Neuron-Specific Response Characteristics Predict the Magnitude of Multisensory Integration

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Perrault, Thomas J. Jr., J. William Vaughan, Barry E. Stein, and Mark T. Wallace. Neuron-specific response characteristics predict the magnitude of multisensory integration. J Neurophysiol 90: 4022–4026, 2003. First published August 20, 2003; 10.1152/jn.00494.2003. Multisensory neurons in the superior colliculus (SC) typically respond to combinations of stimuli from multiple modalities with enhancements and/or depressions in their activity. Although such changes in response have been shown to follow a predictive set of integrative principles, these principles fail to completely account for the full range of interactions seen throughout the SC population. In an effort to better define this variability, we sought to determine if there were additional features of the neuronal response profile that were predictive of the magnitude of the multisensory interaction. To do this, we recorded from 109 visual-auditory SC neurons while systematically manipulating stimulus intensity. Along with the previously described roles of space, time, and stimulus effectiveness, two features of a neuron’s response profile were found to offer predictive value as to the magnitude of the multisensory interaction: spontaneous activity and the level of sensory responsiveness. Multisensory neurons with little or no spontaneous activity and weak sensory responses had the capacity to exhibit large response enhancements. Conversely, neurons with modest spontaneous activity and robust sensory responses exhibited relatively small response enhancements. Together, these results provide a better view into multisensory integration, and suggest substantial heterogeneity in the integrative characteristics of the multisensory SC population.

INTRODUCTION

Neurons receiving convergent input from more than a single sensory modality are found at nearly all levels of the neuraxis (Stein and Meredith 1993). To date, such multisensory neurons have been best-characterized in the superior colliculus (SC), a midbrain structure integrally involved in transforming sensory signals into purposeful action (Sparks 1986; Stein and Meredith 1993).

Multisensory neurons in the SC integrate their different modality-specific inputs according to a set of principles that depend on the spatial and temporal relationships between the stimuli as well as on their physical characteristics (Kadunce et al. 1997; Meredith et al. 1987; Meredith and Stein 1986a,b, 1996; Wallace et al. 1996). Thus two stimuli from different modalities (e.g., visual and auditory) presented in close spatial and temporal proximity typically result in a significant enhancement of the neuronal response. Alternatively, these same stimuli presented in spatial and/or temporal disparity result in either no enhancement or a response depression. In addition, combinations of weakly effective stimuli produce proportionately larger enhancements than when the stimuli are more effective, a principle known as inverse effectiveness. Highlighting the central role of the SC in directing multisensory-mediated behavior, multisensory orientation responses have been found to follow a remarkably parallel set of principles (Stein et al. 1988, 1989) and are selectively compromised by SC lesions (L. R. Burnett, unpublished observations).

Despite the extensive data set outlining the integrative features of multisensory SC neurons, there remain several unresolved issues. One involves the wide variability in the magnitude of the enhancements observed among SC neurons. A review of the literature shows examples of significant response enhancements that range in magnitude from 38% to well in excess of 1000% (Bell et al. 2001; Binns and Salt 1996; Frens and Van Opstal 1998; Jiang et al. 2001; Kadunce et al. 1997; King and Palmer 1985; Meredith and Stein 1986a,b; Peck 1996; Populin and Yin 2002; Wallace et al. 1993, 1996, 1998). Although many of these differences can be explained based on known integrative principles, these principles fail to fully account for the substantial range of interactions seen in this population.

The current study was conducted to provide a better understanding of the heterogeneity within the response gains seen in the multisensory SC population. The principal objective was to determine if there are neuron-specific response characteristics that offer predictive value about the magnitude of the interaction elicited on multisensory stimulation. Two prominent features offer such predictive value: spontaneous activity and the neuron’s level of sensory responsiveness. Portions of this work have been published in abstract form (Perrault et al. 2002).

