 nm λ) placed within the receptive field (see Receptive field mapping). Moving visual stimuli consisted of slits, bars, or spots of light projected onto the translucent hemisphere, the movement speed, amplitude, and

![FIG. 1. Visual and auditory dynamic response ranges were assessed using systematic increases of stimulus intensity. In this theoretical example of how dynamic ranges were determined, neuronal responses at 10 intensity levels are plotted. Note that in this procedure, 3 of the intensities are used to determine threshold (i.e., values 1–3), and 3 are used to determine saturation (i.e., values 8–10). These visual and auditory dynamic ranges were then used as the basis for multisensory testing using a procedure known as index matching. Here, stimuli of intensities at comparable points along the dynamic ranges (e.g., point 4 in the visual and auditory ranges) were paired to evaluate the neuron’s multisensory dynamic range.](http://jn.physiology.org/)

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FIG. 2. Examples and incidence of the different types of dynamic range categories found in multisensory superior colliculus (SC) neurons. Shown in the boxes are examples of visual and auditory dynamic range plots for representative neurons in the dual-modality dynamic range (DMDR, top left), single-modality dynamic range (SMDR, bottom), and no dynamic range (NDR, top right) categories. Note the differences in the response scales for these examples. Central pie graph shows the relative incidence of each of these neuron types.

FIG. 3. The size of the mean dynamic range for the auditory (■) and visual (○) modalities in SMDR neurons (left) and DMDR neurons (right). Note that there were no statistical differences in the size of the mean dynamic ranges between these categories (see text).

FIG. 4. In DMDR neurons, the size of the visual and auditory dynamic ranges was well correlated ($R^2 = 0.656, P < 0.01$). Each point plots the size of the visual dynamic range as a function of size of the auditory dynamic range for an individual neuron.
direction of which could be independently controlled. Whereas the intensity of stationary stimuli was computer controlled, the intensity of moving stimuli was controlled using neutral density filters. In both circumstances stimulus intensity ranged from 0.11 to 13.0 cd/m² with a background luminance of 0.10 cd/m². Auditory stimuli were delivered in a free-field setting and consisted of 50- to 100-ms duration broadband noise bursts (20 Hz to 10 kHz). These stimuli were digitally synthesized and delivered through speakers that could be positioned at any location in auditory space. Auditory stimulus intensities ranged from 50.6 to 70.0 dB sound pressure level (SPL) against a background SPL of 50.0 dB. For quantitative tests of multisensory integration, visual and auditory stimuli were typically delivered at the most sensitive location within the excitatory receptive field (see following text).

FIG. 5. Results of the index matching procedure for a representative DMDR neuron. A: rasters and histograms (10-ms time bins) show the visual (top), auditory (middle), and multisensory (bottom) responses at 3 index-matched points: index 2 (left), index 4 (center); and index 8 (right). B: line graphs show the auditory (○), visual (□), and multisensory (●) dynamic range plots for this neuron. Note that for all points along these response continua, multisensory responses exceed either of the unisensory responses and that the multisensory response saturates at levels far higher than either of the component responses. Square waves above the histograms depict the onset and offset of the visual (V) and auditory (A) stimuli.
Receptive field mapping

The borders of each visual receptive field were mapped onto the translucent hemisphere by moving the optimum stimulus, projected from a handheld pantoscope, from the periphery inward from all directions until an enclosed responsive area was defined. Auditory receptive fields were mapped using brief (50 ms) broadband noise bursts delivered from a speaker that could be positioned at any location on a hoop that could be freely rotated about the animal’s interaural axis. The typical steps in speaker location represented ~15° of auditory angle in both the azimuthal and elevation dimensions. The location of the stimulus was randomly varied, and a positive response (i.e., a location within the receptive field) was one in which the stimulus-evoked response was readily discernible above background activity. For purposes of receptive field mapping, auditory stimuli were 15 dB above the neuron’s previously determined threshold. Receptive fields were transposed from the hemisphere and plotted on standardized representations of visual and auditory space.

