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Université de Montréal

Les neurones voisins de l'aire visuelle 18 réagissent différemment en réponse à l'excitation ou à la dépression de l'aire 17, du chat

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Mémoire présentée a la Faculté des études supérieures
en vue de l'obtention du grade de
Maîtrise (M.Sc.)
en sciences biologiques

Avril 2001

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Page d'identification du jury

Université de Montréal
Faculté des Études supérieures

Ce mémoire intitulé :

Les neurones voisins de l'aire visuelle 18 réagissent différemment en réponse à l'excitation ou à la dépression de l'aire 17, du chat

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Mémoire accepté le : Septembre 2001

RÉSUMÉ

L'organisation en colonnes est une caractéristique commune de l'architecture corticale. Dans le cortex visuel, il est bien connu que les cellules avoisinantes ont une préférence similaire pour l'orientation, pour la dominance oculaire et pour la localisation rétinotopique. La direction est aussi organisée en colonnes. La latence des réponses ainsi que la fréquence temporelle sont classifiées aussi de cette façon. Notre question est la suivante : est-ce que les neurones de l'aire 18 réagissent de la même façon en réponse à une excitation ou à une dépression de l'aire 17 ? L'objectif de cette étude est de comprendre la réponse des cellules voisines dans l'aire 18 en réponse à des stimuli sous forme de réseau lumineux sinusoïdal défilant (grating).

Chez le chat, l'information visuelle émanant de la rétine atteint le cortex via le noyau géniculé latéral (LGN). La majorité des unités de ce relais projettent vers les aires occipitales visuelles 17 et 18. Ces deux aires sont réciproquement liées par des connexions horizontales longues. L'aire 18 du cortex visuel du chat reçoit deux inputs majeurs : un input prend origine dans le LGN, l'autre input projette des fibres corticales de l'aire 17. Il a été bien démontré que dans l'aire 17, les cellules reliées par des connexions horizontales

communiquaient entre elles si elles partageaient la même orientation préférée (OP). Cependant, dans l'aire 18, les connexions horizontales relient des colonnes dont les OP sont plutôt orthogonales. De plus, une cible localisée dans des régions au-delà du champ récepteur classique peut moduler la réponse cellulaire dans l'aire 17. Par ailleurs, il a été montré que les réponses sont modulées par des barres dont l'orientation est la même que celle de la cellule enregistrée, alors que l'influence de l'orientation "croisée" est moins dépendante du circuit à connexions longues. Tout de même, la modulation des réponses par ce type d'orientation demeure encore ambiguë dans l'aire 18. La stimulation de la périphérie a une double influence excitatrice et inhibitrice sur les réponses évoquées à partir du champ récepteur classique. Chez les chats anesthésiés, l'inactivation de l'aire 17 par le GABA montre que les cellules simples sont liées par des connexions excitatrices dont la OP est similaire alors que les cellules complexes apparaissent être liées par des fibres excitatrices provenant de l'aire 17, ce qui leur confère une OP orthogonale.

Les chats sont préparés de façon conventionnelle pour des enregistrements électro-physiologiques dans les aires 17 et 18. La distance entre les deux électrodes était ≥ 3mm (champs récepteurs partiellement chevauchants ou complètement non chevauchants). Les stimuli dont l'orientation, la direction, les

fréquences spatiales et temporelles sont optimales ont été présentés dans les champs récepteurs des aires 17 et 18. Les "histogrammes temporels péri-stimulus" (PSTHs) ont été utilisés pour évaluer les amplitudes des réponses. L'analyse en "corrélogrammes croisée" (XCRGs) a servi pour révéler la connexion inter-corticale. Les réponses unitaires ou multi-unitaires ont été enregistrées dans les aires 17 et 18. Le critère de sélection était la forme de l'onde. Dans tous les cas, la sélection des unités avait une OP qui différait l'une de l'autre par moins de 30°. Deux stratégies ont été employées :

A) *Activation de l'aire 17.* Un grating avec les paramètres optimaux localisés dans le champ récepteur de l'aire 18. Un deuxième grating, positionné dans la périphérie du champ récepteur de cellules de l'aire 18 a été ajouté. Ce grating supplémentaire a une orientation optimale pour le site de l'aire 17. Dans une seconde étape, cette orientation a été rendue orthogonale relative à celle des cellules de l'aire 18.

B) *Inactivation de l'aire 17.* Le GABA a été micro-injecté au même site dans l'aire 17.

J'ai enregistré les activités unitaires et multi-unitaires dans l'aire 18. 20 paires de cellules ont été reteruces de ces enregistrements multi-unitaires. Dans des expériences additionnelles, j'ai enregistré en unitaire 15 cellules. Au

total, 55 cellules ont fait l'objet de ce protocole ainsi que des analyses qui en résultent. Étant donné que chaque cellule obéit à 2 conditions expérimentales, le total des situation expérimentales fut de plus que 100. Les cellules ont été classifiées en groupes relativement aux différences entre l'OP de l'aire 17 et celle de l'aire 18. Aussi, le premier groupe contient des unités dont la disparité est iso-orientationnelle "iso" (0°-30°). Le second groupe englobe des cellules dont la disparité d'orientation est oblique (31°-60°). Le dernier groupe regroupe des neurones dont la différence est orthogonale-orientationnelle (>60°).