Experiments were performed in four adult cats and 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. Implantation and recording procedures were similar to those previously described (Kadunce et al. 2001; Wallace et al. 1993) and are detailed only briefly here. Visual-auditory multisensory neurons were the focus of this study and were isolated in the anesthetized animals using conventional single-unit electrophysiological techniques. Once a neuron was isolated its visual and auditory receptive fields were mapped. Visual stimuli were either stationary (50- to 100-ms illumination of a light emitting diode) or...
moving (galvanometer-driven bars of light projected onto a translucent screen) and ranged in intensity from 0.11 to 13.0 cd/m² on a background luminance of 0.10 cd/m². Auditory stimuli were delivered through freely positionable speakers in a free-field setting and consisted of 50- to 100-ms duration broadband (20 Hz to 20 kHz) noise bursts ranging in intensity from 50.6 to 70.0 dB sound pressure level (SPL) on a background of 45.0 dB SPL (A-weighted). For quantitative tests of multisensory integration, stimuli were presented at the most responsive location within their respective receptive fields. Different stimulus conditions (i.e., visual alone, auditory alone, visual-auditory) and intensities were interleaved in a pseudo-randomized manner. Data from a minimum of 15 trials per condition and intensity were collected.

Multisensory integration was scored using the standard metric for assessing response enhancement (or depression), the Interactive Index (Meredith and Stein 1986b). This index was computed using the formula: \( \left[ \frac{(CM - SM_{max})}{SM_{max}} \right] \times 100 \), where CM is the mean response evoked by the combined-modality (i.e., visual-auditory) stimulus and SM\(_{max}\) is the mean response evoked by the most effective modality-specific stimulus. Significant differences between CM and SM\(_{max}\) were determined using Student’s two-tailed t-test. For each neuron, responses (i.e., number of spikes) were counted within temporal windows that were identical across conditions and that were dictated by the longest duration response. In addition, on each trial, spontaneous activity was assessed for the interval 500 ms prior to stimulus onset and was averaged across all trials.

Data were gathered from a total of 109 visual-auditory neurons (\( n = 38, 52, 17, \) and 2 for each of the 4 animals) isolated in the deep SC (below stratum opticum). In each neuron, attempts were made to assess responses to visual, auditory, and combined visual-auditory stimulation over a range of stimulus intensities from threshold to saturation. A substantial heterogeneity was noted in both the modality-specific and multisensory responses of these neurons along the intensity continuum, and a complete treatment of these data will be presented in a subsequent full report. In this report, we restricted our analyses to identify neuron-specific attributes that carried predictive value as to the magnitude of the resultant multisensory interaction.

The most common outcome of combining visual and auditory stimuli in spatial and temporal coincidence was a significant response enhancement, seen in 74% (\( n = 81 \)) of the sampled population. Figure 1 presents examples of response enhancements in two different multisensory neurons. In both, responses to two selected stimulus intensities (for both the visual and auditory stimuli), referred to as low (i.e., weakly effective on the neuron’s response range, defined as within 1 SD of the threshold intensity) and high (i.e., strongly effective on the neuron’s response range, defined as within 1 SD of the saturating intensity), are shown. In one of these neurons (A), the size of the proportionate gain (i.e., response enhancement) decreased from 94 to 55% as the effectiveness of the individual stimuli increased, a finding consistent with the principle of inverse effectiveness (Meredith and Stein 1986b). In contrast, in the other neuron (B), large response enhancements were seen at both intensities, a result not predicted by inverse effectiveness.

