

Slow intrinsic rhythm in the koniocellular visual pathway

Soon Keen Cheong^{a,b}, Chris Tailby^{c,d}, Paul R. Martin^{a,b,d,1}, Jonathan B. Levitt^e, and Samuel G. Solomon^{a,d}

^aAustralian Research Council Centre of Excellence in Vision Science and ^bSave Sight Institute, University of Sydney, Sydney, New South Wales 2001, Australia; ^cFlorey Neuroscience Institutes (Austin), Heidelberg, Victoria 3084, Australia; ^dDiscipline of Physiology, University of Sydney, Sydney, New South Wales 2006, Australia; and ^eDepartment of Biology, City College of New York, New York, NY 10031

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Slow rhythmic changes in nerve-cell activity are characteristic of unconscious brain states and also may contribute to waking brain function by coordinating activity between cortical and subcortical structures. Here we show that slow rhythms are exhibited by the koniocellular (K) pathway, one of three visual pathways beginning in the eye and projecting through the lateral geniculate visual relay nucleus to the cerebral cortex. We recorded activity in pairs and ensembles of neurons in the lateral geniculate nucleus of anesthetized marmoset monkeys. We found slow rhythms are common in K cells but are rare in parvocellular and magnocellular cell pairs. The time course of slow K rhythms corresponds to subbeta (<10 Hz) EEG frequencies, and high spike rates in K cells are associated with low power in the theta and delta EEG bands. By contrast, spontaneous activity in the parvocellular and magnocellular pathways is neither synchronized nor strongly linked to EEG state. These observations suggest that parallel visual pathways not only carry different kinds of visual signals but also contribute differentially to brain circuits at the first synapse in the thalamus. Differential contribution of sensory streams to rhythmic brain circuits also raises the possibility that sensory stimuli can be tailored to modify brain rhythms.

parallel pathways | visual system | sleep-wake cycles | anesthesia | epilepsy

The thalamus is central to brain networks that generate slow rhythmic neural activity in sleep-wake cycles, anesthesia, and epilepsy (1–5). However, the thalamus also provides parallel pathways to cerebral cortex for conscious sensation. These two aspects of thalamic function are not independent, as shown, for example, when repetitive visual stimuli induce epileptic seizures (6). Anatomical studies of the dorsal lateral geniculate nucleus (LGN) show preferential inputs to the LGN koniocellular (K) layers from midbrain centers regulating eye movements and vigilance state (1, 2, 7–9), suggesting that activity in the K system is concerned with brain state as well as with faithful transmission of retinal signals. We found evidence supporting this idea from an unexpected observation on K cells.

Results

During extracellular recordings from LGN in anesthetized marmoset monkeys (Fig. 1*A–D*), we found that in the absence of patterned visual stimuli the spike rate of K cells showed slow fluctuations over the course of several seconds to minutes. An example of these slow intrinsic rhythms in three simultaneously recorded K cells is shown in Fig. 1*E*. By contrast the spike rate of parvocellular (P) cells (Fig. 1*F*) and magnocellular (M) cells (Fig. 1*G*) was stable in the absence of patterned visual stimulus. Retinal ganglion cell inputs to K, P, and M layers show low variation in steady discharges at frequencies below 3 Hz (10); this fact implies that the fluctuations do not arise in the retina. Frequency analysis of maintained spike rates showed that below 1 Hz, K-cell spike rates ($n = 56$) on average were 33% more variable than P-cell spike rates ($n = 71$) and 65% more variable than M-cell spike rates ($n = 74$). The rhythmic activity in K cells was not overtly synchronized to activity in simultaneously re-

corded M cells or P cells (Fig. 1*H*), ruling out the possibility that the animal was drifting through physiological states affecting the entire LGN.

If K-cell activity is related to brain state, we expect that, compared with P- and M-cell activity, K-cell activity should be more tightly coupled to other measures of brain state, be less tightly coupled to the effects of visual stimuli, and show greater synchronization across ensembles of like-class cells. In two marmosets, we quantified the relation of K-cell rhythms to EEG signals. Frequency analysis of EEG recorded over primary visual cortex ipsilateral to the recorded LGN (Fig. 2*A, C, and D*) showed the expected pattern for surgical anesthesia, with dominance of delta (0.3–5 Hz) and theta (5–10 Hz) frequencies. Alignment of the EEG record with the spike train of recorded K cells (Fig. 2*B*) revealed that high spike rate in K cells is associated with shift in EEG power from lower-frequency (delta and theta) EEG bands to higher-frequency (alpha/beta) EEG bands (Fig. 2*C and D*). The spike rates of K cells and subbeta (<10 Hz) EEG power were correlated negatively over a time-scale of several seconds (Fig. 2*E*). By contrast, spike rates of P and M cells were not overtly time locked to low-frequency EEG activity (Fig. 2*F*). These results show that K cells do carry information about brain state as well as carrying visual signals.

