

RESEARCH ARTICLE | Higher Neural Functions and Behavior

Neural correlate of auditory spatial attention allocation in the superior colliculus

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Submitted 30 November 2017; accepted in final form 21 December 2017

Rajala AZ, Jenison RL, Populin LC. Neural correlate of auditory spatial attention allocation in the superior colliculus. *J Neurophysiol* 119: 1450–1460, 2018. First published December 27, 2017; doi: 10.1152/jn.00854.2017.—This study is the physiological complement to previous behavioral work that demonstrated that rhesus monkeys are able to allocate attention about the surrounding space based on brief, broadband auditory cues. Single-unit recordings were taken from the intermediate layers of the superior colliculus (iSC) while the subjects oriented to visual and auditory targets in the context of a cuing task with their heads unrestrained. The results show a correlation between behavioral manifestations of attention allocation, attention capture and inhibition of return, and modulation of target-evoked responses in single iSC neurons.

NEW & NOTEWORTHY These results show for the first time a neural correlate of attention capture and inhibition of return in response to auditory stimuli in the superior colliculus of the head-unrestrained monkey.

auditory attention; gaze shifts; head-unrestrained; monkey; superior colliculus

INTRODUCTION

In a previous behavioral study, we addressed a major discrepancy between results from humans and monkeys concerning the allocation of spatial attention in the auditory modality (Populin and Rajala 2010). Specifically, it had been demonstrated that humans could allocate spatial attention about the surrounding space based on auditory signals, provided that the sources of the signals were localized, not just detected (McDonald and Ward 1999; Posner 1978; Rhodes 1987; Roberts et al. 2009; Spence and Driver 1994); however, rhesus monkeys, the animal model closest to humans for studies of the function of the nervous system, and specifically for the mechanisms underlying the allocation of visual attention (Bisley and Goldberg 2010; Colby and Goldberg 1999; Desimone and Duncan 1995; Reynolds and Chelazzi 2004; Squire et al. 2013), could not (Bell et al. 2004).

Using gaze latency as the dependent variable, our data demonstrated that rhesus monkeys could indeed allocate spatial attention based on auditory spatial information. Moreover, they

showed that the effects followed the classical attention capture (AC) (Jonides 1981) and inhibition of return (IOR; Posner and Cohen 1984) pattern that characterizes the allocation of spatial attention in the visual modality, albeit with a faster time course (Populin and Rajala 2010).

Importantly, Bell et al. (2004) demonstrated a neural correlate of AC and IOR brought about by a visual but not an auditory cue in the peak discharge rate of visual target-evoked responses of neurons in the intermediate layers of the superior colliculus (iSC). The SC is a midbrain structure known to play a central role in essential functions such as sensorimotor integration (Sparks 1986; Wurtz and Albano 1980), multisensory integration (Populin and Yin 2002; Stein and Meredith 1993), and the allocation of spatial attention, including the implementation of IOR (Dorris et al. 2002; Posner et al. 1985). Bell et al. (2004) proposed that AC results from the summing of responses evoked by a visual cue and the target, whereas for IOR they attribute the reduction in the magnitude of target-evoked responses to descending inhibitory inputs, as proposed by Dorris et al. (2002), not to long-lasting inhibitory effects local to the SC. Importantly, their lack of behavioral effects in the auditory cue modality were accompanied by no modulation of target-evoked responses in the iSC, which they attributed to the meager amplitude of auditory-evoked responses as well as their short latency.

A detailed comparison between the two studies led us to conclude that methodological discrepancies might be responsible for the differences. Specifically, the subjects in our study were trained to localize auditory stimuli by pointing with their gaze to the perceived location of the sources, which in successful trials led to the administration of a reward. Hence, this reinforcement may have led them to attribute behavioral significance to the processing of spatial auditory information. For the subjects studied by Bell et al. (2004), on the other hand, auditory information carried no behavioral significance based on the description of their experimental task. In addition, our subjects were allowed to orient with their heads unrestrained, whereas those of Bell et al. (2004) were studied with their heads restrained.

Accordingly, because we had demonstrated that auditory cues do lead to the attentional effects of AC and IOR under specific task conditions (Populin and Rajala 2010), we hypothesized that iSC neurons should exhibit similar cue-target interactions in animals that have been trained to orient to the

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sources of auditory stimulation with their heads unrestrained for rewards. The results from two rhesus monkeys tested with broadband auditory cues revealed that a similar correlation between behavioral manifestations of spatial attention allocation, AC and IOR, and modulation of target-evoked responses is found in iSC neurons.

MATERIALS AND METHODS

Subjects and surgery. Two adult male rhesus monkeys (*Macaca mulatta*), weighing 7.5 and 10 kg, participated in this study. One of them, *subject G*, had contributed to our previous behavioral report (Populin and Rajala 2010). The animals were prepared for eye movement recordings with the scleral search coil technique (Robinson 1963) by implanting coils constructed from teflon-coated stainless-steel wire (SA632; Cooner Wire, Chatsworth, CA), using the approach described by Judge et al. (1980). A lightweight titanium head post was also implanted to restrain the head to care for the implant area and to hold a spout for the delivery of water rewards while the animals oriented with their head unrestrained. After behavioral training in sound localization (Populin 2006), a second surgery was performed in which a recording cylinder, placed on the midline at a $\sim 37^\circ$ angle, was implanted to allow the insertion of recording electrodes into the right and left SC. All surgical procedures were approved by the University of Wisconsin Institutional Animal Care and Use Committee (IACUC) and were in accordance with the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*.

Experimental setup, gaze and head movement measurement, and stimulus presentation. The experimental setup is described in Rajala et al. (2013). Briefly, all behavioral and experimental sessions were carried out in a $3 \times 3 \times 2$ m double-walled acoustic chamber (Acoustic Systems, Austin, TX), with the interior walls covered with 2-in. reticulated foam to attenuate acoustic reflections. Eye and head position were measured with the scleral search coil technique (Robinson 1963) using a phase angle system (CNC Engineering, Seattle, WA). Horizontal and vertical position signals from one eye and the head were low-pass filtered at 250 Hz (Krohn-Hite, Brockton, MA), digitally sampled at 500 Hz with an analog-to-digital converter (National Instruments, Austin, TX), processed online to reward the animals when their responses met the required temporal and spatial criteria, and stored in a hard drive for offline analyses.

The monkeys sat in a primate chair, facing a hemisphere with their head at the center. Twenty-four speakers (Morel MDT-20 28-mm soft dome tweeters; Morel America, Elmont, NY) were affixed to the frame of the hemisphere. Light-emitting diodes (LEDs) were positioned immediately in front of the center of some of the speakers. The transducers were positioned at 10° intervals along the horizontal and vertical axes. Acoustic signals were generated with Tucker Davis Technologies System 3 (TDT, Alachua, FL) using two separate hardware channels under the control of a custom switch box designed to present acoustic stimuli with microsecond accuracy without introducing unwanted transient noise at the time of speaker selection. Both LEDs and speakers were positioned 84 cm from the subject's head. The subject's view of all transducers was obstructed with a black cheesecloth-like material that allowed acoustic signals to pass and LEDs to be seen. Liquid rewards (water) were delivered at the end of all successful trials with a stainless-steel spout attached to the head post by a lightweight bracket, with its tip positioned immediately in front of the subject's lips.