When the activity profiles of the neurons depicted in Fig. 1 were carefully examined, several fundamental differences were apparent. The first was the difference in their level of sensory responsiveness. Thus whereas the neuron shown in A exhibited robust responses, even with slightly suprathreshold stimuli, the neuron shown in B exhibited weak responses, even when the stimuli were near maximal effectiveness. When the magnitudes of significant multisensory interactions were plotted as a function of sensory responsiveness for the entire sampled population, a clear relationship was apparent (Fig. 2A). High levels of modality-specific response were almost never associated with large multisensory enhancements. More specifically, when the modality-specific response exceeded 15 spikes/trial, the probability of generating a large response enhancement was nearly zero, seen in only 2 of the 298 interactions in which the gain was >100%. Conversely, at low levels of modality-specific response (i.e., <3 spikes/trial), enhancements exceeding 100% were common, seen in 38% (266/699) of all tested interactions. These differences in sensory responsiveness were not readily attributable to either a strong bias in the dominant modality for each of the neurons (visual dominant, \( n = 59 \); auditory dominant, \( n = 50 \)) or a strong bias in the magnitude of the average maximal dominant modality response (maximal visual response = 10.67 spikes/trial, maximal auditory response = 11.83 spikes/trial).

In addition to sensory responsiveness, a second factor appeared to carry significant predictive value for multisensory interactive magnitude. This feature is also evident in Fig. 1, where the two neurons can be seen to differ dramatically in their level of spontaneous activity. When examined as a population, an inverse relationship between spontaneous activity and the magnitude of response enhancement can readily be seen (Fig. 2B).

Sensory responsiveness and spontaneous activity were found to be well correlated (Pearson’s correlation, \( r^2 = 0.6656, P < 0.01 \)), and multiple regression analysis revealed that these two factors are significant contributors to multisensory enhancement \( [r^2 = 0.505, F(2,108) = 54.035, P < 0.0001] \). Although each independently contributed to the multisensory interaction, sensory responsiveness (standardized partial correlation coefficient \( \beta = -0.520, P < 0.001 \)) was found to be a larger contributor when compared with spontaneous activity (\( \beta = -0.226, P < 0.05 \)).

The population of visual-auditory multisensory SC neurons studied here closely resembles those that have been extensively studied in both the anesthetized and awake cat, as well as in the rhesus monkey (Bell et al. 2001; Binns and Salt 1996; Frens and Van Opstal 1998; Jiang et al. 2001; Kadunce et al. 1997; King and Palmer 1985; Meredith and Stein 1986a,b; Peck 1996; Populin and Yin 2002; Wallace et al. 1993, 1996, 1998). For example, these neurons were activated individually by visual and auditory stimuli, showed a capacity to integrate these inputs, and largely abided by the same neural principles of multisensory integration described previously (Kadunce et al. 1997; Meredith et al. 1987; Meredith and Stein 1986a,b, 1996; Wallace et al. 1993, 1998). The goal of the current study, rather than to further detail these principles, was to determine if there are features of an individual neuron’s response profile that are predictive of the multisensory interaction seen on stimulus combination. Two features offered such predictive value. First, the level of overall sensory responsiveness was an important factor in determining the magnitude of the multisensory interaction, such that robust responses were typically
FIG. 1. Depicted are the responses of 2 (A and B) visual-auditory neurons to modality-specific and multisensory stimuli. Rasters and histograms display the neuronal activity for 3 sensory conditions (visual, auditory, and multisensory) presented at both low (left) and high (right) intensities. At the bottom of each column, the mean sensory responses for each condition as well as the interactive index are represented. Note that although both neurons exhibited significant multisensory enhancements at both levels of stimulus effectiveness, the magnitude of these enhancements and the corresponding response profiles of the neurons were very different. Thus the neuron shown in A, which exhibits a decline in response enhancement at high levels of sensory effectiveness, had a relatively high rate of spontaneous activity (6.8 spikes per trial) and robust sensory responses at both low (14.9 spikes per trial) and high (28.2 spikes per trial) levels of stimulus effectiveness. In contrast, the neuron shown in B, which exhibited large response enhancements at both intensities, had a low rate of spontaneous activity (0.03 spikes per trial) and weak sensory responses at both low (0.6 spikes per trial) and high (1.1 spikes/trial) levels of stimulus effectiveness. (*P < 0.05, **P < 0.01)
associated with small proportionate enhancements, and weak responses were often accompanied by large enhancements. This result is consistent with the principle of inverse effectiveness, such that within a given neuron increasing levels of stimulus effectiveness result in proportionately smaller multisensory interactions (Jiang et al. 2001; Meredith and Stein 1986b; Wallace et al. 1996). The current study extends this finding to encompass the responses across the multisensory population. Thus in those neurons in which weakly effective stimuli resulted in fairly vigorous responses, proportionate enhancements were relatively low. Alternatively, in those neurons that exhibited relatively low levels of activity regardless of stimulus effectiveness, the proportionate multisensory gain was typically quite large. Interestingly, neurons with weak sensory responses also had the largest variability in the magnitude of their multisensory interactions, a feature that is likely to be a result of both the proportionate nature of the derived metric (i.e., low firing rates provide the potential for the greatest proportionate gain as well as the potential for the greatest variability in this gain) as well as fundamental differences in input-derived and/or intrinsic neuronal features. These two global classes of multisensory response profiles (i.e., high sensory response – small multisensory interaction, low sensory response – large multisensory interaction) may reflect two distinct multisensory operational modes. Alternatively, multisensory response profiles may be distributed continuously without clear categorical distinctions. An answer to this question, which will undoubtedly offer insights into the mechanistic processes underlying multisensory integration, awaits a full detailing of these responses over the full dynamic range of the multisensory population.