Dragoi et Sur (2000) proposent le mécanisme "push-pull" pour illustrer la relation entre les neurones excitatrices et inhibitrices. Notre discussion porte sur le même schéma auquel nous avons apporté quelques légères modifications pour mettre en lumière nos différents résultats. Ce modèle en réseau montre que les décharges excitatrices des cellules corticales sont le résultat de l'activation de diverses connexions synaptiques empiétant sur un neurone. Ce dernier reçoit divers inputs excitateurs de plusieurs origines, qui sont des cellules voisines ayant des OP similaires ou différentes, des longs axones horizontaux émanant d'autres aires (des axones feed-forward et feed-back), et des contacts inhibiteurs. Les cellules inhibitrices ont des relations réciproques permettant la

désinhibition. Les résultats de cette présente étude indique que la balance synaptique évoquée dans les cellules voisines peut dévier dans des directions opposées.

La présente étude soulève diverses conclusions : les cellules voisines de l'aire 18 ayant la même OP réagissent différemment quand le deuxième grating est appliqué dans l'aire 17 ou dans la périphérie lointaine du champ récepteur de l'aire 18. L'inactivation du même site dans l'aire 17 produit des réactions différentes dans les neurones appartenant au même "pool" de cellules. Elle montre aussi que les cellules de l'aire 17 contribuent à la constitution de la périphérie du champ récepteur des cellules de l'aire 18. Malgré que les "aires" périphériques demeurent silencieuses (aucune réponse n'est évoquée) quand présentés seulement, ils modulent néanmoins les réponses centrales. La direction de la modulation des réponses des cellules dépend de plusieurs facteurs. La facilitation des réponses dépend de l'orientation dominante du site stimulé ou inactivé. En fait, la condition orthogonale-orientationnelle produit une facilitation plus significative que celle produite par la condition iso-orientationnelle. La dépression de l'aire 17 inverse cette relation. Au contraire, la diminution des réponses apparaît être indépendante des différences de l'orientation entre les deux sites. L'inactivation de l'aire 17 n'arrive pas à influencer les diminutions des réponses résultant de la double

condition de stimuli, indépendamment de la disparité de l'orientation. Ceci peut être expliqué par le fait que l'inhibition peut être due à une connexion locale et que par conséquent les connexions les plus longues ne peuvent avoir exercé qu'un rôle mineur dans la diminution des réponses.

En conclusion, mes résultats appuient l'idée que les neurones corticaux voisins tendent à partager des inputs afférents. Cependant, leurs propriétés de réponses paraissent plus flexibles que les travaux antérieurs avaient permis d'anticiper. De même que ces résultats ne pourront pas être obtenus par la technique de l'imagerie cérébrale.

Il a été suggéré que les neurones situés dans des singularités d'orientation puissent exhiber des dissimilitudes concernant leurs caractéristiques visuelles. D'un coté, DeAngelis et al., (1999) ont montré que les cellules voisines partagent globalement des préférences à l'orientation et d'autres propriétés. Laquelle étude démontre donc que les neurones même quand ils exhibent des PO quasi-similaires peuvent réagir de façon différente aux mêmes présentations de stimuli.

Mots-clés :

Chat, aire 17, aire 18, iso-orientationnelle, orthogonale-orientationnelle, cellules voisines, inhibition, facilitation, corrélogrammes croisée(XCRGs).

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LIST OF ABBREVIATIONS

AC: area centralis
CAMP: adenosine 3′,5′-cyclic monophosphate
Cont.: control, prior to GABA injection in area 17
Cross: cross-orientation $\geq 60^0$
Cro-F (I): cross-orientation facilitation (inhibition)
CRF: classical receptive field
deg: degree
DI: detectability index
Diff.: different
ECG: electrocardiogram
EEG: electroencephalogram
FFT: fast fourier transform
GABA: γ-aminobutyric acid
GAD: glutamic acid decarboxylase
Glu: glutamate
Iden.: identical
im: intramuscle
iv: intravein
Inj.: injection, during inactivation area 17
Iso: iso-orientation $\leq 30^0$
Iso-F (I): iso-orientation facilitation (inhibition)
LGN: lateral geniculate nucleus
M pathway: magnocellular
mm: millimeter
ms: millisecond
MT: medial temporal area
N: number
Obl: oblique-orientation $30^0 \sim 60^0$
Obl-F (I): oblique-orientation facilitation (inhibition)
Opt.: optimal orientation
Orth.: orthogonal orientation
P pathway: parvocellular
PSTH: peristimulus time histogram
Rec.: recovery, after injection during recovery phase
s: second
s.c.: subcuticular
SE: standard error
XCRG: cross-correlogram
μm: microns
μv: microvolt
2-DG: 2-deoxyglucose

REMERCIEMENTS

Je tiens à remercier mon directeur Dr. Stéphane Molotchnikoff pour son aide, ses encouragements et son support financier tout au long de mes études en maîtrise.

Je voudrais également remercier Dr. Svetlana Shumikhina pour son aide technique et ses conseils dans l'analyse des données.

Merci également au Dr. Jean-Paul Guillemot pour ses précieux conseils concernant l'article de ce mémoire.

Je remercie également Mme. Louise Pelletier pour la tâche histologique.

Merci aux membres du laboratoire, et en particulier Jamila Aïtoubah et Frédéric Bretzner.

Je tiens à remercier le Fond des Bourses en Sciences Biologiques du Département de Sciences Biologiques (F.B.S.B.) et le Groupe de Recherche en Neuropsychologie Expérimentale (G.R.E.N.E) pour leur support financier.

