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Cortical Neurons Combine Visual Cues about Self-Movement

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Abstract

Visual cues about self-movement are derived from the patterns of optic flow and the relative motion of discrete objects. We recorded dorsal medial superior temporal (MSTd) cortical neurons in monkeys that held centered visual fixation while viewing optic flow and object motion stimuli simulating the self-movement cues seen during translation on a circular path. Twenty stimulus configurations presented naturalistic combinations of optic flow with superimposed objects that simulated either earth-fixed landmark objects or independently moving animate objects.

Landmarks and animate objects yield the same response interactions with optic flow; mainly additive effects, with a substantial number of sub- and super-additive responses. Sub- and super-additive interactions reflect each neuron's local and global motion sensitivities: Local motion sensitivity is based on the spatial arrangement of directions created by object motion and the surrounding optic flow. Global motion sensitivity is based on the temporal sequence of self-movement headings that define a simulated path through the environment. We conclude that MST neurons' spatio-temporal response properties combine object motion and optic flow cues to represent self-movement in diverse, naturalistic circumstances.

Keywords

object motion; optic flow; visual motion; extrastriate; cortex

INTRODUCTION

Visual information about self-movement is derived from the global pattern of visual motion in optic flow and the relative visual motion of discrete, salient objects. Object motion that is congruent with the surrounding optic flow suggests an earth-fixed landmark object. Object motion that is not congruent with the surrounding optic flow suggests that it represents an object that is moving through the environment independent of the observer. Thus, the combined processing of optic flow and object motion provides important cues for navigation and for the detection of animate movers that are potential predators, partners, or prey. Critically, the integration of these cues enables the differentiation between landmarks and animate objects.

Neurons in the dorsal medial superior temporal area (MSTd) of macaque monkey cerebral cortex integrate visual and non-visual cues about self-movement. Individual neurons respond to optic flow (Saito et al., 1986) (Duffy and Wurtz, 1991a) (Graziano et al., 1994)

with clear preferences for stimuli simulating particular self-movement heading directions (Duffy and Wurtz, 1995) (Lappe et al., 1996). These neurons show idiosyncratic response interactions between visual and vestibular self-movement signals (Duffy, 1998) (Gu et al., 2006) (Takahashi et al., 2007) and integrate those cues over time to represent the continually changing headings that define naturalistic paths through the environment (Froehner and Duffy, 2002). In some neurons, heading estimation is confounded by pursuit eye movements made during observer self-movement (Bradley et al., 1996) (Page and Duffy, 1999), but other neurons, and the neuronal population responses, appear to compensate for pursuit effects (Page and Duffy, 2003; Bremmer et al., 2010).

MSTd neurons combine optic flow and object motion cues about self-movement (Komatsu and Wurtz, 1988a). Their responses may contribute to figure-ground separation based on a variety of object-defining cues (Geesaman and Andersen, 1996) with a range of figure-ground interactions (Recanzone et al., 1997). We previously found that superimposing optic flow and object motion simulating the same self-movement heading direction yields responses that mimic those evoked by optic flow alone. In contrast, when superimposed optic flow and object motion have opposite heading directions, single neuron and neuronal population responses can be altered dramatically. When such an object moves across the central visual field in a direction opposite to the surrounding optic flow, MSTd's population responses shift from representing self-movement through the surround to representing self-movement relative to the object (Logan et al., 2006).

We hypothesized that interactions between the object motion and optic flow responses of individual MSTd neurons might create stable population responses to the visual aspects of self-movement. We have tested this hypothesis by combining optic flow and object motion using a variety of stimulus configurations to characterize the context in which inter-modal visual-vestibular interactions must occur. We find that idiosyncratic single neuron response properties include a wide variety of interactions between optic flow and object motion. This variety creates an unbiased population representation of stimulus conditions, with no particular preference for one or another condition. This representation encompasses diverse naturalistic self-movement circumstances so that no particular condition fails to evoke a response or causes excessive responsiveness.

MATERIALS and METHODS

Animal Preparation

Both of the monkeys were new to the laboratory at the beginning of this experiment. After the animals were accommodated to the laboratory routine they underwent surgery in preparation for single neuron recording sessions. Surgical procedures were preceded by sedation with Ketamine (15 mg/kg im) and Robinul (0.011 mg/kg im), followed by venous catheterization, endotracheal intubation, and general anesthesia using inhaled Isoflurane. Heart rate, core temperature, and expired CO₂ were monitored along with continual verification of the surgical plane of anesthesia.

We excised a 3 cm × 4 cm section of scalp and cleaned the exposed calvarium. Sixteen to 24 dental pins (Pearson Dental, Sylmar, CA, USA) were inserted around the edge of the exposed bone to stabilize the implant. We placed bilateral scleral search coils by perilimbotomy, tunneling the leads to the edge of the scalp excision (Judge et al., 1980). A head holder socket was placed over the frontal midline and bilateral recording cylinders were placed over 2 cm trephine holes above area MSTd (AP -2mm, ML+/- 15mm, angle 0). The dental pins, coil connectors, head holder, and recording chambers were then encased in a dental acrylic cap.

Postoperatively, the animal was returned to its home cage when it could maintain postural stability and coordinated limb movements. Close monitoring of its behavior guided analgesia with Banamine (1 mg/kg im) as judged appropriate by veterinary staff. Daily cleaning of the excised scalp edge and of the recording chambers was maintained thereafter. All protocols were approved by the University of Rochester Committee on Animal Research and complied with U. S. Public Health Service and Society for Neuroscience policy on the care of laboratory animals.