A second line of evidence linking K-cell activity to brain state is the presence of synchronizations between K cells in absence of visual stimuli. In multielectrode recordings using tetrodes, pairs and ensembles of M cells and P cells showed little coherence (Fig. 1*F and G*). By contrast, the spike rates of simultaneously recorded K cells showed high variance and large coherent fluctuations (Fig. 1*E*). These slow intrinsic rhythms in K cells are manifest as a broad peak over a 15-s pairwise correlation window (Fig. 3*C*).

Analysis of correlation at very short (<1.5 ms) timescales was possible for cell pairs in which each cell was recorded from distinct tetrode surfaces. Of 70 such pairs, only four (one K, one P, two M) showed narrow correlation peaks at time lags below 20 ms, implying shared retinal input. Of 57 other pairs recorded from the same tetrode surfaces (so that we could not measure correlations within 1.5 ms), one P pair showed a significant correlation peak at time lags below 20 ms. Furthermore, synchronized activity was present in pairs of blue-on (color-selective) K cells (11, 12) as well as between color-selective and pattern-selective K cells (Fig. 1*E*). Where measured, 35% of M-cell pairs ($n = 17/49$) and 55% of K pairs ($n = 12/22$) show partially overlapping receptive fields, but synchronizations in partially overlapping pairs were not stronger than in nonoverlapping pairs ($P > 0.5$; Wilcoxon rank-sum test). In sum, our sample of neurons

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¹To whom correspondence should be addressed. E-mail: prmartin@physiol.usyd.edu.au.

normally 5 Hz. Each contrast was presented for 2 s with an interstimulus interval of 0.5 s. Stimuli were presented in pseudorandom order. Maintained activity was measured at the time and space average mean luminance.

The P, K, and M layers were distinguished during recording by changes in eye dominance and by the receptive field properties of recorded cells (Fig. 1 A–D) (23, 25, 26). Recorded neurons were tested for spatial frequency selectivity, achromatic contrast selectivity, temporal frequency selectivity, and responsivity to specific modulation of short wavelength-sensitive (S or “blue”) cone photoreceptors (11, 26). The P layers contained receptive fields that were small, gave sustained responses to contrast steps, and showed low contrast sensitivity (Fig. 1 B and F). The K layers contained receptive fields with heterogeneous properties (25) including S cone-driven (“blue-on” and “blue-off”) fields (11, 12, 26) (Fig. 1 C, E, and H). The M layers contained fields that were large, gave transient responses, and showed high contrast sensitivity (Fig. 1 D and G). Recorded cell locations histologically reconstructed in four animals were consistent with our previous studies of anatomical segregation of functional P, M, and K pathways in marmosets (11, 25, 26). An example of a reconstructed recording track (case MY128) is shown in Fig. 1 A–D. At the majority of recording sites we also characterized the spatial and temporal profile of receptive fields by calculating spike-triggered average (STA) responses to pseudorandom modulated 16×16 checkerboard patterns (Fig. 1 E–H, *Insets*). Checkerboard size was optimized for the receptive field size(s) at the recording site. Luminance of each checkerboard element was drawn from a Gaussian distribution with SD one-third of the mean luminance and was updated every 30 ms. STA receptive fields were estimated as described (27). We estimated spatial overlap of receptive fields by fitting spatial profiles (at the optimal response latency) to a difference-of-Gaussians model, then dividing their separation by the rms SD of the center Gaussians. Receptive fields were considered to overlap if the “d-prime” metric was <2 .

Variance in spike rate of individual cells was determined in absence of patterned visual stimulus. Histograms of the recorded spike train were made at a resolution of 0.5 s. Nonoverlapping segments of 60-s duration were used to extract the maintained spike rate and Fourier power at frequencies from 0.033–1 Hz. The maintained spike rate, on average, for M cells was 8.6 spikes/s (SD 4.0 spikes/s, $n = 74$), for P cells was 10.7 spikes/s (SD 7.9 spikes/s, $n = 71$), and for K cells was 10.3 spikes/s (SD 6.9 spikes/s, $n = 56$). The Fourier power at a given frequency characterizes the variance in spike rate at that frequency. To compare variance between cell classes, we took the ratio of Fourier power between classes at each frequency and then calculated the geometric mean of these ratios.