Behavioral training and experimental task. All behavioral training was based on positive reinforcement. Complete descriptions of the procedures are found in Populin (2006), Populin and Rajala (2010), and Rajala et al. (2013). Briefly, monkeys were first trained to enter a primate chair for a fruit reward, and subsequently, using operant procedures, they were trained to direct their gaze to visual stimuli for a water reward. After the monkeys were able to earn the daily

minimum amount of water required by the IACUC, their heads were unrestrained, and delayed and memory-guided saccade tasks were included in their training. Subsequently, they were presented with acoustic targets from spatial locations never associated with visual stimuli and tested with spatial acoustic illusions such as summing localization (Populin 2006) and the Franssen illusion (Rajala et al. 2013), which create the perception of sound location where no sound is actually presented, to ensure that their behavioral responses were driven by perceived sound location.

The cuing task (Posner 1978) was introduced later during training (Fig. 1). This oculomotor version of the task did not present much difficulty because, as implemented, it was a variant of the memory-guided saccade task, which the monkeys had already mastered. Specifically, the cue was used to provide the subject information about the potential location of an impending sensory event, a target, which required the overt response of pointing gaze to its perceived location upon presentation. Importantly, no overt response to the cue was allowed, and movement detected in either the eyes or the head during the cue-to-target onset asynchrony (CTOA) period led to immediate termination of the trial.

Emphasis was placed in studying the effects of auditory over visual cues on sensory responses to ensuing visual and auditory targets. Figure 1A illustrates the spatial arrangement of the cuing task with an auditory cue followed by a visual target in both the valid and invalid configurations. Seventy-five percent of all cuing trials were of the valid type and the remaining 25% of the invalid type. The cues were always presented at the same (valid) or exact opposite (invalid) location as the targets, depending on the receptive fields of the units under study, ± 10 , 20, and 30° , at 0° elevation. For *subject G*, the auditory cue was a 120- μ s click, and for *subject A*, it was a 10-ms broadband noise burst (5 ms linear rise/fall). The auditory target was a 250-ms broadband noise burst, with 10 ms linear rise/fall. The background sound level in the experimental room was 27–30 dB SPL (Extech 407740; Extech, Waltham, MA), and the sound level of the auditory cue and auditory target stimuli was 55–65 dB SPL. The expectation was that the presentation of the auditory cue would prompt the subjects to covertly allocate attention to the location from which it was presented, which in turn would affect the latency of the gaze shifts to the ensuing targets. The visual target was a red LED lit for 250 ms.

Figure 1B illustrates the cuing task as a function time, with the occurrence of relevant events (e.g., the onset of the cue and the onset of the target) illustrated with tick marks. Successful performance in this task required the monkeys to refrain from overtly orienting to the cue and to maintain fixation of the visual stimulus at the center. The windows for the fixation epoch were $\pm 3^\circ$ for both gaze and head position. In addition, trials in which either gaze or head moved by less than $\pm 3^\circ$ during the CTOA period were excluded from analyses. The task also required an accurate response to the target, i.e., within $\pm 3^\circ$ for visual targets and within $\pm 7^\circ$ for acoustic targets. In trials in which the monkey's responses fulfilled both the temporal and the spatial criteria, a small amount of water was delivered at the end as a reward.

Two CTOAs were selected for these physiological recordings to produce maximal behavioral effects for AC (10 ms for the single 120- μ s click cue used for *subject G* and 20 ms for the 10-ms broadband noise cue used for *subject A*) and IOR (400 ms) based on our previous findings (Populin and Rajala 2010). In all recording sessions, trials of different types were presented in random order. Approximately 60–70% were of the cuing type, and the remaining 30–40% were a mixture of fixation and standard- and memory-guided saccade trials; the latter were inserted to present variety in an effort to keep the subjects interested in participating. Three-quarters of all cuing trials were of the valid type, and the remaining one-quarter invalid.

Single-unit recordings. Recording sessions started 5–7 days following placement of the recording cylinder and took place four to six

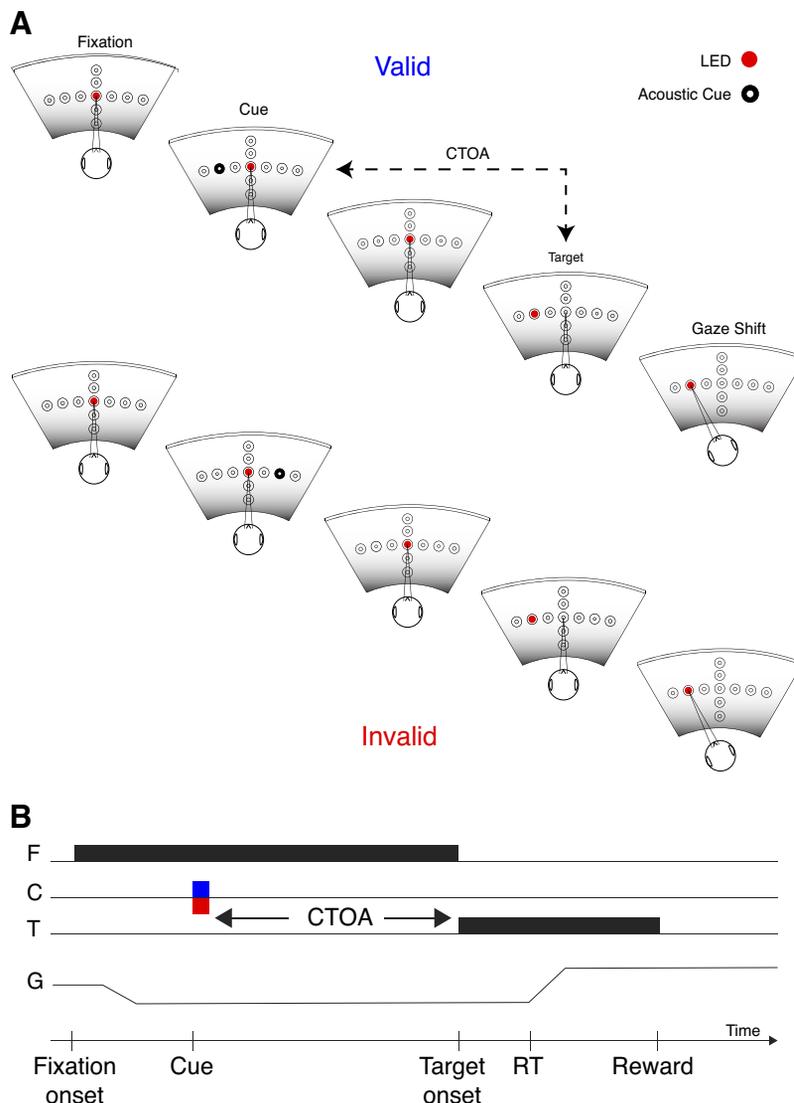


Fig. 1. Schematic representation of the cuing task. *A*: examples of the spatial arrangement of the valid and invalid configurations of the cuing task; an auditory cue preceding a visual target by a cue-to-target onset asynchrony (CTOA) is illustrated. *B*: timeline of the task illustrating the timing of relevant behavioral events. RT, reaction time; F, fixation; C, cue; T, target.

times per week. Single-unit activity was recorded extracellularly in the SC using tungsten electrodes (Fine Science Tools, Foster City, CA, or Microprobe, Potomac, MD). Electrodes were lowered into the brain using a hydraulic microdrive (MO-95; Narishige, Tokyo, Japan) through a 23-gauge stainless-steel guide tube held in place by a custom grid secured within the recording cylinder. The neural signals were amplified (Bak Electronics, Mount Airy, MD) and band-pass filtered (0.6–3.0 kHz; Krohn-Hite, Brockton, MA). The occurrence of action potentials was recorded by saving the time of TTL pulses produced by a window discriminator (Tucker Davis Technologies, Alachua, FL). All data presented were collected from unequivocally well-isolated single units.

