Published in final edited form as:

Neuroscience. 2014 January 3; 256: . doi:10.1016/j.neuroscience.2013.10.044.

Heterogeneity in the spatial receptive field architecture of multisensory neurons of the superior colliculus and its effects on multisensory integration

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Abstract

Multisensory integration has been widely studied in neurons of the mammalian superior colliculus (SC). This has led to the description of various determinants of multisensory integration, including those based on stimulus- and neuron-specific factors. The most widely characterized of these illustrate the importance of the spatial and temporal relationships of the paired stimuli as well as their relative effectiveness in eliciting a response in determining the final integrated output. Although these stimulus-specific factors have generally been considered in isolation (i.e., manipulating stimulus location while holding all other factors constant), they have an intrinsic interdependency that has yet to be fully elucidated. For example, changes in stimulus location will likely also impact both the temporal profile of response and the effectiveness of the stimulus. The importance of better describing this interdependency is further reinforced by the fact that SC neurons have large receptive fields, and that responses at different locations within these receptive fields are far from equivalent. To address these issues, the current study was designed to examine the interdependency between the stimulus factors of space and effectiveness in dictating the multisensory responses of SC neurons. The results show that neuronal responsiveness changes dramatically with changes in stimulus location – highlighting a marked heterogeneity in the spatial receptive fields of SC neurons. More importantly, this receptive field heterogeneity played a major role in the integrative product exhibited by stimulus pairings, such that pairings at weakly responsive locations of the receptive fields resulted in the largest multisensory interactions. Together these results provide greater insight into the interrelationship of the factors underlying multisensory integration in SC neurons, and may have important mechanistic implications for multisensory integration and the role it plays in shaping SC mediated behaviors.

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Author contributions: The study was designed by Dipanwita Ghose and Mark T. Wallace. Data collection and data analysis was performed by Dipanwita Ghose. Dipanwita Ghose and Mark Wallace wrote the paper.

Keywords

cross-modal; visual-auditory; Inverse effectiveness; interdependency; principles of integration

Introduction

Multisensory integration refers to the process by which information from the different senses converges and is synthesized in the brain, often resulting in dramatic changes for behavior and perception (Calvert et al., 2000, Stein and Stanford, 2008; Stein BE 2012; Murray and Wallace 2012). The neural underpinnings of multisensory integration have been widely studied, with much of the work being carried out in the mammalian superior colliculus (SC) (Meredith and Stein, 1983, 1986b, a, Meredith et al., 1987, Meredith and Stein, 1996, Perrault et al., 2003, 2005), a major convergence site for visual, auditory and somatosensory information. Seminal studies characterizing the responses of individual SC neurons showed that they integrate their different sensory inputs based on a number of factors, the most important of which appeared to be founded on the physical characteristics of the stimuli that are combined (Meredith and Stein, 1986b, a, Meredith et al., 1987, Meredith and Stein, 1996). From this work three key “principles” of multisensory integration were identified. The spatial and temporal principles highlight the importance of physical and temporal stimulus proximity, such that stimuli that are spatially and temporally coincident typically give rise to the greatest response gains when combined. The principle of inverse effectiveness reflects the fact that the greatest proportionate gains in response are typically seen when stimuli that are weakly effective in eliciting a response on their own are combined (Meredith and Stein, 1986b, a, Meredith et al., 1987, Meredith and Stein, 1996). Although initially established in individual SC neurons, these principles appear to provide a universal framework for understanding multisensory interactions, in that they have also been shown to apply to multisensory neurons in other brain regions, to behavioral, psychophysical and perceptual phenomena, and in neuroimaging studies indexing the activity of large neuronal ensembles (Wallace et al., 1992, Bushara et al., 2001, Murray et al., 2001, Molholm et al., 2002, Hairston et al., 2003a, Hairston et al., 2003b, Macaluso et al., 2004, Bolognini et al., 2005, Kayser et al., 2005, 2007, Serino et al., 2007a, Serino et al., 2007b, Mozolic et al., 2008, Stevenson and James, 2009; Murray and Wallace 2012)

However, despite the fact that these principles have provided extraordinary insight, they are not the only factors that affect the integrative operations that characterize multisensory neurons and networks. Along these lines, recent work has begun to suggest that there is interdependency between the various stimulus dependent factors that shape the final integrated response (Perrault et al., 2005, Carriere et al., 2008, Royal et al., 2009). In addition, along with these stimulus-specific factors, other studies have illustrated the importance of neuron-specific factors in dictating multisensory interactions, with neuronal responsiveness and dynamic range being previously underappreciated contributors (Perrault et al., 2003, 2005). Collectively, these studies have brought to light a previously unrecognized complexity to the factors that underlie multisensory integration in individual neurons, a complexity very likely to provide important mechanistic clues as to the cellular operations that result in the ultimate product of a multisensory interaction.

These prior studies provide the framework for the hypothesis that motivated the current study: that the location of a paired audiovisual stimulus within the receptive fields of SC neurons will dramatically alter neuronal responsiveness – with a consequent effect on the magnitude of the resultant interaction. To address this question, physically identical stimuli were presented at multiple locations within the receptive fields of individual neurons during single unit extracellular recordings, thus resulting in the creation of spatial receptive field

(SRF) plots that details how changes in stimulus location impact response strength. These SRFs were then used to provide the predictive framework for the responses generated by various multisensory stimulus combinations, and comparison with these predictions revealed the nature of the integrative response (e.g., superadditive, subadditive, etc.). The results revealed that SC neurons exhibit significant heterogeneity in their SRFs, and that this heterogeneity played a key deterministic role in the magnitude of the resultant interaction.

Methods

General procedures

Experiments were conducted in adult cats ($n=3$) raised under standard housing conditions. All experiments were done in an anesthetized and paralyzed semichronic preparation. The experiments consisted of single unit extracellular recordings from the superior colliculus (SC) in the midbrain. Experiments were performed on a weekly basis on each animal. All surgical and recording procedures were performed in compliance with the Guide for the Care and Use of Laboratory Animals and under a protocol approved by the Institutional Animal Care and Use Committee at Vanderbilt University Medical Center, which is accredited by the American Association for Accreditation of Laboratory Animal Care.