Measurements of correlated activity were based on recordings from pairs and ensembles of cells. Correlations were analyzed for all pairs where both cells generated at least 100 spikes over the recording epoch. Anatomical segregation of K layers from the main P and M layers is not complete (9, 11, 12, 28, 29). We recorded 22 pairs of mixed P and K cells and four pairs of mixed K and M cells. (Fig. 1H shows an example of a mixed P/K-cell pair). For simplicity we restricted our analysis to cell pairs in which both members of the pair could be assigned unambiguously to the same functional (P, M, or K) pathway (23, 25, 26). To measure correlations in absence of patterned visual stimulus, 58 P pairs were drawn from a total of 48 P cells at 22 recording sites in 10 animals, 51 M pairs were drawn from 53 M cells (22 recording sites, nine animals), and 26 K pairs were drawn from 34 K cells (14 recording sites, five animals). Nine pairs of cortical cells were drawn from 15 cells (13 complex cells, 2 simple cells) at six recording sites in layers IV, V, and VI of the primary visual cortex in one animal. Correlations in presence of patterned visual

stimuli also were obtained for most of these pairs (46 P-cell pairs, 36 M-cell pairs, 22 K-cell pairs, 5 cortical-cell pairs). In four animals the P, M, and K divisions were targeted sequentially or simultaneously for recordings (e.g., Fig. 1H); in other animals recordings were predominantly from one (P, M, or K) division. There were interanimal differences, presumably attributable to anesthetic response, in mean firing rates of all cell divisions. However, no consistent differences between results from P, M, and K cells were apparent on comparing different animals, so data were pooled for analysis. Strength of correlation between cell pairs did not depend on average spike rate across the recording epoch, which ranged from 2–20 min (mean 6.0 min): K cells, $r = 0.20$, $P = 0.33$, $n = 26$; M cells, $r = 0.11$, $P = 0.45$; $n = 48$; P cells, $r = 0.17$, $P = 0.26$, $n = 47$. Recordings from LGN were not made in the animal in which cortical recordings were made.

Correlations in maintained spike rate in the absence of patterned visual stimulus (Fig. 3 A–D) were measured directly (13). Activity was divided into nonoverlapping 60-s fragments and binned at 300-ms resolution. The correlation coefficient was calculated for each temporal displacement between -50 and $+50$ bins, averaged across fragments, and then averaged across pairs.

We used previously established methods described by Bair et al. (17) and Smith and Kohn (16) to disentangle different temporal contributions to spike count correlations in the presence or absence of patterned visual stimuli. The correlation (r) in the total spike count (SC), (henceforth, rSC) was calculated by z-transforming the mean spike rate for each cell to a given stimulus condition, then calculating the correlation coefficient across all stimulus conditions at zero time lag (17). Long-term (rLT, >20 s) and short-term (rST, <20 s) contributions to rSC were estimated by temporal filtering. Briefly, rLT is estimated by convolving the rSC values at multiple time lags with a low-pass temporal filter to emphasize contributions to rSC from processes acting at timescales longer than ~ 20 s (17). To estimate rST, an ideal high-pass filter is applied to the z-transformed spike counts to emphasize contributions to rSC from processes acting at timescales shorter than ~ 20 s (17).

Very short timescale correlations (that is, within periods <100 ms; Fig. 4 A and B) were analyzed as described (16, 17). Spike trains were binned at a resolution of 1 ms. The average cross-correlogram was calculated for the raw spike trains and for “shifted” spike trains in which the spike train for one cell was drawn from a subsequent presentation of the same stimulus. The shift-corrected cross-correlogram is the difference between these two measures. A shift-corrected auto-correlogram for each member of the pair was estimated in parallel fashion. The strength of correlation at each time lag (that is, at each x axis point on Fig. 4 A and B) is the area under the cross-correlogram curve within the time-lag window, divided by the geometric mean of the auto-correlogram areas for each member of the pair within the same time-lag window. To provide comparable measures for correlations in absence of spatial or temporal modulation of stimulus intensity (indicated by the “no stim” icon in Fig. 4), we repeated the above analysis for spike train segments of length 2.5 s, that is, the normal duration of stimulus presentation.

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