At the start of a recording session, the electrode was lowered into the vicinity of the SC, ~1–2 mm above the superficial layers, with the head of the monkey restrained. After the integrity of the electrode was verified and the leads connecting to the preamplifier and the reward tube were arranged to allow the animal to move its head without interference, the head was unrestrained. Subsequently, the monkey was presented with visual and acoustic targets in the context of the standard- and memory-guided saccade tasks (Rajala et al. 2013) while the electrode was lowered into the intermediate layers of the SC searching for single units. The intermediate layers of the SC were identified based on the sensory motor properties of the neuronal responses (Gandhi and Katnani 2011; Sparks 1986; Wurtz and Albano

1980). Upon isolation of a single unit, the experimental session was reconfigured on the fly to present trials of the cuing type with cues and targets in the receptive field of the isolated unit and in the opposite position in the contralateral hemifield outside of the receptive field.

Data analysis. Eye and head movement data were analyzed offline with custom graphics software written in MATLAB (The MathWorks, Natick, MA) that displayed the vertical and horizontal components of gaze, head, and eye (in the orbit) position and the corresponding time derivatives. The results were stored in a relational database. The method used to determine movement onset and offset has been described previously (Populin and Rajala 2011). Essential to this aspect of the analysis was to exclude trials in which the latency of overt responses was shorter than 50 ms, which would have indicated that the subject had anticipated the location of the target, and trials in which there was movement of the eyes and/or head during the CTOA. Only data from properly executed trials are included in this report.

Spike density functions (MacPherson and Aldridge 1979; Richmond et al. 1987) were constructed by convolving the action potentials from each trial with a time function shaped like Gaussian pulse ($\sigma = 10$ ms). The responsiveness of each neuron to auditory and visual targets was determined using the methods described by Bell et al. (2004). Briefly, the peak response from 0 to 150 ms after the presentation of the cue was measured in the 400-ms CTOA trials. A neuron was considered visual and/or auditory responsive if the mag-

nitude of the cue-aligned activity was significantly greater than the baseline activity, defined as the average rate between 100 and 0 ms before cue onset (Wilcoxon rank-sum test, $P < 0.05$). To determine the saccade-related response of a neuron, the peak activity was measured 10 ms before and after the saccade onset, and the neuron was considered saccade-related if the peak saccade-aligned activity was consistently >80 spikes/s for saccades in the preferred direction. Neurons were used for analysis in the modality (visual and/or auditory) for which they met these criteria. All incorrect trials were excluded, as well as trials in which gaze latency was shorter than 50 ms or longer than 500 ms. Finally, for each condition, more than one correct trial was required for inclusion in the analysis.

The use of a compact set of basis functions (Laguerre), which model the responses of the neurons in the time after target presentation, arose from the need to determine objectively the analysis window given the differences in discharge characteristics between the visual and auditory conditions. Target-evoked activity must be measured within a restrictive epoch that excludes motor-related activity and in some instances cue-related activity. Bell et al. (2004) and Fecteau et al. (2004) resolved this problem by taking into account the magnitude of responses of neurons that have only visual activity as well as saccade latency to calculate the duration of the target-related epoch within which to measure target-related activity. For the present auditory-related data, such an approach proved to be unreliable because the latency of behavioral responses to auditory targets is much shorter (Populin and Rajala 2011) and the magnitude of such responses in the SC were more variable in the auditory condition than in the visual.

System transfer functions can be modeled as a linear combination of exponentially decaying orthonormal Laguerre basis functions (Wahlberg 1991). In the frequency domain, all Laguerre functions have the identical magnitude spectra for the given parameter α ; however, the phase spectra are different (Marmarelis 1993) and can be used to decompose the causal effects of the cue and target on neural spiking activity.

Discrete Laguerre basis functions $V_k(t)$ were computed recursively using the following established formulas (Marmarelis and Berger 2005).

The relation was first initialized by a δ -function $\delta(t)$:

$$v_0(t) = \sqrt{\alpha} v_0(t-1) + \sqrt{1-\alpha} \delta(t) \quad (1)$$

and then recursed an adequate number of times to cover the expected posttarget interval

$$v_k(t) = \sqrt{\alpha} v_k(t-1) + \sqrt{\alpha} v_{k-1}(t) - v_{k-1}(t-1), \quad (2)$$

where $\alpha = 0.08$ is the parameter value that determines the exponential decay, which in this case sufficiently decays for a time interval of 250 ms and k ranges from 1 to 15. The first five basis function orders generated for this study are shown as a function of time and k in Fig. 2A.

The linear combination of weighted Laguerre basis functions forms an impulse response relative to the target event that optimally predicts each trial's neural response (Saha et al. 2004). Each basis function can be considered as a filter orthogonal to the others and having a characteristic group delay determined by each filter's step response. Each component filter then reflects a unique feature of the neural process and its relative timing to the target.

A generalized linear model using the Laguerre bases was fit using stepwise regression. The design matrix was constructed by convolving the set of Laguerre basis functions with δ -functions centered at the time of target presentation. The distribution of spikes is assumed to be an inhomogeneous Poisson process, where the expected discharge rate at time t is defined as

$$\lambda(t) = \exp \left\{ b_0 + \sum_{k=1}^K b_k v_k(t) * \delta(t-T) \right\}, \quad (3)$$

where T is the time of target presentation and $*$ denotes convolution. It is expected that a compact set of basis functions will be able to

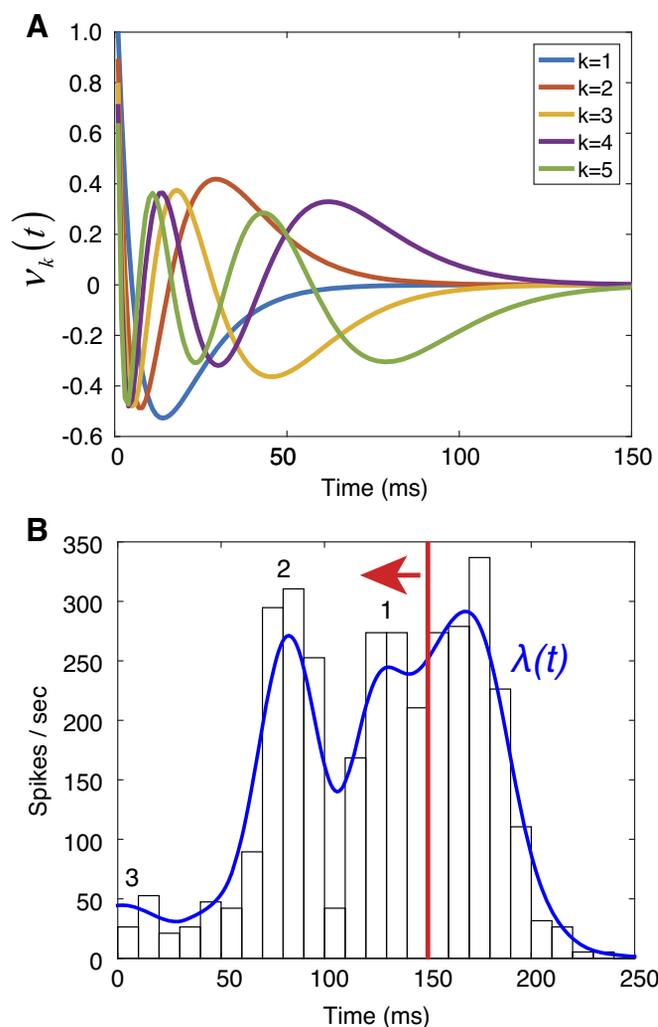


Fig. 2. A: 2-dimensional representation of Laguerre functions $v_k(t)$ of order $k = 1:15$ as a function of lag time; $\alpha = 0.8$. B: $\lambda(t)$ (Eq. 3) fit to single unit data overlaid on binned spike counts. Vertical red line represents the defined end of the analysis window, 150 ms after target presentation, used to identify the target-related epoch. The 2nd mode (peak) was chosen, going backward in time from the red line.