Implantation and recording procedures

For anesthesia during the initial surgical procedure animals were first induced with ketamine hydrochloride (20 mg/kg, administered intramuscularly(im)) and acepromazine maleate (0.04mg/kg im). For implantation of the recording chamber over the SC animals were intubated and artificially respired. A stable plane of surgical anesthesia was achieved using inhalation isoflurane (1%–3%). Body temperature, expiratory CO₂, blood pressure and heart rate were continuously monitored (VSM7, Vetspecs/SCIL), recorded and maintained within ranges consistent with a deep and stable plane of anesthesia. A craniotomy was made to allow access to SC and a head holder was attached to the cranium using stainless steel screws and orthopedic cement to hold the animal during recording sessions without obstructing the face and ears. Postoperative care (antibiotics and analgesics) was done in close consultation with veterinary staff.

For recording animals were administered an initial dose of ketamine (20mg/kg im) and acepromazine maleate (0.04mg/kg im) and maintained throughout the procedure with constant rate infusion of ketamine (5mg/kg/hr iv) delivered through a cannula placed in the saphenous vein. The head holding system was then used to suspend the animal comfortably in the recumbent position. To prevent ocular drift animals were paralyzed using pancuronium or vecuronium bromide (0.1mg/kg/hr, iv for pancuronium bromide and 0.1–0.2mg/kg/hr for vecuronium bromide) and artificially respired for the duration of recording. Parylene insulated tungsten electrodes ($Z = 3\text{--}5\text{ M}\Omega$) were advanced into the SC using an electronically controlled mechanical microdrive. Single unit neural activity (Signal to noise ratio $\geq 3:1$) was recorded (Sort Client software, Plexon Inc., Texas), amplified and routed to an oscilloscope, audio monitor and computer for performing online and offline analysis. On the completion of the recording session the animals were given 60–100 ml of lactated Ringer solution subcutaneously to facilitate recovery.

Stimulus presentation and search strategy

Extracellular single unit recordings targeted multisensory (visual-auditory) neurons in the intermediate and deep layers of the SC. A multisensory neuron was defined as one in which the response in the multisensory condition (mean spikes/trial) was statistically different from the best unisensory response as determined by the Wilcoxon Rank test. Neurons were defined as “overt multisensory neurons” if they showed a change in spiking to both the

visual and auditory stimuli when presented individually. In contrast, “modulatory multisensory neurons” showed an overt response to stimulation in one of the modalities, and this response was altered by presentation of a stimulus in the second modality. Once a neuron was isolated (SNR = 3:1), the borders of its receptive field were coarsely mapped by presenting visual and auditory stimuli. Visual stimuli consisted of the illumination of stationary light emitting diodes (LEDs; 100 ms duration, luminance 104 cd/m²) while auditory stimuli were delivered through positionable speakers and consisted of 100 ms duration broadband noise (20Hz-20kHz) with an intensity of 67dB SPL on a background of 45 dB SPL. Both the LEDs and speakers were mounted on a hoop placed 60 cm in front of the cat at azimuthal locations ranging from 0° to 90° (10° increments) on either side of the midline. The hoop could be rotated along different elevations that allowed sampling numerous locations within and just outside the receptive field. Stimuli and stimulus combinations were randomly presented at different azimuthal locations along a given elevation. This procedure allowed the spatial receptive field (SRF) architecture of the neuron to be defined (Fig. 1). Visual and auditory stimuli were presented in a randomized interleaved manner at multiple azimuthal locations along a single elevation at a time. Multisensory combinations always consisted of visual and auditory stimuli being presented at the same spatial location. Unisensory and multisensory stimulus conditions were randomly interleaved until a minimum of 60 trials (20 visual, 20 auditory, 20 multisensory) were collected for a given stimulus location. Consecutive stimulus presentations were separated by at least 1.5 s to avoid response habituation.

During each recording session, after the boundaries of each neuron’s receptive fields were mapped, a location of robust responsiveness was chosen within the spatial receptive field and this location was tested using 6 different stimulus onset asynchronies (SOAs). These included the combinations: V50A0, V0A0, V0A50, V0A100, V0A150 and V0A200 where V50A0 represents the auditory stimulus preceding the visual stimulus by 50ms, V0A0 represents simultaneous presentation of visual and auditory stimuli, and V0A50, V0A100, V0A150, V0A200 represents conditions in which the visual stimulus preceded the auditory stimulus. Based on this preliminary testing the SOA that optimized the opportunity for multisensory interactions was used to test all other locations for that neuron.

Data acquisition and analysis

A custom built PC-based real time data acquisition system controlled the structure of the trials and the timing of the stimulus (Labview. National Instruments). The analog waveform picked up by the electrode was transferred to a Plexon MAP system (Plexon Inc., Texas) where they were digitized at 40kHz. Single units were isolated online using Sort Client software (Plexon Inc., Texas) and also stored for further offline analysis. Neuronal responses were detailed through construction of peristimulus time histograms (PSTHs) for each condition (visual only (V), auditory only (A), paired visual-auditory (VA)) for each location tested within the SRF. Baseline for each PSTH was calculated as mean firing rate during the 500 ms immediately preceding the stimulus onset for each of the 3 conditions. Response threshold was set at 2 SD above this baseline in order to delimit the stimulus evoked response. Mean spontaneous firing rate was subtracted from the response. The time at which the PSTH crossed above the 2 SD line (and remained so for at least 30ms) was determined to be response onset. Response offset was the latest time at which the PSTH fell below the 2SD line and stayed below this line for ≥ 30 ms. PSTHs were so constructed that resolution of each time bin of the PSTH was =10ms. Response duration was defined as time interval between response onset and response offset. Mean stimulus evoked response was calculated as the average number of spikes elicited per trial during the defined response duration interval.

Spatial Receptive Field (SRF) analyses

To create the SRF plots, the mean stimulus evoked responses are normalized to the highest stimulus evoked response recorded from all tested conditions and locations. This procedure resulted in response values ranging from 0 to 1, which was then used to produce pseudo color spatial receptive field (SRF) plots that show relative activity as a function of stimulus location. SRF plots were created for each of the unisensory conditions (visual and auditory) and for the multisensory condition. In addition, a predicted SRF plot was created by summing the visual and auditory SRFs. The predicted SRF was then subtracted from the actual multisensory SRF to generate a contrast plot. In this contrast plot the warmer colors represent superadditive interactions while the cooler colors represent subadditive interactions (Carriere et al., 2008). To help better visualize these SRF plots, the SRF structure was then interpolated using a 2D gaussian filter (filter size=100deg, resize factor=100).