Introduction

1-1. Organization of the cortex

To understand how a system works, we need to analyze the organization of the centers. It is known that the nerve cells of the cerebral cortex are distributed in layers. On the basis of the number of layers and their developmental origin, anatomists have subdivided the cortex into three regions: *archicortex*, *paleocortex*, and *neocortex*. Archicortex (hippocampus), and paleocortex (portions of the medial temporal lobe) contain only three cell layers. They are simpler than the six-layered neocortex, which covers most of the cerebrum.

The cerebral cortex of human is a sheet of cells that ranges from 2 to 4mm in thickness and folds into gyri and sulci. If the cortex were flattened, it would occupy approximately 2.5 ft^2. The cortex that is visible when the brain is viewed from the outside is called neocortex. The neocortex is by far the largest component of the cerebral hemisphere in the brain and includes four lobes, which are named frontal lobe, parietal lobe, temporal lobe, occipital lobe. The most striking morphological feature of the neocortex is that its cells are arranged in six well-defined layers, numbered from the pial surface to the

underlying white matter. Layer I, the upmost layer, contains only a few neuronal cell bodies. It is made up largely of glial cells and of axonal processes running parallel to the pial surface and presumably inter-connecting local cortical areas. In contrast, layer II is densely cellular, containing mostly small pyramidal cells. Layer III is composed primarily of somewhat larger pyramidal cells. Layers II and III provide the output that goes to other cortical regions. Layer IV is rich in stellate cells and is the layer that receives most of the afferent input from the thalamus. Layer V has the largest pyramidal cells, they give rise to the long descending pathways that leave the cortex and run to the corpus striatum, the brain stem, and the spinal cord. Layer VI is composed of neurons that project back to thalamus. Just below layer VI is the white matter that carries axons to and from the cortex.

Each cortical region has a characteristic layering pattern that usually results from subdivisions and expansion of one or more of these layers and thinning of other. In primary sensory areas there is a large thalamic input; consequently, layer IV is usually expanded in these areas. Because it contains the stellate cells that are

important for the initial stages of input processing. For example, in the primary visual cortex, layer IV is so thick that it can readily be subdivided into three distinct sublayers: IVa, IVb, IVc. In motor areas that give rise to long descending pathways, layer V, with its longer pyramidal cells, is prominent and layer IV is much reduced in size. The association cortex has a layering pattern that is somewhat intermediate between that of the sensory and the motor cortices.

Although these general principles apply to all areas of the cortices, each area has a slightly different layering pattern. This diversity was shown most clearly by Korbinian Brodmann, who examined the organization of the cell bodies and the fibers in the cortex using the Nissl stain to recognize cell bodies and myelin satins for axons. On the basis of these studies, Brodmann divided the human cerebral cortex into 52 unique cytoarchitectonic areas according to the size of the cells, their packing density, the number of layers in each region, and the density of myelinated axons. Figure 1 is a map of Brodmann's subdivisions that shows the relative contribution of the major cortical areas to the total cortical surface.

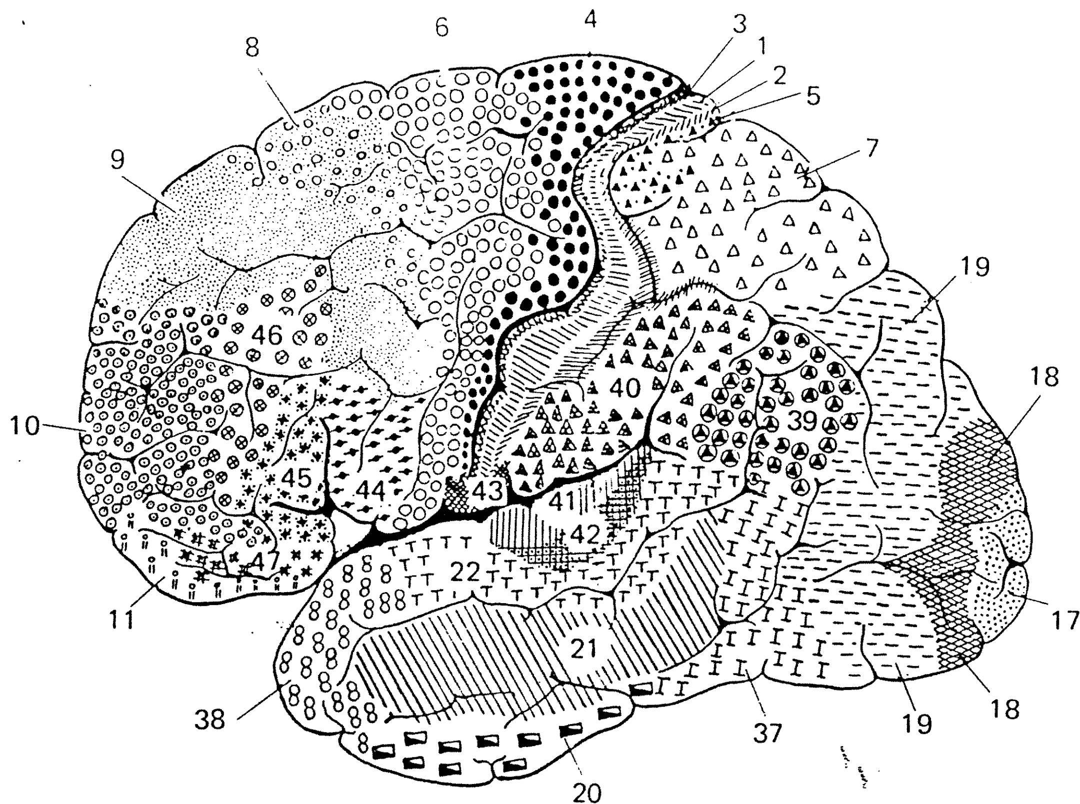

Figure 1: Cytoarchitectural map of the cerebral cortex. The different areas are identified by the thickness of their layers and types cells within them. Some of the most important specific areas are as follow: Motor cortex: motor stripe, area 4; premotor area, area 6; frontal eye fields, area 8. Somatosensory cortex: area 3, 1, 2. Visual cortex: area 17, 18, 19. Auditory cortex: area 41 and 42. Wernick´s speech area: approximately area 22. Broca´s speech area: approximately area 44 (in the left hemisphere). (From Brodmann, in Brodal, 1981)