characterize different temporal components related to the cue (for short CTOAs), target, and eye movement. Stepwise fitting of the model was based on Akaike Information Criteria (AIC) to prune the set of Laguerre basis functions down to relevant orthogonal time-delayed bases. The stepwise AIC method is a model selection method that is simple and can be extended to generalized models based on point process data (Yamashita et al. 2007). It proceeds as follows: 1) fit the full model and 2) remove a regressor from the model fit. If the change in AIC value is more than a threshold change (0.01), then keep the regressor out of the model and repeat this step until no further regressors can be removed. There are several problems associated with stepwise regression that are related primarily to the bias introduced using the same data to stepwise prune the reduced set of regressors (Copas 1983). However, in this particular model selection application, the method provides a principled exploratory method to select a small number of basis functions to guide the target interval over which valid and invalid cues were compared.

Using this method, the time delays of modes (peaks) in the first 150 ms following target presentation were identified. Moving from the end of the 150-ms window backward, the target-related epoch was determined by identifying the second major mode to the left of the 150-ms point (Fig. 2B) for each neuron in the population for both the visual

and auditory target conditions. The upper limit of the time delay for this mode was found for each neuron, and the latter of the two most frequent values for each condition was used as the end point of the target-related epoch. The window was then extended back in *time* 65 to fully capture the responses across the population of neurons in both the valid and invalid conditions that were then applied to all neurons for analysis. For visual targets, the window was set at 50–115 ms following target presentation and for auditory targets 25–90 ms.

The mean discharge rates from this epoch were used in the population analyses for each neuron in each condition. Significance was determined for the population using Wilcoxon rank sum test, $\alpha = 0.05$. Correlation analyses were performed by comparing both gaze onset and head onset from each specific trial of each condition to the corresponding peak in the neural activity during the target-related epoch on the same trial. Significance was determined for each neuron using a *t*-test, $\alpha = 0.05$.

RESULTS

The activity of 35 unequivocally isolated single neurons from the iSC of two monkeys (25 from monkey G and 10 from monkey A) were recorded while they performed the cuing task with their heads unrestrained. The approximate location of the center of their receptive fields ranged between 10 and 30° of eccentricity at approximately eye level.

Behavioral effects. To maximize the number of trials that could be acquired while recording from single units in the SC of the head-unrestrained monkey, we used a small set of CTOAs, 10 or 20 ms for the short range, which were expected to reveal AC, and 400 ms for the long, which was expected to elicit IOR based on the results of our previous study (Populin and Rajala 2010).

Figure 3 illustrates the behavioral effects of auditory cues documented in the present study. Gaze latencies from the valid and invalid configurations were significantly different in each of the two cue-to-target combinations studied (Fig. 3A and Table 1). As indicated above, our emphasis was placed on studying the effects of auditory cues on responses evoked by visual and auditory targets. To determine whether the differences in latency between the valid and invalid cue conditions revealed AC and/or IOR, we subtracted the valid from the invalid and plotted them separately for each target modality (Fecteau et al. 2004). Figure 3B illustrates the results of this analysis. Data corresponding to the short CTOA condition fell above the no-difference line indicating AC, whereas data corresponding to the long CTOA fell below the no-difference line indicating IOR. This pattern of effects brought about by

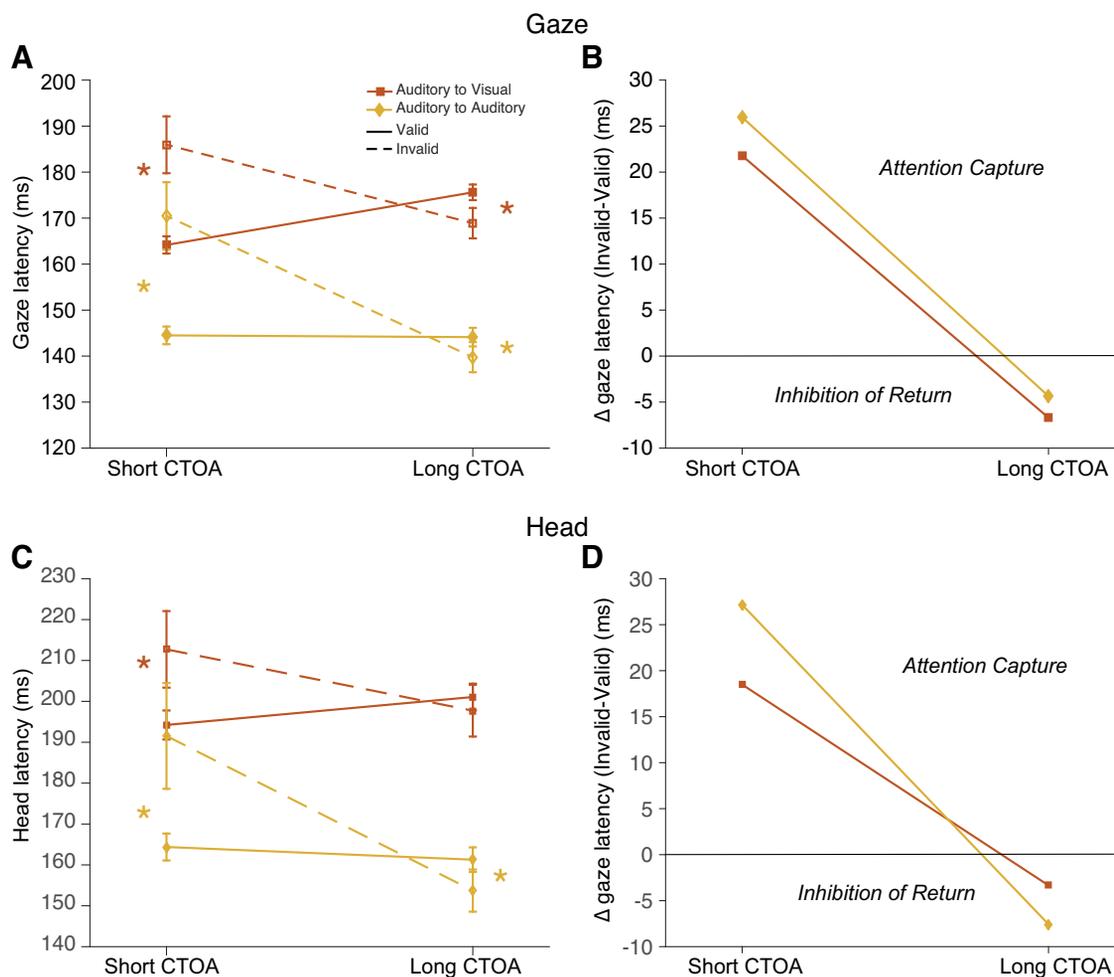


Fig. 3. Behavioral effects of broadband auditory cues on gaze and head movement latency. *A*: average gaze latency to visual and auditory targets for the short cue-to-target onset asynchronies (CTOAs: 10-ms CTOA for *subject G* and 20-ms CTOA for *subject A*) and the long CTOA (400-ms CTOA for both monkeys). The error bars represent 95% confidence intervals. *t*-Test results are presented in Table 1. *B*: difference in latency between the invalid and valid conditions for short and long CTOA conditions. Values >0 indicate shorter latencies in the valid condition (attention capture); values <0 indicate shorter latencies in the invalid condition (IOR).