Spatiotemporal Receptive Field (STRF) analyses

For these STRF plots, pseudo color representations were created for each neuron by normalizing the spikes generated in the epoch spanning from 100ms prestimulus to 200ms poststimulus across all azimuthal locations, all conditions (visual, auditory, multisensory and predicted), and for each tested elevation separately. The predicted STRF obtained by summing the visual and auditory STRFs was then subtracted from the actual multisensory STRF to produce the contrast STRF. In the contrast STRF warmer colors represent superadditive interactions while cooler colors represent subadditive interactions. The contrast plots are scaled from -1 to 1 where statistically significant negative values are sub-additive interactions and statistically significant positive values are superadditive interactions.

Measures for evaluating multisensory integration

Two measures were used to quantify multisensory integration. The first was the interactive index (ii), which measures how the multisensory response differs from the best unisensory response. The magnitude of this change was calculated as

$$[(CM - SM_{max})/SM_{max}] \times 100 = \% \text{interaction}$$

where CM is the mean response evoked by the combined modality (i.e., multisensory) stimulus and SM_{max} is the mean response evoked by the most effective single modality stimulus (Meredith and Stein, 1983, 1986b). Statistical comparisons between the mean stimulus evoked responses of the multisensory and best unisensory conditions were done using a Wilcoxon Rank test for each spatial location tested within the receptive field. The second measure used is mean statistical contrast (msc). This metric evaluates the multisensory response as a function of the response predicted by the addition of the two unisensory responses. Multisensory contrast is calculated using the formula

$$msc = \frac{[\sum AV_i - (A_i + V_i)]}{n}$$

where, A_i is the evoked auditory response on a given trial (i), V_i is the evoked visual response on a given trial, AV_i is the evoked multisensory response on a given trial and n is the number of trials. The model assumes independence between the visual and auditory inputs and uses additive factors logic to distinguish between subadditive (contrast < 0), additive (contrast = 0) and superadditive (contrast > 0) modes of response (Perrault et al.,

2003, 2005, Stanford et al., 2005, Stanford and Stein, 2007). Significant differences from a contrast value of 0 were determined by the Wilcoxon Rank test for each location.

Analyses of SRF “hotspots”

After neuronal responses were collected across different locations in order to derive the SRF plots, the mean stimulus evoked spike counts were then normalized across all locations and all conditions. For each condition, all locations exhibiting at least 70% of the maximum response were considered to be within the hotspot of the receptive field. An areal measurement was used to quantify the size of the hotspots under the different stimulus conditions. In addition, the criterion for demarcating multiple hotspots was that two locations exhibiting >70% of maximum response had to be separated by a minimum of 10° in either elevation or azimuth.

In order to determine the degree of overlap between the visual and auditory hotspots, the area of the hotspots was first computed for both the visual and auditory SRF. Next, the modality that exhibited the smaller hotspot was chosen, and the amount of the total area of that hotspot that overlapped with the hotspot of the other modality was expressed as a percentage of its total area. For example if the area of the visual hotspot was 100 deg² of which only 10 deg² overlapped with the auditory hotspot, the percentage of overlap was 10%.

RESULTS

The spatial receptive fields (SRFs) of multisensory superior colliculus neurons are large and heterogeneous

Data was collected from 72 multisensory (visual-auditory) neurons in the intermediate and deep SC layers of 3 adult cats. A detailed mapping of each of the SRFs (i.e., visual, auditory and visual-auditory) was possible for 64 of these neurons, which often entailed isolation of the neuron for periods of several hours. In accordance with the previous literature (Meredith and Stein, 1983, Stein BE 1993, Kadunce et al., 2001; Meredith and Stein 1996; Meredith and Stein 1986; Meredith and Stein 1990; Stein BE 1993), the majority of these multisensory neurons demonstrated considerable overlap in the spatial extent of their visual and auditory receptive fields.

Following a coarse delimitation of a neuron's receptive fields, an SRF plot for each modality was then created using physically identical stimuli that differed only in spatial location. These analyses revealed significant differences in both the unisensory (i.e., visual alone, auditory alone) and multisensory (combined visual-auditory) responses as a function of stimulus location within the SRF. Figure 2 illustrates several representative examples of these SRF plots for individual SC neurons.

For practical purposes, SC neurons were divided into two general classes: overt neurons and modulatory neurons. Overt neurons are responsive to stimulation in both the visual and auditory modalities, whereas in modulatory neurons responses can be driven by only one modality yet have this driven response significantly influenced when a stimulus from the other modality is presented at or around the same time.

For overt neurons, the visual (26/33=78.8%), auditory (15/33=45.5%), and multisensory (22/33=66.7%) SRFs were characterized by a single region of elevated response (single hotspot) surrounded by regions of weaker response (see methods for a description of how the hotspots were defined and delineated; Fig. 2A). In the remaining overt neurons the SRF architecture was more complex, with multiple regions of elevated responses (multiple hotspots) (Fig. 2B).

For modulatory neurons (which could either be visual modulatory (23/31=74.2%) or auditory modulatory (8/31=25.8%) depending on the driving modality), the pattern of results was very similar. The majority of auditory modulatory neurons (6/8=75%) exhibited single hotspots under both auditory and multisensory conditions while the remainder exhibited multiple hotspots under both these conditions. Similarly, the vast majority of the visual modulatory neurons (21/23=91.3%) exhibited single hotspots under both visual and multisensory conditions. The other two neurons exhibited multiple hotspots under both these conditions.

A more detailed analysis of these SRFs revealed that there was a considerable degree of overlap between the visual and auditory receptive fields in overt neurons (such extent could not be examined in modulatory neurons because of their lack of a driven response in two modalities). Thus, for the large majority of these overt neurons (23/33 = 70%), there was almost complete overlap (i.e., >90%) between the visual and auditory hotspots (Fig 3B). There were no apparent differences (e.g., location in SC, SRF size) between neurons that showed greater and lesser correspondence in these unisensory hotspots.

In neurons with single hotspots, the total area of the visual hotspot was significantly smaller (mean area = 32.5 deg²) when compared with the size of the auditory (mean area = 81.7 deg²) and multisensory (mean area = 101.7 deg²) hotspots (visual vs. auditory: Student t test, $t=-2.20, p=0.03$, visual vs multisensory : Student t test: $t=-2.06, p=0.05$). The size of the auditory and multisensory hotspots were not significantly different (Student t test $t=0.89, p=.388$).