When the animal had fully recovered from surgery, it was trained to maintain visual fixation during visual stimulus presentation as confirmed by eye position monitoring using the magnetic search coils (Robinson, 1963). Trials began with a stationary, red fixation point centered at eye height directly in front of the animal. The monkeys were required to maintain fixation ($\pm 3^\circ$) while viewing a combination of object motion and/or optic flow stimuli simulating translational self-movement. The trial length was gradually increased over a period of several months to train the monkeys to maintain appropriate fixation for prolonged intervals of time, often greater than 8s. At the conclusion of a trial, the stimulus was turned off and free viewing was allowed for ~ 1 s. Successful completion of a trial was accompanied by the sounding of an auditory tone and the delivering of a liquid reward. Single neuron recording sessions were begun after the animal consistently completed $>90\%$ of the stimulus presentation trials.

Experimental Protocol: Behavioral Paradigms and Visual Stimuli

The stimuli were generated by a personal computer driving a television projector (Electrohome ECP4100) at 60 Hz to illuminate a rear projection screen that covered the monkeys' central visual field ($90^\circ \times 90^\circ$). All stimuli were composed of white pixel dots (0.19° at 2.61 cd/m²) presented on a dark background (0.18 cd/m²) and presented 6–8 times in pseudo-random order. The monkey viewed radial optic-flow and object motion stimuli while maintaining centered fixation of a small spot as monitored using the magnetic search coil technique (Judge et al. 1980).

Behavioral Paradigm—The monkey's task was to maintain centered fixation within a 3° window around the fixation spot during the presentation of all visual stimuli. The eye position records were not stored and were not used in other analyses. Stimulus presentation trials consisted of an 8 s display of object motion and/or optic flow that continuously changed to simulate the observer's translational self-movement on a circular path. The visual display created object motion stimuli simulating a pair of landmarks and optic flow stimuli simulating a remote light array. Movement of the stimuli simulated the scene viewed by an observer translating along a clockwise (CW) or counter-clockwise (CC) circular path during straight-ahead gaze (Figure 1A). A close approximation to the laboratory stimulus display can be viewed on the web at http://www.urmc.rochester.edu/labs/Cognitive-Neuroscience-Lab/projects/neuronal_integration_of_visual_cues.

Object Motion—The object motion stimuli consisted of two simple shapes moving on the horizontal meridian at eye height. The object on the left formed three concentric triangles and the object on the right formed three concentric circles, each with transparent segments between the structural features. Each object was formed by an outline of 35 (far) to 120 (near) single pixel dots, varying with object size in a given stimulus frame to maintain visible structure and comparable dot densities across all stimulus frames. The size of the objects was intended to approximate that of a face viewed at the distances of common social interactions covered by the circular path. The height and width of each object varied with simulated distance from the observer to the object, being 3.4° at simulated far viewing to

11.3° at simulated near viewing, with the center separation of the objects varying over twice that range. This dual-object stimulus was chosen when we noticed that it can create a distinct two-pulse response in some MST neurons that facilitates attribution in simple and combined stimuli (e.g., Figure 4, top left, paired arrows at center crossings).

The paired object stimuli were also used to probe the dimensions and selectivities of receptive field segments that might yield transient responses to object motion, with the paired stimuli creating double bumps in the response profiles. While such effects were commonly seen when object motion was presented alone, interactions with superimposed optic flow often altered response properties so that such transients could not be discerned. The shape and position of both object stimuli were visible throughout all stimuli. (Figure 1B)

Optic Flow—The optic flow stimuli simulated self-movement in front of a large volume filled with illuminated points. Motion parallax cues from the relative speeds of dots in the display indicated a range of relative distances from those points extending from 1 to 9 m from the observer. The observer's self-movement simulated a circular path that was 8 m diameter with the observer's simulated speeds being 3.1 m/s. The optic flow stimuli were composed of a maximum of 1000 illuminated white pixels (0.19° at 2.61 cd/m²) presented on a dark background (0.18 cd/m²). The optic flow dots moved in a radial pattern simulating translational movement of the observer. In the first frame, dots were distributed in a random pattern filtered to smooth dot density across the screen. The dots were evenly distributed in a random pattern in the first frame and were assigned a random lifetime of 1–60 frames. Dots were replaced at expiration or if they moved off the screen by a smoothing algorithm to maintain a uniform dot density across all frames in all stimuli. Dot speed was a sin² function of dot eccentricity measured as the angle between the monkey's line of sight and each dot's location on the screen (Nakayama and Loomis, 1974; Lee and Young, 1985; Hatsopoulos et al., 1991) and simulated distance. An average dot speed of ~20°/s was maintained across all stimuli to match the range of speed preferences of MSTd neurons (Duffy and Wurtz, 1997). (Figure 1C)

Combined Stimuli—Object motion and optic flow were superimposed to create 16 unique stimulus configurations that were presented in a pseudorandom sequence. When combined, the object simulated movement within the depth of view simulated by the cloud of dots in the optic flow display. In same direction combined stimuli (CC-CC, CW-CW) the object moved as an element of the flow field to simulate an earth-fixed object. In combined stimuli with opposite directions (CC-CW, CW-CC), the object motion violated the surrounding optic flow field to simulate independently moving (animate) objects on a heading 180 offset from the heading in the optic flow. In combined stimuli with matching and opposite directions, phase shifting of the object motion and optic flow resulted in object motion that violated the surrounding optic flow to simulate independently moving objects. The object did not occlude the flow; that is, pixels within the bounds of an object, which were not illuminated as part of the object, could be illuminated as part of the superimposed optic flow. (Figure 1D)