1-2. Location of the visual cortex

The occipital lobe lies at the caudal margin of the hemisphere and contains the visual cortex. The visual cortex is about 3 mm thick and consists of six layers. The primary visual cortex (Borden's area 17 or visual area V1) lies posteriority in the occipital lobe. This area is also called the striate cortex because it contains a prominent stripe of white matter, which can be seen by the naked eye, hence the name striate. The area immediately surrounding V1 is called extrastriate cortex (Brodmann's area 18 or area V2). The exact boundaries of V2, V3, V4, V5 cannot be defined by simple inspection of the brain. The border of area 17 and 18 is often histologically ambiguous, but it can be estimated from the following criteria: layer III is wider in area 18 than area 17; layer IV is narrower in area 18 than area 17; layer V widens in area 18, adjacent to area 17; a number of large pyramidal cells are located in layer III at the border of area 17 and 18 (Hubel and Wiesel, 1965; Movshon et al., 1978a; Tusa et al., 1978; Sclar and Freeman, 1983; Payne, 1990; Olavarria, 1996).

From the lateral geniculate nucleus, neurons project via the optic radiation to the primary visual cortex. From

the primary visual cortex, neurons project to the higher order, extrastriate cortex. Neurons from area 17 also project to the superior colliculus and back to the lateral geniculate nucleus (LGN). From area 18, neurons project to the medial temporal cortex (area 19), to the inferotemporal cortex (area 20 and 21), and to the posterior parietal cortex (area 17). The inferotemporal cortex and area 18 also receive input from the pulvinar of the thalamus.

1-3. Pyramidal and stellate cells

There are two main varieties of cortical neurons, *pyramidal* and *stellate* cells. Pyramidal cells have a conical body, and the apex of the cone usually points toward the pial surface of the brain. The axon of the pyramidal cell does not stay confined to the local cortical region, it gives off several collateral branches that terminate nearby and then enter the white matter, running toward some distant site in the central nervous system. They are excitatory neurons and are the major projection neurons of the cerebral cortex. In addition, the dendrites contain booster zones that amplify synaptic currents,

thereby enabling distant synaptic sites to be effective. Pharmacological experiments suggest that an amino acid (either glutamate or aspartate) is the neurotransmitter of pyramidal cells (Kandel et al., 2000).

Stellate cells have round bodies that are smaller than pyramidal cells. Dendrites arise from all aspects of the cell body, giving it a star-shaped appearance. Stellate cells are primarily involved in local intracortical processing of afferent inputs; thus the stellate cells are interneurons and serve to establish the appropriate connection within cortical columns. One important class of stellate cells has axons that are oriented vertically in the plane of the cortical columns. These cells receive information directly from thalamic neurons which they convey to other interneurons or pyramidal cells. An example of this kind of stellate interneuron is the spiny stellate cell of the visual cortex. Stellate interneurons are quite heterogeneous and use various transmitters. One class, with vertically oriented axons, contains either vasoactive intestinal polypeptide or cholecystokinin. When administered to cortical neurons, both of these peptides are excitatory, and this suggests that the interneurons that contain them are excitatory. Some stellate cells have

axons that are oriented horizontally, in the plane of the cortical layers. An important cell with this axonal configuration is the basket cell, which forms dense synaptic connections that envelop some of the postsynaptic neuron (hence the name "basket"). The terminal of basket cells contains large amounts of the enzyme glutamic acid decarboxylase, which catalyzes the synthesis of the inhibitory neurontransmitter γ-aminobutyric acid (GABA). For this reason, this cell is likely to be an inhibitory interneuron. The basket cell is thought to produce surround or pericolumnar inhibition, which enables neurons in a given cortical column to function in relative isolation from neighboring columns (Kandel et al., 2000). In the cat visual cortex, the functional topography of large basket cell axons indicate that the some basket cell can mediate iso-orientation ($\pm 0^0 \sim 30^0$), oblique ($\pm 30^0 \sim 60^0$) and cross-orientation ($\pm 60^0 \sim 90^0$) inhibition at different sites. Hence, we assume that large basket cells serve on a complex physiological role depending on the location of the target cells in the orientation map (Kisvàrday et al., 1993).