Despite this similarity in size of the auditory and multisensory hotspots, response levels differed significantly between conditions. For neurons with single hotspots, when expressed as normalized values (in order to be able to compare across neurons), response magnitude within the multisensory hotspots was highest (0.94), followed by visual (0.65) and then auditory (0.33). Each of these values differed significantly from the other (Student t test: V vs VA: $t=-3.12, p<0.01$, A vs VA: $t=-7.3, p<0.01$, V vs A: $t=2.83, p<0.01$).

Similarly 86% of the neurons with multiple hotspots in either the visual or auditory SRFs also exhibited multiple hotspots within their multisensory SRFs. For these neurons with multiple hotspots, the size of the largest hotspots were compared. This analysis revealed that area of the auditory hotspots were largest compared to that of visual and multisensory hotspots but the differences were not statistically significant (mean area of auditory hotspot = 83.7 deg²; mean area of visual hotspot = 34.3 deg²; mean area of multisensory hotspot = 70 deg²; Student t test: V vs A: $t=-1.59, p=0.13$ V vs VA = $t=-0.69, p=0.49$; A vs VA: $t=0.25, p=0.8$). However, when strength of responses were compared it was found that the multisensory responses were strongest (mean = 0.93) followed by visual (0.65) and auditory responses (0.39). All these differences were statistically significant. (Student t test: VvsVA: $t=-2.99, p<0.01$, A vs VA: $t=-8.31, p<0.01$, V vs A: $t=-2.95, p<0.01$)

For modulatory neurons (visual and auditory), 87.1% (27/31) of the neurons exhibited single hotspots under both unisensory and multisensory conditions. In contrast to the overt neurons, the area of the visual (mean area=33.5 deg²) and multisensory (mean area =36.5 deg²) hotspots for the visual modulatory neurons (visual stimulus being the driving modality) were not significantly different (Student t test: $t=-0.35, p=0.72$). Similarly, for auditory modulatory neurons, the area of the auditory (mean area= 134.2 deg²) and multisensory (mean area =144.2 deg²) hotspots were not significantly different (Student t test: $t=-0.2, p=0.84$). In contrast to the data for overt neurons, for visual modulatory neurons, the strength of responses within the visual (mean normalized response= 0.96) and multisensory (mean normalized response=0.85) hotspots were not significantly different

from each other (Student t test: $t=1.7$, $p=0.08$). However, for auditory modulatory neurons, the response strength of multisensory hotspots (0.98) was significantly higher than that of auditory hotspots (mean normalized response =0.94; Student t test: $t=-2.2$, $p=0.03$).

The architecture of the visual and auditory SRFs was next used to provide a prediction of the multisensory SRF based on a simple summation of the unisensory SRFs. In virtually all neurons, the measured multisensory SRF differed significantly from the predicted multisensory SRF, as evident by the contrast plots that compared these measured and modeled responses. When compared to the size of the best unisensory SRFs, the mean size of the multisensory SRFs were 14.6% larger for overt neurons. For modulatory neurons the mean size of the multisensory SRFs were 11% larger than that of the best unisensory SRFs.

As described in the sections above, by quantifying the total size of the SRFs, the size of the hotspots, and the strength of response at the hotspots under different stimulus conditions for both overt and modulatory neurons, an important difference emerged between the two neuronal classes. The total size of the SRFs as well as the size of the hotspots under visual and auditory conditions did not differ when compared between overt and modulatory neurons (SRF sizes: Student t test: visual: $t=1.64$, $p=0.1$; auditory: $t=1.07$, $p=0.2$; Hotspot sizes: Student t test: visual: $t=0.13$, $p=0.89$; auditory: $t=-1.2$, $p=0.2$). However, the strength of the responses within the hotspots were significantly larger for modulatory neurons than for overt neurons under both visual and auditory conditions (visual: Student t test: $t=-4.38$, $p<0.01$, auditory: Student t test: $t=-6.4$, $p<0.01$). This suggests that the modulatory neurons that are dominated by one sensory modality exhibit higher sensory responsiveness to that dominant modality when compared to overt neurons. This is important for the differences in the nature of multisensory interactions exhibited by these two groups of neurons as described in detail later.

For both overt and modulatory neurons, the most dramatic difference was not in the size of the multisensory SRF, but rather in the magnitude of the responses elicited under multisensory conditions when compared with those predicted from the component unisensory responses.

Relationship between SRF heterogeneity and multisensory interactions

An analysis of the SRF plots revealed that multisensory interactions differed dramatically from location-to-location (Fig. 4–5). For the overt neuron represented in figure 4, pairings of visual and auditory stimuli at locations within the SRFs where the individual responses are weak (circle and asterisk) resulted in significant multisensory enhancements. In contrast, pairings of these stimuli at locations that showed robust auditory responses (triangle) resulted in no significant interactions. These differences are further reinforced by the contrast plot that compares the multisensory responses to the predicted additive model. Here it can be seen that significant superadditive interactions accompany the pairing of weakly effective stimuli, whereas the interaction is purely additive at the location in which responses to the auditory stimulus is robust. For the modulatory neuron depicted in figure 5, despite the qualitative differences in this neuron from the overt neuron represented in figure 4, the influence of SRF architecture on the nature of the multisensory interactions was very similar. Thus, whereas stimulus pairings at locations within the SRF that showed weak auditory responses (triangle) resulted in a significant superadditive response enhancement, pairings at highly effective locations resulted in significant subadditive interactions (circle and asterisk). Collectively, these single neuron examples are highly representative of the behavior of the entire neuronal population, and underscore the conclusion that multisensory interactions are critically dependent on the effectiveness of stimuli at different locations within the SRF.

Inverse effectiveness forms the basis of spatial influences on multisensory interactions

The data illustrated in figures 4 and 5 strongly suggest that the magnitude of the unisensory response (i.e., stimulus effectiveness) plays an integral role in the degree of gain seen in the resultant multisensory interaction, and that spatial location in turn determines these interactions. To reinforce the role of effectiveness in multisensory gain (i.e., interactive magnitude), an analysis of all of the tested interactions was conducted. For the overt neurons (n=33) a total of 1843 locations were tested, of which 46.0% (843/1843) exhibited statistically significant interactions. In contrast, for modulatory neurons (n=31), a total of 985 receptive field locations were tested, of which only 27.2% (268/985) exhibited significant multisensory interactions. This difference between overt and modulatory neurons was highly significant (Chi Square test : $\chi^2=92.4$, $p<0.01$).

