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RESEARCH ARTICLE

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Visual processing in the ketamine-anesthetized monkey

Optokinetic and blood oxygenation level-dependent responses

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Abstract We used optokinetic responses and functional magnetic resonance imaging (fMRI) to examine visual processing in monkeys whose conscious state was modulated by low doses (1–2 mg/kg) of the dissociative anesthetic ketamine. We found that, despite the animal's dissociated state and despite specific influences of ketamine on the oculomotor system, optokinetic nystagmus (OKN) could be reliably elicited with large, moving visual patterns. Responses were horizontally bidirectional for monocular stimulation, indicating that ketamine did not eliminate cortical processing of the motion stimulus. Also, results from fMRI directly demonstrated that the cortical blood oxygenation level-dependent (BOLD) response to visual patterns was preserved at the same ketamine doses used to elicit OKN. Finally, in the ketamine-anesthetized state, perceptually bistable motion stimuli produced patterns of spontaneously alternating OKN that normally would be tightly coupled to perceptual changes. These results, taken together, demonstrate that after ketamine administration cortical circuits continue to processes visual patterns in a dose-dependent manner despite the animal's behavioral dissociation. While perceptual experience is difficult to evaluate under these conditions, oculomotor patterns revealed that the brain not only registers but also acts upon its sensory input, employing it to drive a sensorimotor loop and even responding to a sensory conflict by engaging in spontaneous perception-related state changes. The ketamine-anesthetized monkey preparation thereby offers a safe and viable paradigm for the behavioral and electrophysiological investigation of issues related to conscious perception and anesthesia, as well as neural mechanisms of basic sensory processing.

Keywords Ketamine · Optokinetic nystagmus · Binocular rivalry · Visual perception · Monkey

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Introduction

Much of the brain's capacity to register and respond to sensory patterns is irrespective of an animal's conscious state. It is interesting that much if not most of our current knowledge of neural responses in visual cortex was initially revealed through electrophysiological recordings in animals under general anesthesia (Hubel and Wiesel 1968; Gross et al. 1969; Dubner and Zeki 1971). Recently, functional imaging results in anesthetized monkeys have reemphasized the degree to which the brain can be responsive to visual patterns during anesthesia (Logothetis et al. 1999; Sereno et al. 2000), revealing activation not only in primary visual cortex, but also in numerous cortical and subcortical structures whose activity is normally associated with complex stimulus representations, spatial orientation, attention, and even memory and motor planning. This "automatic" activation of a diversity of brain structures raises a number of questions regarding mechanisms of basic sensory processing, as well as those related specifically to perception.

Unfortunately, the anesthetized preparation lacks the means to directly examine the relationship between neural responses and more active elements of vision such as attention, recognition, and subjective perception. Largely for this reason, the last decades have witnessed the emergence of the alert, behaving monkey preparation as the prominent electrophysiological paradigm for assessing the neural mechanisms of vision. Since anesthetized and awake electrophysiological preparations are both technically challenging, yet require different expertise, they are often carried out by different individuals in different laboratories. Comparison of data arising from the two techniques has therefore been difficult, both with regard to basic mechanisms of vision and the specific effects of anesthesia. Few if any studies have sought to assess visual processing as an animal is brought systematically in and out of wakefulness by varying levels of an anesthetic agent.

Mechanisms of anesthesia are complex and remain poorly understood despite a long history of inquiry into

their action (Angel 1993; Franks and Lieb 1994; Urban and Friederich 1998; Antkowiak 2001). It is unclear, for example, whether anesthetics' primary impact is directly on cortical and subcortical neurons or whether they also act more indirectly by triggering natural sleep-related mechanisms (Lydic and Biebuyck 1994). A paradigm that would allow for a continuous transition between the awake and anesthetized state would not only afford a convenient preparation for testing aspects of visual processing, but would also provide an excellent means by which to test hypotheses related to mechanisms of anesthesia. For example, might a distinct physiological transition occur in the quality of sensory processing upon an animal's loss of consciousness? Similarly, might waking represent the only state of consciousness in which sensory and motor areas can be coordinated to form a functional sensorimotor circuit? Finally, beyond simple sensory responses, is it possible that more active elements of vision survive anesthesia, including mechanisms related to perceptual organization? Answers to such questions may provide important insights regarding the relationship between the brain's gross state-changes and specific mechanisms related to the registration and perception of sensory patterns.

Ketamine, a derivative of the hallucinogenic drug phencyclidine (PCP), is an example of an anesthetic agent thought to act upon a ligand-gated ion channel. Specifically, it is suspected to exert its influence through noncompetitive blockade of the *N*-methyl-D-aspartate (NMDA) glutamate receptors (Anis et al. 1983; Yamamura et al. 1990; Orser et al. 1997). However, like many anesthetics, its receptor action is not completely specific, as inhibition of neuronal nicotinic acetylcholine receptors might also contribute to its action (Anis et al. 1983; Krasowski and Harrison 1999). Ketamine is a unique anesthetic with respect to its global action on the brain. In contrast to volatile anesthetics, barbiturates, and propofol, ketamine does not strongly depress sensory-evoked potentials elicited by somatosensory, auditory, and visual stimuli (Schubert et al. 1990; Plourde et al. 1997). Nor does it appear to suppress the excitability of cortical neurons, an action shared by most general anesthetics (Kalkman et al. 1994).

Ketamine was first introduced as a "dissociative anesthetic" for man in 1965 (Domino et al. 1965). Tested originally on prison inmates, it was reported to produce profound analgesia accompanied by both parasympathetic signs (hypersalivation) and sympathomimetic signs (elevated heart rate and blood pressure), without significant respiratory depression. In the initial report, ketamine injection is described as producing a cataleptic state resembling coma: "After 1.0 mg per kilogram or more of CI-581 [ketamine], the subject would open his eyes and at the same time lose contact with the environment." This trance-like uncoupling from sensory events in the world is the hallmark of ketamine anesthesia, and makes it suitable for short, spontaneous-ventilation, office-surgery procedures, where it is often used together with propofol or midazolam (Friedberg 1999; Haeseler et al. 2000; Reyle-Hahn et al. 2000). Its analgesia is so profound that it has even been used alone for maintenance of anesthesia during open-heart surgery (Kumar et al. 1978). Its safety, intramuscular delivery, and fast induction have made it the drug of choice for animal restraint in both veterinary medicine and laboratory research (Bree et al. 1967). Yet despite its many advantages over other anesthetics, it remains controversial, primarily because if its common psychotropic effects that affect up to 30% of patients (White et al. 1982; Engelhardt 1997; Oye 1998), but also because it is thought to exacerbate symptoms of schizophrenia (Lahti et al. 1995). Recently, ketamine has also been increasingly identified as a drug prone to abuse, both in medical and social settings (Dotson et al. 1995).

In the current study, we examined the effect of ketamine on cortical function by exploiting evoked eye movements. Oculomotor patterns are often tightly linked to the spatiotemporal structure of visual input, usually in association with stabilizing objects on the retina when either an object or observer is in motion. Many stimulus-evoked eye movements have extremely short latencies and appear to be reflexive in nature, but are nonetheless considered to engage cortical mechanisms in primates (Yo and Demer 1992; Harris et al. 1993; Miles 1997, 1998). In fact, many evoked oculomotor responses including optokinetic nystagmus (OKN) are more tightly coupled to what is *perceived* at each point in time than to the precise pattern of motion on the retina (Steinbach 1976; Fox et al. 1978; Kowler 1990; Manny and Fern 1990; Ringach et al. 1996), providing further evidence for cortical processing. Optokinetic responses during binocular motion rivalry serve as an excellent example of this point. When oppositely moving patterns are presented separately to the two eyes, perceptual dominance alternates sequentially between the patterns in the left and right eyes. Coupled with this, the polarity of the OKN reflex changes reliably with each perceptual transition. Optokinetic movements have therefore been used to objectively monitor the pattern of perceptual changes in both humans and monkeys (Fox et al. 1975; Logothetis and Schall 1990; Leopold et al. 1995).

Ketamine, in addition to its general behavioral dissociation, also has specific effects on the oculomotor system. Shortly following a medium-dose injection, many species including humans develop nystagmic movements. These movements have been described in some cases as being primarily horizontal (Radant et al. 1998; Porro et al. 1999), in others as primarily vertical (Bon and Lucchetti 1990), and in yet others as rotatory (Domino et al. 1965). Ketamine has also been reported to have specific effects on the gaze-holding system in cats and has been postulated to specifically induce failure of the oculomotor neural integrator without altering saccade dynamics (Godaux et al. 1990).

We used optokinetic movements to investigate several aspects of visual function in monkeys experiencing different levels of ketamine dissociation. The ultimate goal of our research is to measure the impact of ketamine and

other anesthetics upon neural responses to sensory stimulation in order to gain a better understanding of mechanisms related to visual perception. In the present paper, we introduce the "awake/anesthetized" setup that allows us to vary the animal's state of consciousness by varying blood anesthetic concentrations along a continuum. We first demonstrate that OKN responses can be reliably elicited in ketamine-anesthetized, dissociated monkeys, and that these responses necessarily derive from cortical motion processing. Using functional magnetic resonance imaging (fMRI), we then show that, for the range of ketamine doses that allow for OKN, cortical BOLD responses to visual stimuli remain largely intact. Finally, we demonstrate that, when dissociated monkeys are presented with bistable motion patterns, OKN tends to alternate its polarity in a manner consistent with brain state-changes that would normally accompany perceptual reversals. We conclude that the ketamine-anesthetized monkey preparation, in which the drug level and conscious state can be continuously manipulated, is well suited for both behavioral and electrophysiological investigations into mechanisms of visual processing.

