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RESEARCH ARTICLE

Influence of visually guided tracking arm movements on single cell activity in area MT

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Abstract The behavioral relevance of neuronal activity in primate area MT for motion perception and control of visually guided eye movements is well documented. The projections of area MT comprise connections to subcortical structures and to the parietal network, both of which play a role in visuospatial transformation for guiding eyes and hands. Here, we have investigated, whether area MT is involved in the network needed to control visually guided arm movements. Our results show that half of the neurons tested significantly modulated their activity during visually guided arm movements. We conclude that the main reason for the neuronal modulation is not the arm movement per se, but the use of information from MT for visual feedback in the tracking movement. Moreover, control experiments show that attentional effects cannot solely cause the neuronal modulation. Thus, our study provides strong evidence that area MT is involved in processing visual information for visually guided manual tracking movements.

Keywords Area MT · Manual tracking · Visuomotor integration · Visual feedback

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Introduction

Visual information is crucial for goal-directed arm movements. The neural events associated with visually guided hand movements begin with an image on the retina and end with impulses to the muscles. Reduced to the cortical level, this process takes place while visual information is transferred between the primary visual area V1 and the primary motor area M1. During hand movements, activity of M1 neurons is related to the muscular activity, the force, the velocity vector or even the workspace of the hand (Georgopoulos et al. 1992; Kakei et al. 1999; Moran and Schwartz 1999; Graziano et al. 2002). A hybrid model is more or less accepted to represent feedforward and feedback control of the arm (Wolpert et al. 1995). The feedforward control comprises a rough motor plan and predictions assembled before movement onset which is updated and refined through powerful sensory feedback loops (for reviews see Miall et al. 2001; Desmurget and Grafton 2000). But where does the visual feedback during a hand tracking task with unpredictable target movements come from? The spatial information about hand and target position is originally encoded in retinal coordinates and has to be transformed into the coordinate frame of the muscles or joints involved in moving the arm. The cortical areas along the 'dorsal stream' seem to be possible candidates for such a transformation (Goodale 1998; Burnod et al. 1999). The extrastriate visual areas MT and MST of the dorsal stream project to the posterior parietal cortex (PPC). Together with the premotor areas in the frontal cortex, the PPC builds the parieto-frontal network, which has been suggested to be the neuronal substrate for visuomotor transformation (Pesaran et al. 2006, 2008). Different regions of PPC are specialized for planning different types of hand movements (Rizzolatti et al. 1997; Snyder et al.

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1997, 2000; Scherberger and Andersen 2007; Chang et al. 2008) like reaches [parietal reach region (PRR); medial intraparietal area (MIP)] and for grasping [anterior intraparietal area (AIP)]. Moreover, also one part of the middle superior temporal area (MST) was shown to be not only involved in the generation of goal-directed eye movements (Thier and Erickson 1992), but also in the generation of goal-directed hand movements (Ilg and Schumann 2007). In a functional MRI study, we could discern the role of human extrastriate area V5 (hMT+), which corresponds to monkey area MT and its satellite regions MST, in the control of visually guided hand movements (Oreja-Guevara et al. 2004). The results indicate that visual monitoring during tracking with central fixation requires the involvement of area V5 (hMT+).

Moreover, we have shown that during a visual tracking task visual (area MT/MST) and motor (M1) populations which code for similar directions of movement are co-activated with considerable temporal overlap, though we failed to observe any significant synchronization between these two areas (Kruse et al. 2002). Nevertheless, we could demonstrate that the population vector recorded from area MT/MST represents the target velocity during a manual tracking task.

It has been proposed in some studies that a common command signal is driving both ocular and manual tracking responses. A study from Engel et al. (2000) showed that if the trajectory of a moving target presents an abrupt change in direction, eye and hand tracking movements show similarities in kinematics despite the considerable inertial differences of the two systems. Furthermore, the fact that effects of adaptive modifications imposed on the smooth pursuit system could subsequently be observed in the manual motor system implied that the adaptation occurred at a level common to both systems, probably in structures concerned with visual motion processing (Van Donkelaar et al. 1994a). Another study from Van Donkelaar (1994b) demonstrates that the limb motor control system uses both retinal and extraretinal signals when attempting to accurately track a target moving at constant velocity.

The functional importance of area MT for visual guidance of eye movements, for motion perception as well as for forming categorical decisions about moving stimuli has been studied extensively (Newsome et al. 1985; Newsome and Paré 1988; Komatsu and Wurtz 1988; Pasternak and Merigan 1994; Lisberger and Movshon 1999). However, so far, no study shows how single cell activity in area MT is involved in the online control of visually guided hand movements. Therefore, we have conducted experiments with a paradigm designed to reveal the role of area MT during visually guided manual tracking movements (Oreja-Guevara et al. 2004). The behavioral paradigm consists of two different conditions that are identical in terms of visual (retinal) stimulation: we compare the activity of MT neurons during "active manual tracking" of a visual target against the activity evoked during "passive" visual stimulation. Differences in activity due to visual stimulation are ruled out by using the identical visual target/cursor movements stored from the active condition for the "passive (replay)" stimulation. The goal of this study was to verify a modulation of activity in area MT that can be assigned to an extraretinal influence like the behavioral context of visually guided manual tracking movements.

Methods

Subjects

Two adult male rhesus monkeys (*Macaca mulatta*, TO and TI), weighing between 9 and 10 kg, were used in the present study. The animals were trained using liquid reinforcement. Body weight, skin turgor, activity levels, and food consumption were monitored on a daily basis to be sure that dehydration, weight loss, or symptoms of other illness did not occur. All procedures were approved by the local Animal Care Committee in compliance with the guidelines of European Community on Animal Care.

Surgical preparation

Animals were prepared for chronic recording of eye position and single neuron activity in the superior temporal sulcus (STS). Anaethesia was induced with ketamine hydrochloride (Ketanest 10 mg/kg) and atropine (0.04 mg/kg) and maintained under pentobarbital sodium anesthesia (Narkoren, 25 mg/kg i.v.). Deep analgesia was introduced by intravenous application of 3 μg/kg/h of fentanyl. A search coil was implanted subconjunctivally to measure eye position (Judge et al. 1980), and a head-restraining post was implanted on the skull. In both animals the recording chambers were implanted over the occipital cortex in a parasagittal, stereotaxic plane tilted back 60° from the vertical (in monkey TO on the right and left, in monkey TI only on the left side). The placement of the chamber was guided by magnetic resonance images, which were taken from each animal before the first surgery. The recording chamber and the eye coil plug as well as the head holder from one monkey (TO) were embedded in dental acrylic. In the second monkey (TI) the head-restraining post was anchored to the skull by self-tapping screws only. Analgesics were applied postoperatively and recordings started no sooner than 8 weeks after surgery.

