antibody to rat non-helper T cells) was from Sera-lab, Sussex, England.
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# Dormancy of Inhibitory Interneurons in a Model of Temporal Lobe Epilepsy

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**In humans temporal lobe epilepsy (TLE) is characterized by recurrent seizures, neuronal hyperexcitability, and selective loss of certain neuronal populations in the hippocampus. Animal models of the condition indicate that a diminution of inhibition mediated by gamma-aminobutyric acid (GABA) accounts for the altered function, and it has been hypothesized that the diminution arises because GABAergic basket interneurons are "dormant" as a result of their being disconnected from excitatory inputs. In hippocampal slices, inhibitory postsynaptic potentials (IPSPs) were elicited in CA1 pyramidal cells by activation of basket cells; responses from an animal model of TLE were compared to those from control tissue. IPSPs evoked indirectly by activation of terminals that then excited basket cells were reduced in the epileptic tissue, whereas IPSPs evoked by direct activation of basket cells, when excitatory neurotransmission was blocked, were not different from controls. These results provide support for the "dormant basket cell" hypothesis and have implications for the pathophysiology and treatment of human TLE.**

There has been long-standing controversy over whether a diminution of inhibition mediated by the amino acid GABA causes epilepsy and, if so, how this comes about. The premise that a decrease in GABAergic inhibition participates in epileptogenesis arose from observations made decades ago that several drugs that block GABA-mediated inhibition produce acute seizures (*1*). However, proper investigation of this issue requires the study of tissue from a persistently epileptic brain. This approach has been hampered by limited availability of brain tissue from humans with epilepsy. Recently, appropriate animal models of epilepsy, sharing critical characteristics with the condition in human patients, have been developed (*2–4*). These features include neuronal hyperexcitability, distinctive neuropathological changes such as loss of neurons and sprouting of certain axon terminals, and recurrent spontaneous seizures.

Models of epilepsy established with electrical stimulation are associated with an enduring, apparently permanent loss of GABAergic inhibition (*3–5*). Furthermore, in one of these models, an intriguing paradox was reported: physiological studies indicated loss of GABA-mediated inhibition of principal cells in the hippocampus, whereas immunohistochemical studies revealed survival of GABAergic interneurons in that structure (*3*). This led to the concept that the basket cell interneurons that exert an inhibitory effect in the hippocampus by releasing GABA onto principal cells (pyramidal cells in Ammon's horn and granule cells in the dentate gyrus) are "dormant" rather than dysfunctional (*4*). There has been controversy (*6*) over whether GABAergic interneurons do survive in this situation and, if so, how this relates to heightened epileptogenesis.

If the dormant basket cell hypothesis is correct, several predictions can be made. The first two relate to stimuli delivered at a site distant to a CA1 pyramidal cell that indirectly engage basket cells by initially exciting terminals presynaptic to the basket cell (Fig. 1). Under these conditions, intracellular recordings would be predicted to show inhibitory postsynaptic potentials (IPSPs) elicited in CA1 pyramidal cells from epileptic tissue that are smaller than corresponding IPSPs in neurons from control tissue. The second prediction is that under these conditions $GABA_A$ IPSPs and $GABA_B$ IPSPs should be affected to the same degree. The third prediction is that IPSPs evoked in CA1 pyramidal cells by direct near-site stimulation of basket cells, in the presence of agents that block excitatory neurotransmission, should not differ between epileptic and control tissue. Thus, there should be substantial differences between the results with near- and far-site stimulation.

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We have now tested these predictions. Experimental arrangements are schematized in Fig. 1. Intracellular recordings were taken from pyramidal cells in CA1. Slices were obtained either from control animals or from animals that had experienced a previous episode of self-sustaining limbic status epilepticus (*9, 10*), which leads to persistent sequelae of hyperexcitability of hippocampal slices under conditions that precipitate epileptiform discharges (*5*), neuropathological changes like mesial temporal sclerosis (*11*), and recurrent hippocampal seizures (*5*). Stimuli were given at three sites. Near-site stimulation was done in the presence of pharmacological antagonists 6-cyano-7-nitro-quinoxaline-2,3-dione (CNQX) and D-2-amino-5-phosphonovalerate (APV) to block excitatory synapses utilizing non-*N*-methyl-D-aspartate (non-NMDA) and NMDA-type glutamate receptors, respectively. Far-site stimulations, done without the antagonists, activated GABAergic basket cells either "antidromically," by first discharging CA1 pyramidal cells, or "orthodromically," by first activating Schaeffer collaterals.