Methods

Two adult, healthy monkeys, G97 (monkey A) and L97 (monkey B), were used in the main study. monkey A was also tested with fMRI, as was an additional monkey F97 (monkey C). All experiments were performed in compliance with the guidelines of the local authorities (Regierungspraesidium), as well as the European Community (EUVD 86/609/EEC), for the care and use of laboratory animals.

Ketamine was injected primarily intramuscularly (IM) in monkey A and intravenously (IV) in monkey B. In solution, ketamine usually consists of a mixture of two optical enantiomers, *S*-(+)-ketamine and *R*-(–)-ketamine. Recent results have demonstrated differential effects of the two enantiomers at molecular, physiological, and behavioral levels (Zeilhofer et al. 1992; Vollenweider et al. 1997a). In the current study, monkey A was always given a racemic ketamine mixture, while monkey B was in some cases given purified *S*-(+)-ketamine. We observed no qualitative differences in oculomotor behavior arising from two ketamine preparations, although we did not specifically compare either the dose response or time course of the isomeric versus racemic mixtures. In the current paper, specific dosages always refer to the racemic mixture.

Surgery

Each animal was implanted with a custom-made, single-piece, plastic (Tecapeek, GF 30; Ensinger, Germany) head holder, consisting of a cylindrical post and five legs shaped to fit the individual monkey's skull. Surgery was performed under sterile conditions as described previously (Logothetis et al. 1999). In addition, monkey B was implanted with a scleral search coil (Judge et al. 1980). Eye coil implantation began with a circular incision 2 mm exterior to the limbal margin. A double loop of eye-coil wire was inserted around the iris, underneath the scleral conjunctive, and attached to the sclera with both nonabsorbable sutures as well as surgical adhesive. A loop of wire was embedded in a dissected pouch lateral between the pleural and parietal conjuctival layers lateral to the eyeball, and the coil lead was passed out through a hole in the lateral side of the orbit to attach to the head post. The scleral conjunctiva was then sutured. After surgery, the animals spent 10 days in a recovery chair, which allowed them to stand and move freely, but did not permit them to touch their fresh implants with their hands. They received an analgesic (Finadyne, 1.0 mg/kg) for the first 2 days, as well as an antibiotic (Veracin Composite, 0.25 ml/kg) for 8 days after the surgery.

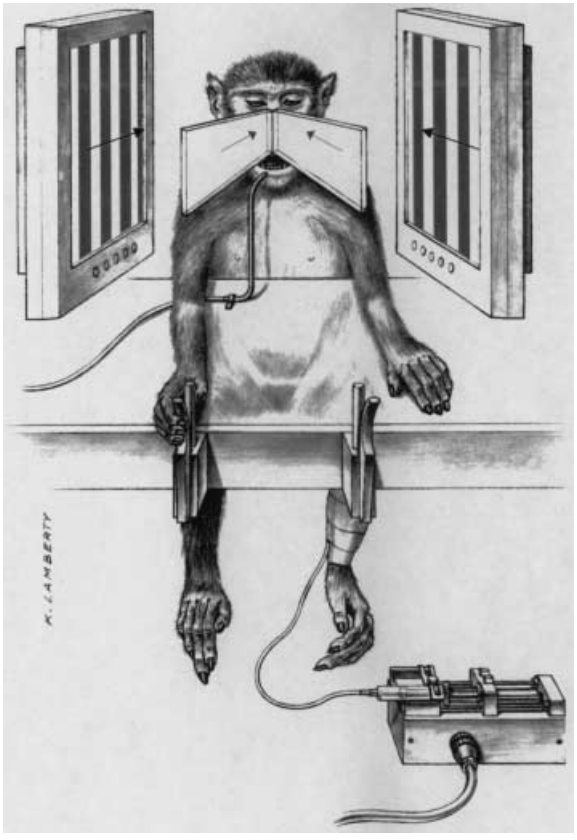

Fig. 1 Awake/anesthetized setup. Monkeys were trained to accept an intravenous catheter and pulled one of two levers situated in front of them to report in the discrimination task. Directly in front of their nose was a mirror stereoscope, which afforded a large-field view of stimuli presented on two monitors situated to either side. Motion stimuli were in some cases congruent, in others monocular, and in others rivalrous (depicted here). During the task, anesthetic agents were silently infused into the animal's bloodstream, modulating his state of consciousness. In the case of ketamine, the eyes would generally remain open, allowing one to present visual stimuli during a state of dissociation

Experimental protocol

Each day, the monkey was brought to the setup fully awake. Fifteen minutes prior to the beginning of the experiment, the animal was given an IM injection of glycopyrrolate (Robinul, 0.01 mg/kg) in order to prevent hypersalivation during the experiment. A session began with calibration of the eye-tracking system. Each monkey was trained to fixate small spots of light flashed in a number of eccentric locations, allowing us to adjust the offset and calculate the gain of the eye signal. Before the administration of any drug, eye movements were recorded while the animal made normal scanning movements within the lit room. In addition, the animal learned to make restricted scanning movements within the extent of the screen for a small juice reward. During this "gazing" task, a variety of more or less interesting stimuli such as faces, photographs, and geometrical figures were shown. We also presented the optokinetic patterns during this time, allowing us to collect some periods of OKN during the awake condition. The color of a briefly flashed dot at the end of the observation period indi-

cated which of two levers to press in order to obtain an apple juice reward.

In monkey A, ketamine was delivered IM in a bolus injection while he sat in his chair. Unless otherwise stated, bolus doses were always 1–2 mg/kg. In monkey B, it was delivered through an IV line (Fig. 1). This monkey had been previously conditioned to sit in a special chair that allowed only minimal motion of the legs and prevented his reaching the catheter. Each day he offered his leg and allowed the insertion of a 20-gauge catheter into his saphenous vein. The leg was secured in a partially extended position with a wooden splint underneath the foot, as well as gauze and tape to support the leg. Drug delivery was achieved by means of an infusion pump (Harvard Apparatus PHD 2000) containing a ketamine solution (1 mg/ml concentration). The pump was controlled remotely from the experimenter's control desk as the monkey sat alone in a sound-isolated room. This setup allowed for the covert delivery of the drug with an arbitrary time course. In addition to bolus injections, we infused at constant and decreasing rates to achieve a steady state level of anesthetic potency, as assayed by the frequency of evoked eye movements. This was typically achieved by starting with a rate of 0.03–0.08 mg/kg per minute, and reducing the rate to 0.01–0.015 mg/kg per minute as soon as periods of OKN appeared after several minutes. In contrast to the IM case, we generally tried to maintain a "steady state" of ketamine efficacy for the IV experiments. As we were not able to monitor blood concentration, nor did we have electrophysiological measurements, this entailed our using the number of evoked saccades during optokinetic stimulation as an empirical measurement with which to monitor the level of the drug effect.

Stimuli

Visual stimulation was presented through a mirror stereoscope (see Fig. 1). This allowed us to show large-field images separately to the two eyes under monocular, binocular (dioptic), or rivalrous (dichoptic) conditions. Flat-screen LCD monitors were mounted on either side of his head, inside the driving magnetic coils. Each day, fine adjustments were made in the positions and angles of the mirrors and monitors, with a pair of parallel lasers in the normal position of the monkey's eyes. The eye-screen distance was 30.0 cm, and the monitor size was 30.0×24.0 cm, resulting in a visual stimulus that was approx. 55×45° in visual extent. The animal's head was restrained during the experiment. In monkey A, eye position was monitored by an image-based tracking system (Eyelink; Sensomotoric Instruments, Teltow, Germany). A camera was mounted in front of either the left or right eye. In monkey B, position was measured with a scleral search-coil apparatus (C-N-C Engineering). In both cases, the analog eye traces were sampled at 200 Hz and saved onto a computer. Optokinetic stimuli generally consisted of vertically oriented, horizontally moving, full-field square-wave gratings (contrast 0.75, spatial frequency 0.2 cycles/°, speed 30°/s, mean luminance 39.4 cd/m^2). Other patterns such as large faces, counterphase flickering gratings, and briefly flashed spots were also shown as "interesting" stimuli.

Functional imaging

fMRI was conducted in a vertical 4.7-T scanner with a 40-cm bore (Biospec 47/40v; Bruker Medical, Ettlingen, Germany). The animals were under general anesthesia when placed into the scanner. Ketamine was administered in addition to the basic anesthetic regimen to determine its effect upon the evoked blood oxygenation level-dependent (BOLD) responses. An extensive description of both the scanning and basic anesthesia protocol are available in the paper by Logothetis et al. (1999). Briefly, balanced anesthesia was maintained with isoflurane (0.3% end-tidal concentration) and fentanyl (3 μg/kg per hour). Muscle relaxation was achieved with mivacurium (5 mg/kg per hour). Contact lenses were placed in the eyes of the animals for refractive correction. Visual stimuli were shown separately to each eye through a fiber-optic system (Avotec, Silent Vision, Fla.). Each eye's fiber optic stimulator was driven by a dedicated graphics computer and was precisely aligned with the optical axis and centered on the foveola by means of a modified fundoscope. Stimuli consisted of high-contrast, rotating, polar-transformed checkerboard patterns (Fig. 8b). The effective resolution was 800 horizontal × 225 vertical pixels. The rotation speed was 60–180 angular degrees per second, and patterns reversed direction once per second. The stimulus alternated between on periods (48 s) and off periods (48 s). Functional scans were collected using a segmented echo planar imaging (EPI) sequence. Thirty coronal slices were selected, with a within-slice resolution of 1.0 mm and 2.5 mm between slices. Each functional volume was collected in 8 segments and required 12.0 s of data collection. A total of 128 time points (25.6 min) were collected per condition.

Data analysis

All data analysis was performed using custom software written with MATLAB (MathWorks). Offline processing of the eye movement data began by converting the horizontal and vertical traces into cubic spline representations and then resampling at 1 kHz. Individual saccades were then extracted using an iterative algorithm that relied on first identifying potential saccades based on eye velocity and then accepting or rejecting each candidate by comparing several parameters to the well-known parameters of saccades (Carpenter 1988). For each saccade, a number of parameters and statistics were calculated, including the direction, amplitude, peak velocity, and duration.