1-4. Neurotransmitter GABA

Nerve cells differ from other cells by their ability to communicate rapidly with one another, sometimes over great distances and with great precision, Axonal conduction and synaptic transmission provide the means for this rapid and precise communication. Charles Sherrington introduced the term synapse to refer to the specialized contact zone, where one neuron communicates with another. On the basis of morphological criteria, synapses are classified into two type (type I and type II). Most type I synapses end on dendritic spines and are excitatory. Type II synapses end on both dendrites and cell bodies, and usually are inhibitory. Inhibitory synapses generally are located closer to the cell body than excitatory synapses, and this is important for information processing. For example, basket cells synapse on the cell bodies of pyramidal cells in the cortex, thus exerting an inhibitory veto on whether or not an impulse is generated at the initial segment of the pyramidal cell. Synaptic transmission can be electrical or chemical. Electrical synapses, which have bridges (gap junctions) interconnecting the cytoplasms of the pre- and

postsynaptic cells. Chemical synapses are not bridged in the cytoplasm and are separated by a cleft. Chemical transmission can be divided mechanistically into sets of processes. The presynaptic transmitting processes determine the release of the chemical mediator (a transmitter substance). The postsynaptic receptive processes determine the interaction between the transmitter and the receptor molecule in the postsynaptic cell. Neuromuscular junction and the central synapses with rapid excitatory and inhibitory actions are regarded as the simplest types of synapses. More complex types of synapses act on different receptors, activating different second messenger systems. Examples are Ca^{++}, G-protein, and adenosine 3',5'-cyclic monophosphate (cAMP) (Shepherd, 1988).

GABA has been studied extensively. GABA is generally associated with inhibitory actions. GABA is almost uniquely present in the nervous system. Most GABAergic neurons are intrinsic neurons, in regions such as cortex, olfactory bulb, hippocampus, cerebellum, and retina. Within these regions, GABA is present in high concentrations, The predominant action of GABA is inhibitory, by increasing Cl^- or K^+ conductance, causing the membrane potential to become relatively hyperpolarized. These actions are exerted at

both axonal and dendritic output synapses. The inhibitory actions are important for many functions, such as sensory processing, negative feedback, gating of rhythmic discharges, timing and coordination of motor output. Drugs like picrotoxin and bicuculline, which block GABA receptors, cause seizures, which has suggested that dysfunction of GABAergic interneurons in the cortex may be critical in the development of epilepsy. GABA is synthesized from glutamate (Glu), by the enzyme glutamic acid decarboxylase (GAD). The GABA receptor is actually quite complicated. A basic distinction is made between $GABA_A$ receptors, linked directly to the Cl^- channel, and $GABA_B$ receptors linked via the G protein of cAMP to K^+ and Ca^{++} channels (Shepherd, 1988).

GABA is the major inhibitory neurotransmitter in the visual cortex. Every fifth neuron and 15% of synaptic boutons in cat visual cortex contain GABA (Gabbott and Somogyi, 1986; Beaulieu and Somogyi, 1990), and every cortex cell receives a rich GABAergic input (Freund et al., 1983; Somogyi, 1989). Results of experiments employing iontophoretic applications of the $GABA_A$ antagonist bicuculline close to a recorded cell (Sillito, 1977; Tsumoto et al., 1979) established the importance of

GABAergic inhibitory processes for orientation tuning and direction selectivity in cat visual cortex. Bicuculline application also substantially increased response rates. These results argue for a critical role for intracortical inhibition in orientation selectivity (Sillito et al., 1980; Wolf et al., 1986). Furthermore, blockade of GABAergic inhibition has revealed inhibitory contributions to the spatial organization of ON and OFF subregions in area 17 simple cells (Sillito, 1975b; Eysel and Shevelev, 1994), and shifted a simple receptive field into a complex one, and caused a loss of spatial separation of antagonist ON and OFF subfields.

Inactivation by GABA is a powerful tool for studying the function of specific cortical areas. It is especially useful in electrophysiology, because inactivation is reversible within short time periods. Iontophesis of GABA inactivates neurons up to 300μm around the micropipette. Pressure injection of GABA inactivates neurons further away. Chevalier and his collaborators (1985) could inactivate neurons 600μm away from the injection pipette, and Nealay and Maunsell (1994) have shown that GABA was not able to inactivate neurons 1mm away from the pipette. GABA is ideally suited to make possible repeated, fast acting

and precisely localized inactivations without affecting on passant fibers, and is therefore readily applicable for electrophysiological studies, even when the regions of study are very close to each other. Inactivating area 17 by GABA led to various results. In monkeys, inactivating area V1 results in silencing cells of area V2. (Schiller and Malpeli, 1977; Girard and Bullier, 1989; Bullier et al., 1994). In cats (Sherk, 1978) and rats (Molotchnikoff and Hubert, 1990), however, inactivating area 17 fails to modify in a substantial way several specific properties of area 18 neurons. There are also evidences of generalized decreases of responses in area 18 (Donaldson and Dash, 1975; Dreher and Cottee, 1975; Chabli et al., 1998).

1-5. Organization of the receptive fields of areas 17 and 18

Receptive field properties differ from area to area. It is well established that both area 17 area 18 of the cat's visual cortex receive a direct projection from lateral geniculate nucleus. The terminals of geniculocortical axons are distributed to the same cortical layers in the two areas. The relay cells of the LGN can be classified into

three functionally types of cells, X-cells, Y-cells and W-cells. In the latter group most of the axons of reach the superior colliculus. The axons of Y-cells are markedly faster conducting, and presumably larger in caliber than X-cell axons. The axons of X-cells terminate predominantly in area 17, while the axon of many, perhaps all, Y-cells project more widely to cortical area 17, 18 and 19 (Orban, 1984). The distinction between X and Y cells is in several properties. The most important one is the existence of a phase-null position when cells are stimulated with sine-wave gratings in the classical receptive field (Enroth-Cugell and Robson, 1966). Hence the X-cell is characterized by a high degree of linearity of summation, whereas the Y-cell exhibits linear summation only to low spatial frequencies of the stimulating sine-wave grating. This pattern of projection endows cells of area 17 and 18 with distinct properties. Neurons in area 17 prefer relatively high spatial frequencies and respond well to very low temporal frequencies, while neurons in area 18 prefer lower spatial frequencies and respond poorly to very low temporal frequencies (Movshon et al., 1978a; Berardi et al., 1982). X and simple cells feature distinct ON and OFF areas and linear summation. By contrast, Y and complex cells exhibit nonlinear spatial summation properties (Movshon et al.,

1978b). Quite interestingly, previous investigations have reported overlapping inputs from X and Y geniculate cells onto simple and complex cortical cells (Tanaka, 1983).