In response to challenges with elevated concentrations of extracellular potassium ($[K^+]_o$), slices from epileptic animals are hyperexcitable relative to slices from control animals, as determined by measurements of population spikes in the stratum pyramidale of CA1 (*5*). However, under conditions with $[K^+]_o$ of 3 mM, the normal concentration in brain and the value used in the current study, population spike responses from the two types of slices are the same, without epileptiform discharges. This latter condition was maintained in the present study. There were no differences in intrinsic membrane properties between neurons studied in slices from normal animals and in those from epileptic animals (Table 1).

In slices from control animals, the two far-site stimuli produced IPSPs in CA1 pyramidal cells (Fig. 2) identical to those previously described (*12–14*). Orthodromic stimulation elicited a biphasic IPSP, with an earlier peak occurring at about 40 ms and a later peak at about 110 ms. Antidromic stimulation evoked a monophasic IPSP, with a peak at about 40 ms. Investigators (*12, 13*) have previously established that (i) all three IPSPs are mediated by GABA; (ii) both the earlier component of the orthodromic IPSP and the antidromic IPSP result from activation of $GABA_A$ receptors that open $Cl^-$ channels, whereas the later component of the orthodromic IPSP arises from activation of $GABA_B$ receptors that open $K^+$ channels; and (iii) the magnitude of the IPSPs increases with stimulus strength to reach maximal values. Thus, stimulus intensity was adjusted in our

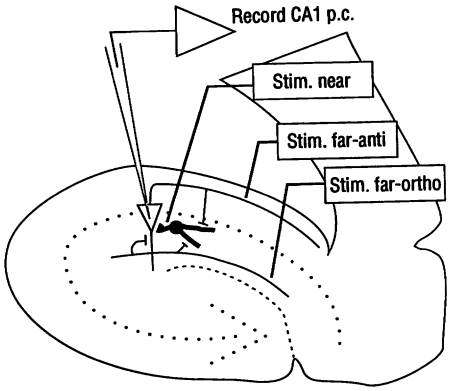


**Fig. 1.** Experimental setup for recording IPSPs in CA1 pyramidal cells (p.c.). Hippocampal slices (*7*) were prepared from two groups of animals. One group of rats had experienced a period of self-sustaining, nonconvulsive limbic status epilepticus evoked by 90 min of "continuous" electrical stimulation through a bipolar ventral hippocampal electrode 2 to 5 months previously (*9, 10*). One week after the status epilepticus had abated, the rats were anesthetized with halothane and the electrodes removed. The second group of rats was age-matched controls. Previous studies (*5*) have shown that electrode implantation without stimulation does not affect morphological or functional aspects of the contralateral hippocampus (the aspect examined in our experiments).