Table 1. *t*-Test results of gaze and head latency comparing reaction time in the valid vs. invalid cue conditions

Condition and CTOA	df	<i>t</i> Value	<i>P</i> Value (2-Tailed)
<i>Gaze</i>			
Auditory to visual			
10/20 ms	180	6.725	<0.0001
400 ms	786	3.6472	0.0028
Auditory to auditory			
10/20 ms	174	7.4283	<0.0001
400 ms	716	2.15234	0.0317
<i>Head</i>			
Auditory to visual			
10/20 ms	127	3.69439	0.0033
400 ms	605	0.9264	0.3546
Auditory to auditory			
10/20 ms	87	4.07078	0.0001
400 ms	554	2.4552	0.0144

CTOA, cue-to-target onset asynchrony; df, degrees of freedom.

the auditory cue was observed for both target modalities. Accordingly, these data replicate our previous findings in a behavioral study that demonstrated that acoustic cues can effectively guide the allocation of spatial attention (Populin and Rajala 2010). Thus, they set the stage for the analysis of the single-unit data recorded during the same trials from the iSC.

In addition, because of the importance of head movements for orienting behavior toward auditory stimuli (Populin 2006; Populin and Rajala 2011; Sparks 2005), we performed the same analyses on head movement data. In general, the head movements yielded a pattern similar to the gaze, with the exception of the auditory cue to visual target, the long-CTOA condition, which, despite showing a pattern consistent with IOR (Fig. 3, *C* and *D*), did not reach statistical significance (Table 1).

Single-unit recordings: general. As indicated above, the recording sessions were configured with a limited subset of CTOAs to obtain data from as many auditory cue trials as possible. Hence, a full comparison of basic physiological response properties evoked by visual and auditory targets on SC units is not possible. Nevertheless, in general, single-unit responses evoked by the auditory stimuli were weaker than those evoked by visual stimuli in the SC of the monkey. This was accentuated by the brief duration of the auditory cues, a single 120- μ s click for *subject G*, who was a more proficient and experienced localizer of sound sources than *subject A*, who required stimuli easier to localize; the cue for *subject A* was a 10-ms (5-ms linear rise/fall) broadband noise burst. These brief acoustic cues did not evoke sensory responses in some neurons but were nevertheless effective in prompting the subjects to covertly allocate spatial attention (Fig. 3 and Table 1) and in modulating single-unit responses to visual targets in the SC.

Effects of acoustic cue preceding visual targets. Representative single-unit responses to an auditory cue and ensuing visual target are shown in Fig. 4. All data are plotted as a function of time and synchronized to the onset of the target at 0 ms. The experimental task is shown in schematic form at the bottom of each part of the figure. The rasters illustrate the units' responses, with single tick marks representing the time of occurrence of action potentials and each row representing a trial. The red (Fig. 4, *top*) and blue triangles embedded in the

rasters represent the time of gaze onset in individual trials for the invalid and valid cue conditions, respectively, and are sorted from top to bottom based on gaze latency. The corresponding spike density functions are plotted in Fig. 4, *bottom*, with a gray box representing the target-related epoch from which the peak firing rate for each condition was computed.

The unit illustrating the effect of the auditory cue, a 120- μ s single click, in the short, 10-ms CTOA condition on the responses evoked by a visual target (Fig. 4A) did not overtly respond to the presentation of the cue with action potentials, but the amplitude of the target-driven activity (gray box) in the valid condition (blue spike density function) was higher compared with the invalid (red) condition. Note that the only difference between the valid and invalid conditions was the position of the auditory cue that preceded the same visual target presented within the unit's receptive field. In this example, there was an AC effect on gaze latency, as illustrated by the blue and red triangles overlaid on the rasters, with the latter occurring much later in time.

For the long, 400-ms CTOA condition, we chose two example units to illustrate the effects of the single, 120- μ s click cue. In the example in Fig. 4B, the single-click cue, the time of presentation of which is illustrated with a thin vertical broken line, did not evoke a sensory response, but the magnitude of the target-evoked responses (gray box) was modulated, with the response in the valid condition (blue spike density function) being smaller compared with that of the invalid (red) cue condition, consistent with the observed IOR. Note, however, that the unit did discharge at a low rate during the CTOA, starting \sim 100 ms after the presentation of cue, which may represent some sensory-driven activity given that it was seen only in the valid condition, when the cue was presented within the receptive field. In the example in Fig. 4C, on the other hand, the single 120- μ s click cue evoked a single spike response in some of the trials; the time of presentation of the single click cue is also highlighted with a thin broken line at the -400 -ms mark. In this example the sensory responses to the visual target presented within the unit's receptive field depict a pattern of modulation similar to that observed in Fig. 4B. This reduction in the magnitude of sensory evoked responses by the target is thought to be consistent with a pattern of activity that could mediate IOR (Bell et al. 2004; Fecteau et al. 2004).

A summary of the effects of the acoustic cues on the magnitude of the sensory responses evoked by the visual target at the population level is shown in Fig. 6A. Values from the invalid condition are plotted as a function of the valid condition. For short CTOAs, 10 and 20 ms, larger target-related sensory responses were evoked by the visual target in the valid compared with the invalid condition, given that most values lie below the unity line, whereas for the long, 400-ms CTOA, larger sensory responses were observed in the invalid condition, as indicated by the fact that most values lie above the unity line (Wilcoxon rank-sum test, $P < 0.05$). These observations, which are consistent with the findings of Bell et al. (2004), with visual cues and visual targets, indicate that auditory cues lead to changes in the encoding of sensory targets in the SC in a manner that correlates with the animals' behavioral output.