In monkey, the visual system is composed of multiple, functionally specialized cortical areas. The retino-geniculo-cortical system, parallel magnocellular (M) and parvocellular (P) pathways converge on V1, where they segregate their inputs. The M pathway is believed to provide information about motion and contrast, because neurons in the M pathway have relatively large receptive fields. Neurons in the P pathway have smaller receptive fields, convey fine spatial information, detect color contrast. So P pathway is believed to provide information about shape and color (Shapley and Lennie, 1985; Casagiand and Nortonit, 1991). It is speculated that the P pathway to interblobs is a "X-like" linear system, whereas blobs also receive nonlinear "Y-like" M input (Desimone and Ungerleider, 1989). These relationships suggest a further similarity between the cat and monkey visual systems. In area 17 of cats, blobs receive direct input from nonlinear Y cells (Shoham et al., 1997).

1-6. Simple cells and complex cells

When stimulated with stationary or moving bar or sine-wave grating, cells in the visual cortex gave response that could be interpreted in term of the arrangements of excitatory and inhibitory regions in their receptive fields (Hubel and Wiesel, 1962). Some cells responded in a more complex manner. The great majority of fields seem to fall naturally into groups, which we have termed "simple" and "complex" cells. Simple cells and complex cells have been shown to have different types of facilitatory and inhibitory interactions within the receptive fields (Movshon et al., 1978a, b; Baker 1988; Mclean and Palmer 1989). Complex cells also differ from simple cells in the spatial relationship between ON and OFF subregions. In simple cells, ON and OFF subregions are largely nonoverlapping, and there is antagonism between ON and OFF subregions, whereas in complex cell, the ON and OFF regions overlap. Simple cells exhibit linear spatial and temporal summation, which is clearly not the case for complex cells. (Movshon et al., 1978 b). Simple and complex cell types are identified by classical criteria (Hubel and Wiesel, 1962), and also by the ratio of AC/DC response rate (Skottun et al., 1991). Simple cell response to a drifting grating is

highly modulated, whereas complex cell response is relatively unmodulated. Cells for which the AC/DC ratio exceeded 1.0 were considered to be simple while those with a AC/DC ratio less than 1.0 were classified as complex cells.

According to Hubel and Wiesel (1962, 1965), simple cells comprise the first stage of cortical information processing while complex cells form the second stage of this process. The size of complex receptive fields is larger than that of simple cells. There is also evidence contrary to Hubel and Wiesel's (1962) original report, showing that there is no significant difference in receptive field size between single and complex cell types (Walker et al., 2000). Some properties (large receptive fields, overlapping ON and OFF subregions) of complex cells can be explained by the convergence of afferents of simple cells. In addition, not all complex cells receive their inputs from simple cells; some complex cells can receive their inputs directly from concentric receptive field cells in layer IVc.

Simple cells are often recorded in layers III, IV and VI, and less in layer II and V. (Hubel and Wiese, 1962; Gilbert, 1977). There is a general agreement that simple

cells are the main recipient cell type for LGN axon (Bullier and Henry, 1979a, b; Ferster, 1981). Complex cells are uncommon in layer IV and are more often recorded in layers II, III, and V (Gilbert, 1977; Martin and Witteridge, 1984). While some of the complex cells (20-40%) are directly contacted by geniculate fibers, most receive additional connections from callosal fibers, from recurrent collaterals of corticofugal axons and other intrinsic cortical afferents (Singer et al., 1975; Bullier and Henry, 1979a, b).

1-7. Columnar organization of the visual cortex

The visual cortex is organized into narrow columns of cells. Each column is about 30 to 100μm wide and 2mm deep, running from the pial surface to the white matter. The visual cortex is organized into two sets of interconnections: one vertical, consisting of functional columns spanning the different cortical layers, and another horizontal, connecting functional columns with the same response properties in different columns. In vertical interconnections, orientation selectivity is generated

independently in different layers with a cortical column, and it is conceivable that different mechanisms operate at different sites, which have the same orientation preferred orientation (Malpeli, 1983; Malpeli et al., 1986). The horizontal connections integrate information over many millimeters of cortex. As a result, a cell can be influenced by stimuli outside its receptive field.

Knowledge of the column organization has important implications for population response properties. Columnar organization is most commonly studied using multiple electrode penetrations for single cell recordings (Hubel and Wiesel, 1974; Tusa et al., 1978, 1979; Kaas et al., 1979; Swindale et al., 1987), metabolic labeling by 2-deoxyglucose (2-DG) (Sokoloff, 1977; Hubel et al., 1978), and optimal imagine techniques (Ts'o et al., 1990; Bonhoeffer and Grinvald, 1991, 1993; Buzas et al., 1998) based on intrinsic signals which obtains population activities. Most of these studies have mapped how the response properties change onto the surface of the cortex. In the visual cortex, it is well documented that orientation preference, ocular dominance, and retinotopic location are organized in columns (Hubel and Wiesel, 1962). In addition, directionality columns have been reported

(Payne et al., 1980; Tolhurst et al., 1981; Berman et al., 1987; Weliky et al., 1996). Response latency and temporal frequency are also clustered (DeAngelis, 1999). In an orientation column, different neurons have similar orientation preference and overlapping receptive field. Furthermore, the preferred orientation changes gradually, forming orientation maps (Hubel and Wiesel, 1962, 1963, 1965). The typical organization of orientation maps in the cat visual cortex is arranged radially (the pinwheel-like organization). The salient feature of these maps is that various orientation preferences are grouped around orientation centers in a pinwheel fashion. Swindale and colleagues (1987) report that the average cortical orientation cycle length is 1.25mm±0.13, based on 21 orientation maps, but it has also been demonstrated that long linear sequences (1.7mm) of orientation coexist in area 18 of cats (Shmuel and Grinvald, 2000).