Single Neuron Recording

We recorded the time of action potentials from single neurons using epoxy-coated tungsten microelectrodes (FHC, Inc. and Microprobe, Inc.) that were passed through a trans-dural guide tube previously inserted through a positioning grid fixed within a recording chamber (Crist et al., 1988). As the electrode was advanced, we monitored neural activity to identify transitions between gray and white matter and the relative depth of physiological landmarks. After isolating the responses of a neuron, the boundaries of its receptive field

were mapped using hand-held projectors. MSTd neurons were identified by their physiologic characteristics: large receptive fields ($>20^\circ$) beyond central eccentricities which included the fixation point and showed a preference for large moving patterns, rather than moving bars or spots, with direction selective responses evident in the audible representation of their activity (Komatsu and Wurtz, 1988a) (Duffy and Wurtz, 1991a) (Duffy and Wurtz, 1995). A dual window discriminator was used to digitize neuronal discharge times that were stored with stimulus and behavioral event markers for off-line analysis using the REX system (Hays et al., 1982).

Recording Sites

Single neuron recordings were directed in to cortical area MSTd using the stereotaxic positioning of the recording chambers and the depths of microelectrode penetrations. When all experiments were completed, electrolytic marks ($25 \text{ A} \times 25 \text{ s}$) were made at selected depths in several guide tubes in six hemispheres of four monkeys with another monkey continuing in ongoing experiments. After pentobarbital euthanasia, the animal was perfused with buffered formalin and the brain removed. When formalin fixation was complete, posterior cortical regional blocks were obtained and cut in to 50 μm thick sections. Every fourth and fifth section was stained by the Nissl and Luxol Fast Blue methods, respectively. We identified the electrolytic lesions relative to anatomic landmarks to extrapolate the position of the recording sites. This analysis indicates that the neurons studied were located in the anterior bank of the superior temporal sulcus that is included in cortical area MSTd (Komatsu and Wurtz, 1988b). Although the boundaries between areas within the STS are somewhat nebulous, we did not record neurons further up the STS in to area 7a, further anteriorly along the STS in to fundal superior temporal cortex (FST), nor across the STS in to the middle temporal area (MT). The boundary between dorsal and ventro-lateral medial superior temporal areas (MSTd and MSTl) is best defined physiologically. In this regard, we have consistently applied the rule that gray matter layers that include neurons with the large, direction selective, pattern motion preferring receptive fields of MSTd are considered to be part of MSTd (Duffy and Wurtz, 1991a) (Duffy and Wurtz, 1995). In these areas, we occasionally encounter neurons with smaller, more central receptive fields or receptive fields that do not respond to our hand controlled stimuli. Review of our findings reveals a highly variable relationship between responses to mapping stimuli and computer controlled stimuli, prompting us to include all stably recorded neurons in the data set (Supplement Figure 1).

Data Analysis

Neuronal activity was convolved with a 20 ms Gaussian to produce trial-wise spike density functions that were averaged over the six to eight presentations of each stimulus. Average spike densities were plotted on a time line to relate changes in firing rates to the parameters of object motion and optic flow. We did not make explicit changes in an attempt to account for response latency differences within or between neurons. Averaged spike densities were also plotted on a circle. In circular spike densities distance from the center of the polar coordinate system represents firing rate and angular position around the coordinate system represents the simulated position of the animal on the circular path at the time that rate was recorded. In all circular spike densities, the simulated position of the animal was determined relative to the optic flow stimulus.

We used regression analysis to examine relations between neuronal firing rates in the combined stimulus conditions as a function of firing rates in the object motion and optic flow alone conditions. To do so, we compared activity in each 250 ms interval of each combined condition to activity in the 250 ms intervals from the alone conditions that presented the corresponding component stimuli. Our approach was to separately examine

firing rate relations in each combined stimulus condition, although we also created analyses that collapsed across various combined stimulus conditions that did not lead to any unique revelations about the responses.

We tested a variety of regression analyses, with the result that multiple linear regression worked as well as any other approach with comparable degrees of freedom. That is, just about every approach yielded a better fit in some small number of neurons, but no other approach yielded a better distribution of fits across neurons. In addition, we explored fits to sigmoidal response functions, and the addition of higher-order variables such as multiplicative combinations of our primary response variables. We compared models across degrees of freedom using Akaike Information Criteria (AIC). None of these approaches yielded consistently better fits to the recorded neuronal responses (Supplement Figures 2 and 3).

In other analyses, we compared the evoked activity in each interval with the activity recorded in that trial's baseline activity as measured by the average firing rate recorded in the final 250 ms half of the 1 s fixation intervals that preceded stimulus onset. We tested the significance of differences ($p < .05$) between the evoked and baseline activity using Student's t-test. All statistical analyses were carried-out using SPSS (SPSS Inc., 2007).

RESULTS

We completed studies of 61 neurons from three hemispheres of two adult Rhesus monkeys. All recordings were made at sites that included neurons with large receptive fields, often more than a full quadrant of the visual field, including the fovea. All neurons showed direction selective responses, preferring large pattern motion to moving bars; characteristics typical of MSTd neurons (Komatsu and Wurtz, 1988b) (Supplement Figure 1).