Analysis of the functional imaging data centered upon identifying voxels that were reliably activated by a visual pattern and mapping their time course over several minutes before and after injection of ketamine. Responsive voxels were first identified by computing the correlation in their time course with the on and off periods of the stimulus. Time courses were first linearly detrended, and then high-pass filtered (6th-order Butterworth filter, 0.005-Hz cutoff). The correlation map was smoothed with a Gaussian filter with a 1-pixel standard deviation. A correlation coefficient threshold of 0.3 was then applied to this map to identify voxels that were activated by the stimulus in the first 8 min, before ketamine was injected. The mean time course for these selected voxels was then evaluated over the entire scan duration to determine the influence of ketamine on the responses.

Results

After IM injection of ketamine, spontaneous nystagmic movements began after 2–3 min. After 8–12 min, the monkey was unresponsive to environmental stimuli that would normally cause a strong reaction, such as a light poke in the abdomen or a visual threat gesture. With IV infusion, this process was accelerated, with the first symptoms generally appearing within the 1st min, and complete trance-like state occurring after 5 min. In this dissociated condition, the monkey stared straight ahead with his eyes open, blinking at more or less normal intervals. He would occasionally smack his lips or make uncoordinated gestures with his limbs. While he was in this state, it was easy to present a variety of visual stimuli and measure eye position with a high degree of precision.

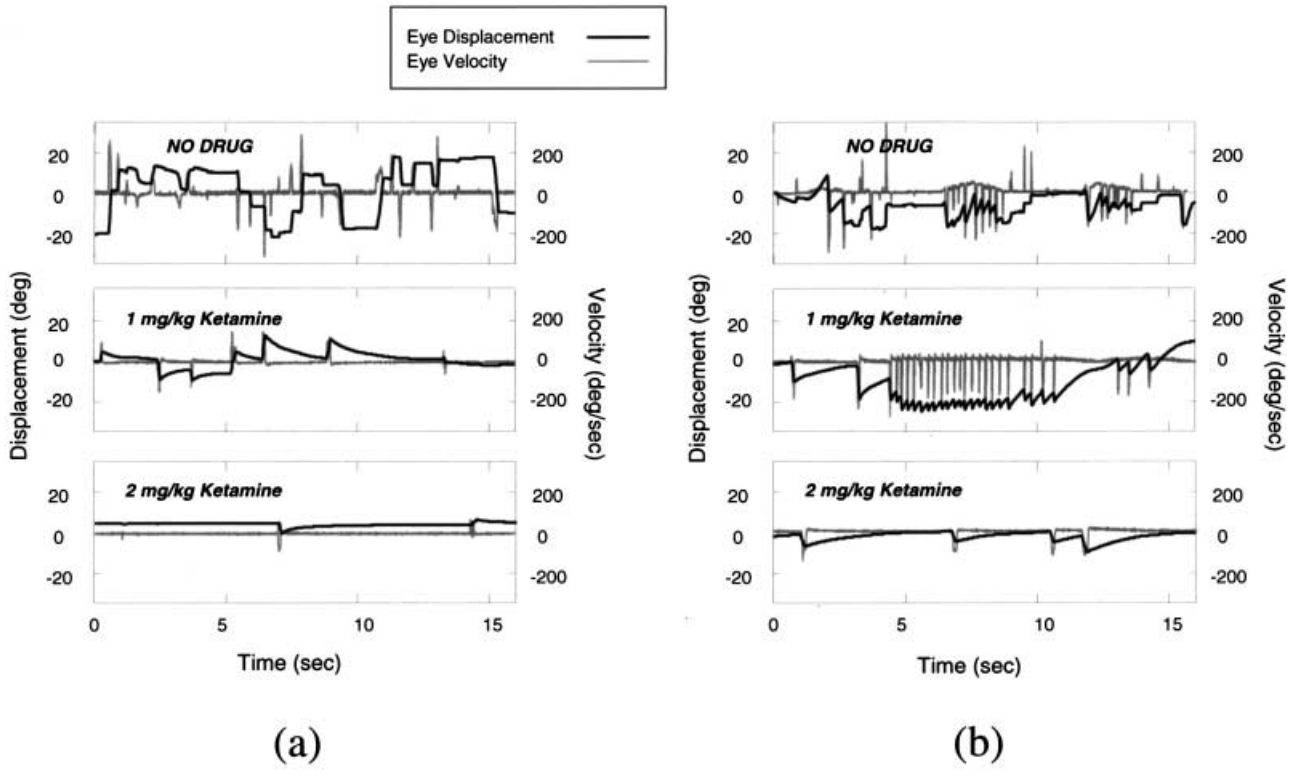

Fig. 2a, b Effect of intramuscular ketamine bolus on spontaneous and stimulus-evoked eye movements. *Black traces* represent horizontal eye position and *gray traces* horizontal eye velocity. **a** Spontaneous movements. Before any drug is administered, the monkey tended to make normal scanning movements, consisting of frequent saccades followed by stable periods of fixation. A few minutes after a bolus of 1 mg/kg ketamine, both the frequency and amplitude of saccades decreased. In addition, periods of stable fixation were replaced by exponential decays of the position to a *null point* (shown here for horizontal only, but also present in the vertical traces). When the bolus was 2 mg/kg, the eyes remained largely motionless (although the eyelids remained open), periodically showing small, jerky movements that immediately decayed back to the null point. **b** Optokinetic movements during continuous horizontal stimulation. When a large moving stimulus was present, optokinetic response were elicited both before drug administration and in a dose-dependent manner following ketamine

Spontaneous eye movements

In the absence of any stimulus, "nystagmic" movements could be observed in all directions following ketamine injection. Figure 2a illustrates a typical pattern of such movements (horizontal components only) for a monkey sitting quietly in a dimly lit room approx. 15 min after receiving no ketamine, 1.0 mg/kg, or 2.0 mg/kg IM, respectively. Following ketamine administration, there was a dose-dependent decrease in saccade frequency. Most striking, however, was the apparent inability of the animal to hold an eccentric position of gaze. Each saccade was followed by a slow decay back to a *null point*, where the eyes temporarily remained until the next saccade. This demonstrates that the failure in gaze-holding after ketamine administration as previously reported in cats (Godaux et al. 1990) is also present in monkeys. However, in contrast to the study in cats, we found that the dynamic structure of individual saccades was also influenced by ketamine. Figure 3a and c compares eye traces shortly before and for several hundred milliseconds after spontaneous saccades, demonstrating the decay in eye position was present only after ketamine administration. In Fig. 3b and d, plots of peak velocity versus amplitude, in which saccades of different amplitudes generally fall on a straight line referred to as the *main sequence* (Carpenter 1988), demonstrated a shift of higher and lower saccade velocities toward intermediate values (Fig. 3b, d).

Optokinetic responses

A main result of the current study was that optokinetic eye movements could be reliably elicited during ketamine dissociation. In some ways, the OKN resembled that found in the awake condition (Fig. 2b): nystagmic movements occurred in bursts of periodic alternating fast and slow phases, where the fast phase was opposite to the direction of stimulus movement. Periods of such bursting were often flanked by periods in which OKN was entirely absent. However, there were also a number of differences from normal optokinetic nystagmus. First, the slow phases were not straight lines, indicating a constant velocity (i.e., gain), but were instead curved, reflecting a deceleration in eye motion. A second difference related to the patterning of fast and slow phases with respect to the center of vision. In normal OKN, the slow phase, working to stabilize the image on the retina, brings the gaze direction away from the center. Each

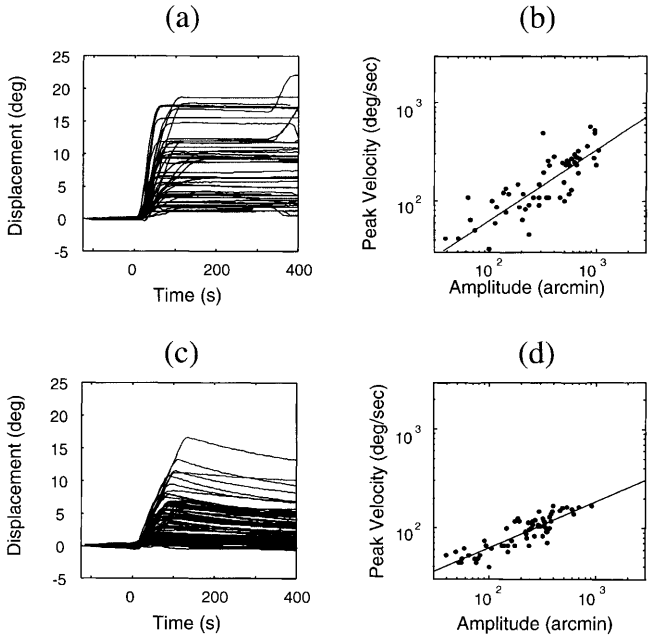

Fig. 3a–d Spontaneous eye movements collected before and after the administration of 1 mg/kg ketamine. Ketamine had an immediate effect upon gaze holding. While post-saccadic periods consisted of steady fixation in the control condition (**a**), the consistently decayed with time toward the null point following ketamine (**c**). Ketamine also influenced the saccade dynamics themselves. Before ketamine (**b**), saccade peak-velocity plotted versus amplitude had a linear relationship, with a slope and offset of 0.728 s^{-1} and 2.22°/s, respectively. Following ketamine (**d**), the peak velocity decreases for a given saccade amplitude, resulting in a slope and offset of 0.475 s^{-1} and 7.3°/s, respectively

slow phase is followed by a rapid fast phase bringing it more or less back to the center. However, following ketamine administration, OKN sequences tended to begin with fast phases that directed the eyes *away* from the center of gaze. The subsequent, curved slow phases then represented a decay in position, bringing the eye back toward the center of the screen. Finally, the spatial distribution of the optokinetic movements differed from normal OKN, which can occurr at any position on the moving stimulus. After ketamine, trains of OKN responses were consistently restricted to the "upstream" half of the stimulus (on the side of the screen representing the source of the motion). This tendency can be seen for the horizontal direction in Fig. 2b, and for two dimensions in Fig. 4c, f.