1-8. Connections of areas 17 and 18

Visual information arriving indirectly from the retina through the lateral geniculate nucleus (LGN) of the thalamus enters occipital visual areas 17 and 18. The

analysis of visual images is performed with two models. The hierarchical model proposes that visual features are processed sequentially (Hubel and Wiesel, 1962). The primary visual cortex is at the bottom of such a hierarchy, cells in this area responding to elementary features, whereas in high areas, cells are tuned to different aspects of complex stimuli (Mausell and Newsome, 1987). This suggests that visual processing goes through several stages, from low-level feature extraction in primary areas to complex processing related to perceptual interpretation in higher areas. Anatomical connections, however, indicate that cortical processing is not strictly hierarchical. That is the parallel model which allows simultaneous analysis in different cortical areas (Van Essen and Maunsell, 1962). Moreover, horizontal connections link neurons across large distances within each area (Gilbert, 1993, 1996). For example, area 18 of cat's visual cortex receives two major inputs, one originating in the lateral geniculate nucleus, and another in fibers leaving area 17 (Bullier et al., 1994; Symonds and Rosenquist, 1984). In addition, some studies concluded that all cortical cells could receive direct LGN inputs (Bullier, 1986; Spitzer and Hochstein, 1988). The cortical visual system consists of many richly interconnected areas. Each area is characterized by more or

less specific receptive field tuning properties. The pioneering work of Hubel and Wiesel (1968) triggered an enormous amount of work on receptive field tuning properties of neurons in visual cortical areas, and the receptive field properties differ from area to area.

The connections of the cortical layers in area 17 in cat have been studied by retrograde tracing with peroxidase. Cells in layers IV that receive input from the lateral geniculate nucleus send their axons superficially to layer II and III. Cells in layer II and III project to higher visual areas, such as area 18 and the medial temporal lobe. Cells in layers II and III are the major sources of ipsilateral cortico-cortical connections. In monkey, area V2 does not receive strong direct connections from the lateral geniculate nucleus but receives outputs from area 17. Cells in layer V project to the superior colliculus. Cells in layer VI project back to the lateral geniculate nucleus. Thus this layer exerts a feedback control over visual input reaching the cortex from the thalamus (Kandel et al., 2000).

Areas 17 and 18 of the cat are reciprocally linked through long horizontal connections, which may extend up to several millimeters (Bullier et al., 1994; Salin and

Bullier, 1995). It has been demonstrated that cells connected through horizontal connections in area 17 tended to communicate with each other by sharing a similar preferred orientation (Mitchison and Crick, 1982; Gilbert and Wiesel, 1983, 1989). It is also in accordance with an earlier cross-correlation study showing that horizontal projections in the superficial layers connect cells with the same orientation specificity (Ts'o et al., 1986). This is not the case in area 18, where horizontal connections displayed a bias for interconnecting columns with orthogonal orientation preference (Matsubara et al., 1985, 1987). It is possible that there are differences in the extrinsic connections between areas 17 and 18. Inactivation of area 17 could affect specific receptive field properties of cells in area 18. The main specific effect was a loss of direction selectivity of a number of cells in area 18. The change in direction selectivity came either from a disinhibitory effect in the nonpreferred direction or from a reduction of response in the preferred direction (Casanova et al., 1992). In most simple cells, whenever the difference in orientation was in the iso-range, area 17 decreased the response in area 18, but it augmented the evoked firing rate when the difference was in the cross-range. By contrast, inactivation of area 17 enhanced the

response of complex cells of area 18 when the difference between the two areas was in iso-range. When the difference was in cross-range, area 17 depression produced weaker evoked firing. These investigations suggest that the path connecting area 17 to area 18 may be functionally discriminated on the basis of the orientation domain and cell types (Chabli et al., 1998).

1-9. Objective:

In spite of data reported in the literature, little is known about the mechanisms of response modulation in area 18. In order to further understand feed-forward processes the aim of the present investigation is to examine the reaction of neighboring neurons sharing the same orientation domain in area 18 while a localized zone of area 17 is either excited or inactivated. In anesthetized cats, responses in area 18 were recorded under three basic paradigms. First, a primary stimulus using a sine-wave grating with optimal parameters was placed in the classical receptive field (CRF) of an area 18 unit, while a second grating was positioned in the receptive field of area 17 (the second grating was thus in the periphery of the receptive field of area 18 cells). This supplementary grating had optimal parameters for the area 17 site. Second, the orientation of the patch of area 17 was rotated to be orthogonal relative to the area 18 cells. This dual stimulation was followed by the third step in which the same area 17 site was reversibly inactivated with a micro-injection of GABA.