Experimental setup

The monkeys were seated comfortably in individually adjustable primate chairs, with the head fixed to the chair by a head post. The animals were trained to use their right hand only for moving a two-joint manipulandum placed in front of them in a horizontal plane, which was attached to the primate chair at the level of the hip. The hand position data were digitized as position values of the optical rotary position transducers at the shoulder and elbow joint and sampled with 75 Hz by a PC with a spatial resolution of 0.1 mm. The workspace of the hand was restricted to 30×30 cm^2 due to the spatial dimensions of the primate chair. The position data were displayed in real time as a feedback cursor (red dot, radius between 0.8° for monkey TI and 1.25° for monkey TO) on a translucent vertical screen, placed 62 cm away from the animal. The gain ratio between hand distance in space and cursor distance on the screen (visual space) was adjustable by the software and varied across studies (0.3–0.9 cm/°). The visual stimuli were generated by a PC and were back-projected onto the screen with a video projection system (75 Hz frame rate, 800×600-pixel video resolution; Electrohome ECP 4100, Kitchener, Ontario, Canada). The screen covered 131° azimuth and 98° elevation of the visual field. During the experiments, the room was darkened.

All experiments were controlled by a DOS-based software that was developed in the laboratory by one of the authors (W. Kruse). The software controlled the time course of the experiment, monitored the behavior of the animal, generated the entire visual stimulation, sampled the hand position and eye position data, as well as the spike activity of monkey TO. The neuronal activity of monkey TI was recorded using Cortex (Salk Institute for Biological Studies, La Jolla, CA, USA) and the data could be synchronized with the behavioral events offline.

Neuronal activity was recorded from areas MT and MST in monkey TO using a seven-electrode device (Thomas Recording, Giessen, Germany). Activity of single cells was detected in real time by means of a computer controlled multi-channel spike sorter (Plexon Inc., Dallas, TX). Spikes were stored with 10-μs resolution. In the second monkey TI, the neuronal activity was recorded extracellularly using tungsten in glass electrodes driven by a Narishige microdrive attached to the recording chamber. Spike detection was achieved with a MSD (Multi Spike Detector: Alpha Omega).

Eye positions were measured using implanted search coils (Judge et al. 1980). These analog signals were sampled with a rate of 500 Hz by an A/D-converter (Intelligent Instrumentation Inc., Tucson, Arizona) for horizontal and vertical eye position. Instantaneous voltage values of the eye coils were converted into position units of the screen (pixel) in time with the graphical update (75 Hz) and served mainly for the control of the ocular behavior of the monkey. During all tested paradigms, the animals had to maintain fixation of a small green square (Ø 0.7°) and a trial would be aborted if the animal left a virtual fixation window of a diameter of 5.16°. Only trials with successful fixation were further analyzed.

Experimental paradigm

The behavioral paradigm applied in this study featured two conditions that were identical in terms of visual (retinal) stimulation. In the active condition (tracking condition), the monkey tracked a moving target with a cursor controlled by his hand via a manipulandum. In the passive condition (replay condition), the prior recorded movements of target and cursor were replayed, while the monkey held his hand at a constant position (monkey TO, "replay condition I") or while he was free to move the manipulandum, but without a visual feedback of his motor behavior (monkey TI, "replay condition II"). This procedure yielded pairs of trials with identical visual stimulation. The trajectory of the tracking target was adjusted to the functional properties of MT neurons according to the position of their receptive fields and to their preferred direction (PD). Once typical MT activity was isolated at the tip of the electrode, the monkey was required to perform three types of behavioral paradigms.

Direction tuning paradigm

First, we estimated the preferred directions of the visual cells at the recording site. The monkeys fixated a central green square of 0.7° width and a whole field random dot pattern (0.8 cycle/°) was moved on a circular pathway in clockwise and counterclockwise direction (31°/s). The continuous change of stimulus direction modulated the activity of all direction-selective cells within the time course of one trial (Schoppmann and Hoffmann 1976). In a single trial, the pattern moved for 3.5 s. A trial was cancelled if the distance of the eye position to the fixation point exceeded 4° (TO) or 3° (TI). After successful completion of a trial, the animal got a liquid reward. For the circular pattern stimulus, the PD was calculated separately for clockwise and counterclockwise pathway. The PD was defined as the mean vector derived from the average firing rates in 15° bins. If mean vectors of clockwise and counterclockwise directions reached significance ($P > 0.05$, Raleigh test), the overall PD was defined as their mean direction. By averaging the mean direction of clockwise and counterclockwise stimuli, a possible influence of the response latency on the PD of a cell was cancelled out. The computation of the preferred

directions is described in more detail by Kruse et al. (2002).

In some cases, a white bar (orientation perpendicular to moving direction, 0.7° × 2.4°) moving in eight equally spaced directions at a speed of 12°/s across the center of the receptive field of a MT neuron was used as another stimulus. Here, we calculated the average firing rate during stimulus motion for every direction. The PD was then defined as the resulting mean vector.

Receptive field mapping

Additionally, the receptive fields (RFs) of all tested visual neurons were determined qualitatively by means of a hand-held lamp, while the animals were required to fixate a green square (Ø 0.7°) in the center of the screen. RFs were mapped onto a translucent screen and the center of the RF was determined.

Tracking and replay paradigm

After we determined the RF-position, we shifted the fixation point so that the center of the RF was aligned with the center of the screen. This arrangement ensured that during the replay paradigm all cells were tested with arm movements in a similar workspace.

The replay task differed somewhat between the two animals. Monkey TO was initially instructed by the color of the cursor. In case of a red cursor as shown in Fig. 1b, he had to track the upcoming moving target (active or tracking condition). In case of a blue cursor, the following trial was passive (replay condition I) and the monkey had to hold his hand in a defined stationary position (Fig. 1c). In tracking as well as in replay condition I, a trial was initiated if the monkey guided the cursor to a start position indicated by a white unfilled circle (Ø 6.5°) and maintained fixation of a small green square (Ø 0.7°). The start position was constant for replay condition I and differed for the start positions of active tracking trials which depended on the direction of tracking movement. The start positions of active tracking were positioned on the trajectory of the upcoming target movement outside of the particular RF. In active tracking conditions after a random time of 1.5–2 s, a target (white filled circle, Ø 2.3°, 12°/s) appeared moving on a linear trajectory that crossed the start position of the cursor and the center of the screen, which corresponded to the RF (grey shaded square) of the MT neuron. At a time of 500 ms before the onset of the tracking, the white circle indicating the start position was switched off. At the same time, the recording of the cursor position started for the later replay in the passive condition. When the target crossed the start position of the cursor (trajectory of the target indicated by the white arrow) after a time of 250 ms, the monkey was required to initiate a tracking movement (cursor movement indicated by the red arrow). The target stopped to move after a tracking distance that usually covered 20° of visual angle. The monkey received a reward after holding the final target position for another second. Tracking accuracy in active tracking trials was controlled by a virtual window (3.3° radius) around the moving target not visible to the monkey. In replay condition I (Fig. 1c), the blue cursor and the circle indicating the start position were switched off 500 ms prior to the onset of the replayed tracking target. The replay of the red (active) cursor and the target started immediately after switching of the blue cursor. The replay of an active trial lasted until the end of the target hold period of the active trial. Hence, the visual stimulation of active and replay conditions was identical from a time of 500 ms prior to target movement onset. The animals had to fixate the same position on the screen and the target as well as the cursor trajectories were the same under both conditions. This would be important to avoid luminance differences which could cause a modulation of the activity. Throughout the course of a passive condition I trial, the monkey had to keep his hand stationary at the start position, indicated by the blue circle, but visible only before the start of the replay. A deviation from this position exceeding 3.3° led to an abortion of the trial.