Responses to Combined Stimuli

Stimulus presentation trials consisted of an 8 s display of object motion and/or optic flow that continuously changed to simulate the observer's translational self-movement on a circular path. A circular path was used: 1) to present the full range of headings across 360° in every trial, 2) to limit movement discontinuities with changes in linear heading direction, and 3) to evoke previously observed heading path effects seen when following a prolonged circular path (Froehler and Duffy, 2002). The visual display created object motion stimuli simulating a pair of landmarks and optic flow stimuli simulating a remote light array. Movement of the stimuli simulated the scene viewed by an observer translating along a clockwise (CW) or counter-clockwise (CC) circular path during straight-ahead gaze (Figure 1A).

The 20 stimulus configurations were presented in a pseudorandom sequence with 6–8 repetitions recorded for each trial type. Superimposed object motion and optic flow often evoked larger responses than the component stimuli presented separately. In most neurons, one or two of the 16 direction-by-phase combined stimulus conditions yielded much larger responses than those evoked by separate stimuli or the other combined stimulus conditions (Figure 2). Typically, these effects were not obviously related to the responses to object motion and optic flow alone.

We compared responses to object motion, optic flow, and combined stimuli by dividing the 8 s averaged responses from all 20 conditions in to 32 intervals of 250 ms. The sum of the object motion and optic flow responses was compared to the responses to the corresponding combined stimuli. These comparisons revealed a wide range of effects, from sub-additive responses in which the combined firing rates were less than the sum of the firing rates in the

responses to the corresponding periods of optic flow and object motion presented alone, to super-additive responses in which the combined firing rates were greater than the sum.

We combined data across neurons to examine the net effects of combining object motion and optic flow stimuli. The firing rate for each interval of each condition was normalized to the peak response for each neuron, and the sum of the response amplitudes evoked by object motion and optic flow alone was subtracted from that evoked by the corresponding combined stimulus. We first noted what appears to be a clear sub-additivity of responses with mean sub-additivities in the range of -25% to -28% of the normalized firing rates (Figure 3, green curves). However, when we subtracted the baseline firing rate from the alone and combined responses, recorded in the 250 ms prior to stimulus onset in each trial, we found that there was a substantial shift in the distribution toward overall net additivity (Figure 3, red curves).

Baseline subtraction also narrowed the distributions, shifting the standard deviation from 30.5% without baseline adjustment to 25.2% with baseline adjustment. Thus, accounting for trial-by-trial variation in unstimulated firing rate shows net additivity in the sample of neurons across diverse combined stimulus conditions.

Neuron response interactions show no preference for any particular combined stimulus condition across the sample of neurons. The two conditions corresponding to the simulation of earth-fixed objects viewed during observer self-movement (Figure 3, left side of the top row) evoke the same interval distributions seen across the other combined stimulus conditions. Thus, while we found that individual neurons show idiosyncratic preferences for specific combined stimuli, there is no population bias for representing any particular naturalistic circumstance. Nevertheless, such idiosyncratic response properties in neurons from our small sample may represent sub-populations that play a significant role in representing particular circumstances.

Stimulus Specific Interactions

To better understand the unique response interactions seen in many neurons we focused on specific interactions with combined object motion and optic flow stimuli. Object motion often evoked transient paired activity peaks, the paired peaks being the intended signature of the paired objects (red and blue arrows) (Figure 4A, far and near left panels, object alone stimuli). Optic flow typically evoked more sustained responses referable to the center of motion, or to a recognizable local motion component of the pattern, distinguishable by comparing responses to the in and outward optic flow's regions of left-or rightward local motion (filled and open green arrows) (Fig. 4A, near and far right panels, flow alone stimuli). As expected, the coincidence of object motion and optic flow responses were sometimes associated with strong excitatory effects (Figure 4B: 0° phase, object CC, flow CC). In other cases from the same neuron, very similar responses to optic flow and object motion alone yielded much smaller responses to the corresponding combined stimuli, evoking little activity (Figure 4B: 0° phase, object CW, flow CW).

In some neurons, idiosyncratic responses occurred when an object moved across one location in a particular direction, when there was a particular pattern of overlapping optic flow at that location. To explore these effects, we divided the 90° range of object positions on the horizontal meridian in to nine 10° segments. The interactions between the object motion and the local motion in optic flow was assessed by classifying each stimulus segment with respect to the relative directions of the object and optic flow: uniform leftward motion from object motion and optic flow, uniform rightward motion from object motion and optic flow, and conflicting leftward and rightward motion from object motion and optic flow (Figure 5A).

For each location in each neuron, we plotted the summed normalized, averaged response amplitudes to object motion and optic flow presented alone versus the responses to the corresponding combined stimuli. The color coding of directional conditions highlights our finding that some neurons showed large responses when specific directional patterns were presented at specific locations (Figure 5B–C). Those large responses were limited to cases of uniform local motion, with much smaller responses when similar object locations and optic flow patterns presented conflicting motion at that location. This dependency on relative directions in the object motion and optic flow was evident even when comparing summed responses of identical net magnitude that yielded super-additive interactions when the object motion and optic flow presented the same directions of motion at that location versus sub-additive interactions when they presented different directions of motion at that location. We used 2-way ANOVA to test the significance of object relative direction and location effects in each of the neurons. Most neurons showed significant effects of object-flow relative direction (69%, $F_{2, 705} = 3.01$, $p < .05$); whether the direction of object motion and the optic flow immediately surrounding the object were uniformly rightward, leftward, or opposite. The effects of object location were significant in one-third of the neurons (33%, $F_{8, 705} = 1.96$, $p < .05$) and were fewer significant relative direction X location interaction effects (23%, $F_{16, 705} = 1.66$, $p < .05$). We did not find clear relations between these response properties and receptive field dimensions derived from hand-mapping.