Figure 5 shows several representative time courses for the IM injections. Note that the number of saccades per minute declines sharply in the first 5–8 min, reaching a minimum value after approx. 10 min. This time course is very similar to that in a recent study of Cebus monkeys, where bradykinesia, locomotor activity, and reactivity to environmental stimuli was measured following 1.0 mg/kg IM ketamine administration (Shiigi and Casey 1999).

Monocular asymmetry

In contrast to afoveate animals, primate horizontal OKN is largely directionally symmetrical for monocular stimuli. However, following lesions to the striate cortex, monocular OKN in monkeys becomes very asymmetrical. Specifically, temporonasal (TN) stimuli continue to pro-

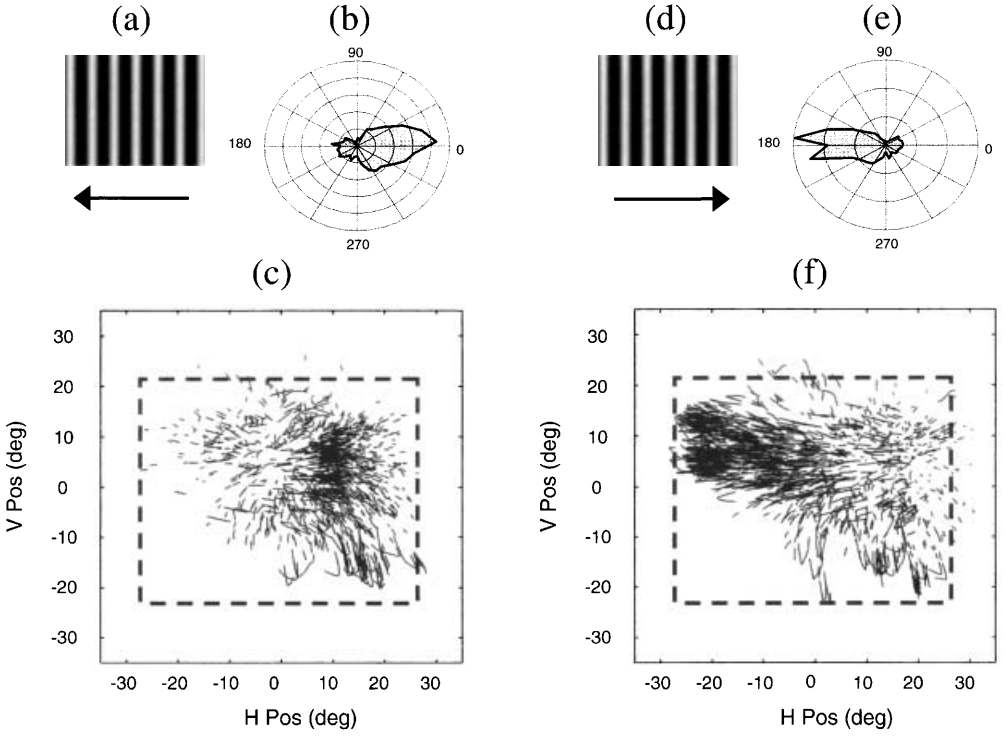

Fig. 4a–f Stimulus-driven eye movements during ketamine dissociation. Leftward- (**a**) and rightward-moving (**d**) grating patterns elicited optokinetic responses that were highly dependent on the stimulus. Saccades were frequent and were strongly (although not exclusively) in the direction opposite the moving stimulus, as expected from the optokinetic fast phase. The histograms in **b** and **e** show the distribution of saccade directions during leftward and rightward stimulation, respectively. The spatial trajectories of the "slow phases" are shown in **c** and **f**. Slow phases would generally begin at the "upstream" edge of the screen. Subsequent slow phases would generally consist of an exponential decay of position back toward the screen center. In **c**, this corresponds to slow phases on the right side of the screen moving from right to left, while in **f** slow phases started on the left and moved to the right (*V Pos* vertical position, *H Pos* horizontal position)

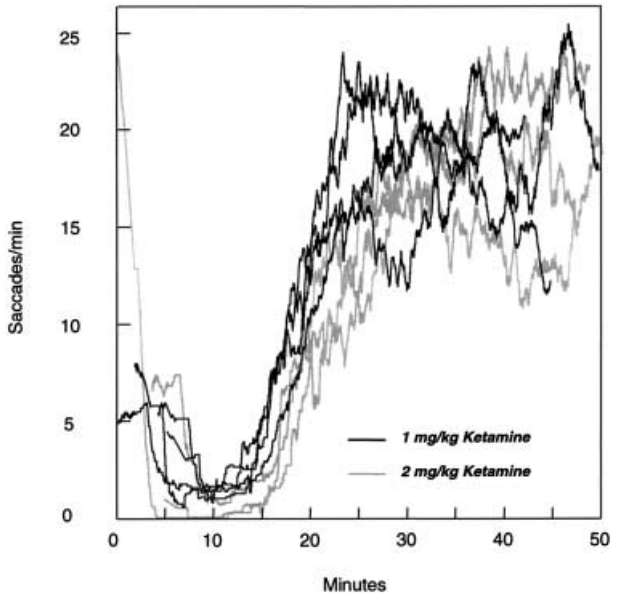

Fig. 5 Time course of ketamine action during optokinetic stimulus conditions. Each trace represents the total number of saccades per minute shortly following IM injection of ketamine at time zero. In most of the traces the initial rates are low, reflecting the fact that recording started shortly after the drug had begun to take effect

duce OKN, while nasotemporal (NT) stimuli are largely ineffective (Zee et al. 1987). This result has been attributed to the balancing influence of the cortex upon an asymmetric subcortical OKN system (see Discussion). We therefore assessed ketamine's effect on the degree of OKN directional asymmetry with monocular stimuli. A comparison between OKN responses during several dozen 1-min monocular TN and NT stimulus presentations is shown in Fig. 6 for two monkeys. Note that while in both cases there is indeed a slight bias toward TN stimulation, there are still many NT-elicited saccades, and the distributions are almost entirely overlapping. This lack of directional asymmetry provides indirect evidence that the stimuli are processed by the visual cortex despite the effects of the drug, and that this processed information is passed back to brainstem structures that generate OKN, completing the sensorimotor circuit.

Null point

During relatively quiescent periods of eye movement, between vigorous trains of OKN for example, postsaccadic decay brought the gaze direction back to a particular point in visual space. We noticed that this point was not fixed, but tended to change position according to the stimulus that was being shown. In particular, although trains of OKN movements tended to occur at the upstream edge of the display, the null point was pushed downstream by the motion stimulus, toward the other side of the monitor. We found this puzzling and decided to investigate it further by increasing the intravenous infusion rate to eliminate saccades entirely, and then randomly changing the direction of stimulus motion from minute to minute. The results of one representative experiment are shown in Fig. 7. For this experiment, the IV infusion was switched from 0.04 mg/kg per minute to 0.1 mg/kg per minute at t=0, and then stopped entirely at t=17.5 min. During the first 5 min, the eye trace was dominated by OKN-like saccades determined by the direction of the stimulus. This reflects the relatively low level of drug in the animal prior to raising the infusion rate at t=0. As the drug's influence increased, the number of saccades declined to nearly zero, but the null point was pushed slowly and reliably in the direction of the stimulus. This movement resembled in some ways a smooth pursuit of remarkably low speed (0.2°/s, gain

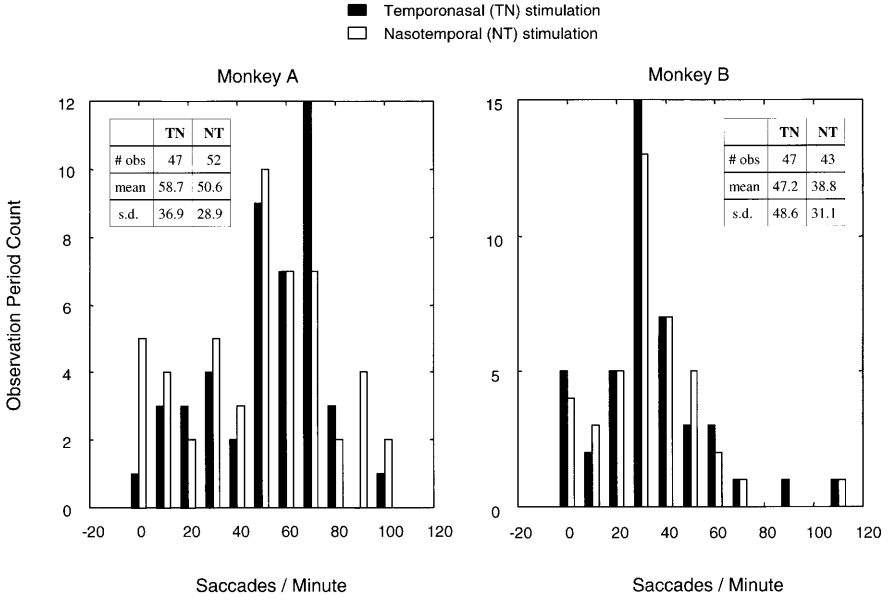

Fig. 6 Optokinetic responses during monocular presentation for two monkeys. Each histogram shows the distribution of OKN rates (saccades per minute) over many 1-min observation periods for temporonasal (*TN*, *black bars*) and nasotemporal (*NT*, *white bars*) motion stimuli. The number of observation periods for each condition, as well as the corresponding mean and standard deviation rates, is shown in the *tables*. Note that the calculation of rate here was aimed at identifying trains of optokinetic fast phases, and therefore only include those saccades that were detected between 150 ms and 600 ms following the previous fast phase