In replay condition I, monkey TO was instructed by the blue cursor to hold his arm in a stationary position and to neglect the tracking target. That might cause a difference in neuronal activity between active and passive conditions that is solely due to a difference in the monkey's attention to the tracking target (Treue and Maunsell 1996). To reduce the possible influence of attentional mechanisms, monkey TI was not cued by a blue cursor to hold his arm in a stationary position (replay condition II). Instead, he was free to move the manipulandum during the replay of the active condition, but without a visual feedback of his actual motor behavior (Fig. 1d). The time course of the two replay conditions was otherwise the same.

Paradigm

Active tracking and replay conditions (replay I and II) were compared for three directions of target movement. One direction was aligned to the PD of the particular MT neuron. The target trajectory was centered on the RF of the neuron under study. The other directions were shifted clockwise and counterclockwise at 30° from the PD. Figure 3 shows the arrangement of the three trajectories according to the directional tuning and the spatial receptive field (Fig. 3a) of an example cell. This arrangement ensured that cells were tested along the most responsive directions. However, since we recorded neurons from more than one electrode during a single session and sometimes

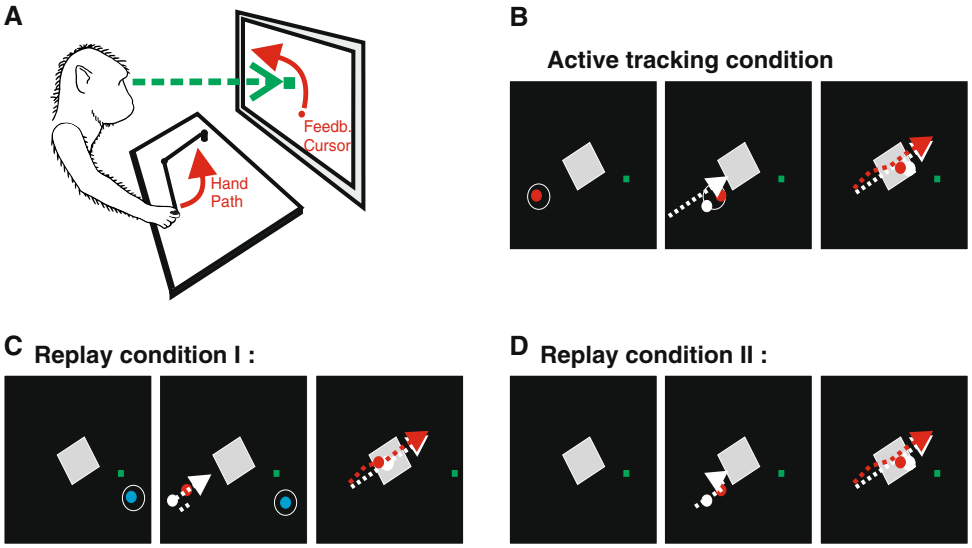

Fig. 1 Setup and basic behavioral paradigm. **a** The monkey controlled the movement of the cursor (*red filled circle*) via a two-dimensional manipulandum, while keeping his gaze on a fixation spot (*green square*). Visual targets and the cursor were back-projected onto a translucent screen. **b** The monkey initiated a trial by guiding the cursor (*red filled circle*) into a start window presented on the screen (*white unfilled circle*). After a random time a moving target appeared (*white filled circle*), moving on a linear trajectory (*white dotted arrow*) that crossed the start position of the cursor, then the center of the receptive field of a MT neuron (*grey square*). **c** In replay condition I, the monkey held the cursor (*blue dot*) in a defined stationary position (*white circle*). This cursor was switched off 500 ms before the onset of the replay, to provide the same visual stimulation, but the monkey was still required to keep the arm stationary. **d** The monkey had no visual control about his arm movements in replay condition II, since he got no feedback about his movements via the red cursor. The visual stimulation was the same for all three conditions in a predefined time window

more than one neuron from one electrode, we also recorded neurons with suboptimal directions, which were not aligned to the neurons direction preference.

It is also important to mention, that the moving tracking target had always the same velocity (12°/s) though we were conscious that MT neurons showed a wide range of preferred speeds (Mikami et al. 1986). We chose this speed, because the animal had to be able to follow the target with the cursor and the velocity had to be in the range where many neurons showed a modulation. However, we cannot exclude the possibility that we therefore missed some neurons sensitive to other velocities.

Data analysis

The analysis was based on the paired comparison of the firing rates in active tracking and replay trials. Since cursor trajectories naturally differed from trial to trial, a passive trial was paired with that particular active trial in which the target and cursor movements were recorded for the replay. We calculated the mean firing rate in a fixed window of 1-s width for every trial. The time window was centered on the trajectory of target movement to cover the epoch when target and cursor moved through the receptive field. The difference in firing rates for every pair of active and passive trials was quantified by a modulation index (MI, Michelson contrast):

$$\mathrm{MI} = R_{\mathrm{active}} - R_{\mathrm{passive}} / R_{\mathrm{active}} + R_{\mathrm{passive}}$$

MI values ranged from −1 to 1 with positive values indicating higher rates in the active condition (R_{active}), whereas higher rates in passive conditions (R_{passive}) would result in negative values. To get an estimate of the overall modulation of a cell for a certain direction of tracking, we calculated the median MI of the MIs of single trial pairs. The differences in firing rates of active and passive conditions were tested for significance by means of non-parametric test for paired samples (Wilcoxon sign-rank test).

Histology

After completion of data collection in one monkey (TO) several defined positions were permanently marked by electrolytic lesions (12 s, 15 μA) or injections of physiologically inactive dye. These marks were made at selected locations to serve as reference points during reconstruction of electrode tracks on sections. Following deep anesthesia with pentobarbital, the animal was perfused with 0.9% saline and 4% paraformaldehyde (PFA)–lysine–periodate. After cryoprotection in 10% (24 h) and 20% glycerol (48–72 h), the brain was frozen in isopentane and stored at −70°C. Frozen 50-μm thick sections were cut in a sagittal plane. Alternating sections were stained for cytoarchitecture and myeloarchitecture. Individual recording sites were

reconstructed in relation to mircolesions, tracer deposits and penetration scheme. The reconstruction of the histology is shown in Fig. 2. The recording sites which could be found in area MT are indicated by red open circles. There were also some recordings made in area V4t, but these cells have been discarded.