Interval plots of summed versus combined object motion and optic flow responses revealed two other sources of variability in response interactions. First, the distribution of intervals within response additivity space differed between the CW and CC self-movement directions on the simulated circular path. These effects are most evident as the clustering of circular direction specific intervals in plots superimposing additivity distributions across all 16 combined stimulus conditions, with one set of path specific responses clustering above the additivity line and other path specific responses clustering below the additivity line (Figure 6A).

Second, the interval plots also reveal effects of phase relations between object motion and optic flow in combined stimuli. These effects are most evident as a layering of phase specific intervals in plots that superimpose additivity distributions across all 16 combined stimulus conditions, with one set of phase specific responses layered over others relative to the additivity line (Figure 6B). Thus, we again see that the summing of two responses having identical net magnitude can result in very different combined response magnitudes. In this case, the global motion parameters that are captured by the path (CC vs. CW) and phase (0° , 90° , 180° , 270°) of each stimulus condition, explain some of that variability in responses to combined stimuli.

Two-way ANOVAs in each neuron showed robust path and phase effects. The effects of CC vs. CW circular paths were significant in most of the neurons (90%, $F_{3, 93} = 2.71$, $p < .05$) as were the effects of the object motion / optic flow phase relations (84%, $F_{3, 93} = 2.71$, $p < .05$), with significant path-by-phase interactions in almost all of the neurons (98%, $F_{9, 279} = 1.92$, $p < .05$).

Net Effects of Response Interactions

To further characterize response interactions we used multiple linear regression to describe the responses to combined stimuli as a function of responses related to various stimulus parameters. Initially, we used only the object motion and optic flow responses finding that 89% (54/61) of the neurons yielded significant models ($p < .05$) but with a mean R^2 of only .11 (mean AIC = 2688). In these regression analyses, individual neurons often showed substantially different multiple linear regression fits across the 16 combined stimulus

conditions (Supplement Figure 2). However, across neurons, we could not discover any consistent pattern in the variation of fit parameters across conditions. We also explored the use of non-linear regression fits, such as the inclusion of multiplicative factors (flow X object, flow², etc.) and the use of sigmoidal functions (Suppl. Fig. 3), that yielded better fits in some individual neurons. However, there was no general benefit on the quality of the fits either across neurons or conditions.

We extended the regression analyses by adding the effects of other stimulus parameters: object location and relative direction, and the global path and phase conditions. In this analysis, all of the neurons yielded significant models (all p values < .001) with a number of neurons showing the substantial explanatory power of these models (Figure 7A). The relative significance of these stimulus parameters on the responses to the combined stimuli is reflected in the p values of these factors in the multiple linear regression. As expected from the previously cited ANOVAs, the path and phase parameters yielded the strongest effects in the largest number of neurons (Supplement Figure 4).

Overall, these models accounted for only a modest amount of the total variance in responses across all stimulus conditions with a mean $R^2 = .24$ (AIC = 2583) (Figure 7B). The inclusion of other, higher-order interaction effects (e.g., multiplicative interactions between the included factors) improved these regression models ($R^2 = .38$). However, the addition of the multiplicative effects led to only minor improvements of the fits (AIC = 2519). Again, no single stimulus parameters substantially improved fits across neurons. Thus, stimulus parameters do not account for a great deal of the total variation seen in single neurons' responses to naturalistically combined stimuli.

We pursued the alternative approach of joining all of the interval response data, across neurons and conditions, to characterize the relationship between the responses to optic flow and object motion and responses to combined stimuli. A linear regression through all of the combined response intervals yielded an $R^2 = 0.47$ (slope = 0.38, y-int = 1.25) (Figure 8A). The near zero intercept reflects the additivity of the near baseline activity seen in substantial periods of each stimulus presentation that did not greatly influence neuronal activity. The flat slope reflects the general finding that large excitatory responses yield sub-additive interactions (below the additivity line), whereas large inhibitory responses yield super-additive interactions (above the additivity line).

To focus on the more significant responses, we binned the optic flow and object motion responses by the p value derived from a t-test comparing their response amplitudes to the pre-stimulus fixation period's baseline activity of that neuron. Seven significance levels ($p < .1$, $p < .2$, $p < .3$ for excitatory and inhibitory responses and $p \geq .3$) for object motion and optic flow responses created 49 bins that included all combined response intervals from all neurons (Supplement Figure 5). The centroids of each bin were co-plotted in summed versus combined space to clarify the relationship between the significance of object motion and optic flow responses and their additivity in generating responses to the corresponding combined stimuli (Figure 8B). This plot emphasizes that the more significant excitatory responses lead to greater sub-additivity and the more significant inhibitory responses lead to greater super-additivity. These data describe the predominant tendencies in MSTd's neuronal activation-response function, constraining their excitatory and inhibitory responses to diverse, naturalistic stimuli. The relatively few responses generated by MSTd neurons beyond the bounds of this function appear to reflect their idiosyncratic sensitivities to the net effects of a wide variety of stimulus parameters.