Dynamic range determination

To determine the intensities to be used in dynamic range testing, threshold and saturating stimulus intensities were first determined. For threshold determination, stimulus intensity was progressively lowered until no response was elicited from the neuron. The minimum intensity value that resulted in an observable response was set as threshold. For saturation determination, stimulus intensity was progressively raised until no observable increase in response was noted. The first intensity value at which the response no longer increased was set as the saturating intensity. For quantitative analysis of dynamic range, these two qualitatively chosen intensity values served as the upper and lower bounds, and a minimum of 10 intervening intensities were chosen to examine the neuron’s visual and auditory dynamic ranges. To determine the neuron’s multisensory dynamic range, these same 10+ intensities were then index-matched (Fig. 1). For example, a visual stimulus intensity that elicited a threshold response was paired with an auditory stimulus intensity that elicited a threshold response. Post hoc tests were used to determine if the chosen stimuli were adequate for assessing the neuron’s dynamic range. Using these tests, threshold was defined as the intensity that elicited a response that was 1 SD above mean spontaneous activity. Saturation was defined as the minimum intensity at which three successive increases in stimulus intensity failed to result in a significant increase in response. Neurons were said to have a dynamic range in a given modality if they contained a minimum of three intensity values that resulted in responses that could be statistically distinguished from one another. Conversely, neurons were determined to lack a dynamic range in a given modality if manipulations of stimulus intensity failed to yield any significant differences in response.

For all neurons, visual, auditory and combined visual-auditory (i.e., multisensory) trials were pseudorandomly interleaved, allowing for the simultaneous determination of uni- and multisensory dynamic ranges as well as the interactions elicited under multisensory conditions. For all trials, neuronal activity was recorded for 2–3 s with a 500-ms interval prior to stimulus presentation used to determine spontaneous activity. An interstimulus interval of 5–10 s was used to minimize adaptation, and a minimum of 15 trials per condition were collected.

Analyses

Two principal methods of analysis were used to examine the integrative characteristics of the sampled neurons. The first method was one that has been used in many prior studies of multisensory integration (Meredith and Stein 1983, 1986a,b; Wallace et al. 1993) and is termed the interactive index. This metric represents the relative change in a multisensory neuron’s dominant unisensory response (e.g., visual) induced by the concurrent presentation of a stimulus from the nondominant modality (e.g., auditory). The interactive index was computed using the following formula

\[
\left[\frac{CM - SM_{\text{max}}}{SM_{\text{max}}} \right] \times 100 = \% \text{ Interaction}
\]

where CM is the response evoked by the combined-modality stimulus, and SM_{\text{max}} is the response evoked by the most effective unisensory stimulus. Significant differences between CM and SM_{\text{max}} were determined using Student’s two-tailed t-test.

The second method of analysis was a calculation of multisensory contrast. This metric serves as a way of evaluating the multisensory response as a function of the response predicted by an addition of the two unisensory responses. Mean multisensory contrast was computed using the following formula

\[
\sum \left( \frac{A_{\text{off}}V_{\text{off}} - A_{\text{off}}V_{\text{on}} - (A_{\text{on}}V_{\text{on}} - A_{\text{on}}V_{\text{off}})}{n} \right)
\]

where \(n\) is the total number of trials; \(A_{\text{off}}V_{\text{off}}\) = response when no stimulus is present (i.e., spontaneous activity); \(A_{\text{on}}V_{\text{off}}\) = auditory re-

![Image](http://jn.physiology.org/doi/10.1152/jn.01084.2004)

**Fig. 6.** A: the mean size of the maximal multisensory response significantly exceeded that of either the visual or auditory responses (**t-test \(P < 0.01\)). B: when examined on a neuron-by-neuron basis, it can be seen that the maximal multisensory response was always larger than the maximal unisensory response. Line of unity represents equivalent multisensory and unisensory responses.
response; $A_{on}^* V_{on}$ = visual response; $A_{on} V_{on}$ = multisensory response. The model assumes that the visual and auditory inputs are independent, therefore additive factors logic was used to distinguish between subadditive (contrast < 0), additive (contrast = 0), and superadditive (contrast > 0) modes of response. Significant differences from zero (i.e., additivity) were assessed by means of a $t$-test (Nozawa et al. 1994).