Results

The present report is based on the analysis of a sample of 108 neurons recorded in area MT of two monkeys. All neurons presented from monkey TO ($n = 26$) were verified by histology to belong to area MT (Fig. 2). For the second

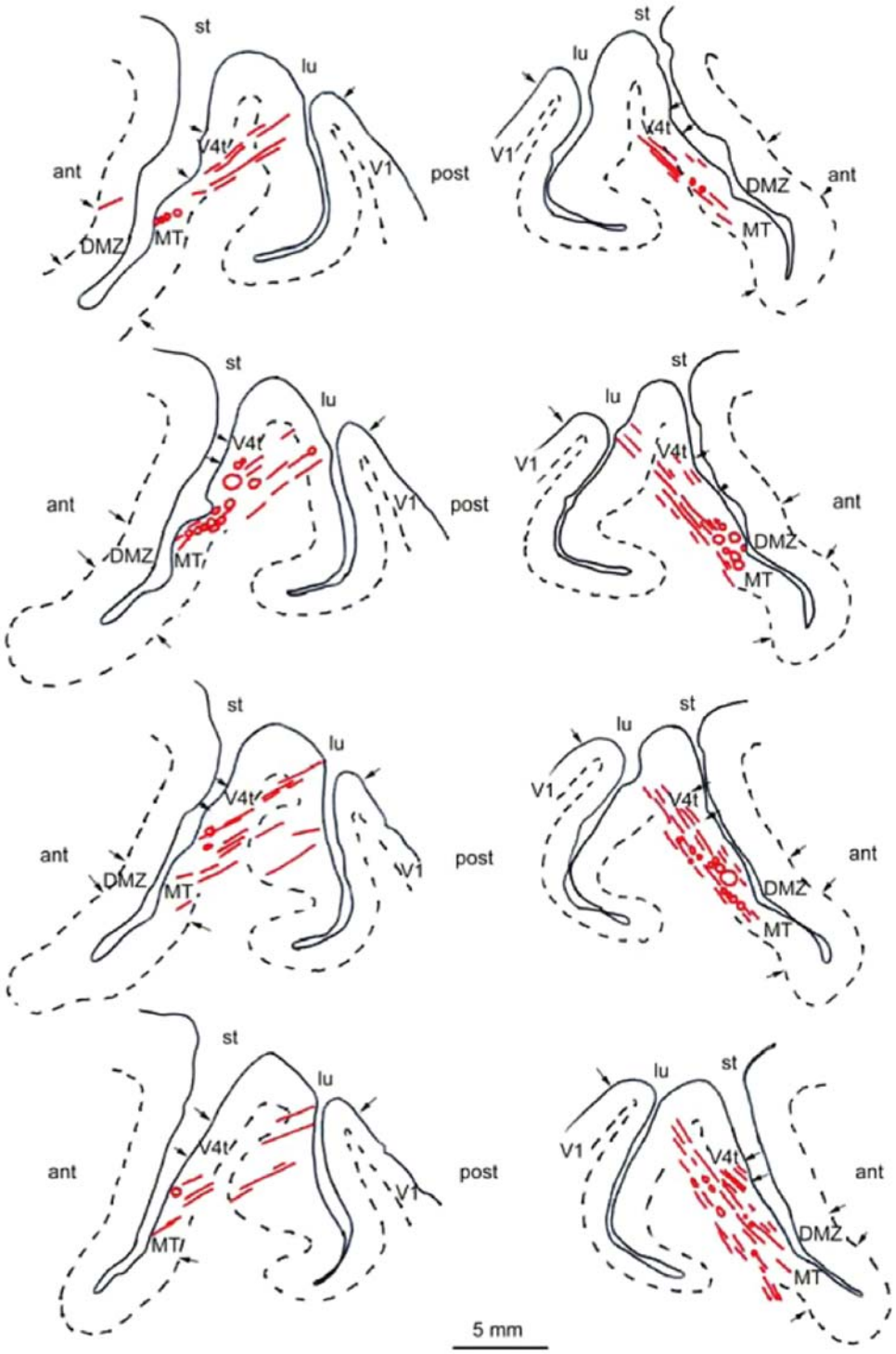

Fig. 2 Serial parasagittal sections through the left (*left column*) and right (*right column*) cortical hemispheres of monkey TO. The sections are arranged from lateral (*top*) to medial (*bottom*), intersection distance is 600 µm. *Solid lines* present the outline of the sections, *broken lines* give the border between grey and white matter. Areal borders based on myeloarchitecture are indicated by *arrows*. *Red lines* indicate penetration tracks, *red circles* indicate the recording/injection sites. *ant* anterior, *DMZ* densely myelinated zone of MST, *lu* lunate sulcus, *MT* medial temporal area, *st* superior temporal sulcus, *V1* primary visual cortex, *V4t* transition zone of visual area V4, *post* posterior. The *scale bar* represents 5 mm