DISCUSSION

Response Interactions with Combined Stimuli

We varied object motion and optic flow stimulus relations to simulate the diversity of naturalistic scenes during circular path self-movement in the ground plane (Figure 1). Each neuron responded to a sub-set of the stimuli, preferring certain stimulus intervals in certain combined stimulus conditions (Fig.2). This is consistent with our earlier finding that MST neurons respond to both object motion and optic flow stimuli to depicting self-movement (Logan et al., 2006). Our current results extend the previous findings by showing that there are no special stimulus conditions that uniquely activate the neuronal population (Fig. 3). In particular, congruent cue conditions that simulate earth-fixed landmarks in a self-movement scene are not more activating than other naturalistic combined stimulus conditions.

Interactions between object motion and optic flow responses are consistent with human psychophysical evidence that superimposing such cues complicates heading estimation (Warren, Jr. and Saunders, 1995) (Habak et al., 2002). The large perceptual errors seen when objects cross peri-central headings in an overlapping optic flow field suggest that local motion vector subtraction plays an important role in determining MSTd neuronal responsiveness (Royden, 2002) (Royden and Conti, 2003). The recent finding that the perception of object motion is enhanced by differences between the direction and speed of the object motion and that of the surrounding optic flow (Royden and Connors, 2010) is consistent with the relative local motion effects seen in two-thirds of our neurons (Figures 4 and 5).

The local motion perspective does not contradict the suggestion that interactions between MSTd's neuronal responses to object motion and optic flow might conform to weighted summation for heading estimation (Hanada, 2005). Weighted summation models are well-suited to the global motion effects seen in many neurons (Figure 6) with robust but widely varying influences across the population (Fig. 7 and Suppl. Fig. 4). Local motion vector subtraction models might be reconciled with global pattern weighted summation models by considering a dynamic balance between such influences.

We previously found that spatial attention may dynamically shift the balance between local motion and global pattern responsiveness in MSTd, and that monkeys can implement local or global strategies to suit task demands (Page and Duffy, 2008a). Likewise, we have found that Alzheimer's disease has a selective impact on global strategies for heading perception, while local strategies are preserved (O'Brien et al., 2001). We consider that findings from psychophysical studies favoring local versus global models might reflect human subjects' implementing different perceptual strategies for heading estimation depending on testing conditions.

Additivity of Response Interactions

The net additivity of object motion and optic flow evoked activity (Figure 3) reflects the summation of small effects with non-additive interactions between larger responses: Inhibitory responses yield higher firing rates than predicted by additivity; super-additive interactions. Excitatory responses yield lower firing rates than predicted by additivity; sub-additive interactions. The limits of these generalities are seen when equally sized summed responses evoke very differently sized combined responses (Figs. 5 and 6).

The co-activation of spatially separated and directionally disparate receptive field segments has long been thought to play an important role in MSTd's selectivity for the patterned visual motion of optic flow (Tanaka et al., 1989a) and the segmentation of object motion from surrounding optic flow fields (Komatsu and Wurtz, 1988a) (Recanzone et al., 1997).

However, the analysis of MSTd neuronal receptive field segments and their optic flow selectivity have not yielded consistent compatibility with such structural models (Tanaka et al., 1989b) (Duffy and Wurtz, 1991b) (Graziano et al., 1994). We consider that non-additive interactions between optic flow and object motion stimuli might reflect mechanisms underlying interactions between different directions of motion at multiple sites in MSTd neuronal receptive fields.

Comparisons between the local motion and global pattern responses of MSTd neurons provides evidence that non-additive interactions across receptive field segments supports optic flow selectivity. Modeling of these receptive field interactions suggests that the central visual field along the vertical meridian may be suppressed by larger field stimuli to enhance selectivity for optic flow (Yu et al., 2010). Thus, the non-additive interactions we have seen in MSTd neurons might contribute to differences between their local motion responses and their optic flow selectivities produced by simultaneous activation of separate response mechanisms across the visual field.

An alternative view is that optic flow selectivity in MSTd is not locally derived from receptive field architecture, but is inherited in the higher-order attributes of input from adjacent medial temporal cortex (MT). Diverse response interactions are evident in both MT and MST, seen as contrast sensitivity in MT (Heuer and Britten, 2002) and motion coherence sensitivity in MST (Heuer and Britten, 2007). MT contains intermixed neuronal sub-populations that respond to either the motion components of patterned motion stimuli versus the composite effects of those patterns (Adelson and Movshon, 1982; Movshon et al., 1986). These effects comport with a model of sequential linear and non-linear response mechanisms combined through direction selective suppressive responses in some MT neurons (Rust et al., 2006). The influence of such effects may create a spectrum of integrative and segmentative motion integration in MT (Huang et al., 2007) which may reflect interactions across receptive field segments (Majaj et al., 2007).

In this context, MSTd neurons in which optic flow selectivity can be explained by local motion effects, and those in which non-additive interactions are required, may constitute a similar spectrum of neuronal diversity (Yu et al., 2010). Thus, one might recognize comparable varieties of motion component versus motion pattern sensitive neurons in MT and MST. This implies that MT and MST may use similar non-additive mechanisms of response integration, differing mainly by the size of their receptive fields and receptive field sub-units.