**Histology and euthanasia**

The $x$-$y$ coordinates of each electrode penetration and the depth of each neuron from the dorsal surface of the SC were systematically recorded. During the final few recording sessions, a series of electrolytic lesions were made by injecting small currents (10–20 $\mu$A DC for
5–10 s) through the recording electrode. At the end of the final experiment, the animal was killed with an overdose of sodium pentobarbital (100 mg/kg iv) and perfused transcardially with saline followed by formalin (10%). The brain was blocked, and the SC was cut into 40–50 μm coronal frozen sections. Neuron locations were reconstructed from histologically prepared Nissl-stained sections using standard methods (Meredith and Stein 1986a,b).

**RESULTS**

**Visual and auditory dynamic ranges of multisensory SC neurons**

A total of 109 visual-auditory neurons were studied in the multisensory (i.e., below stratum opticum) SC layers. The responses from 84 of these neurons were examined in sufficient quantitative detail to allow a determination of their dynamic ranges to visual and auditory stimuli as well as to their multisensory combination. A neuron’s dynamic range was operationally defined as the mean difference in the number of spikes evoked at threshold and at saturation (see Methods for more detail on this procedure).

Multisensory SC neurons were divided into three general dynamic range categories on the basis of their responses to systematic changes in stimulus intensity (Fig. 2). The first category exhibited monotonic changes in response to changes in both visual and auditory stimulus intensity until saturation was achieved [dual-modality dynamic range neurons (DMDR), 29%]. In the second category, changes in stimulus intensity modulated neuronal responsiveness in only one of the two effective modalities. These single-modality dynamic range neurons (SMDR) represented approximately half of the total population with there being a nearly equal incidence of those having a visual (26%) and those having an auditory (23%) dynamic range. Finally, 22% of the neurons were unaffected by changes in stimulus intensity in either modality [no dynamic range neurons (NDR)].

A comparison of the size of the visual and auditory dynamic ranges, when present, of SMDR and DMDR neurons failed to reveal a main effect [ANOVA F(3,84) = 2.57, P = 0.06], even though there appeared to be a trend toward SMDR neurons having smaller dynamic ranges (Fig. 3). It is important to note here that these average values were calculated only for those cases where demonstrable dynamic ranges were apparent. Thus in SMDR neurons, the nonmodulated component of the responses (i.e., the modality in which there was no dynamic range) was not factored into the average. This was done for several reasons. First, the presence or absence of a dynamic range appears to represent a true categorical distinction (consequently, our NDR, SMDR, and DMDR divisions) likely to represent an underlying physiological process. Second, if such averaging was done, it would undoubtedly lower the SMDR dynamic range averages (because a number of 0’s would be factored into the average) and would suggest that SMDR dynamic ranges are more limited than DMDR dynamic ranges, a finding that the comparison shown in Fig. 3 suggests might be potentially misleading. Despite the similarities in the average size of the SMDR and DMDR dynamic ranges, there was substantial variability for any given SC neuron. Thus demonstrable visual dynamic ranges varied from 1.5 to 41.6 spikes/trial, and demonstrable auditory dynamic ranges varied from 1.0 to 40.1 spikes/trial. Interestingly, in dual-modality dynamic range neurons, there was a good correlation between the size of the visual and auditory dynamic ranges (Fig. 4).

**Multisensory dynamic ranges**

Dynamic ranges were also assessed in response to multisensory stimuli. To facilitate this analysis, visual and auditory stimuli were index matched for intensity (see Methods and Fig. 1), enabling an examination of the multisensory response profile at comparable points along the neuron’s unisensory dynamic ranges. An example of the results of this index matching is shown in Fig. 5 for a representative DMDR neuron. Note that the maximal multisensory responses exceeded the maximal unisensory responses. This general finding was found in each of the three dynamic range categories (NDR, SMDR, DMDR) as is evident in Fig. 6. Intriguingly, for a number of NDR neurons the presentation of multisensory stimuli effectively created a dynamic range where none was evident under conditions of unisensory stimulation.