In addition to this difference in the incidence of integration within the SRF for overt and modulatory neurons, substantial differences were noted in the magnitude of integration for these two populations. For both, a significant negative correlation was found between the best unisensory response and the amount of multisensory integration as quantified by interactive index (overt neurons $R = -0.3568$, $p<0.0001$; modulatory neurons $R = -0.2773$, $p<0.0001$) (Fig 6 A and B left panel). However, overt neurons exhibited a greater degree of multisensory gain when compared with modulatory neurons (overt neurons mean ii = 102.4%; modulatory neurons mean ii = 74.0%). This difference was statistically significant (Student t test : $t=-3.73$, $p<0.01$). Furthermore, and likely contributing to this difference, the percentage of receptive field locations exhibiting significant response depressions was much more frequent for modulatory neurons (39.5%) compared to that of overt neurons (15.1%). Thus, this population data is in keeping with the hypothesis that the principle of inverse effectiveness forms the predictive framework for the changes in multisensory integration that take place as a function of changes in stimulus location within the SRFs of SC multisensory neurons.

Along with an analysis of interactive magnitude, which plots gain (or loss) as a function of the best unisensory response, we also conducted parallel analyses to quantify responses relative to an additive model measured by the mean statistical contrast (msc) measure. In this framework, both unisensory responses contribute to the predicted multisensory responses, and these multisensory responses can be characterized as superadditive, additive or subadditive. Analyzed in this way, for overt neurons the majority of the significant interactions were superadditive (488/630 = 76.1%) with the remainder being subadditive in nature. In addition to these significant interactions, a substantial number of the multisensory responses were purely additive in nature (213/843 = 25.2%).

For modulatory neurons, only superadditive (162/268=or 60.5%) or subadditive (106/268or 39.5%) were in evidence (since these neurons were only driven by one modality), with the percentage of subadditive interactions being higher in these neurons than in overt neurons (Overt vs modulatory: ChiSquare Test : $\chi^2=27.2$, $p<0.01$) (Fig 6B right panel) Analysis was done to test if neurons with multiple hotspots are more likely to integrate superadditively. For both overt and modulatory neurons, there were no differences between the percentage of superadditive interactions exhibited by neurons with single and multiple hotspots.

SRFs represent two spatial dimensions of the complex spatiotemporal receptive fields (STRFs) that characterize SC neurons

In addition to examining how spatial location influences the entire epoch of response for SC neurons, we were also interested in testing how different spatial locations influence the temporal profile of the unisensory and multisensory responses. Hence, in a subset of the

neurons ($n=15$) in which a complete set of SRFs was derived, the temporal response profile of the neuron as a function of changes in one spatial dimension (i.e. azimuth) was examined. The partial multisensory spatiotemporal receptive field (STRF) plot derived in this manner again showed dramatic differences from that predicted based on the unisensory responses (fig. 7). Of greatest interest here is the temporal evolution of the multisensory response, which differed depending upon whether the stimuli were positioned within or outside of a SRF hotspot. For locations that are within these unisensory hotspots, interactions shifted from subadditive in the earliest phase of the response (when unisensory firing is robust) to superadditive in later response epochs (when unisensory firing is weaker). In contrast, for locations where unisensory responses were weak, the temporal evolution of the multisensory response is such that there is an initial period of superadditivity followed by subadditivity. Collectively, these temporally-based analyses reinforced the results of the spatially-based manipulation in highlighting responsiveness (i.e., effectiveness) as the key factor in dictating the magnitude of the multisensory interaction.

DISCUSSION

The current study represents the first to provide a more detailed characterization of the complex spatial receptive field architecture of superior colliculus multisensory neurons than has been previously carried out. The study illustrates that this architecture plays an important role in the multisensory interactions that characterize these neurons. Furthermore, the work shows that it is space's impact on sensory responsiveness that appears to be the most important factor in these interactions. Furthermore, we show the SRF architecture for two of the major multisensory neuron classes in the SC – overt and modulatory neurons, and highlight differences in the integrative features of these neuronal classes.

The heterogeneous nature of the receptive fields of SC multisensory neurons

Numerous previous studies have described the large receptive fields of multisensory neurons in the intermediate and deep layers of the superior colliculus (Meredith and Stein, 1990, Wallace and Stein, 1996, Wilkinson et al., 1996; Goldberg and Wurtz, 1972; Gordon, 1973). In addition, several studies have shown in their examples the heterogeneity of these receptive fields, with differing responses to identical stimuli placed at different locations within the receptive field (Kadunce et al., 2001, Perrault et al., 2003, 2005, Krueger et al., 2009, Royal et al., 2009; Meredith and Stein 1986; 1996). However, this heterogeneous nature for the receptive fields of SC multisensory neurons has not been systematically explored. In the current study we provide a more comprehensive (but far from complete) analysis to detail the complex architecture of these receptive fields. First, in order to better characterize the receptive field architecture of these neurons, we classified them depending on the number of hotspots within their receptive fields. In this analysis we show that SC neurons can have spatial receptive fields with single or multiple hot spots.

Previous work on multisensory neurons of the cat SC suggests that there is a great degree of overlap between the visual and auditory receptive fields of these neurons (Meredith and Stein 1996; Meredith and Stein 1986; Stein and Meredith 1993). However, this overlap is not complete, a result reinforced in the current study, and which may be the result of anesthesia-dependent effects or a lack of precise spatial coding in the large receptive fields of SC neurons (and which may be attributable to slight differences in input overlap). Such discrepancies between the visual and auditory receptive fields have been reported in previous studies as well (Meredith and Stein 1996; Gordon 1973; Rauschecker and Harris 1989). Since it is known that auditory receptive fields are influenced by pinnae position (Middlebrooks and Knudsen 1987), and since the pinnae sag inferolaterally during paralysis, the lateral displacement of auditory receptive fields may be a simple result of paralysis (Meredith and Stein 1996). However, it is also possible that these misalignments in certain

neurons may reflect a more complex coding scheme for signaling dynamic multisensory stimuli. For example, azimuthal displacements in receptive fields may be important in signaling the direction and/or velocity of a stimulus moving along a specific trajectory. Secondly, regardless of the slight mis-registry in some neurons, our current results show that this general feature of receptive field overlap and spatial congruence extends to the **hotspots** of the receptive fields as well. Thus, for majority of neurons studied here, not only was there a good correspondence in the extent of the visual and auditory receptive fields, but there was also a considerable degree of alignment of the visual and auditory hotspots. Such an overlap may be functionally important to signal the spatial congruency of an audiovisual stimulus complex (as well as to code for incongruency), one of the key features of the mammalian SC for guiding accurate orientation movements of the eyes, ears, head and body (Sprague and Meikle 1965; Casagrande et al 1972; Harting et al 1973; Stein et al 1976a).