Acoustic cue preceding acoustic target. Figure 5 shows the responses of two units studied with the auditory cue and auditory target configuration to illustrate the effects of short

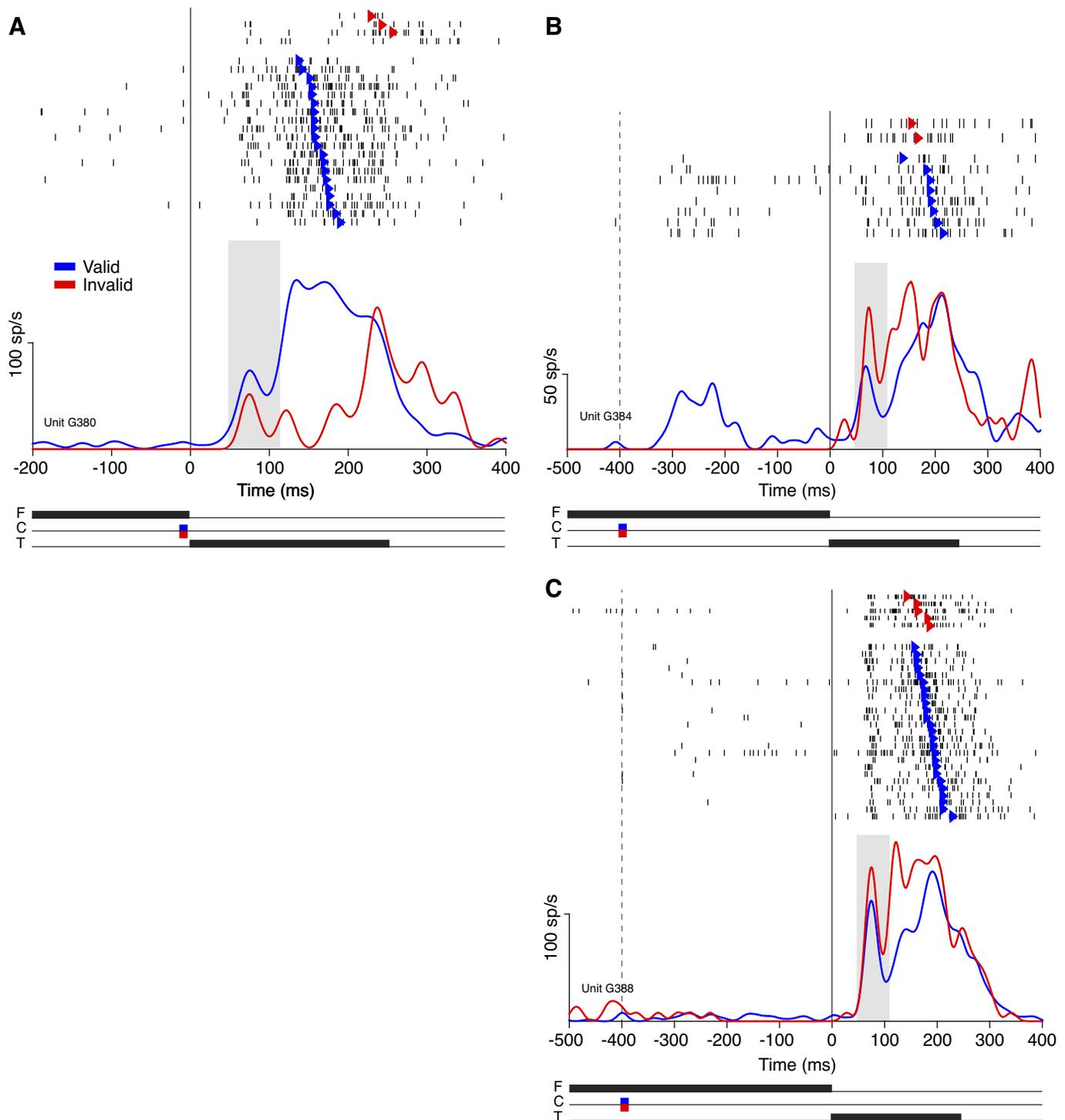


Fig. 4. Examples of neuronal responses from the auditory cue-to-visual target condition. *A*: short cue-to-target onset asynchrony (CTOA). Red and blue triangles overlaid on the raster represent gaze latency in the invalid and valid conditions, respectively. *B*: long, 400-ms CTOA. *C*: long CTOA, different unit. Red and blue spike density functions summarize the responses in the corresponding conditions. The gray boxes represent the target-aligned epoch of analyses (see MATERIALS AND METHODS for details). The time line of the experimental task is shown in *A–C*, bottom: F, fixation; C, cue; T, target. All data are plotted synchronized to the onset of the target at *time 0 ms*. The thin broken lines in *B* and *C* represent the onset of the cue.

and long CTOAs. As indicated, responses to auditory stimuli were generally weak, and in some instances they were very transient, like those of the unit shown in Fig. 5*A*. This unit responded to both the 10-ms broadband noise cue and the 250-ms broadband noise target with short, transient bursts of action potentials and little sustained activity. The spike density

functions do not distinguish between the bursts evoked by the cue and the target, and accordingly we constructed peristimulus time histograms with 10-ms bins to better illustrate the transient nature of the responses (Fig. 5*C*); note that the unit responded to the cue presented both inside (blue) and outside (red) its receptive field, albeit more weakly, likely because the