**Multisensory integration across the dynamic range**

Multisensory integration was assessed at different points along each neuron’s dynamic range using two complementary metrics. First, the standard metric for assessing multisensory integration, the interactive index, was calculated. This measure, which has been the conventional for quantifying multisensory interactions, relates the multisensory response to the larger of the two unisensory responses and illustrates the proportionate gain provided by having a second channel of sensory information. The second metric was multisensory contrast. This measure relates the multisensory response to a model founded on the predicted sum of the two unisensory responses and provides a view as to the integrative operation performed by the neuron on these inputs. A contrast value of zero represents a response that is equivalent to the predicted addition of the two unisensory responses, positive contrast values (i.e., superadditivity) indicate multisensory responses exceeding the additive prediction, and negative contrast values (i.e., subadditivity) indicate responses that are less than the additive prediction. Both the interactive index and multisensory contrast were calculated because they offer somewhat differing views into the integrative process. Perhaps more
importantly, no study to date has attempted to relate between these measures, a feature that was intrinsic to the current study design.

Examples of the results of these analyses are presented for four different SC neurons in Fig. 7. For each of these examples, the principal line graph shows the results of the contrast analyses (i.e., mean contrast as a function of stimulus effectiveness for points along the dynamic range). Furthermore, the three inset bar graphs in each plot show the mean visual, auditory, and multisensory responses at three different points along the dynamic range along with the proportionate multisensory gain (i.e., % interaction) at each of these points. For the neuron depicted in the top left quadrant, the contrast analyses reveal that virtually all tested interactions exceeded the additive prediction. Furthermore, the bar graph insets show that when using the interactive index, large proportionate response enhancements are seen regardless of stimulus effectiveness. Note, however, that the magnitude of these enhancements declined from >1,000% at low levels of effectiveness to 320% at high levels of effectiveness. Because contrast values were invariably positive in these neurons (Fig. 8, top left), they were classified as superadditive, and represented 18% of the population (Fig. 7, pie graph).

For a second type of neuron, a similar pattern was seen when looking at the interactive index in that relatively large multisensory enhancements were elicited at low levels of stimulus effectiveness and progressively smaller enhancements were seen at higher levels of stimulus effectiveness (Figs. 7 and 8, top right). However, in contrast to superadditive neurons, these neurons exhibited shifts from superadditive interactions (i.e., positive contrast values) at low levels of stimulus effectiveness to subadditive interactions (i.e., negative contrast values) at high levels of stimulus effectiveness. Neurons exhibiting such a contrast transition were labeled as superadditive/subadditive and accounted for 10% of the sample. A third group of neurons were found that also exhibited inverse effectiveness (i.e., the decrease in multisensory enhancement with increasing stimulus effectiveness) and which showed a similar trend for contrast to decline with increasing stimulus effectiveness (Figs. 7 and 8, bottom right). However, these neurons were only capable of additive interactions at low levels of effectiveness, and showed progressively more subadditive interactions with increasing effectiveness. These additive/subadditive neurons made up the largest multisensory contrast category (58%). A final neuronal type showed a similar pattern of results but exhibited subadditive interactions at all points along the dynamic range (Figs. 7 and 8, bottom left). These subadditive neurons comprised 14% of the sample.

Neuronal categorization is independent of stimulus features

To determine whether changes in the nature of the stimuli would alter these neuronal categorizations, parallel data sets were gathered in 14 neurons using two different types of visual stimuli. Whereas the first data set employed the standard stationary stimulus described in the preceding text, the second set used a moving visual stimulus. Although the shape of the dynamic range functions evoked by stationary and moving stimuli were generally different (data not shown), the size of the dynamic range was not dependent on the type of stimulus used (Fig. 9A). Most importantly, when multisensory contrast was plotted as a function of stimulus effectiveness for moving versus stationary stimuli in this neuron, the plots were virtually identical (Fig. 9B). This invariance in the shape of the contrast functions for the two different types of visual stimuli was a general feature of the sampled population (Fig. 9C), suggesting that these categories are robust and general features of the multisensory population.

Dynamic range predicts neuronal categorization

In an effort to extend the current predictive framework for multisensory interactions, we examined the relationship between a neuron’s dynamic range and its multisensory contrast category. Indeed, a strong relationship was found between these two (Fig. 10). Most striking was the finding that neurons capable of exhibiting superadditive interactions (i.e., superadditive and superadditive/subadditive neurons) had a strong tendency to have either no or very small dynamic ranges, whereas additive/subadditive and purely subadditive neurons tended to have large dynamic ranges.