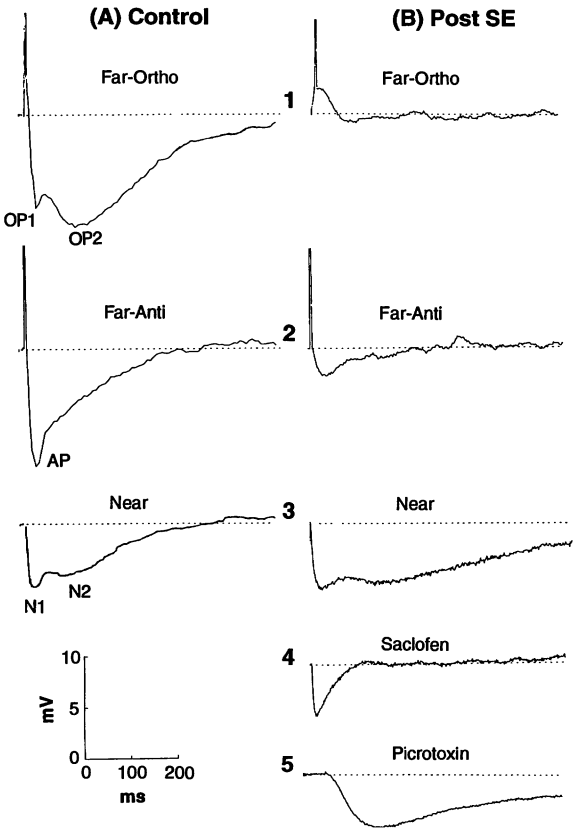


**Fig. 2.** Loss of GABAergic IPSPs evoked by far-site stimulation with retention of IPSPs evoked by near-site stimulation. Responses recorded in CA1 pyramidal cells and evoked by far (trace 1, orthodromic; trace 2, antidromic) and near (traces 3 to 5) stimulation. Intracellular recordings obtained from control group (**A**) or from group with previous limbic status epilepticus (Post SE) (**B**). Separate components of IPSPs are labeled. Far-site stimulation: OP1, first orthodromic peak; OP2, second orthodromic peak; AP, antidromic peak. Near-site stimulation: N1, first peak; N2, second peak. Traces 4 and 5: Near-site stimulation with CNQX and APV together with saclofen (trace 4) or picrotoxin (trace 5). All responses are maximal-amplitude IPSPs. Action potentials are truncated. Calibration is at lower left.

**Table 1.** Comparison of membrane properties of CA1 pyramidal cells recorded in slices from animals with previous limbic status epilepticus and from control animals. There were no significant differences (*t* test, $P > 0.05$) in any of the parameters reported below. Means (± SEM) are for 23 cells in 19 slices for the control group ($n = 12$ animals) and for 21 cells in 16 slices for the post-limbic status epilepticus group ($n = 7$ animals).

| Membrane property | Status epilepticus | Post-limbic control |
|---|---|---|
| Resting membrane potential (mV) | −62.5 ± 1.5 | −62.0 ± 1.8 |
| Action potential height (mV) | 72.5 ± 1.7 | 73.4 ± 1.9 |
| Input resistance (megohm) | 51.2 ± 2.2 | 47.3 ± 0.9 |

experiments to give maximal-amplitude IPSPs. Monitoring of population spikes, measured with extracellular recordings obtained either from another microelectrode positioned in the stratum pyramidale adjacent to the intracellular electrode or from the intracellular electrode before and after penetration of CA1 neurons, assured constant effectiveness of the far-site stimuli.

In slices from control animals, the maximal amplitudes of the three IPSPs under consideration (early $GABA_A$ component of orthodromic response, late $GABA_B$ component of orthodromic response, and $GABA_A$ antidromic response) were comparable in peak amplitude (Fig. 3). In slices from epileptic animals, the three types of maximal IPSPs produced by both types of far-site stimulation were markedly attenuated (Fig. 2), and their amplitudes were statistically different (Fig. 3A) from control values. The stimuli used to elicit maximal-amplitude IPSPs also evoked action potentials in the CA1 pyramidal cells under examination. Because post–action potential potassium conductances could influence measurements of IPSPs, we also studied IPSPs evoked by stimuli that did not cause action potentials. Under these conditions, IPSPs in slices from epileptic animals were also smaller than those in slices from control animals (Fig. 3B). These results confirm the first two predictions made above.

IPSPs produced by near-site stimulation in slices from control animals were as described previously (*15*), consisting of an early peak at about 17 ms and a later peak at about 120 ms. The effectiveness of blockade of non-NMDA and NMDA glutamatergic receptors was corroborated by the absence of excitatory postsynaptic potentials. As with the far-site stimulation, the magnitude of IPSPs increased with stimulus intensity to a maximal value. In contrast to the findings with the far-site stimuli, the maximal IPSPs with near-site stimulation in slices from epileptic animals were the same size as in control animals (Figs. 2 and 4).