The second predictive feature of multisensory interactive magnitude was spontaneous activity; in which neurons with little or no spontaneous activity exhibited the largest response enhancements. Again, although not systematically examined before, this feature is apparent in many of the prior examples of large response enhancements (Kadunce et al. 2001; Meredith and Stein 1986a,b; Wallace et al. 1993, 1996, 1998). Although spontaneous activity is believed to play a role in the development of afferent connectivity within the SC (Galli-Resta et al. 1993; Itaya et al. 1995), and likely is an important contributor to fixation aspects of SC motor function (Munoz and Guitton 1991), little is known about its role in sensory and multisensory processes. In the current study, the high degree of covariance between spontaneous activity and neuronal responsiveness suggest that one factor might underlie the manner in which a given multisensory neuron integrates its different sensory inputs. This factor, which appears to reflect inherent differences in neuronal excitability, might relate to the linear and nonlinear operational modes of activation in these neurons.

How these differences in multisensory integration relate to the behavioral role of the SC remains open to discussion. As a structure intimately involved in sensory and motor processes, and that likely plays an important role in the sensorimotor transform, the impact of alterations in sensory (and multisensory) activity on premotor responses remains a central question. That enhancement and depression of multisensory activity are closely linked to increases and decreases in SC-mediated orientation responses is well documented (Stein et al. 1988, 1989). However, the specific contribution of the different subpopulations of these neurons to this process remains unknown. Similarly, although recent evidence suggests that enhanced
multisensory responses may speed the time to the initiation of premotor activity in the SC (Bell et al. 2001), a result that fits nicely with observations of multisensory-mediated speeding of eye movements (Corneil and Munoz 1996; Frens and Van Opstal 1998; Frens et al. 1995; Harrington and Peck 1998; Hughes et al. 1994), the role of the different subpopulations of SC multisensory neurons to this effect remain to be determined.

From a mechanistic perspective, the current study illustrates that fundamental features of a given neuron’s response characteristics are strong determinants of multisensory integration. As alluded to in the preceding text, these features reflect either intrinsic (e.g., complement of ion channels, dendritic morphology, etc.) or extrinsic (e.g., sensory inputs, modulatory inputs, etc.) features of the neuron or some combination thereof. As such, it is abundantly clear that the multisensory population in the SC is heterogeneous and that different multisensory neurons perform their integrative operations in distinctly different ways. Parsing out such heterogeneity to further our understanding of multisensory processing will entail a series of complementary approaches. These should include but not be limited to: new analytical methods with which multisensory neurons can be categorized on the basis of their physiological responses, computational methods to narrow the array of mechanistic possibilities, and new experimental approaches tailored toward discovering the biophysical principles by which multisensory neurons perform their adaptive and highly integrative functions.

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DISCLOSURES

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REFERENCES