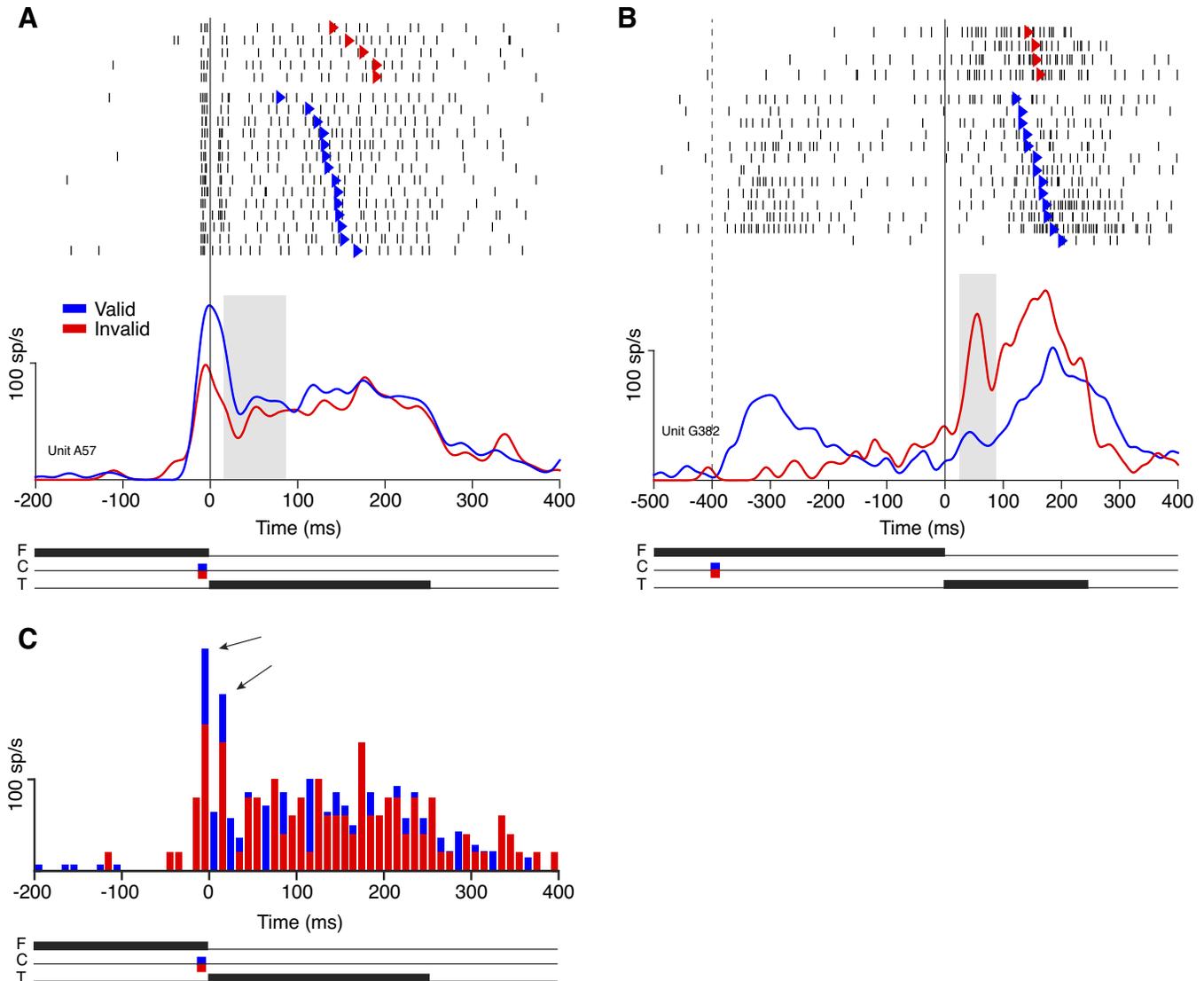


Fig. 5. Examples of neuronal responses from the auditory cue to auditory target condition. *A*: short, 20-ms, cue-to-target onset asynchrony (CTOA). Red and blue triangles overlaid on the raster represent gaze latency in the invalid and valid conditions, respectively. *B*: long, 400-ms CTOA. *C*: peri-stimulus time histograms corresponding to the responses plotted in *A* with 10-ms bins; blue and red bars correspond to the valid and invalid cue conditions, respectively. Red and blue spike density functions summarize the responses in the corresponding conditions. Gray squares represent the target-aligned epoch of analyses (see MATERIALS AND METHODS for details). The timeline of the experimental task is shown below each graph. F, fixation; C, cue; T, target. All data are plotted synchronized to the onset of the target at *time 0 ms*. The thin dashed lines in *B* and *C* represent the onset of the cue.

auditory stimuli had to be presented at a relatively high level for the animal to perform the task.

The location of the cue modulated the responses evoked by the target presented within the unit's receptive field. In the valid configuration, the responses to the target were larger than in the invalid configuration, which is consistent with AC (Fig. 5, *A* and *C*), even though the responses were separated by ≥ 10 ms, as illustrated in Fig. 5*C*. At the population level (Fig. 6*B*), in the short CTOA condition, the amplitude of most of the auditory target-evoked responses fell below the unity line, indicating that they were larger than in the valid condition and hence, consistent with AC (Wilcoxon rank-sum test, $P < 0.05$).

The effects of the auditory cue in the long, 400-ms CTOA are illustrated in Fig. 5*B* with a different example unit. This unit responded weakly to the cue, which consisted of a 120- μ s single click in the valid condition, i.e., when it was

presented within the receptive field, and it did not respond when the cue was presented in the opposite hemifield; the time of presentation of the cue is illustrated by a thin, broken, vertical line at the -400 -ms mark. Note that the unit discharged at a low rate for nearly 200 ms after the presentation of the cue. Comparison of the magnitude of the responses with the auditory target in the valid (blue) vs. the invalid (red) condition within the analysis window (gray box) revealed that the cue in the valid condition significantly attenuated the response to the target, an effect that is consistent with IOR (Bell et al. 2004). At the population level, most units responded in a similar fashion to the presentation of the auditory target, i.e., more strongly in the invalid compared with the valid condition given that most points fall above the unity line (Wilcoxon rank-sum test, $P < 0.05$), and hence, their activity was modulated as expected from a correlate of IOR (Fig. 6*B*).

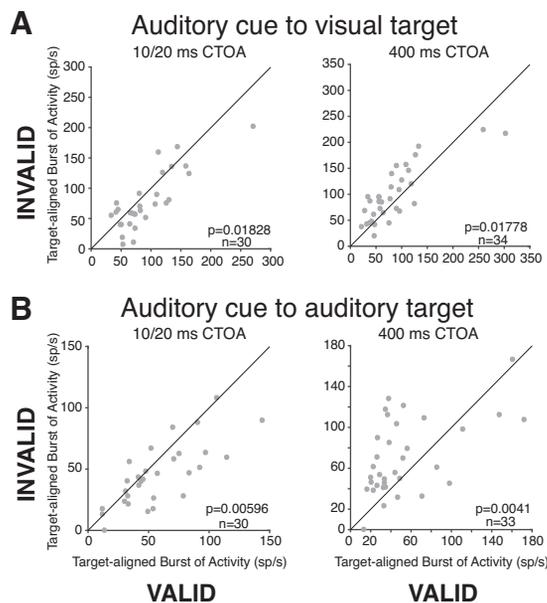


Fig. 6. Summary of effects of the auditory cue on the magnitude of visual and auditory target-evoked responses. Peak firing rate, measured within the target-aligned burst of activity (gray boxes in Figs. 4 and 5), is plotted for the invalid condition as a function of the valid condition. Data points falling below the unity line are hypothesized to be consistent with attention capture, whereas points falling above the unity line are hypothesized to be consistent with inhibition of return. The Wilcoxon signed rank-sum test was used in each condition to test for significance.

Finally, to further examine the relationship between peak discharge rate in the target-related epoch and response latency, we computed a trial-by-trial correlation between these measurements for both gaze and head. Unlike Bell et al. (2004), who found a significant negative correlation between the discharge rate of visual but not auditory-evoked responses and saccade latency on a trial-by-trial basis in the majority of the neurons they studied, we found that in the auditory cue to visual target condition, eight of 34 neurons showed a significant negative correlation between peak discharge rate and gaze latency (mean $r = -0.17$), and nine of 33 between discharge rate and head latency (mean $r = -0.12$). In the auditory cue to auditory target condition, on the other hand, the effect, although modest, was stronger with 14 of 34 neurons showing a significant negative correlation between peak discharge rate and gaze latency (mean $r = -0.26$), and nine of 34 between discharge rate and head latency (mean $r = -0.2$).

DISCUSSION

The monkeys in this study exhibited AC and IOR in trials in which the visual and auditory targets to which they oriented overtly with gaze shifts were preceded by auditory cues at short and long CTOAs, respectively. Hence, these results are consistent with previous observations from our laboratory in the head-unrestrained monkey (Populin and Rajala 2010) and with observations in humans (McDonald and Ward 1999; Reuter-Lorenz and Rosenquist 1996; Spence and Driver 1994; Tassinari and Berlucchi 1995) but inconsistent with the observations of Bell et al. (2004) in the head-restrained monkey. In addition, and central to the goals of this study, single-unit activity recorded in the iSC while monkeys performed the cuing task with the head unrestrained and pointed with their gaze to the

perceived location of auditory and visual targets shows that the neural activity evoked by the targets was modulated by the brief broadband auditory cues that preceded them during an epoch in which no overt responses were allowed. Importantly, the modulation was consistent with changes in neuronal activity hypothesized to correspond to AC and IOR (Bell et al. 2004), that is, higher discharge rates for valid cues correlating to AC and lower discharge rates for valid cues correlating to IOR. Therefore, these neural data represent a neural correlate of the covert allocation of spatial attention to the location of auditory stimuli observed in the orienting behavior of the monkeys.