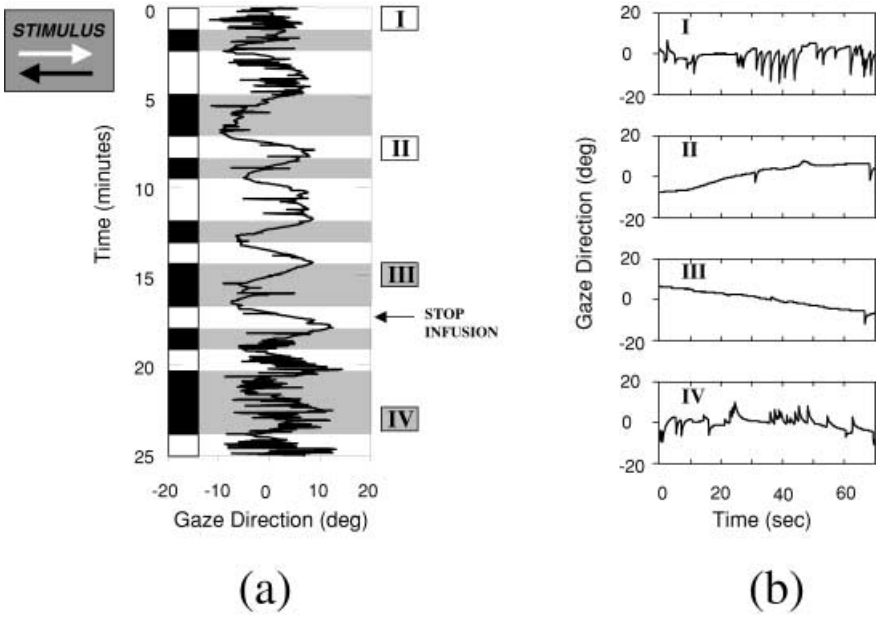

Fig. 7a, b Stimulus driven displacement of the "null point" following relatively high doses of ketamine. **a** Impact of direction-reversing stimulus over 25-min period. The moving grating stimulus changed direction after intervals ranging between 1 and 5 min, depicted by *gray-shaded* and *white areas*. In this example, the intravenous infusion rate of ketamine was adjusted to bring the saccade frequency down to near zero, and then back up again. **b** Four examples of stimulus-induced slow changes in eye position with (*I, IV*) and without (*II, III*) superimposed optokinetic saccades

less than 0.007). With intravenous infusion, such a state could be reliably obtained for periods exceeding 1 h; however we did not test whether longer periods were also possible.

Functional imaging

We wanted to directly measure the impact of a motion stimulus on the brain during ketamine dissociation to establish that information was indeed reaching the cortical areas. We therefore used fMRI to measure BOLD responses to moving patterns following the IV administration of different levels of racemic ketamine. During the scans, the monkeys were under balanced general anesthesia and muscle relaxation, optimized to preserve cortical responses to sensory stimulation (Logothetis et al. 1999). Slices were angled 20° from coronal and covered the majority of primary visual cortex (Fig. 8a). Rotating, high-contrast polar grating patterns (Fig. 8b) were presented periodically, with on and off periods of 48 s, for 25.6 min (one hundred and twenty-eight 12-s scans). Figure 8c–e shows the effects for one session of IV ketamine bolus injection on BOLD responses in the primary visual cortex (1 mg/kg, 5 mg/kg, and 10 mg/kg, respectively). The leftmost image in each panel shows the stimulus-activated voxels before ketamine injection, calculated between t=0.0 and t=8.0 min. The rightmost image then shows the responsiveness shortly following ketamine injection (t=12.8 to 20.8 min). The mean time course for all voxels whose correlation coefficient in the preketamine condition was greater than or equal to 0.3 is shown for the entire 25.6-min duration below. The red arrows represent the moment that the ketamine bolus entered the animal's vein. In this experiment, waiting periods of 30 min intervened between scans in order to ensure that ketamine levels had fallen sufficiently. Note that, while 10 mg/kg ketamine obliterated stimulus-evoked BOLD responses in V1, the doses used in the behavioral portion of the study did not. The 5 mg/kg dose had a slight and short-lived decrease in the amplitude of the response, while the 1 mg/kg dose had no suppressive effect (in some cases even showing enhancement; see Fig. 8c). These results strongly suggest that, at low doses of ketamine, visual information continues to be transmitted and processed by the thalamocortical system.

Binocular rivalry

Given the stimulus-evoked cortical activity for the ketamine concentrations used, we were curious whether we could use OKN to infer whether some active mechanisms of perceptual organization were also spared. We thus used the mirror stereoscope to present opposite-direction (rivalrous) horizontal motion stimuli to the two eyes and monitored the optokinetic responses over several minutes. Under such conditions, it might be possible that optokinetic responses cease entirely, reflecting summation between equal and opposite motion vectors in the two eyes. On the other hand, alternating OKN polarity might reflect state changes within the visual system that would normally underlie our perceptual experience, as in normal rivalry. We found that, during the rivalry condition, the total optokinetic activity was somewhat reduced compared with congruent stimulation, but there remained trains of robust OKN. Interestingly, these trains alternated between rightward and leftward polarity in a manner that was exclusive to binocular rivalry, and was not observed with either rightward-only or leftward-only stimulation. Figure 9 illustrates this finding by comparing a period of nonrivalry (congruent directions of motion in the two eyes) with one of binocular rivalry (rightward motion in right eye, leftward in left eye). Note that

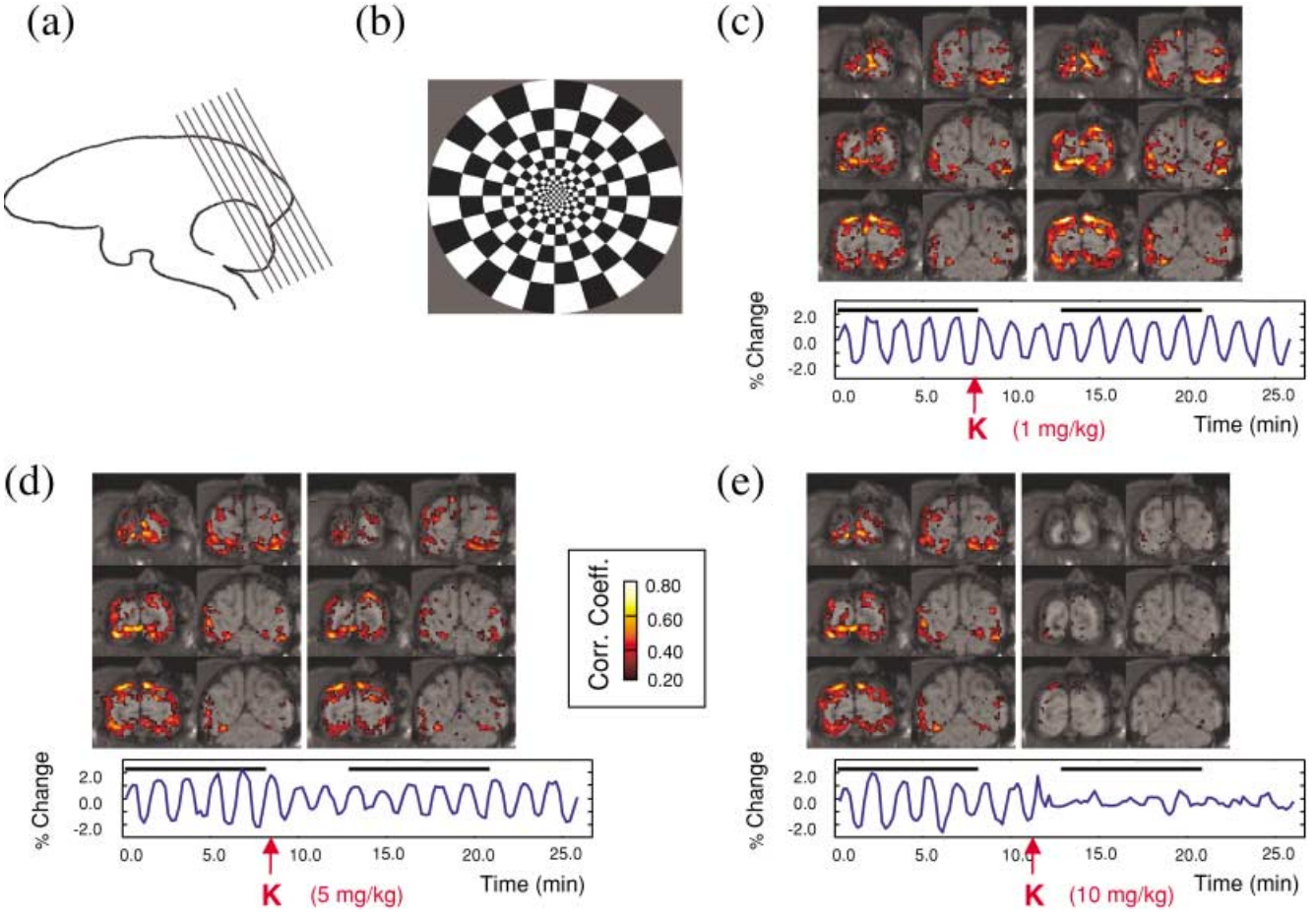

Fig. 8a–e Functional imaging of cortical responsiveness following different doses of ketamine (*K*). **a** Six slices in the posterior brain including primary visual cortex were analyzed. **b** Polar checkerboard rotating stimulus. **c–e** Dose-dependent influence of ketamine on transmission of information to the visual cortex measured by functional magnetic resonance imaging. Each pair of images represents blood level oxygenation-dependent (BOLD) activation of visual cortex by the rotating checkerboard before and after ketamine injection (see Methods). The *traces below* represent the mean time course of all pixels displaying a correlation coefficient greater than 0.3 with the stimulus in the first 8 min (before drug administration). Several minutes into the scan, ketamine (1.0 mg/kg, 5.0 mg/kg, or 10.0 mg/kg) was injected intravenously, reaching the monkey's vein at the point designated by the *red arrows*. Note that while ketamine obliterates the periodic response for the 10 mg/kg, as seen in both the images and the time course, it has only a minor impact at the 5 mg/kg dose, and minimal effect on the signal at 1 mg/kg

during binocular rivalry the state changes were reflected not only in the polarity of OKN, but also in the spatial (upstream) position of the eyes on the screen.