This type of complex receptive field architecture is not uncommon in sensory systems. Indeed, even in the superficial layers of the SC, where receptive fields are substantially smaller in size when compared with the deeper layers, receptive field heterogeneity has been described and implicated in the coding of visual motion and direction (Dreher and Hoffmann, 1973). In addition, and very consistent with the findings of the current study, recent work reveals excitatory and inhibitory domains within the visual receptive fields of neurons of the intermediate and deep layers of the SC in macaques (Churan et al., 2012). This architecture is speculated to play a role in target selection processes that ultimately give rise to oculomotor behaviors (i.e., gaze shifts).

Evidence from structures other than the SC also demonstrates that complex receptive field architecture is a common characteristic within sensory representations. Early work in the cat lateral geniculate nucleus illustrated a surprising complexity to the receptive fields of these neurons, a structure presumed to play a role in the spatial and temporal filtering processes carried out within the LGN (Stevens and Gerstein, 1976). Recent studies have also shown that the spatiotemporal architecture of LGN neurons may contribute to orientation tuning (Soodak et al., 1987, Shou and Leventhal, 1989, Smith et al., 1990, Sillito et al., 1993, Sun et al., 2004, Naito et al., 2007, Suematsu et al., 2012). Similar studies conducted in thalamic and cortical somatosensory structures (i.e., VPM and SI) have elucidated complex spatiotemporal receptive field architecture for the constituent neurons (Simons, 1985, Simons and Carvell, 1989, Nicolelis et al., 1993a, b, Nicolelis and Chapin, 1994). Such receptive field architecture has been implicated to play a critical role in tactile discrimination and pattern recognition (Ghazanfar and Nicolelis, 1997, Shimegi et al., 1999, Ghazanfar and Nicolelis, 2001).

In each of these examples, the complex spatial architecture of these neuronal receptive fields appears integral for the coding of dynamic stimuli, in that this type of organization can provide meaningful information about stimulus direction and velocity (Hyvarinen and Poranen, 1978, Phillips et al., 1988, DiCarlo and Johnson, 2000). Finally, with the addition of the temporal dimension (see discussion below), the spatiotemporal receptive field becomes a powerful tool for coding the salient details of a dynamic stimulus complex, an organization that maps well onto the role of the SC in guiding gaze shifts to stimuli of interest.

Spatial receptive field heterogeneity and its relevance for multisensory interactions

The receptive field architecture of multisensory SC neurons was found to be quite complex, with widely differing responses to the same stimulus presented at different spatial locations. These regions of greater and lesser response were found to be important in determining the magnitude of a multisensory interaction. Thus, for locations within the SRF in which unisensory responsiveness is weak, stimulus combinations typically result in large response

enhancements (i.e., multisensory gain that is frequently superadditive). Conversely, for locations within the SRF of high unisensory responsiveness, this gain is weak or absent (with corresponding additive or subadditive interactions). These data thus provide a compelling argument for the preeminence of inverse effectiveness as a core determinant of multisensory integration (Meredith and Stein, 1986b, a, 1996, Wallace and Stein, 1996). The reductionist nature of this finding has important mechanistic implications, in that it suggests a single overarching process that governs how multisensory neurons integrate their diverse sensory inputs. These data also illustrate the extraordinary interdependency of the previously characterized “rules” or “principles” of multisensory integration (Meredith and Stein, 1983, 1986b, a, Meredith et al., 1987, Meredith and Stein, 1996, Wallace and Stein, 1996). More specifically, these data show that depending on the location of the stimuli within the receptive field, response effectiveness is altered in a manner that ultimately affects the magnitude and nature of multisensory interactions. In many respects such a concept is intuitive, in that changes in one of these factors (e.g., space) have a consequent impact on the others. However, since these rules were necessarily derived in isolation (by manipulating one variable at a time), the importance of the current study is in establishing the nature of this vital interdependency. Indeed, this interdependency seems to be true regardless of brain structure, in that it has been previously shown to apply to cortical multisensory neurons as well (Carriere et al., 2008). Moreover, in our STRF analyses we show interdependencies between three of the classic factors: space, time and effectiveness (albeit just one dimension of space is represented at a time in our data i.e., multiple azimuths at a single elevation). These relationships show that **when** (represented as time) unisensory responsiveness is high in certain spatial locations, multisensory gains are less when compared with time epochs and spatial locations when unisensory responsiveness is weak (and multisensory enhancement is large). Although the functional roles of this interdependency and the importance of effectiveness remain to be determined, they create an interesting local form of gain control that serve to increase the potential impact and functional relevance of weakly responsive regions of the unisensory SRFs.

Nature of integration within the SRF architecture of multisensory neurons

This study also shows that the nature of multisensory integration within the SRF of SC neurons differ depending on the type of multisensory neuron under study (overt vs modulatory). Thus, when compared with modulatory neurons, overt neurons exhibited more response enhancements and super additive interactions. Why such distinctions exist between these different neuronal types is not clear. One possibility is that modulatory neurons lack the synaptic drive necessary to support super-additive interactions. This seems unlikely given the inverse effectiveness observations described earlier. A second related possibility is that modulatory neurons receive their non-dominant modality inputs from the local processing architecture, and this local architecture is insufficient to support large interactions. Congruent with this explanation is prior work showing the multisensory integration in the SC, as evidenced in large super-additive response enhancements, is largely a result of convergent inputs from descending cortical sources (Wallace and Stein 1994). Finally, our results show that the strength of responses of modulatory neurons is significantly higher under unisensory conditions when compared to that of the overt neurons. Hence addition of a spatially coincident second modality stimulus may result in more frequent response depressions and subadditive interactions. Future work should be structured to examine in detail these intriguing differences in the integrative potential of overt vs. modulatory neurons..

Previous work shows that the underlying nature of the computations performed by SC multisensory neurons critically depends on the dynamic range of the individual neuron (Perrault et al 2005). Thus, neurons that show superadditive or superadditive / subadditive

interactions have small dynamic ranges while neurons which show additive and subadditive interactions have larger dynamic ranges. However, all of these earlier studies characterized the nature of integration in overt multisensory neurons only. To the best of our knowledge, this is the first study describing the nature of integration performed by modulatory multisensory neurons in the cat SC. Thus, in the light of our current results and based on previous findings it can be hypothesized that modulatory neurons, which exhibit many more sub-additive interactions when compared to overt neurons, may have a wider dynamic range. However, this remains to be empirically tested.