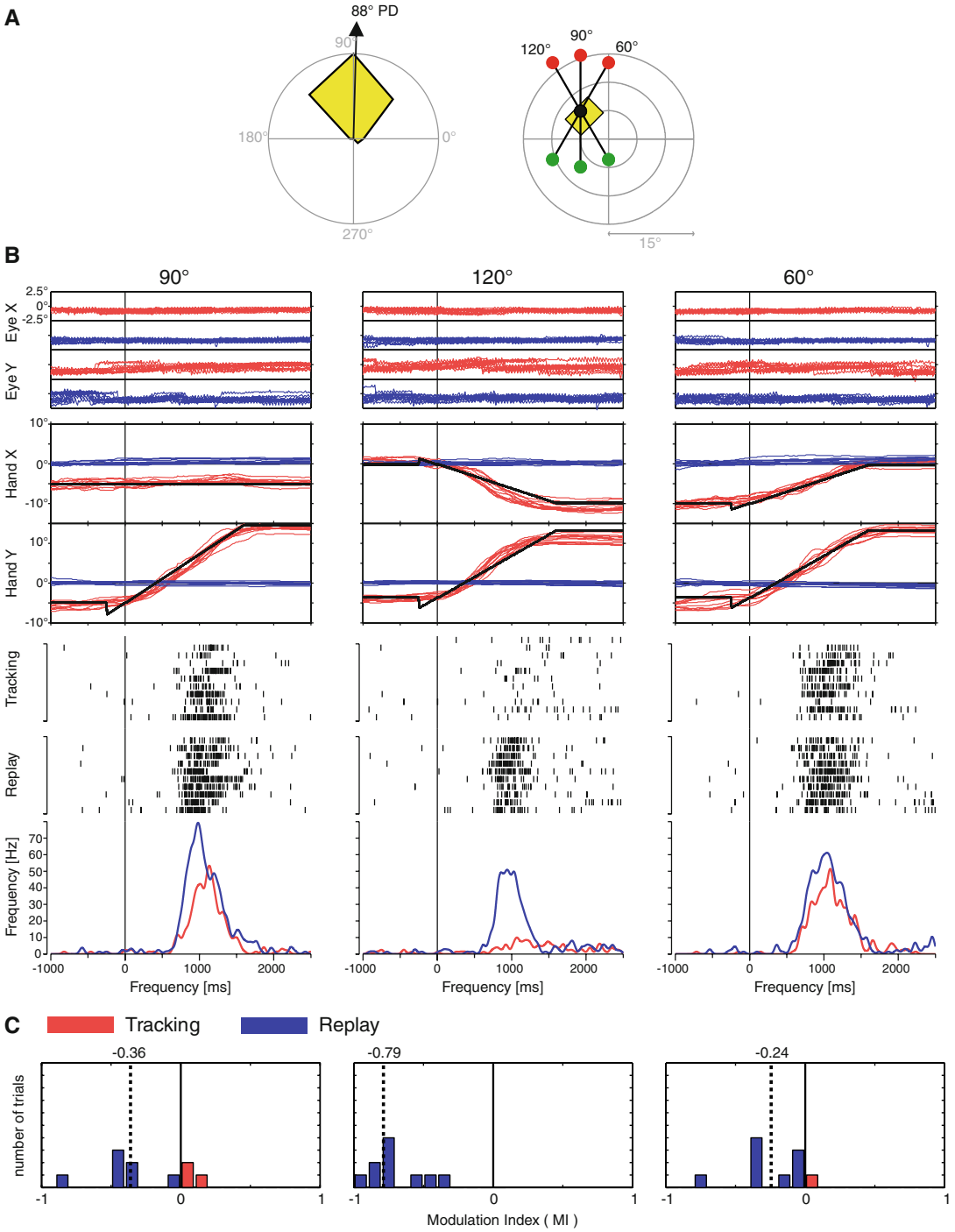

Fig. 3 Comparison of the activity of a MT neuron during the active and replay I tracking paradigm. **a** *Left panel* Polar plot of the direction tuning of the cell. The radius of the circle stands for the maximal firing rate of the neuron elicited during upward stimulus movements (34 imp/s). The *solid arrow* shows the PD of the cell. **a** *Right panel* The RF of the same neuron in the visual space of the monkey is indicated by the *yellow square*. The fixation spot is at the center of the circles. The *lines* indicate the target trajectories for movements in PD (90°), 30° counter clockwise (120°) and 30° clockwise (60°) with the three different start positions (*green circles*) and end positions (*red circles*) for the target. **b** *Top* The *upper panels* show the eye position data against time. **b** *Middle panels* show hand position data against time (*blue* replay condition I, *red* active tracking condition). **b** *Bottom* The figures show the activity over time elicited by active tracking (*in red*) and in the replay condition (*in blue*) in the above illustrated directions. The spike density functions were computed by a Gaussian kernel function with a kernel width of 20 ms. The *black vertical lines* indicate start of the trial. Each *black tic mark* in the raster plots represents one action potential. **c** *Panels* show the results of analysis as the distribution of the modulation indices (MI) for each pair of active tracking and corresponding replay trial. The median MI is indicated by the *dashed vertical line*. Firing rate in active and passive condition were significantly different for all three tracking directions

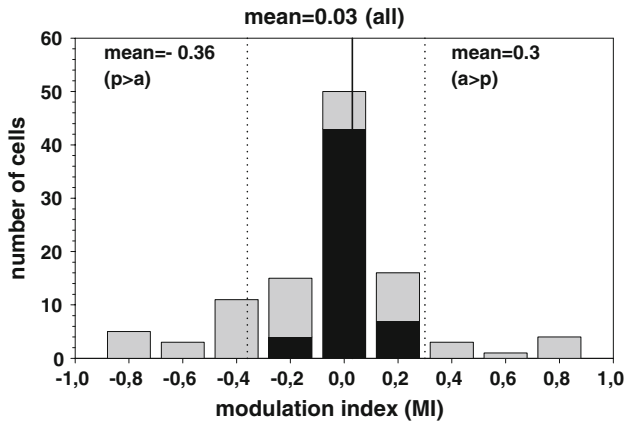

Fig. 4 Distribution of the modulation index (MI) with tracking in PD. MI values ranged from −1 to 1, with positive values indicating higher rates in the active condition, and negative values higher rates in replay conditions. *Grey bars* show the distribution of significantly modulated units ($P < 0.05$, paired Wilcoxon sign-rank test), *black bars* units with no significant modulation

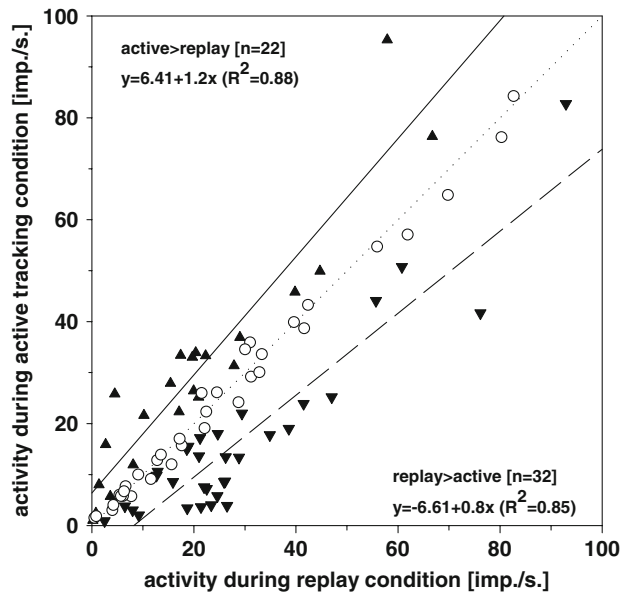

Fig. 5 Scatter plot of the mean activity during active tracking condition versus the mean activity during replay condition for all neurons tested in the tracking and replay task. *Black upwards pointing triangles* indicate neurons with a significant higher activity in the active tracking condition ($n = 22$), *black downwards pointing triangles* neurons with a significantly higher firing rate in the replay condition ($n = 32$). *Open circles* stand for neurons with no significant modulation ($n = 54$)

monkey (TI) the histology is so far missing, since this animal is still involved in other experiments. The 82 neurons from monkey TI presented here fulfilled the functional criteria known of MT neurons: a clear direction preference of motion as well as the size and retinotopic position of the RFs.

Our primary goal was to examine if neurons in MT were differently activated when the monkey executed visually guided tracking movements or when he was presented only with the visual stimulation of the same tracking movements (replay condition). Figure 3 shows an example of a MT neuron with a directional preference for upward motion of bars (Fig. 3a, left). The neuronal activity in active tracking and replay I conditions in the PD (90°) as well as 30° counter clockwise (120°) and 30° clockwise (60°) from the PD through the RF of this neuron is shown in Fig. 3b. The neuronal activity for all three tracking conditions were significantly different in active tracking and replay I conditions ($P < 0.05$, Wilcoxon sign-rank test) with a higher discharge rate in the replay condition I, i.e., when the animal merely observed the movement of target and cursor from a previous active trial but now did not move the arm. The median of the modulation indices (MI) were −0.36 (PD), −0.79 (counter clockwise to PD) and −0.24 (clockwise to PD) (Fig. 3c).

Modulation index as a measurement to classify MT neurons

In a first analysis of MI for tracking movements in PD of the neurons, we found no consistent difference across the cell population (Fig. 4). The means of the distribution were not significantly different from zero. But nevertheless a number of cells in area MT were differentially activated depending on the active or passive nature of the tracking condition. Fifty-four out of 108 MT units (50%) showed a significant difference ($P < 0.05$, Wilcoxon sign-rank test) in firing rates between active tracking and replay conditions. Among these cases were 32 units (29.6%) firing at higher rates in replay conditions with a mean MI of −0.36 and 22 units (20.4%) firing at higher rates in active tracking conditions with a mean MI of 0.3. Half of the tested neurons fired at equal rates, no matter if the tracking was active or replayed. Size or eccentricity of the receptive fields of the tested neurons is not a predictor whether the neuron would be modulated by the tracking or not. Neurons with receptive fields in the fovea could not be analysed because the monkey broke fixation when the target and the cursor would move across the fixation spot. We were not only interested in the modulation index of a neuron for a certain direction of tracking, but in addition we quantified the difference of the mean firing rate of a neuron with respect to active tracking and replay trials. In Fig. 5, we present the distribution of the mean firing rates of all individual neurons tested during active tracking in PD against the replay condition in a scatter diagram. The filled triangles indicate neurons which showed a significant difference, whereas the unfilled circles represent neurons with no significant effect during active tracking against the replay condition. The