Discussion

Our main interest in developing the awake/anesthetized setup was to systematically examine the influence of ketamine and other neuroactive substances on neural mechanisms related to perceptual organization. However, it became increasingly clear that the present methods offer a convenient and safe means by which to study a wide range of issues, from basic visual sensory processing to specific neural mechanisms of anesthesia.

In preliminary experiments, we explored the feasibility of measuring optokinetic movements with two other anesthetics, propofol and isoflurane. While each agent allowed for continuous and efficient manipulation of the conscious state with maintained spontaneous respiration, ketamine proved superior, primarily because the eyelids tended to remain open. With the low dose of the other anesthetics, the eyes spontaneously closed, but the anesthesia was light enough that specula and other devices to keep the eyes open were not tolerated. On occasion, eye closure would occur even with ketamine, most often when experiments were conducted in the evening and the monkey was drowsy. Ironically, we found that the most effective way to combat this problem was to actually increase the ketamine infusion rate for a period. Then, after having received a relatively high drug dosage, the animal would usually spontaneously open his eyes, and in many cases leave them open for the remainder of the experiment. Even the highest ketamine doses we used were lower than the standard doses used for handling monkeys in the laboratory (5–15 mg/kg).

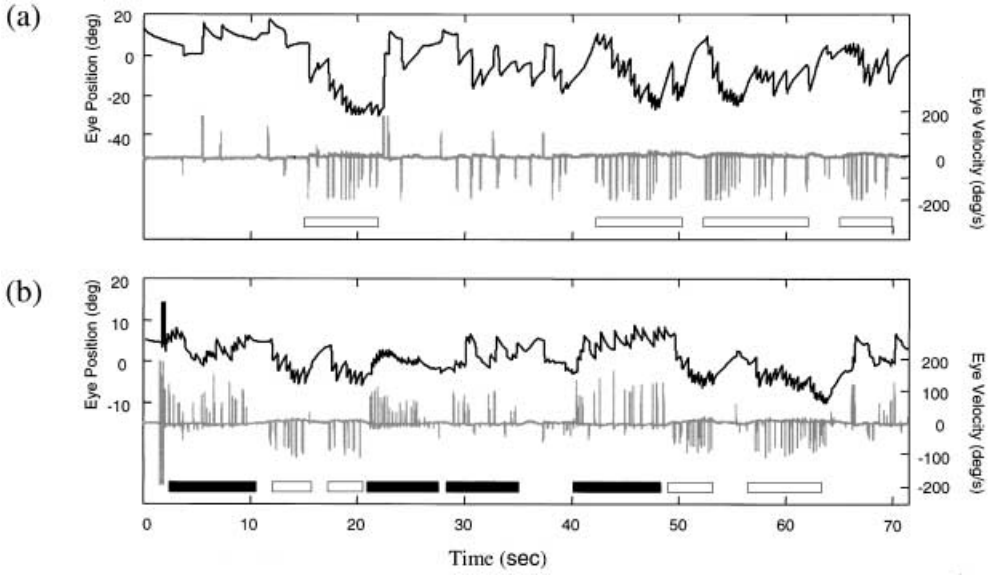

Fig. 9a, b Optokinetic responses during **a** congruous and **b** rivalrous stimulation during ketamine dissociation. **a** Position and velocity of optokinetic eye movements in the dissociated state during one observation period of congruent stimulation. In the resulting optokinetic nystagmus (*OKN*), the majority of "slow phase" movements were in the grating's direction of motion. The corresponding saccades (most easy identified by the *downward-pointing peaks in velocity trace*) were variable in their size and interval, but in the direction corresponding to normal OKN. **b** Example of OKN pattern during binocular motion rivalry stimulation. The *top row* shows the position of the eye, including several alternating epochs of fast OKN movements. The *black bars* show periods in which the slow phase of OKN was clearly in the negative direction and the *white bars*, in the positive direction. Such alternations were never observed during congruent stimulation

Eye movements under ketamine

Prior to the experiments, we were uncertain whether optokinetic responses could be elicited at all in an unconscious animal. It is known that, in addition to ketamine's general effects on the brain and consciousness, it also has specific effects on the oculomotor system. In agreement with previous studies, we found that, following ketamine injection, a spontaneous nystagmus developed (Domino et al. 1965; Bon and Lucchetti 1990; Radant et al. 1998; Porro et al. 1999). However, we did not think that the ketamine was actually inducing uncontrolled eye movements as previously speculated (Bon and Lucchetti 1990), but rather that its specific effect on the gaze-holding mechanism transformed more or less normally programmed voluntary saccades into a series of spontaneous nystagmic movements. We also found that the directional bias in nystagmus was primarily a function of the specific testing conditions, such as the relative positions of the monkey and the experimenter. This is consistent with previous results in cats, in which nystagmic movements following ketamine were significantly less frequent in darkness, and enhanced by waving attractive materials in front of the animal (Godaux et al. 1990).

The deficits we observed with ketamine, much like those previously observed in cats, closely resembled those following lesions or temporary inactivation of brainstem nuclei thought to serve as the oculomotor integrator (Cannon and Robinson 1987; Pastor et al. 1994; Kaneko 1997). However, besides the species differences, there are at least two differences between our results and those from the cat study. First, while ketamine was reported to have no effects on the structure of saccades in cats, we found it had a significant influence on saccadic peak velocity (see Fig. 3), which is consistent with the results of a low-dose ketamine study in humans (Radant et al. 1998). Second, in the cat study, the impact of ketamine was hypothesized to reflect a failure of oculomotor neural integrator. Additional work from the same group clarified that, while this had a specific impact on gaze holding, the velocity storage mechanism was not affected (Mettens et al. 1991). Our observation that the null point can be slowly and predictably shifted over several degrees by a moving visual pattern argues that there is at least some residual integration present. This slow shift may eliminate the most distal oculomotor structures as being implicated in the oculomotor deficits.

Cortical or subcortical motion processing?

Given our main motivation to examine neural mechanisms related to visual perception, it is important to understand whether the oculomotor responses we observed were confined to evolutionarily old reflexive loops in the brainstem, or whether they engaged cortical mechanisms as well. We draw upon three main pieces of evidence that the visual cortex actively processed the stimuli in our animals. First, our functional imaging results were unequivocal– ketamine blocked BOLD responses in the visual cortex in a dose-dependent manner. However, at the doses we used in the current study, 1–2 mg/kg, ketamine had little effect on cortical responsiveness. This

result provides direct evidence that the thalamocortical system is not significantly depressed in the range of doses for which OKN can be elicited.

As a second piece of evidence, we take the lack of directional asymmetry for monocular stimuli in OKN as a strong indication that the cortex actively processes the motion pattern. The brainstem structure thought to represent the afferent limb of horizontal OKN is the nucleus of the optic tract (NOT) in the pretectum (Hoffmann 1989; Mustari and Fuchs 1990). Physiological and lesion studies both suggest that each NOT is responsible for processing one direction of horizontal motion and initiating nystagmus whose slow phase is in that direction (Hoffmann and Schoppmann 1981; Kato et al. 1986; Hoffmann and Distler 1989; Mustari and Fuchs 1990). For many nonprimate species, particularly those who are afoveate, horizontal optokinetic nystagmus is asymmetric under monocular stimulation. This is thought to arise because of the primarily contralateral retinal inputs to the NOT from each eye, allowing only temporonasally moving stimuli to be processed (Montarolo et al. 1981; Distler et al. 1999). In contrast, monocular OKN in primates is generally symmetric (but not entirely; see van den Berg and Collewijn 1988). This has been attributed to the fact that the NOT receives significant input from the cortex as well as directly from the retina. Although recent anatomical experiments have shown that the fraction of ipsilateral retinal connections is significantly higher in primates than many other mammals (36–43% as strong as the contralateral input), the vast majority of NOT inputs arise from cortical sources (Hoffmann et al. 1992; Telkes et al. 2000). In monkeys, following the effective removal of this corticofugal input by occipital lobectomy, monocular OKN is significantly biased for temporonasal stimuli (Zee et al. 1987). This bias can also be observed in primate development (Distler et al. 1999; Naegele and Held 1982), although it is much more pronounced in cats (Van Hof-Van Duin 1978). In our study we found very little temporonasal dominance during ketamine dissociation. This suggests that the cortical circuits involved in the generating symmetric responses remained intact despite the dissociated perceptual state.

Finally, the binocular rivalry results suggest that active mechanisms of vision related to perceptual organization and perhaps even attention are at least partially spared during the dissociated state. Of course, a major limitation in the current experiments is that the perceptual state is not well defined. However, regardless of what is subjectively perceived by the monkey, the alternating OKN responses necessarily reflect state changes of some sort in the brain. These alternations may perhaps be related to those that normally underlie reversals in perceptual dominance. Previous studies have suggested that perceptual reversals are reflected in the responses of a subset of neurons in the visual cortex (Logothetis and Schall 1989; Lehky and Maunsell 1996; Leopold and Logothetis 1996), and moreover that spontaneous alternations themselves are likely to be initiated in frontoparietal networks related to attention (Lumer et al. 1998; Leopold and Logothetis 1999). Thus this observation raises interesting but difficult questions regarding the expression of active elements related to visual perception in the dissociated state.