To establish that the hyperpolarizations detected with the near-site stimulation in the slices from animals with previous limbic status epilepticus were GABA-mediated IPSPs, we compared their properties to those already established for normal CA1 pyramidal cells. In slices from normal rats, Davies and co-workers (*15*) have shown that the earlier component is mediated by $GABA_A$ receptors and has a reversal potential near −75 mV, whereas the later component is mediated by $GABA_B$ receptors and has a reversal potential near −95 mV. In the slices taken from animals with previous limbic system status epilepticus, the early component of the near-site stimulus IPSP was blocked by the $GABA_A$ receptor antagonist picrotoxin (Fig. 2B, trace 5), whereas the late component was blocked by the $GABA_B$ receptor antagonist saclofen (Fig. 2B, trace 4). Determinations of reversal potentials for the near-site stimulation response showed a value of about −75 mV for the early $GABA_A$ component and about −95 mV for the later $GABA_B$ component. Hence, the changes detected in IPSPs with the far-site stimulation cannot be ascribed to changes in their driving force. These results confirm the third prediction of the dormant cell hypothesis presented above, that IPSPs elicited with near-site stimulation should not differ in epileptic and control tissue. Thus, the confirmation of all three predictions provides strong support

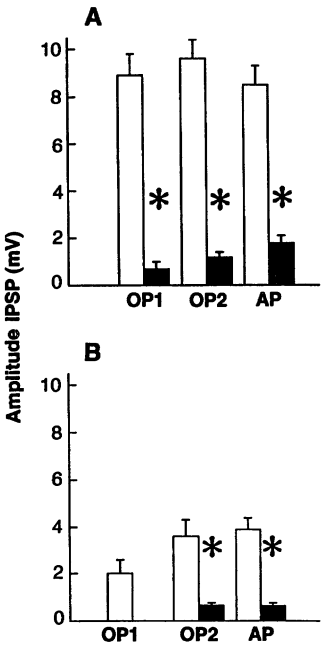


**Fig. 3.** Amplitudes (means ± SEM) of CA1 pyramidal cell IPSPs evoked by far-site stimulation in slices from control animals (open bars) and from animals with previous limbic status epilepticus (filled bars). Statistically significant differences ($P < 0.005$, $t$ tests) are indicated by asterisks. (**A**) Maximal-amplitude IPSPs for ten cells in ten slices from control animals ($n = 7$) and for ten cells in nine slices from post-SE animals ($n = 4$). (**B**) IPSPs for stimulus strength at threshold for population spike. No action potential resulted in the CA1 pyramidal cell under study. IPSPs were obtained for six cells in six slices from control animals ($n = 6$) and for six cells in six slices from post-SE animals ($n = 4$). For the data in (B), there were no discernible OP1 IPSPs for the post-SE condition.

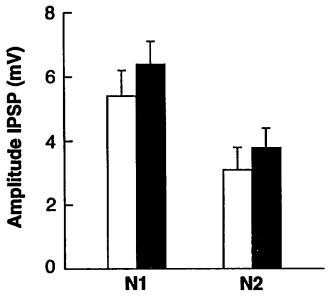


**Fig. 4.** Comparison of maximal-amplitude IPSPs evoked by near-site (N1 and N2) stimulation. Symbols are as in Fig. 3. There were no statistically significant differences ($t$ test). Responses for eight cells in three slices from control animals ($n = 3$) and for eight cells in five slices from post-SE animals ($n = 4$).

for the dormant basket cell hypothesis.

Our experiments focused on basket cells in the CA1 region of Ammon's horn of the hippocampal region. The classic description of the operation of these cells is that they participate in a feedback inhibitory circuit (*16*). More recent work has shown that they also function in a feedforward fashion (*12*, *17*). The two far-site stimulation protocols we used studied both the feedback and feedforward operations of basket cells (Fig. 1). The antidromic protocol examined the feedback mode. Because of the high intensity of the orthodromic far-site stimuli, this protocol activated basket cells by both the feedforward and feedback routes. However, even a high degree of feedback activation with the orthodromic far-site stimulation would not have masked an inability of the Schaeffer collaterals to excite basket cells. Thus, our results indicate that the basket cells are "disconnected" irrespective of the routes by which inhibitory interneurons are excited. Whether the disconnection of inhibitory interneurons is global, including isolation from inhibitory inputs, remains to be explored.