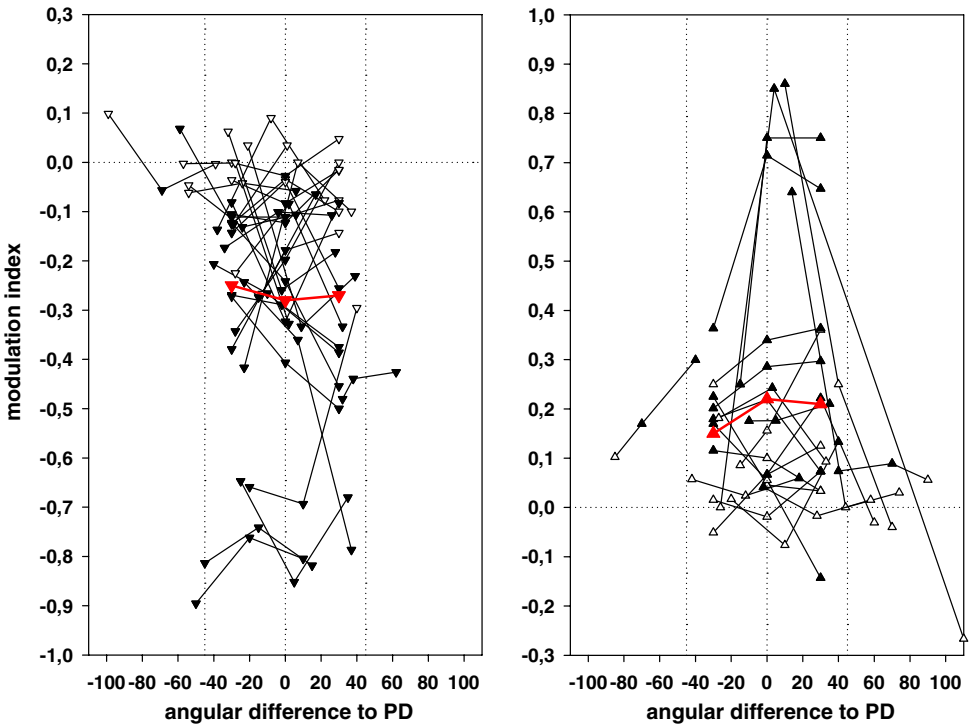

Fig. 6 Comparison of the neuronal modulation during tracking in different directions. The graph shows modulation indices (MI) against the direction of tracking for all neurons with a significant modulation for at least one direction. Directions were normalized to the PD of the unit under study plotted at 0. *Downwards pointing triangles* indicate neurons which show higher activity during the replay condition (*left panel*), *upwards pointing triangles* neurons with higher discharge during the active tracking (*right panel*). *Filled symbols* indicate significant ($P < 0.05$, Wilcoxon sign-rank test) differences in firing rates in active versus passive conditions, *open triangles* no significant differences. *Lines* connect the data points corresponding to the three tracking directions for a single neuron. The *red filled triangles* indicate the mean modulation indices for the MIs in PD $\pm$ 15°, 30° $\pm$ 15° counter clockwise and 30° $\pm$ 15° clockwise. Therefore, only the neurons are included, where the tested directions differs not more than 15° from the PD of the recorded neuron. *Upwards pointing red triangles* indicate the mean modulation index for neurons with higher activity in the active tracking condition (mean of $n = 15$), *downwards pointing red triangles* the mean MI for neurons with higher firing rate in the replay condition (mean of $n = 25$)

time window for the calculation of the mean firing rate was selected according to the time the visual stimulation was completely identical irrespective of the nature of the tracking condition. These results clearly demonstrate that the neuronal activity in MT is influenced by a simultaneously ongoing visually controlled tracking arm movement. But to our surprise, this influence could be a higher discharge during active tracking for some neurons as well as a decrease in firing rate for other neurons.

Modulation for different tracking directions

For the estimation how an extraretinal modulation affected the neuronal responses along the directional tuning curve, we tested two other directions in addition to the PD. As illustrated in Fig. 3b for the example cell, neurons were not only tested in their PD but also in two additional tracking directions: 30° counter clockwise and 30° clockwise from PD. Two response profiles were conceivable. First, only tracking in the PD elicited a modulation of the neuronal response, which resulted in a "sharpening" or "blunting" of the tuning curve. Second, the neuronal modulation is of a "multiplicative" nature, so that the observed response would be modulated by the same proportion irrespective of the tested direction. The latter case could be seen as a modulation in response gain which was shown for MT neurons in case of attended visual stimuli (Treue and Trujillo 1999).

Figure 6 shows the modulation indices of each unit tested in all tracking directions. Directions of conditions were plotted relatively to the particular PD of the single unit. For purpose of clarity, only data of those cells were illustrated that showed a significant modulation at least in one of the tested directions. During cell sampling, it was not possible to measure every single unit in its special PD for the tracking and replay task, since normally more than one cell was recorded simultaneously. Therefore, for some cells we have an angular difference to the preferred direction for all tested directions. Figure 6 clearly shows that not only tracking in the PD of the neurons modulated the neuronal activity, but also tracking with 30° or even more degrees of difference to the PD showed significant