Brain mechanisms of ketamine dissociation

While the inhibition of NMDA receptor transmission by ketamine is well established, the sequence of events in the brain that produces ketamine's trance-like state of dissociation remains poorly understood. Early electrophysiological studies suggested that ketamine's effect involved a functional disorganization between subsystems within the brain, rather than a general depression (Mori et al. 1971; Sparks et al. 1975). It was suggested that the behavioral dissociation associated with ketamine actually reflects an uncoupling between thalamoneocortical and limbic brain systems (Miyasaka and Domino 1968; Weingarten 1972). Reports showed that after ketamine injection the thalamocortical system is generally depressed (with the exception of the frontal cortex), while limbic structures such as the hippocampus was strongly activated (Massopust et al. 1972; Crosby et al. 1982). In fact, studies in humans and cats with implanted deep electrodes demonstrated that the limbic activation sometimes led to epileptiform potentials (Mori et al. 1971; Kayama and Iwama 1972; Ferrer-Allado et al. 1973), which caused ketamine to be considered for a period as a dangerous, proconvulsive agent. More recently, however, this notion has been challenged, and ketamine has been labeled as anticonvulsive and even neuroprotective (Fitzal 1997; Kempski and Proescholdt 1997).

In the context of a model for schizophrenia, a handful of positron emission tomography (PET) studies in healthy humans have attempted to correlate patterns of brain activity elicited by ketamine with its psychomimetic effects. These studies have demonstrated consistent ketamine-induced increases the cerebral metabolic rate of glucose (CMRglu) in the frontal and temporal cortex that were correlated with symptoms of schizophrenic psychosis including visual hallucinations (Breier et al. 1997; Vollenweider et al. 1997a, 1997b). It is also interesting to note that the outward behavior of the ketamine-anesthetized monkeys in our study was quite similar to that of human patients suffering from severe akinetic mutism. This disorder, typically arising from bilateral cortical injury of the anterior cingulate, mediofrontal, or orbitobasal cortex, similarly gives rise to a state in which patients are vigilant but motionless, and where optokinetic movements can be elicited by an external stimulus (Schiff and Plum 2000).

Regarding basic sensory processing, ketamine was shown to affect basic receptive field properties of single neurons in the somatosensory cortex (Duncan et al. 1982). These effects were largely dose-dependent and may or may not transfer to the visual system. An early evoked potential study in monkeys suggested that the visual cortex is only minimally affected by ketamine. This

study found that, following a 10 mg/kg IM injection, evoked potentials were largely unaffected in the primary visual cortex, but became distorted in extrastriate (association) areas (Sparks et al. 1973). This observation is interesting given that the extrastriate visual cortex is thought to be critical for mechanisms of perceptual organization, and that ketamine itself has been reported to cause distortions of visual perception in the form of hallucinations, vivid dreams, or optical illusions (Domino et al. 1965; Krystal et al. 1994; Dotson et al. 1995). Regarding the perceptual consequences of low-dose ketamine, a single previous study measured its impact on sensory thresholds in monkeys (baboons; Lukas et al. 1985). In this experiment, visual thresholds were nearly unchanged with doses up to 1.0 mg/kg, again suggesting basic sensory processing is unaffected during dissociation. Unfortunately, the interpretation of these results is difficult, since the baboons were clearly less affected behaviorally by 1.0 mg/kg ketamine than the rhesus monkeys in the present study.

The primary motivation for developing the awake/anesthetized setup was to investigate issues related sensory versus perceptual visual processing mechanisms of single and multiple neurons. Traditional approaches have examined such questions by simultaneously measuring the impact of a particular stimulus on both perception and neuronal responses. For example, several studies have compared perceptual versus neural sensitivity with threshold-level stimuli (Britten et al. 1992; Parker and Newsome 1998). Others have examined how neural activity is modulated by spontaneous perceptual changes upon viewing bistable patterns (Logothetis 1998; Leopold and Logothetis 1999; Leopold et al. 2000). The current paradigm offers an alternative method to probe neural mechanisms of perception– namely, altering the animal's conscious perception pharmacologically while simultaneously measuring sensory visual responses. The awake/anesthetized setup allows for the comparison of responses between isolated neurons under identical stimulus conditions, but under a continuum of behavioral/perceptual conditions set up by the infusion of a neuroactive agent. A weak point in the paradigm is the current inability to assess or measure the monkey's perceptual condition more directly, since the animal becomes unresponsive long before his cortex stops processing visual information. While this is clearly a limitation, one may gain insights into the extent of perception-related processing by comparing the differential impact of agents on the neural responses at multiple levels of visual representation, such as in the primary visual cortex, the inferotemporal cortex, and the frontal cortex.

Finally, aside from issues related to perception and anesthesia, the current paradigm offers an alternative method to measure basic neural responses in sensory systems. It combines the convenience of the awake setup with many of the aspects of the anesthetized preparation that allow the experimenter a great deal of control. For example, the eyes remain open, with constant blinking to keep the cornea hydrated. The direction of gaze is generally straight ahead and fixed for extended periods. Combined with standard eye position measurement, these properties might facilitate careful electrophysiological mapping of receptive fields, which would be particularly useful at the end of sessions employing multiple electrodes, where time is limited by the animal's participation in a behavioral task.

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Reference

Angel A (1993) Central neuronal pathways and the process of anaesthesia. Br J Anaesth 71:148–163

Anis NA, Berry SC, Burton NR, Lodge D (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by *N*-methyl-aspartate. Br J Pharmacol 79:565–575

Antkowiak B (2001) The molecular basis of general anesthesia. Naturwissenschaften 88:201–213

Berg AV van den, Collewijn H (1988) Directional asymmetries of human optokinetic nystagmus. Exp Brain Res 70:597–604

Bon L, Lucchetti C (1990) Does attention affect the motor programs of pharmacologically induced eye movements? Int J Neurosci 53:103–109

Bree MM, Feller I, Corssen G (1967) Safety and tolerance of repeated anesthesia with CI 581 (ketamine) in monkeys. Anesth Analg 46:596–600

Breier A, Malhotra AK, Pinals DA, Weisenfeld NI, Pickar D (1997) Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. Am J Psychiatry 154:805–811

Britten KH, Shadlen MN, Newsome WT, Movshon JA (1992) The analysis of visual motion: a comparison of neuronal and psychophysical performance. J Neurosci 12:4745–4765

Cannon SC, Robinson DA (1987) Loss of the neural integrator of the oculomotor system from brain stem lesions in monkey. J Neurophysiol 57:1383–1409

Carpenter RHS (1988) Movements of the eyes. Pion, London

Crosby G, Crane AM, Sokoloff L (1982) Local changes in cerebral glucose utilization during ketamine anesthesia. Anesthesiology 56:437–443

Distler C, Vital-Durand F, Korte R, Korbmacher H, Hoffmann KP (1999) Development of the optokinetic system in macaque monkeys. Vision Res 39:3909–3919

Domino EF, Chodoff P, Corssen G (1965) Pharmacological effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6:279–291

Dotson JW, Ackerman DL, West LJ (1995) Ketamine abuse. J Drug Issues 25:751–757

Dubner R, Zeki SM (1971) Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. Brain Res 35:528–532

Duncan GH, Dreyer DA, McKenna TM, Whitsel BL (1982) Dose- and time-dependent effects of ketamine on SI neurons with cutaneous receptive fields. J Neurophysiol 47:677–699

Engelhardt W (1997) Recovery and psychomimetic reactions following *S*-(+)-ketamine (abstract). Anaesthesist 46:38

Ferrer-Allado T, Brechner VL, Dymond A, Cozen H, Crandall P (1973) Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333–344

Fitzal S (1997) Ketamine and neuroprotection. Clinical outlook. Anaesthesist 46:65–70

Fox R, Todd S, Bettinger LA (1975) Optokinetic nystagmus as an objective indicator of binocular rivalry. Vision Res 15:849–853

Fox R, Lehmkuhle S, Leguire LE (1978) Stereoscopic contours induce optokinetic nystagmus. Vision Res 18:1189–1192

Franks NP, Lieb WR (1994) Molecular and cellular mechanisms of general anaesthesia. Nature 367:607–614

Friedberg BL (1999) Propofol-ketamine technique: dissociative anesthesia for office surgery (a 5-year review of 1,264 cases). Aesthetic Plast Surg 23:70–75

Godaux E, Cheron G, Mettens P (1990) Ketamine induces failure of the oculomotor neural integrator in the cat. Neurosci Lett 116:162–167

Gross CG, Bender DB, Rocha-Miranda CE (1969) Visual receptive fields of neurons in inferotemporal cortex of the monkey. Science 166:1303–1306

Haeseler G, Zuzan O, Kohn G, Piepenbrock S, Leuwer M (2000) Anaesthesia with midazolam and *S*-(+)-ketamine in spontaneously breathing paediatric patients during magnetic resonance imaging. Paediatr Anaesth 10:513–519

Harris LR, Lewis TL, Maurer D (1993) Brain stem and cortical contributions to the generation of horizontal optokinetic eye movements in humans. Vis Neurosci 10:247–259

Hoffmann KP (1989) Control of the optokinetic reflex by the nucleus of the optic tract in primates. Prog Brain Res 80:173–182

Hoffmann KP, Distler C (1989) Quantitative analysis of visual receptive fields of neurons in nucleus of the optic tract and dorsal terminal nucleus of the accessory optic tract in macaque monkey. J Neurophysiol 62:416–428

Hoffmann KP, Schoppmann A (1981) A quantitative analysis of the direction-specific response of neurons in the cat's nucleus of the optic tract. Exp Brain Res 42:146–157