Non-additive Signal Integration

The diversity of non-additive visual-visual interactions in MSTd bears some similarity to interactions seen across sensory modalities. In MSTd, visual-vestibular interactions with rotational (Erickson and Thier, 1991) (Shenoy et al., 1999) and translational (Duffy, 1998) (Gu et al., 2006) self-movement stimuli show evidence of the same range of diverse interactions seen in our current studies of visual-visual interactions. Auditory and visual co-stimulation in posterior (Bizley et al., 2007) and anterior cortices (Romanski, 2007) causes non-additive effects that can remarkably transform response properties. These effects may relate to the additive and non-additive interactions seen in the sensory integration of superior colliculus neurons (Stein et al., 1993) (Stanford et al., 2005) (Alvarado et al., 2007). Thus, across brain areas and functional domains, a spectrum from sub-additive to super-additive response interactions, as seen in our populations responses (Figure 8), is more the rule than the exception.

These seemingly ubiquitous interaction effects may reflect non-linear response functions created by a hierarchy of summing nodes combining synaptic drive from different sources

through the various dendritic input compartments of each neuron (Poirazi et al., 2003) (Polsky et al., 2004). Such cellular mechanisms of intra- and inter-modal non-additive response interactions would also present a substrate for the supra-modal control of response interactions by top-down influences. Directing a monkey's attention to different segments of the visual field alters MSTd neuronal responses to local motion patches (Treue and Maunsell, 1996). Likewise, MSTd neuronal responses to global patterns of optic flow are also influenced by spatial attention (Dubin and Duffy, 2007) and directing attention to local and global motion components greatly alters their response properties (Page and Duffy, 2008b). Thus, momentary changes in the monkey's attention to particular cues in a naturalistic array may influence responsiveness to those cues and their role in response interactions.

We did not implement the behavioral control of selective attention in the current studies, other than by demanding continual centered fixation. However, we recognize that the instantaneous details of specific stimuli may dynamically re-allocate attention in a manner that could account for the broad range of apparently idiosyncratic response interactions seen in our neurons. The attentional modulation of response interactions might alter response interactions and the shape of population response profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Object Motion and Optic Flow Stimuli Simulating Observer Movement on a Circular Path

A Simulated Position on Circular Path in Front of Visual Display

B Object Motion Display

C Optic Flow Display

D Combined Stimuli: Object Motion with Optic Flow

Figure 1.

Object motion and optic flow stimuli were used to simulate observer self-movement on a circular path. A. Simulated translational self-movement on a circular path began at a left-sided starting position and moved either in a clockwise (CW) or counterclockwise (CC) direction to return to that position after 8 s. The animals' straight-ahead gaze and head orientation remains directed at the center of the screen throughout the circular path of simulated self-movement. The object and array features of the simulated environment were visible throughout all simulated excursions. B. The object motion display presented two figures, a triangle on the left and a circle on the right, that moved across the horizontal meridian to simulate the visual movement of earth-fixed, eye-height objects seen during

relative self-movement on a circular path (left to right image sequence as during clockwise circular path movement). C. The optic flow display presented randomly positioned white dots simulating an array of white lights scattered across a single, remote tangent plane to create a sequence of radial and planar movement patterns seen during relative self-movement on a circular path (left to right image sequence as during clockwise circular path movement). D. Object motion (blue) and optic flow (red) circular path displays were superimposed to create combined cue stimuli. Four combinations of circular paths were created by combining CW and CC paths of optic flow and object motion stimuli (columns). The start position (arrowheads) of the object motion stimuli were changed to create four types of combined stimuli in which the optic flow and object motion were phase shifted relative to each other (rows). Together, the four circular path combinations and four phase shifts created 16 combination circular path stimuli.

Figure 2.

Responses of an MSTd neuron to the 20 visual motion stimuli presented in this experiment. A. Circular spike density plots of responses to object motion (left) and optic flow (right) presented alone. Each plot shows average neuronal firing rate for six to eight stimulus presentations as eccentricity (green) from the center of the plot. Location around each circle corresponds to the position of the observer on the simulated circular path of self-movement when that firing rate was recorded. B. Responses to the 16 combined object motion and optic flow stimuli. The direction of object motion (blue) and optic flow (red) movement simulating the circular path of translational self-movement is represented in the columns of plots. The phase shift in combined stimuli is represented across the rows of plots with the simulated start position shown in the column on the far left for the CW (blue triangle) and CC (blue circle) object motion and for the optic flow (red diamond). Responses to object motion and optic flow presented alone are smaller than the responses evoked by some combined stimuli, particularly the congruent combination of CC object motion, CC optic flow, at 0° phase shift.

Figure 3.

Neuronal response additivity across all 250 ms response intervals combined across all neurons. Prior to subtraction of the baseline (green), sub-additivity dominates. Subtracting trial-wise baseline activity from all responses (red) results in a narrower additivity distribution centered on zero net additivity. The unbiased representation of stimulus conditions is reflected in no particular condition or phase relationship yielding more sub-additive or super-additive response interactions. In each frame, response additivity (abscissa) is plotted as the comparison of the normalized combined minus the summed responses across all response intervals from all neurons in that condition (ordinate). Each of the upper left 16 frames shows the distribution of normalized response additivities for one of the 16 combined stimulus conditions, with their sum across directional conditions along the bottom row and their sum across phase conditions in the right column. The mean $\pm$ s. d. is given over each frame plot for the raw (top) and baseline subtracted (bottom) distributions.

Figure 4.