DISCUSSION

Consistent with previous work, multisensory SC neurons were found in abundance in the deep SC and had the capacity to exhibit significant response enhancements when presented with stimuli from multiple sensory modalities (Bell et al. 2001; Binns and Salt 1996; Jiang et al. 2001; Kadunce et al. 1997; King and Palmer 1985; Meredith and Stein 1983, 1986a; Peck 1995; Peck et al. 1995; Perrault et al. 2003; Stein and Arigebde 1972; Wallace et al. 1993; Zangenehpur and Chaudhuri 2001). Although the current study focused exclusively on visual-auditory neurons, the broad similarities in the integrative characteristics of SC multisensory neurons suggest that these results may be applicable to the entire population of multisensory neurons in this structure.

Multisensory SC neurons exhibit significant variability in their sensory responses

The response magnitude of multisensory SC neurons to both uni- and multisensory stimuli was found to vary widely in the population of neurons sampled. Although response variability has been apparent in previous studies, it has not been clear to what extent it is due to variations in stimulus characteristics (e.g., intensity, duration, etc.), the pattern of converging inputs, or inherent characteristics of different SC neurons. Here we show that different SC neurons respond very differently to stimuli with similar physical characteristics and that these response differences are predictable when viewed in the context of a given neuron’s dynamic range.

Substantial differences in the responsiveness of different SC neurons were manifested in differences in their dynamic ranges. That these differences in some neurons were likely due to variations in their inputs (e.g., see Huerta and Harting 1984; Jiang and Stein 2003; Jiang et al. 2001, 2002; Meredith 1999; Meredith and Clemo 1989) is suggested by the observation that multisensory neurons often exhibited striking differences in their visual and auditory dynamic ranges with nearly half of the sample having a substantial dynamic range for one modality and no dynamic range for the other modality. Nonetheless, in those neurons with a demonstrable dynamic range in both modalities, there was a
strong correlation between the size of the visual and auditory dynamic ranges, a feature that suggests that there are intrinsic determinants of neuronal responsiveness as well.

Another consistent feature of multisensory neurons was that the size of the multisensory dynamic range was larger than the size of the unisensory dynamic range(s). This finding, which is
in keeping with previous observations, see (Jiang et al. 2001), suggests that the maximum information-carrying content of these neurons is achieved only in response to multisensory stimuli. That the multisensory response is the most robust response of these neurons also has relevance for the principle of inverse effectiveness (Meredith and Stein 1986a; Stein and Meredith 1993). This feature of multisensory integration, in which declining levels of response enhancement are seen with progressive increases in stimulus effectiveness, could be explained by a ceiling effect. However, because maximal multisensory responses always exceed maximal unisensory responses, this possibility seems unlikely.

Multisensory contrast reveals categorical distinctions in the SC population

In comparison to the continuous measure of multisensory integration provided by the interactive index (which ranged from 32% to >1,000% in the current study), measures of multisensory contrast enabled a differentiation of the multisensory population into discrete categories. This metric, which assesses the multisensory response against a prediction using both unisensory responses, is being used increasingly as an effective tool to assess the integrative operation carried out by multisensory neurons (Nozawa et al. 1994).

The present data lend themselves to a division of the multisensory responses of SC neurons into four contrast categories. In three of these categories (superadditive/subadditive, additive/subadditive and subadditive), contrast values became increasingly negative with increases in stimulus effectiveness, and the similarities in the shapes of their response functions suggest that they employ similar mechanisms in their synthesis of multisensory information. The fourth category was distinct in that it showed superadditive interactions regardless of stimulus intensity. As a population, these neurons were found to have either compressed dynamic ranges or, more commonly, no demonstrable dynamic ranges. The enhancement in these neurons appears to involve a nonlinear amplification of the unisensory inputs to produce a superadditive response. Possible candidate mechanisms for supporting superadditive interactions include but are not limited to the integration of subthreshold inputs, specialized biophysical properties of the multisensory neurons (e.g., complement of ion channels, channel kinetics, etc.), local circuit effects that serve to amplify responses, and/or a gating mechanism imposed from an extrinsic source(s).