Hoffmann KP, Distler C, Ilg U (1992) Callosal and superior temporal sulcus contributions to receptive field properties in the macaque monkey's nucleus of the optic tract and dorsal terminal nucleus of the accessory optic tract. J Comp Neurol 321:150–162

Hubel DH, Wiesel TN (1968) Receptive fields and functional architecture of monkey striate cortex. J Physiol (Lond) 195: 215–243

Judge SJ, Richmond BJ, Chu FC (1980) Implantation of magnetic search coils for measurement of eye position: an improved method. Vision Res 20:535–538

Kalkman CJ, Drummond JC, Patel PM, Sano T, Chesnut RM (1994) Effects of droperidol, pentobarbital, and ketamine on myogenic transcranial magnetic motor-evoked responses in humans. Neurosurgery 35:1066–1071

Kaneko CR (1997) Eye movement deficits after ibotenic acid lesions of the nucleus prepositus hypoglossi in monkeys. I. Saccades and fixation. J Neurophysiol 78:1753–1768

Kato I, Harada K, Hasegawa T, Igarashi T, Koike Y, Kawasaki T (1986) Role of the nucleus of the optic tract in monkeys in relation to optokinetic nystagmus. Brain Res 364:12–22

Kayama Y, Iwama K (1972) The EEG, evoked potentials, and single-unit activity during ketamine anesthesia in cats. Anesthesiology 36:316–328

Kempski O, Proescholdt M (1997) Effect of ketamine on global cerebral ischemia. Anaesthesist 46:61–64

Kowler E (1990) The role of visual and cognitive processes in the control of eye movement. Rev Oculomot Res 4:1–70

Krasowski MD, Harrison NL (1999) General anaesthetic actions on ligand-gated ion channels. Cell Mol Life Sci 55:1278–1303

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Kumar SM, Pandit SK, Jackson PF (1978) Recall following ketamine anesthesia for open-heart surgery: report of a case. Anesth Analg 57:267–269

Lahti AC, Koffel B, LaPorte D, Tamminga CA (1995) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19

Lehky SR, Maunsell JH (1996) No binocular rivalry in the LGN of alert macaque monkeys. Vision Res 36:1225–1234

Leopold DA, Logothetis NK (1996) Activity changes in early visual cortex reflect monkeys' percepts during binocular rivalry. Nature 379:549–553

Leopold DA, Logothetis NK (1999) Multistable phenomena: changing views in perception. Trends Cognit Sci 3:254–264

Leopold DA, Fitzgibbons JC, Logothetis NK (1995) The role of attention in binocular rivalry as revealed through optokinetic nystagmus. A I Memo 1554:1–13

Leopold DA, Murayama Y, Logothetis NK (2000) Intra- and interareal covariation of neural activity during multistable perception in the monkey. Soc Neurosci Abstr 26:498.10

Logothetis NK (1998) Single units and conscious vision. Philos Trans R Soc B Biol Sci 353:1801–1818

Logothetis NK, Schall JD (1989) Neuronal correlates of subjective visual perception. Science 245:761–763

Logothetis NK, Schall JD (1990) Binocular motion rivalry in macaque monkeys: eye dominance and tracking eye movements. Vision Res 30:1409–1419

Logothetis NK, Guggenberger H, Peled S, Pauls J (1999) Functional imaging of the monkey brain. Nat Neurosci 2:555–562

Lukas SE, Hienz RD, Brady JV (1985) The effects of phencyclidine and ketamine on sensory thresholds and reaction times in the baboon. Pharmacol Biochem Behav 23:743–747

Lumer ED, Friston KJ, Rees G (1998) Neural correlates of perceptual rivalry in the human brain. Science 280:1930–1934

Lydic R, Biebuyck JF (1994) Sleep neurobiology: relevance for mechanistic studies of anaesthesia. Br J Anaesth 72:506–508

Manny RE, Fern KD (1990) Motion coherence in infants. Vision Res 30:1319–1329

Massopust LC Jr, Wolin LR, Albin MS (1972) Electrophysiologic and behavioral responses to ketamine hydrochloride in the rhesus monkey. Anesth Analg 51:329–341

Mettens P, Godaux E, Cheron G (1991) Effects of ketamine on ocular movements of the cat. J Vestib Res 1:325–338

Miles FA (1997) Visual stabilization of the eyes in primates. Curr Opin Neurobiol 7:867–871

Miles FA (1998) The neural processing of 3-D visual information: evidence from eye movements. Eur J Neurosci 10:811–822

Miyasaka M, Domino EF (1968) Neural mechanisms of ketamine-induced anesthesia. Int J Neuropharmacol 7:557–573

Montarolo PG, Precht W, Strata P (1981) Functional organization of the mechanisms subserving the optokinetic nystagmus in the cat. Neuroscience 6:231–246

Mori K, Kawamata M, Mitani H, Yamazaki Y, Fujita M (1971) A neurophysiologic study of ketamine anesthesia in the cat. Anesthesiology 35:373–383

Mustari MJ, Fuchs AF (1990) Discharge patterns of neurons in the pretectal nucleus of the optic tract (NOT) in the behaving primate. J Neurophysiol 64:77–90

Naegele JR, Held R (1982) The postnatal development of monocular optokinetic nystagmus in infants. Vision Res 22:341–346

Orser BA, Pennefather PS, MacDonald JF (1997) Multiple mechanisms of ketamine blockade of *N*-methyl-D-aspartate receptors. Anesthesiology 86:903–917

Oye I (1998) Ketamine analgesia, NMDA receptors and the gates of perception. Acta Anaesth Scand 42:747–749

Parker AJ, Newsome WT (1998) Sense and the single neuron: probing the physiology of perception. Annu Rev Neurosci 21:227–277

Pastor AM, De la Cruz RR, Baker R (1994) Eye position and eye velocity integrators reside in separate brainstem nuclei. Proc Natl Acad Sci USA 91:807–811

Plourde G, Baribeau J, Bonhomme V (1997) Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. Br J Anaesth 78:524–529

Porro CA, Biral GP, Benassi C, Cavazzuti M, Baraldi P, Lui F, Corazza R (1999) Neural circuits underlying ketamine-in-

duced oculomotor behavior in the rat: 2-deoxyglucose studies. Exp Brain Res 124:8–16
Radant AD, Bowdle TA, Cowley DS, Kharasch ED, Roy-Byrne PP (1998) Does ketamine-mediated *N*-methyl-D-aspartate receptor antagonism cause schizophrenia-like oculomotor abnormalities? Neuropsychopharmacology 19:434–444
Reyle-Hahn M, Niggemann B, Max M, Streich R, Rossaint R (2000) Remifentanil and propofol for sedation in children and young adolescents undergoing diagnostic flexible bronchoscopy. Paediatr Anaesth 10:59–63
Ringach DL, Hawken MJ, Shapley R (1996) Binocular eye movements caused by the perception of three-dimensional structure from motion. Vision Res 36:1479–1492
Schiff ND, Plum F (2000) The role of arousal and "gating" systems in the neurology of impaired consciousness. J Clin Neurophysiol 17:438–452
Schubert A, Licina MG, Lineberry PJ (1990) The effect of ketamine on human somatosensory evoked potentials and its modification by nitrous oxide. Anesthesiology 72:33–39
Sereno ME, Trinath T, Augath MA, Logotetis NK (2000) The representation of 3-D shape in visual cortex: a monkey fMRI study. Soc Neurosci Abstr 26:498.11
Shiigi Y, Casey DE (1999) Behavioral effects of ketamine, an NMDA glutamatergic antagonist, in nonhuman primates. Psychopharmacology 146:67–72
Sparks DL, Corssen G, Sides J, Black J, Kholeif A (1973) Ketamine-induced anesthesia: neural mechanisms in the rhesus monkey. Anesth Analg 52:288–297
Sparks DL, Corssen G, Aizenman B, Black J (1975) Further studies of the neural mechanisms of ketamine-induced anesthesia in the rhesus monkey. Anesth Analg 54:189–195
Steinbach MJ (1976) Pursuing the perceptual rather than the retinal stimulus. Vision Res 16:1371–1376
Telkes I, Distler C, Hoffmann KP (2000) Retinal ganglion cells projecting to the nucleus of the optic tract and the dorsal terminal nucleus of the accessory optic system in macaque monkeys. Eur J Neurosci 12:2367–2375
Urban BW, Friederich P (1998) Anesthetic mechanisms in-vitro and in general anesthesia. Toxicol Lett 100–101:9–16
Van Hof-Van Duin J (1978) Direction preference of optokinetic responses in monocularly tested normal kittens and light deprived cats. Arch Ital Biol 116:471–477
Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J (1997a) Differential psychopathology and patterns of cerebral glucose utilisation produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 7:25–38
Vollenweider FX, Leenders KL, Scharfetter C, Antonini A, Maguire P, Missimer J, Angst J (1997b) Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG). Eur Neuropsychopharmacol 7:9–24
Weingarten SM (1972) Dissociation of limbic and neocortical EEG patterns in cats under ketamine anesthesia. J Neurosurg 37:429–433
White PF, Way WL, Trevor AJ (1982) Ketamine – its pharmacology and therapeutic uses. Anesthesiology 56:119–136
Yamamura T, Harada K, Okamura A, Kemmotsu O (1990) Is the site of action of ketamine anesthesia the *N*-methyl-D-aspartate receptor? Anesthesiology 72:704–710
Yo C, Demer JL (1992) Two-dimensional optokinetic nystagmus induced by moving plaids and texture boundaries. Evidence for multiple visual pathways. Investigative Ophthalmol Vis Sci 33:2490–2500
Zee DS, Tusa RJ, Herdman SJ, Butler PH, Gucer G (1987) Effects of occipital lobectomy upon eye movements in primate. J Neurophysiol 58:883–907
Zeilhofer HU, Swandulla D, Geisslinger G, Brune K (1992) Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. Eur J Pharmacol 213:155–158