Behavioral results. The present behavioral results were expected given that the behavioral training used to prepare the animals for single-unit recordings and the general experimental methods were very similar to those employed previously in this laboratory (Populin and Rajala 2010). The only major procedural changes involved testing with only two CTOAs per recording session, selected to produce large AC and IOR effects (Populin and Rajala 2010), to acquire a large number of trials for each condition and the inclusion of a search procedure to find and isolate single units at the start of recording sessions and after losing a unit early enough in a recording session to warrant restarting.

Operant procedures were used to train the monkeys to overtly orient to broadband auditory targets and to do so in the context of the standard- and memory-guided saccade tasks. As demonstrated previously (Populin 2006), this required that the monkeys were allowed to orient with their heads unrestrained. Accordingly, the goal of the training was to convey to the monkeys the behavioral relevance, i.e., receipt of a reward, of orienting to the sources of auditory stimulation accurately and timely and to accomplish it without training to direct their gaze to specific, learned, spatial locations (Populin 2006). We hypothesized that Bell et al.'s (2004) monkeys, in addition to being tested with their heads restrained, may not have attributed any relevance to auditory stimuli, given that they could successfully complete the cuing task and receive rewards without regard for the auditory cue. Finally, the present behavioral data are also consistent with those of humans, showing that the spatial requirements of an auditory task play an essential role in driving the allocation of spatial attention in this modality (McDonald and Ward 1999; Spence and Driver 1994), as postulated by Rhodes (1987).

Physiological results. Having demonstrated that the monkeys in this study exhibited AC and IOR in their overt orienting responses to visual and auditory targets that were preceded by auditory cues presented with short and long CTOAs (Fig. 3), respectively, the question arises as to whether a neural correlate could be found in responses evoked by such targets in single units of the iSC. The SC is a logical choice for the search of a neural correlate of the present behavioral effects because of its integration properties and detailed representations of visual and auditory space (Gordon 1973; Middlebrooks and Knudsen 1984). Furthermore, it is the structure where Bell et al. (2004) demonstrated a neural correlate of AC and IOR in trials in which visual targets were preceded by visual cues presented at short and long CTOAs, respectively.

Although contrary to results in Bell et al. (2004), the physiological correlate of AC and IOR found in the responses of SC neurons in the present study is not surprising given that we also

observed behavioral effects on the latency of gaze shifts (Fig. 3) (Populin and Rajala 2010). This discrepancy likely results from two separate, albeit related, methodological differences between the studies, which concern the training administered to the subjects before the physiological recordings and the unrestrained condition of the head.

The subjects in this study oriented with their heads unrestrained when an overt response was required. Our previous work showed that this is a necessity for animals to accurately orient to the sources of auditory stimulation (Populin 2006; Tollin et al. 2005), although the mechanism underlying this requirement remains to be determined. This is particularly important for rhesus monkeys, who, due to testing under head-restrained conditions, were thought to be unable to orient to sound sources (Grunewald et al. 1999). Accurate orienting to sound sources, in turn, resulted in reinforcement, which must have conveyed behavioral importance to stimuli of this type. The subjects in the study by Bell et al. (2004), on the other hand, were not trained to attribute significance to auditory stimuli and were presented with auditory cues that were not predictive; thus they may have treated such cues as distractors or irrelevant noise, and hence, it follows that they would not have allocated attention to them or their sources. Therefore, auditory cues appeared not to have led to either AC or IOR.

From an ethological standpoint, we argue that this should be expected given that the environment is filled with many sounds, most of which are irrelevant to an animal and thus need to be filtered out. As a higher order sensorimotor integration center and a gateway for oculomotor behavior, the SC is ideally positioned along the neural circuits responsible for orienting to underlie these effects. For instance, it is well documented that structures further upstream, such as the substantia nigra pars reticulata (SNr), an output of the basal ganglia, inhibit the SC and the generation of eye movements (Hikosaka and Wurtz 1983, 1985). The basal ganglia play an important role in oculomotor behavior and have been proposed to control the allocation of attention via the SNr-SC circuit (Hikosaka et al. 2000). Although this has been shown only in the visual modality, it stands to reason that the same could be true for auditory stimuli given that the SC also integrates sensory information to drive gaze shifts to auditory stimuli (Jay and Sparks 1984, 1987; Populin et al. 2004).

In terms of the potential neural mechanisms that may underlie the behavioral effects shown above, it has been shown that in the iSC larger target-evoked responses are associated with decreases in saccade latency, and hence, they correspond to AC (Fecteau et al. 2004), and conversely, that decreases in the magnitude of target-evoked responses are associated with longer saccade latency; thus they correspond to IOR (Dorris et al. 2002). Bell et al. (2004) hypothesized that interactions between the responses evoked by the cue and target are responsible for the associated changes. They further hypothesized that the lack of effect in the auditory cue condition resulted from the meager nature of the responses evoked by the auditory cue, as well as their short latency, which precluded their interacting with the responses evoked by the target. In other words, the responses evoked by the auditory cue were too insignificant and too far apart from the responses evoked by the target to interact.

Therefore, for the short CTOA condition, which led to AC, it is possible that the signals evoked by the auditory cue in our

study were of large enough magnitude to modulate the target-evoked responses, as expected by the mechanism proposed by Bell et al. (2004). This explanation would suggest that our subjects' training may have conveyed behavioral significance to auditory stimuli and were worth localizing because of the associated rewards and thus were responsible for larger, more effective auditory cue-evoked responses.

For IOR, as illustrated in Fig. 4, reduction in target-evoked activity takes place in the presence of very weak cue-evoked activity approximately occurring 400 ms before the target (Fig. 4C) or in the absence of any cue-evoked activity (Fig. 4B). The present data, although agnostic to the potential mechanism, are consistent with the conclusion by Dorris et al. (2002) that although the SC likely contributes to the expression of IOR, the origin of the reduction of target-evoked neural activity may result from some upstream input. A potential candidate is the posterior parietal cortex (Klein 2000), which projects to the SC and plays an important role in sensorimotor integration, attention, and higher order, sensory input- and motor output-independent representations of space (Andersen and Buneo 2002).

Overall, the data show that in monkeys trained to localize sound sources with the head unrestrained, attention is allocated to auditory stimuli, resulting in the behavioral effects of AC and IOR, and a neural correlate of this effect on gaze latency is found in the target-related discharges of neurons in the iSC.

ACKNOWLEDGMENTS

We thank Yonghe Yan and Jane Sekulski for computer programming and Michael Gallardo and his staff (C. Daly, P. Esser, K. Sayles, and C. Tegt) for outstanding animal care.

GRANTS

This work was supported by National Institutes of Health (NIH) Grant DC-003693 and National Science Foundation Grant IOB-0517458. A. Z. Rajala was supported by NIH Grant T32-GM-007507. R. L. Jenison was supported by NIH Grant AA-018736. Research reported in this publication was supported in part by the Office Of The Director, NIH, under award no. P51-OD-011106 to the Wisconsin National Primate Research Center, University of Wisconsin-Madison.

DISCLAIMERS

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.Z.R., R.L.J., and L.C.P. conceived and designed research; A.Z.R., R.L.J., and L.C.P. performed experiments; A.Z.R., R.L.J., and L.C.P. analyzed data; A.Z.R., R.L.J., and L.C.P. interpreted results of experiments; A.Z.R., R.L.J., and L.C.P. prepared figures; A.Z.R., R.L.J., and L.C.P. drafted manuscript; A.Z.R., R.L.J., and L.C.P. edited and revised manuscript; A.Z.R., R.L.J., and L.C.P. approved final version of manuscript.

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