In support of an extrinsic gating mechanism is recent data suggesting that two cortical areas are critical for the manifestation of integrated multisensory responses in SC neurons.

![FIG. 9. A neuron’s multisensory contrast category does not depend on the nature of the visual stimuli. A: plotted for a representative neuron are the visual dynamic ranges determined in response to a stationary (○) and moving visual stimulus (●) and that have been transformed onto an effectiveness scale. Note that the response functions are indistinguishable. B: plots of multisensory contrast as a function of stimulus effectiveness are nearly identical, regardless of whether the visual stimulus is stationary or moving. Note that for this analysis, the visual stimulus was of fixed intensity (and either stationary or moving), and the effectiveness of the auditory stimulus was varied. This neuron was categorized as additive/subadditive. C: the average multisensory contrast value was binned and averaged across all 14 neurons tested. t-test were used to evaluate any differences between moving and stationary conditions at each bin and no significant differences were found.](#)

![FIG. 10. Multisensory dynamic range (i.e., the mean difference in activity from threshold to saturation) appears to be predictive of multisensory contrast category with superadditive and superadditive/subadditive neurons almost invariably having small multisensory dynamic ranges. In this figure, multisensory dynamic ranges are binned into 5 spike intervals.](#)
(Jiang and Stein 2003; Jiang et al. 2001, 2002; Wallace et al. 1992, 1993). Thus selective and reversible deactivation of the anterior ectosylvian sulcus (AES) and the rostral lateral suprasylvian cortex (rLS) compromises the integrative capacity of their multisensory SC targets. Such deactivation renders the multisensory responses of these neurons indistinguishable from their constituent unisensory responses. Intriguingly, these cortical inputs appear to be essential for multisensory integration regardless of the contrast operation (i.e., superadditive, subadditive, etc.) utilized by the neuron. Thus it appears that along with the role of extrinsic cortical influences in gating the capacity of multisensory neurons to integrate their multiple channels of sensory input, other factors play an integral role in determining the end product of these integrative operations.

One clue as to the identity of these factors may lie in the relationship found to exist between dynamic range and contrast category. Thus neurons capable of exhibiting superadditive interactions (i.e., superadditive and superadditive/subadditive neurons) were very likely to have no or small dynamic ranges, whereas neurons exhibiting only additive or subadditive interactions typically had extensive dynamic ranges. Such a result points to neuronal responsiveness as a major determinant of multisensory operational mode. In further support of this suggestion is the finding that multisensory interactions appear to be dependent on both levels of spontaneous activity and absolute sensory responsiveness (Perrault et al. 2003).

Unresolved questions include potential differences that might exist in the projection patterns of these different multisensory neuronal types, and in a related question, the functional significance of these different operational modes. Although no obvious differences were noted in the location of each of the multisensory neuronal types, the sample size is too small to support any firm conclusions about spatial distributions. Given our observation of higher spontaneous firing rates in the rostral SC and the strong relationship between spontaneous firing rates and neuronal responsiveness (Perrault et al. 2003), one might predict that neurons with larger dynamic ranges and thus less superadditive potential would be found in these rostral locations. Such a result would fit within the framework of rostral SC zones being concerned with fixation-related processes mediated by intrinsic connectivity, and more caudal SC locations being concerned with localization functions that are dependent on SC outputs to premotor circuits (Meredith and Ramoa 1998; Munoz and Guitton 1989; Munoz and Wurtz 1993; Peck and Baro 1997). It is in such extrinsic projections that nonlinear enhancements may serve an important role, possibly by increasing the probability of an action and/or speeding response times.

Together, the results of the current study illustrate that multisensory integration in SC neurons, in addition to being strongly dependent on stimulus factors (i.e., their spatial and temporal relationship, their relative effectiveness), also appears to be governed by neuron-specific factors. Although the relative contributions of these intrinsic and extrinsic factors are likely to differ from neuron to neuron, it is now clear that the stimulus-dependent modulations of multisensory integration in SC neurons take place within intrinsic limitations characteristic of each neuron. In addition to their obvious mechanistic implications, these results should be used to guide more biologically plausible models of multisensory integration, a rapidly emerging field of inquiry.

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