Spatial receptive fields and their possible role in multisensory-mediated SC behaviors

The long standing role attributed to the SC has been in the detection and localization of a stimulus or stimulus complex and the subsequent production of an orientation response involving movements of the eyes, head and ears (Sprague and Meikle, 1965, Casagrande et al., 1972, Sprague, 1996). Prior work has shown that SC-mediated behaviors are facilitated under multisensory circumstances, with improvements being seen in both the speed and accuracy of responses (Stein et al., 1988, Hughes et al., 1994, Nozawa et al., 1994, Frens et al., 1995, Wilkinson et al., 1996, Jiang et al., 2002, Diederich and Colonius, 2004, Bell et al., 2005). The current study provides a more mechanistic view into this process, by illustrating *how* the complex receptive fields of SC neurons may contribute to these behavioral improvements. The most straightforward interpretation of these results is that the multisensory SRF serves as a “smoothing” filter, boosting gain for regions of weak response and thus equilibrating performance across space. At first, this may seem counterintuitive because by serving as a smoothing filter, the SRF architecture will result in decreased spatial accuracy at the level of individual neurons. However, this concept is in accordance with previous literature, which shows that although the spatial resolution of individual neurons is rather coarse, it can be envisioned that when neurons are pooled at the population level, the system can have substantially better resolution (Kadunce et al 2001). This is because the high degree of spatial overlap between the receptive field of these neurons insures that spatially coincident multisensory stimuli will fall within the excitatory receptive fields of a large number of multisensory neurons and consequently evoke a large population response. Conversely, progressive increases in spatial disparity decreases the population response in two ways. First, increasing spatial disparity decreases the likelihood that the two different stimuli will encroach on the two excitatory receptive fields of the same neuron, thus decreasing the likelihood of multisensory enhancement and lowering the magnitude of population response. Second, increasing spatial disparity increases the incidence of multisensory inhibition generated when one stimulus is within its excitatory receptive field while the other stimulus is within its inhibitory receptive field (Kadunce et al. 1997). Consequently, the multisensory population response reflects an underlying spatial resolution that cannot be predicted by the absolute sizes of the receptive fields of individual SC neurons or their areas of receptive field overlap.

Although an intriguing possibility, this interpretation requires empirical validation by examining behavioral performance while recording the activity of SC multisensory neurons. Current work in the laboratory is exploring this linkage. A similar boosting of multisensory responses in regions of the receptive field that have weaker unisensory responses after pairing visual and auditory stimuli across space has been seen in auditory cortex of anesthetized ferret (Bizley and King, 2008, King and Walker, 2012). They demonstrated that spatially coincident visual and auditory cues increased the amount of information conveyed by the neurons about stimulus location. The authors suggested that such multisensory information enhancement could underlie improved localization accuracy observed when visual and auditory stimuli are presented in the same spatial location. A similar explanation can be valid for our results as well.

Spatial receptive fields as a component of the spatiotemporal receptive field

Although the current description of the SRFs of multisensory SC neurons represents an important step in furthering our mechanistic understanding of these neurons, a complete description will only be obtained with the inclusion of the temporal dimension as well. Here we begin this analysis by creating partial spatiotemporal receptive fields (STRFs) for a subset of the recorded neurons. Although very preliminary, these STRFs illustrates that complex temporal dynamics characterize the response profile of SC neurons, a finding in keeping with numerous studies looking at the response characteristics of these neurons (Sterling, 1971, Walker et al., 1995, Waleszczyk et al., 1999, Waleszczyk et al., 2003, Rowland et al., 2007, Rowland and Stein, 2007, Waleszczyk et al., 2007, Wang et al., 2010)

However, from the perspective of multisensory processing, once again it appears that this complexity can be substantially resolved by taking into account a single factor – sensory responsiveness. Thus, temporal epochs of the response in which firing is low under unisensory conditions are those that have the highest potential for gain upon stimulus pairing. Such a finding is concordant with prior work looking at the temporal elements of the multisensory response (Rowland et al., 2007, Rowland and Stein, 2007, Royal et al., 2009). One important caveat for the current data is that the STRF mappings conducted here are quite low resolution and limited to a single spatial dimension (multiple azimuths across a single elevation). Ongoing work in the lab is focused on creating more complete STRF representations where these temporal properties are analyzed for both azimuth and elevation.

Sensory signals in the natural environment are complex with time varying properties, and necessitate brain mechanisms to code for these spatiotemporal features in order to guide adaptive behavior. Indeed, the concept of spatiotemporal (or spectrotemporal) receptive fields is becoming a standard in studies of sensory processing, where this architecture provides important clues into both functional circuitry and functional utility (Dawis et al., 1984, McLean and Palmer, 1989, Reid and Shapley, 1992, Eckhorn et al., 1993, Golomb et al., 1994, Victor JD, 1994, Cai et al., 1997, Reid et al., 1997, Ringach et al., 1997, Cottaris and De Valois, 1998, Li Y, 2008). In the auditory system, the spectrotemporal RF architecture of auditory cortical neurons has been suggested to code for species-specific vocal signals used for prey hunting and/or communication among conspecifics (Suga et al., 1987). In addition, work in the primate auditory system have implicated STRFs in the encoding of stimulus edges, stimulus transitions in frequency or intensity and conjunctions of different stimulus features (deCharms et al., 1998). In the somatosensory system, STRF architecture has been implicated to play a role in identifying patterns of tactile stimulation (Nicoletis et al., 1993a, b, Nicoletis and Chapin, 1994). The current study represents the first to extend the description and analysis of STRFs to the multisensory layers of the mammalian SC, a structure in which the well-established spatial architecture and behavioral output make it particularly amenable to psychometric-neurometric studies to further elucidate the importance of STRFs in dynamic stimulus encoding.

Conclusion

To summarize, in this study we show that multisensory neurons of the cat SC have complex spatial and spatiotemporal receptive fields, and that this receptive field architecture plays an integral role in the integrative abilities of these neurons. Thus, changes in sensory responsiveness brought about by changes in stimulus location represent an important determinant of the nature and amount of multisensory integration. Hence, regions of the receptive field that show weak unisensory responsiveness are those that show the greatest response gain under multisensory conditions.