Because the dormant inhibitory interneurons establish a defect presynaptic to the CA1 pyramidal cell, both $GABA_A$ and $GABA_B$ responses were attenuated. The relative role of these two subclasses of inhibitory responses in opposing the generation and elaboration of epileptiform discharges is not known. Nevertheless, the therapeutic implications of the current study are twofold. First, the CA1 pyramidal cells, which are responsible for generating epileptic discharges in this region (*18*), are fully capable of responding in a normal fashion to the inhibitory neurotransmitter GABA. Therefore, a firm rationale is provided for strategies that seek to promote GABA-mediated inhibitory events in epileptic tissue. Second, the local circuit composed of the CA1 pyramidal cell and its associated basket cell is intact, opening up the possibility of activating the inhibitory interneuron so that it, in turn, provides appropriate regulation of the pyramidal cells.

Changes in GABAergic inhibition in the hippocampus have been examined in other models of temporal lobe epilepsy. A diminution of GABA-mediated IPSPs in CA1 pyramidal cells and dentate granule cells follows direct injections of the excitotoxin kainic acid into the hippocampus (*19*). However, GABA-mediated inhibition also recovers over several weeks after the injection. Alternatives to kainic acid in establishing experimental epilepsy are the models that develop as sequelae to acute limbic system status epilepticus triggered with electrical stimulation (*3*, *5*). Under these circumstances, changes in inhibition appear to be permanent (*4*). In the model we studied, the disturbance of inhibition lasts at least 5 months, the longest time interval so far examined. Understanding why inhibition recovers in the kainic acid model but not in the electrical stimulation models should provide important insight into the pathophysiology of epilepsy. Our model also has striking parallels with a common human clinical condition, the mesial temporal lobe epilepsy syndrome (*20*).

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7. Adult, male (450 g) Sprague-Dawley rats were anesthetized with ether. Brains were removed from the skull and blocked by dissection away of the cerebellum, coronal sectioning at the level of the midthalamus, and removal of the dorsal half of the posterior section of the forebrain. The brain block containing the ventral hippocampus and adjacent parahippocampal region was then sectioned (450-μm thick) on a vibratome in chilled (4°C) and oxygenated (bubbled with 95% $O_2$–5% $CO_2$) artificial cerebrospinal fluid [153 mM $Na^+$, 3.1 mM $K^+$, 130.5 mM $Cl^-$, 26 mM $HCO_3^-$, 1.5 mM $Ca^{2+}$, 1.5 mM $Mg^{2+}$, 1.5 mM $SO_4^{2-}$, and 1.1 mM $PO_4^{2-}$ (pH 7.4)]. After a minimum of 1 hour of recovery (22°C), slices were placed in an interface chamber and maintained at 36°C in artificial cerebrospinal fluid and humidified 95% $O_2$–5% $CO_2$ gas (4 to 5 liter/min). In some cases CNQX (20 μM) (Cambridge Research Biochemicals, Wilmington, DE), APV (40 μm) (Cambridge Research Biochemicals), picrotoxin (100 μM) (Sigma), or 2-hydroxysaclofen (100 μM) (RBI, Natuck, MA) were used as described in the text. Intracellular recordings were made with glass microelectrodes (80 to 140 megohms) filled with 2 M potassium methylsulfate positioned in the stratum pyramidale. Neurons identified as CA1 pyramidal cells by electrophysiological criteria (*8*) with stable penetrations (membrane potentials more negative than −60 mV, action potential overshoots) were studied. Stimuli were given through bipolar stainless-steel electrodes (Rhodes, Woodland Hills, CA). For far-site stimuli, electrodes with 200-μm tip separation were positioned 1 to 1.5 mm away from the recording site on the subicular side either in the stratum radiatum (to activate Schaeffer collaterals) or in the alveus (to activate axons of pyramidal cells). For near-site stimulation, electrodes with 70-μm tip separation were positioned in the stratum pyramidale toward the stratum radiatum at a distance less than 100 μm from the recording electrode.
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# Selectivity for Polar, Hyperbolic, and Cartesian Gratings in Macaque Visual Cortex

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**The neural basis of pattern recognition is a central problem in visual neuroscience. Responses of single cells were recorded in area V4 of macaque monkey to three classes of periodic stimuli that are based on spatial derivative operators: polar (concentric and radial), hyperbolic, and conventional sinusoidal (Cartesian) gratings. Of 118 cells tested, 16 percent responded significantly more to polar or hyperbolic (non-Cartesian) gratings than to Cartesian gratings and only 8 percent showed a significant preference for Cartesian gratings. Among cells selective for non-Cartesian gratings, those that preferred concentric gratings were most common. Cells selective for non-Cartesian gratings may constitute an important intermediate stage in pattern recognition and the representation of surface shape.**