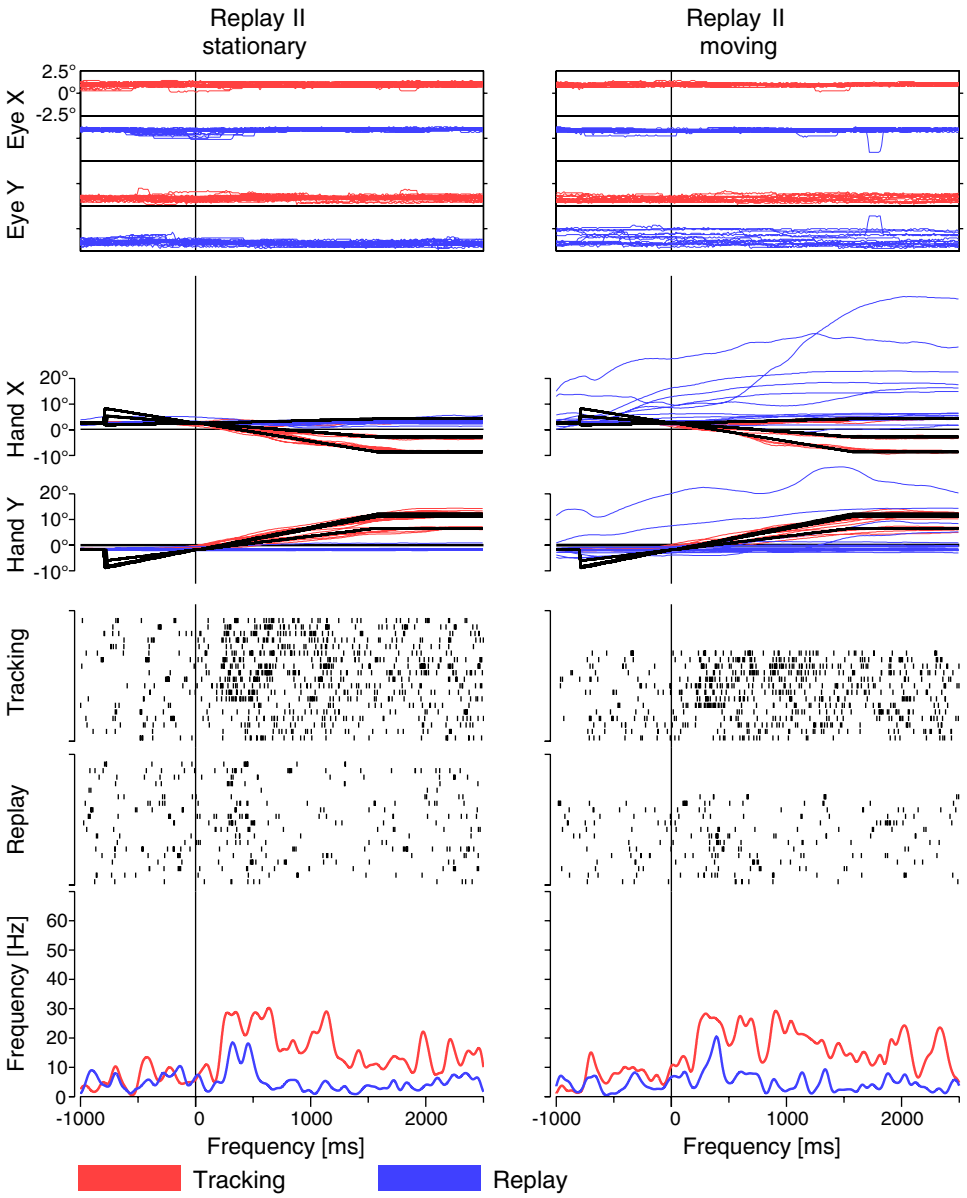

Fig. 7 Activity of an MT cell plotted separately for replay condition II stationary (*left*) and replay condition II moving (*right*). The *upper panels* show the eye position data against time. The *middle panels* illustrate the hand position data for three different tracking directions (*blue* replay condition II, *red* active tracking condition). The *lower panels* show the activity over time elicited by active tracking (*in red*) and in the replay condition (*in blue*). The spike density functions were computed as in Fig. 3. The *black vertical lines* indicate start of the trial. Each *black tic mark* in the *raster plots* represents one action potential

effects. Neurons which where tested in tracking directions up to 45° apart from the PD (in PD ± 15°, 30° ± 15° counter clockwise and 30° ± 15° clockwise) showed no significant differences in their modulation strength as compared to PD (mean modulation indices were marked by the red filled triangles) ($P = 0.84$, rank-sum test, for neurons with a higher firing rate in the replay condition and $P = 0.62$ for neurons with higher activity in the active tracking condition). This finding is in line with a "multiplicative" gain modulating mechanism.

Activity of MT neurons during replay condition II

A difference in neuronal activity in active and passive trials in monkey TO might have been introduced by a difference in the degree of visual attention the monkey employed in the two conditions. Since monkey TO was instructed to omit any hand movements in passive trials (replay condition I), he might have simply neglected the replayed visual stimulus. To rule out this explanation for the observed modulation, we examined the behavior of monkey TI in the replay condition II. We divided the replay II condition data offline into replay trials, where the monkey still made open loop tracking movements to the target though this was not required (replay condition II moving) and replay trials, where the monkey held the hand nearly constant at a certain position on the tracking table (replay condition II stationary). The division of passive condition II trials was done by inspection of the hand position data from the manipulandum (Fig. 7) during the critical tracking phase, when the visual stimulation was identical for active tracking trials and the associated replay condition II.

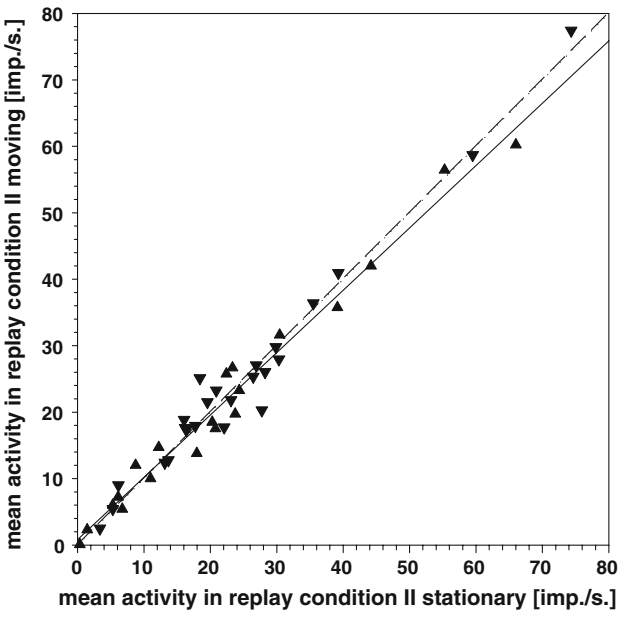

Fig. 8 Scatter plot of the mean activity during replay condition II moving versus the mean activity during replay condition II stationary for all neurons with a significant modulation. *Upwards pointing triangles* indicate neurons with higher activity in the active tracking condition, *downwards pointing triangles* with higher firing rate in the replay condition

Figure 7 shows an example of monkey TI replay tracking after the offline breakdown of replay condition II in stationary (Fig. 7 left, blue) and moving (Fig. 7 right, blue) trials. The respective active conditions are shown in red. On the right side of Fig. 7, the situation is shown where a tracking movement was carried out, despite the fact that this was not necessary for the monkey to get a reward. During this condition, we had clear evidence that the monkey paid attention to the visual stimulation because he tried to follow with the manipulandum the course of the target though he had no visual feedback about his actual cursor position. In other trials the animal made no movements with the manipulandum (Fig. 7, left).

If attention would be the critical factor in the difference in firing rate between active tracking and replay trials than the activity in the replay condition II moving and in the active tracking condition should be identical, because under both conditions it would be absolutely necessary that the animal paid attention to the visual target to follow it. But as it is shown in Fig. 7 this was not the case. The activity of this neuron was not significantly different during replay condition II stationary (Fig. 7, left) and replay condition II moving (Fig. 7, right; $P > 0.05$, Wilcoxon sign-rank test), but both replay conditions were significantly different from the active conditions ($P < 0.001$, Wilcoxon sign-rank test).

This effect was obvious for all 44 neurons (all tested directions included) which showed a significant modulation in the replay paradigm and where tested with the replay II condition (Fig. 8). None of the tested neurons showed a significant difference in their modulation during replay condition II moving and replay condition II stationary, but the activity is significantly different with regard to the corresponding active tracking conditions. This analysis also showed that arm movements per se were not enough to modulate activity in area MT. The important factor leading to the difference between the active tracking and the replay situation was that the visual stimulation was used for the online guidance of the monkey's hand.

To ensure that the difference in the neuronal modulation between replay and active tracking conditions was not an effect of eye movements like microsaccades, we also analyzed the eye position data under this aspect. We could not find any correlation between microsaccades and consistent changes of neuronal activity.