Acknowledgments

We thank Zachary Barnett who contributed towards setting up the stimulus paradigm and providing the analytic tools and Aaron Nidiffer for help in constructing some of the figures. We also thank the Vanderbilt University Division of Animal Care.

Grants: This work was supported by National Institute of Mental Health Grant MH-63861 and Vanderbilt Kennedy Center and Vanderbilt Brain Institute Development Funds.

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Highlights

- The spatial receptive field of overt and modulatory multisensory neurons in SC are characterized
- The complex SRF architecture plays a vital role in dictating a resultant multisensory interaction
- Response effectiveness appears to be a primary determinant for multisensory interactions
- Integrative profile differs between overt and modulatory neurons.

Figure 1.

Construction of spatial receptive field (SRF) plots. A. The schematic depicts multiple locations within the spatial receptive field of a neuron. The dots are color coded to represent different azimuths in a single elevation. The top and bottom rows represent an upper and lower elevation, respectively. B. Exemplar single unit activity (SUA) recorded at each of the tested locations, depicted as peristimulus time histograms (PSTHs). The inset shows a representative multisensory response at a single location. Stimulus onset and offset (visual (V), auditory (A)) is depicted by square waves on the top. Below the stimulus representation is a raster plot in which each dot represents an action potential and each row of dots represents a single trial. The solid vertical line marks stimulus onset. Shown below the rasters is the PSTH for this location. The dashed horizontal line represents the threshold criterion for response (2SD above the baseline), the solid vertical line represents response onset and the dotted vertical line represents response offset. C. The evoked response is then normalized across all locations and all conditions to produce a response range from 0 to 1 where 0 represents no response and 1 represents the maximum response. This is then represented as a pseudo color SRF plot in which warmer colors represent greater response magnitudes and cooler colors represent lower response magnitudes.

Figure 2.

SRF plots for a pair of representative SC neurons. A. Shown on the top row are responses to the visual, auditory and multisensory conditions. In each of these conditions, the neuronal response changes as a function of stimulus location within the receptive field. This neuron exhibits a single hotspot in the multisensory condition. Shown on the bottom row is the predicted multisensory response based on additive factors logic, as well as a contrast plot showing how the actual multisensory response differs from the predicted response. Note the regions of superadditivity (warmer colors) and subadditivity (cooler colors) in this representation. B. Representative example of a second multisensory neuron showing a more complex SRF architecture with multiple hotspots in the multisensory condition (highlighted

by the circles). As for the neuron represented in A, the contrast plot highlights that the multisensory SRF differs substantially from the predicted SRF. Dotted lines outline the hotspots in both A and B.

Figure 3. Frequency distribution of the area of overlap (in %) between the visual and auditory hotspots for multisensory SC neurons. A visual depiction of the overlap is shown along the x axis.

Figure 4. Influence of spatial receptive field architecture on nature of multisensory interactions. **A.** Visual, auditory and multisensory SRF plotted for a representative multisensory SC neuron with overt responses to both visual and auditory stimuli. Symbols (circle, triangle, star) depict 3 locations within the SRF where visual and auditory stimuli were delivered individually (in the unisensory conditions) and in combination (for the multisensory condition). The contrast plot at the bottom is obtained by subtracting the predicted SRF ($V + A$) from the multisensory SRF (VA). **B.** Rasters and PSTHs show this neuron's response at each of the 3 locations (represented by symbols) in each of the 3 stimulus conditions represented in the top, middle and bottom panels. **C.** Bar graphs illustrating the mean visual, auditory and multisensory response for each location and the magnitude of multisensory interaction as calculated using both interactive index (ii) and multisensory contrast (msc). Asterisks represent statistically significant ($p < 0.05$) changes in the multisensory condition.

Note that despite the physical characteristics of the stimulus being identical, the responses are dramatically different for each of the different locations. Note also that the nature of the multisensory interactions differed dramatically from location-to-location. Whereas locations with lower visual and auditory responses (circle and star panels) show large superadditive interactions, locations with high visual and auditory responses (triangle panel) shows no significant interaction. Dotted lines in color plots outline the hotspots under different stimulus conditions.

Figure 5.

A second example of the influence of spatial receptive field architecture on the nature of multisensory interactions. Conventions are identical to those for figure 4. Note that this neuron is an example from the modulatory class, in which no overt response to the visual stimulus is evident. Nonetheless, the visual stimulus had the ability to modulate responses to the auditory stimulus. Note also the more complex and heterogeneous SRF architecture of this neuron. Nonetheless, the same general guidelines evident for the neuron shown in figure 4 are evident here, with weakly responsive regions of the SRF being where the largest multisensory interactions are seen. Dotted lines in color plots outline the hotspots under different stimulus conditions.

Figure 6.

A. Population data for all 33 overt multisensory neurons recorded from the intermediate/ deep layers of the SC and which plots statistically significant interactive index (ii) and mean statistical contrast (msc) as a function of the normalized best unisensory response. For ii, positive values signify response enhancements while negative values signify response depressions. The red line represents the trend of the dataset represented by the equation $y = -255.01x + 139.19$. For msc, the blue circles represent superadditive and subadditive interactions while the red circles represent additive interactions. B. Population data for all 31 modulatory multisensory neurons recorded from the intermediate/ deep layers of the SC and which plots statistically significant interactive index (ii) and mean statistical contrast (msc) as a function of the normalized best unisensory response. For ii, positive values signify response enhancements while negative values signify response depressions. The red line represents the trend of the dataset represented by the equation $y = -114.89x + 58.093$. For msc, the blue circles represent superadditive and subadditive interactions. By definition, modulatory neurons do not exhibit additive interactions.

Figure 7.

Example of a series of spatiotemporal receptive field (STRF) plots for a multisensory SC neuron. For these plots a single dimension of stimulus location (i.e., azimuth) is plotted on the y-axis and peristimulus time is plotted on the x-axis (stimulus onset = 0). Note that the temporal characteristics of the neuronal response changes as a function of both space and time for each of the different conditions. Once again note that the multisensory STRF differs considerably from the predicted STRF obtained by summing the visual and auditory STRF, with the differences best highlighted in the contrast plot at the bottom. Here we see that the temporal dynamics of the response also play an important role in multisensory interactions, such that weakly responsive regions of the STRF are those in which the largest multisensory

interactions are seen. The circles in the contrast plot highlight this for two azimuthal locations, and in which the temporal dynamics of the multisensory interaction follow the temporal dynamics of the unisensory response profiles