Neurons in the primary visual cortex (area V1) typically display tuning for elementary stimulus dimensions such as position, orientation, and spatial frequency (*1*). In the macaque monkey, subsequent stages of form processing are believed to take place in a hierarchy of extrastriate areas that includes areas V2, V4, and the inferotemporal cortex (IT) (*2*, *3*). Although complex pattern recognition probably occurs in area IT and some IT cells are selective for faces, hands, or other highly complex stimuli (*4*, *5*), little is known about the intermediate stages of processing involved in the generation of these higher order receptive field properties. We have addressed this problem by analyzing the receptive field characteristics of cells in area V4, an intermediate stage of the visual hierarchy. The stimulus set used in our experiments (Fig. 1A) was designed to meet several criteria: (i) it is rich enough to elicit responses from cells with complex tuning properties, (ii) it is mathematically defined and permits calculation of tuning curves, (iii) it is based on specific computational theories of vision, and (iv) psychophysical and physiological observations have suggested the existence of cells tuned to these stimuli.

The stimuli were sinusoidally modulated gratings from three distinct classes, which we call Cartesian, polar, and hyperbolic. Each class is defined by the coordinate system in which the modulation functions form a linear, orthogonal basis. Thus, the Cartesian modulation functions form a basis in Cartesian coordinates whose cardinal axes generate conventional horizontal and vertical gratings. The intermediate functions generate Cartesian gratings at intermediate orientations. The polar functions form a basis in polar coordinates whose cardinal axes generate concentric and radial gratings, and the intermediate functions generate spiral gratings. Finally, the hyperbolic functions form a basis in hyperbolic coordinates whose cardinal axes generate hyperbolic gratings that differ in orientation by 45°, and the intermediate functions generate hyperbolic gratings at intermediate orientations. The three stimulus classes are closely related to Lie differential operators, which take continuous derivatives of an image with respect to different coordinate systems. These operators may aid perceptual constancy by compensating for affine transformations of the retinal image that arise from changes in viewpoint and object orientation (*6*–*8*). The stimulus classes are also related to those used to identify cells in the medial superior temporal area that are selective for changes in rotation and in expansion and contraction (*9*): when integrated over time, rotating flow fields form concentric patterns, and expanding and contracting flow fields form radial patterns. Similar stimuli have been used in psychophysical studies (*10*) and have provided some support for mechanisms selective for polar or hyperbolic stimuli.

We first looked for cells in area V4 that respond more strongly to polar or hyperbolic gratings than to any Cartesian grating. We recorded extracellularly from single units in area V4 of anesthetized, paralyzed macaque monkeys (*11*, *12*). In our primary test, we used polar and hyperbolic gratings that varied in spatial frequency and phase and Cartesian gratings that varied in orientation, spatial frequency, and phase (Fig. 1A). Figure 1, B to D, illustrates three types of selectivity that we encountered. The cell represented in Fig. 1B responded vigorously to concentric stimuli but poorly to all Cartesian gratings. The cell represented in Fig. 1C also preferred non-Cartesian stimuli, but the most effective stimulus was a hyperbolic grating. The cell represented in Fig. 1D preferred Cartesian gratings and was tuned for both orientation and spatial frequency.

All 118 V4 neurons studied with this stimulus set gave responses significantly above the base-line rate. With a *t* test, we compared the normalized firing rate obtained with the best Cartesian grating to that obtained with the best non-Cartesian grating (*13*). By this measure, 19 cells (16%) showed a statistically significant preference for non-Cartesian gratings, whereas 10 (8%) preferred Cartesian gratings (*14*). Out of 19 cells classified as non-Cartesian, 12 preferred concentric gratings, only 3 preferred radial gratings, and 4 preferred hyperbolic gratings. The preferences seem to reflect a continuum of selectivity rather than distinct cell classes. For the remaining 89 cells (78%), the responses to the best Cartesian and non-Cartesian gratings could not be distinguished statistically. Many cells in this last category showed sharp tuning profiles in both Cartesian and non-Cartesian stimulus spaces, which suggests a form of multiplexing in the representation of pattern information.

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