With these results, we demonstrated for the first time that neurons in MT participate in visuomotor integration, strictly speaking, that visual online monitoring during tracking with central fixation modulates activity of neurons in area MT.

Discussion

The main goal of this study was to show an extraretinal non-visual signal influencing the activity of MT neurons during visually guided manual tracking movements. For this purpose, we created a behavioral paradigm with an active tracking and a passive replay condition with identical visual stimulation designed to reveal the role of area MT in action. We were able to show for the first time that neurons in area MT significantly modulated their activity due to the context of visually controlled manual tracking movements. It was manifested in different firing rates of neurons depending on whether the monkey is in the context of performing visually guided hand movements (active tracking) or is passively observing the visual stimulus (replay condition). Out of 108 neurons examined in area MT in two monkeys, 29.6% showed a significantly higher firing rate during the passive replay condition and 20.4% showed a significantly higher firing rate during active tracking. A comparison of the modulation in different tracking directions indicates a multiplicative effect along the tuning curve of directionally selective neurons in MT.

Extraretinal factors modulating neuronal activity in area MT

Modulation of neuronal activity by extraretinal factors like attention or eye position is a known phenomenon in MT and throughout the extrastriate and parietal cortex. It was

found in connection with a shift in the attentive state of the monkey (Treue and Maunsell 1996; Seidemann and Newsome 1999; Recanzone and Wurtz 2000). Also the change of eye position or ongoing eye movements can modulate the response of some neurons in MT (Newsome et al. 1988; Bremmer et al. 1997), although these effects are more striking in MST.

However, in contrast to MST area MT is not influenced by eye velocity during pursuit, though this is also an extraretinal signal (Ilg and Thier 2003). The extraretinal signals found with the experimental paradigm applied in this study cannot entirely be attributed to attentional influences. In the active tracking condition, the monkey was required to track the moving target with a sufficient amount of accuracy. Since this task involves spatial attention to the moving target, it was crucial to exclude the possibility of spatial attention being the sole factor causing the observed modulatory effects. In the replay condition with the instruction to hold the cursor at a constant position (replay I), the monkey could have just neglected the replayed stimulus. Nevertheless, the visual stimulus instructed the monkey how long he had to hold his hand still and when to expect a reward. There are two reasons that let us conclude that the observed modulation of MT activity derives from the involvement of MT into a closed visuomotor control loop rather than from a simple enhancement of neuronal activity by attentional processes. First, in the second monkey we observed that in the replay condition where he was not instructed to hold and where he moved his hand with the stimulus (replay II moving), the activity was still different compared to the active tracking condition. Assuming that both of these tracking conditions required the monkey to direct its attention to the visual target, the only factor that could have modulated the neuronal activity is the visual stimulus representing the actual hand movement in the active tracking, making the visual information suitable to serve as a feedback signal. Second, replay conditions II where the monkey held his hand still showed no difference from replay conditions where he initiated an open loop tracking movement (Fig. 8). The initiation of a tracking movement could be interpreted as an attempt to retrieve information from visual areas to guide the hand movement and hence could be interpreted as a top down or attentional process. The lack of modulation despite the monkey trying to exploit the visual signal showed the importance of area MT being embedded in a sustained visuomotor loop to show extraretinal modulation. Another hint that the modulation in area MT during the control of manual tracking was not only an attentional mechanism came from the result that the modulation of neuronal activity could be an increase as well as a decrease depending on the tracking condition. Assuming that the passive conditions in the tracking and replay paradigm correspond to a "non attentive" condition, this result seems to be contradictory to the findings of most attentional studies. However, neurophysiological as well as fMRI studies in awake behaving monkeys showed that attention is able to inhibit neuronal activity for non-preferred stimulus parameter (Treue and Maunsell 1999; Vanduffel et al. 2000; Slotnick et al. 2003). In general, attention to a visual stimulus enhanced the activity of neurons encoding the parameter of this stimulus. Thus, the more important factor for the observed modulation of neuronal activity in area MT is the sensorimotor integration of the visual stimulus for feedback control.

Modulation of MT neurons depends on the nature of the tracking movement

To our surprise, we found no significant difference in the neuronal response of MT neurons during the open loop arm movements (replay condition II moving) compared to the situation where the monkey made no arm movement (replay condition II stationary). Only when the monkey got visual feedback about his cursor position during the manual tracking, activity in area MT changed consistently compared to the pure visual stimulation. Under the open loop condition, the animal got no feedback how accurate he tracked and which position on the screen corresponded to his actual hand position. He got a reward as long as he maintained fixation throughout the trial, independent of his arm movement. The different requirement during the active tracking was that an online control, i.e., an alignment between cursor (the position of which depended upon the hand position of the monkey) and the visual moving target, was absolutely necessary to finish a trial successful. If the animal left a virtual window around the target with the cursor, the trial would be aborted and the animal not rewarded. Thus, area MT is not involved in arm movements per se, but in tracking objects which are moved by the arm movement. The importance of MT for motion perception has been convincingly shown in single unit, microstimulation as well as lesion studies (Britten et al. 1996; Rudolph and Pasternak 1999; Bisley and Pasternak 2000; Ditterich et al. 2003). The common attribute of all these studies is that there was a visual stimulus present which triggered the behavior. This fact seems to be also essential for the arm movement task.

It is well known from a large number of studies that when arm and eyes are simultaneously involved in a tracking task, the performance of both systems considerably improves compared with when they move alone (Koken and Erkelens 1992; Vercher et al. 1994). A transcranial magnetic stimulation study from Maioli et al. (2007) demonstrated for the first time that tracking a moving object with the eyes inherently involves

excitability changes in the motor control system of the arm, in the absence of any overt limb movement or sign of EMG activation. This result is a strong argument for the existence of a common drive to both eye and hand tracking systems. It is in a good agreement with the observation of Van Donkelaar et al. (1994a) that gain adaptation imposed to the ocular pursuit influences also manual tracking responses, indicating that plastic changes must occur in a common neural substrate. Another investigation of the behavioral similarity between the manual-following response and the ocular-following response also proposes a hypothesis that these different visuomotor responses may share some common neural process through which visual motion signals directly drive motor responses (Gomi et al. 2006).

Area MT subserves the control of hand movements

This study gives us strong evidence that area MT plays a considerable role in the cortical network controlling hand movements. Extraretinal modulation of MT activity depends on the context of hand movement performance in combination with the processing of a certain, selected visual stimuli. Such modulations were also found in tasks related to eye movements (Recanzone and Wurtz 2000) and motion perception (Treue and Maunsell 1996; Seidemann and Newsome 1999). It has been commonly accepted that MT is a purely sensory area. This can be concluded from a large amount of existing data (Orban 1997; Eskandar and Assad 2002; Britten 2003). The earliest stage where motor related signals were found was MST (Newsome et al. 1988; Thier and Erickson 1992) which is believed to directly follow MT within the cortical hierarchy. Considering the results of this study, it is getting more difficult to hold up the notion of MT being strictly sensory. Due to the findings here, one has to generalize its functional significance to the hand and probably in general to the limb movement system. Thus, MT has to be positioned before a hypothetical branching point to different motor systems within the cortical visuomotor circuitry.

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