Responses of a single MST neuron in all 20 stimulus conditions co-plotted with stimulus parameters to compare responses to various attributes of the stimuli. Neuronal firing rate (black lines) is shown with the screen position of the moving object stimuli (red and blue lines) and the radial center of motion in the optic flow (green lines) along the horizontal meridian. Each frame shows responses obtained under one of the alone (A) or combined (B) stimulus conditions, arranged as in Figure 2. The abscissa is time in the 8 s circular path simulated translational motion stimulus. The left side ordinate is horizontal location (positive right, negative left) of the two objects (red and blue lines) and of the focus of expansion (solid green line) or focus of contraction (dashed green line). The right side ordinate is the firing rate of the neuron plotted in spk/s (solid black line). The stimulus traces show the center of motion in its rotation around the observer as an outward radial focus of expansion or an inward radial focus of contraction. The paired object stimulus moves across the screen along the horizontal meridian, its simulated motion in depth indicated by the separation of the lines, near being widely separated and far being closely so.

A. This neuron shows robust optic flow responses: In CW motion backwards (open green arrow) and leftwards (filled green arrow) simulated self-movement evokes large responses. In CC motion right-forward (filled green arrow) simulated self-movement is the most prominent response. Object motion alone evokes smaller, transient responses: The circular (blue) and triangular (red) objects evoke distinct response transients (paired blue and red arrows) regardless of whether they are moving to the right or left across the midline, when the paired objects loom large in the simulation. However, they evoke only a single transient when they have receded to form a smaller image in the simulation (lone arrows), again regardless of direction. B. Specific combined stimuli reveal stronger responses, with distinct direction selectivities, that are not clearly referable to responses seen when the object motion and optic flow are presented alone. A distinctly super-additive response is seen when CC object motion (blue box) and CC optic flow (red box), each of which evokes moderate responses, are combined (green box) to produce a large response.

Figure 5.

Neurons showing interactions between object motion location and direction and the overlapping motion of optic flow. A. Approach to assessing object motion effects on single neuron response additivity: The horizontal range of object positions is binned into 10° intervals for leftward (left) and rightward (right) object motion exemplified for left- and right-sided foci of expansion (FOEs) in optic flow. The bins are color-coded for the relationship between object motion direction and the local motion direction in overlapping optic flow: leftward object and flow (red), opposite directions of object and flow (green), rightward object and flow (blue). B–C. Summed (abscissas) versus combined (ordinates) response relations for each of the nine 10° object location segments with points for each of

the 250 ms response intervals color-coded for the relative directions of object motion and optic flow as depicted in A. B. Response intervals of the neuron illustrated in Figures 2 and 4 showing its largest responses as super-additive effects of uniform leftward local motion in optic flow and leftward object motion in the central, $+10^\circ$, and $+20^\circ$ locations. C. Response intervals of a second neuron showing additive effects attributable to uniform leftward optic flow and leftward object motion in the central and the $+10^\circ$ locations that is suppressed by overlapping rightward local motion in optic flow.

Figure 6.

Scatter plot of relations between summed (abscissas) and corresponding combined (ordinates) responses demonstrating path effects on response additivity. Each plot shows the baseline subtracted, averaged firing rates in the thirty-two 250 ms intervals for the 16 combined stimulus conditions with the row- and column-wise sums. All responses are normalized to the largest response (object motion, optic flow, or combined); negative numbers reflect firing rates below that recorded in the baseline period of fixation without visual motion stimuli. A. In this neuron, CC object motion (green and blue) evoked mild excitation and is associated with closer aggregation around additivity (along unity line [red] in row X column summed display of the lower right corner). In contrast, CW object motion

(red and yellow) evoked inhibitory responses that combined to yield super-additivity evident above red unity line in row X column summed display (lower right plot). B. In this neuron, the 90° phase condition uniquely yields a range of combined responses from more inhibitory effects (CW/CC condition, green) to more excitatory effects (CC/CC condition, red) most evident in the layering of the color-coded response intervals in the far right column. These effects dominate the range of super-additivities evident relative to the red line in the row X column summed display (lower right plot).

Figure 7.

Multiple linear regression analyses of responses to combined stimuli in relation to response object motion, optic flow, and their multiplicative interaction. A. Example of a neuron with a good fit plotting all response intervals from all combined stimulus conditions in which all predictors played a significant role. B. The distribution of regression fits produced by the 61 neurons. All of the neurons produced significant fits but only 25% (15/61) yielded $R^2 > .3$. The significance of each factor differed widely across neurons (see Supplement Fig. 4).

Figure 8.

Summary of response additivity of all responses recorded in experiment 1. A. Scatter plot of relations between summed (abscissa) and corresponding combined (ordinate) responses from the thirty-two 250 ms intervals of the 16-combined stimulus conditions from all neurons. All responses are normalized to the largest object motion, optic flow, or combined response elicited from that neuron. Larger excitatory responses (far right) show more sub-additive interactions, falling below the additivity line (blue). Larger inhibitory responses (far left) show more super-additive interactions, falling above the additivity line. These effects are confirmed by the linear regression's fit to the data (red line) having a slope of .38 ($R^2 = .47$, $p < .001$). B. The sub-additivity large excitatory responses, additivity of small responses,

and super-additivity of large inhibitory responses is shown in relation to the significance of responses to the object motion and optic flow stimuli. All combined responses were sorted into 49 significance bins based on their object motion and optic flow responses (see Supplement Fig. 5). The location of the centroids of responses in each bin are co-plotted as points in summed versus combined response space with the diameter of the circle around each point being proportionate to the number of combined response intervals in that class. The most significant excitatory responses (far right) are substantially sub-additive (far below the additivity line (blue). The most significant inhibitory responses (far left) are substantially super-additive (far above the additivity line). A regression line through the centroids (red) is shown for comparison to A (above).