Paper

Neighboring neurons in area 18 react differently in response to excitation or depression of area 17 in cats

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- This manuscript was submitted (August 1st 2001) to Journal of Neuroscience.
- I have done all the experiments, the data analysis and wrote the first draft of the manuscript.
- Master students J. Aïtoubah and F. Bretzner helped in experiment preparation and participated in the discussion of the results and paper.
- Dr. S. Shumikhina provided process technical help for the experiments, computer programming and discussion of the results and paper.
- Prof. F. Lepore participated in the discussion of the results and paper.
- Prof. S. Molotchnikoff initiated the hypothesis and was directly involved in all steps of this study.

Dr. S. G. Lisberger
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Montréal 30th July 2001

Dear Sir:

We are pleased to submit for publication a manuscript entitled "Responses of area 18 cells to excitation and inactivation of area 17 in cats".

We investigated the modulations of cellular responses of area 18 in the visual cortex when a peripheral target is added outside the neuronal receptive field. Our paper discloses following results: A) When two sine-wave patches are positioned in the visual field the cross influence between these targets modifies the evoked firing rate. The facilitation of responses depends on the orientation disparity between the two patches. In contrast inhibition of the same responses is independent of orientation differences. B) Inactivation of area 17 inverses the relation observed for facilitation whereas inhibition remains unaffected by area 17 depression. C) We also show that two neighbouring cells react in OPPOSITE fashion to the same experimental paradigm, suggesting that even if neurons belong to the same functional domain such as orientation they convey different information. This latter result seems to us very challenging.

We hope that paper will be positively evaluated and I remain.

Cordially yours

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Responses of Area 18 Cells to Excitation and Inactivation of Area 17 in Cats

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Responses of Area 18 Cells

Text: 45 pages Figure: 8

Abstract: 249 words Introduction: 497 words Discussion: 1240 words

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Acknowledgments: We wish to thank Professors M. Anctil, S.K. Itaya and M. Volgushew for helpful comments on this manuscript. This work was supported by NSERC grants to S.M.

Abstract:

The goal of this study is to examine the reaction of neighboring neurons in area 18 while a localized zone of area 17 is either excited or inactivated, in anesthetized cats prepared in conventional fashion for electrophysiology. In area 18 two or more individual neurons were selected from a pool of neurons using a waveform template process. All neurons selected from a single pool had similar optimal orientation (difference $<30^0$). Responses in area 18 were recorded under three basic paradigms. First, a primary stimulus using a sine-wave grating with optimal parameters was placed in the classical receptive field (CRF) of an area 18 unit, while a second grating was positioned in the receptive field of area 17 (the second grating was thus in the periphery of the receptive field of area 18 cells). This supplementary grating had optimal parameters for the area 17 site. Second, the orientation of the patch of area 17 was rotated to be orthogonal relative to the area 18 cells. This dual stimulation was followed by the third step in which the same area 17 site was reversibly inactivated with a micro-injection of GABA. Dual stimulation and inactivation showed that neighboring cells in area 18 displayed opposite

reactions. Cross-orientation inhibition is the most frequent occurrence. Because facilitation is more susceptible than inhibition to GABA inactivation, it is proposed that the former depends on long horizontal fibers while the latter is supported by local circuitry. Results suggest that neurons in the visual cortex simultaneously process independent information.

Key words: iso-orientation, cross-orientation, neighboring cells, stimulus interactions, receptive field, cross-correlograms (XCRGs).

1. Introduction:

Cortical organization rests on the principle that cells exhibiting similar properties are clustered together. This led to the view of columnar architecture as a common feature of cortical organization. In the visual cortex, neighboring cells are well documented to have similar orientation preference, ocular dominance, and retinotopic location (Hubel and Wiesel, 1962). In addition, directionality columns have also been reported (Payne et al., 1980; Tolhurst et al., 1981; Berman et al., 1987; Shmuel and Grinvald, 1996; Weliky et al., 1996). Response latency and temporal frequency are clustered as well (DeAngelis et al., 1999).

In cats, visual information from the retina reaches the cortex (areas 17 and 18) through the lateral geniculate nucleus (LGN). Furthermore, these two areas are reciprocally linked through long horizontal connections (Gilbert and Wiesel, 1979; Swadlow, 1983; Bullier et al., 1994; Salin and Bullier, 1995). Hence, area 18 of cat's visual cortex receives two major inputs: one from the LGN (Orban, 1984), and another from area 17 (Bullier et al., 1984, Symonds and Rosenquist, 1984, Bullier et al., 1994). It has been demonstrated that cells with horizontal

connections in area 17 tend to communicate with each other if they share similar preferred orientation (Mitchison and Crick, 1982, Gilbert and Wiesel, 1983, 1989). However, it has been reported that in area 18, horizontal connections may display a bias for interconnecting columns with orthogonal orientation preference (Matsubara et al., 1985, 1987; Volgushev et al., 1993). Moreover a target located in regions beyond the CRF can influence cellular responses in area 17 of the cat (Walker et al., 1999).

Little is known about the mechanisms of response modulation in area 18. Stimulation of the periphery has both inhibitory and excitatory influences on responses evoked from the CRF (Allman et al., 1985; Nelson and Frost, 1985; Orban et al., 1987; Gilbert and Wiesel, 1989, 1990). Furthermore, in anaesthetized cats inactivation of area 17 by GABA shows that simple and complex cells of area 18 react in an opposite fashion (Chabli et al., 1998).

In order to further understand feed-forward processes the aim of the present investigation was to examine whether nearby neurons sharing the same orientation domain behave in the same fashion. Two or more individual neurons were sorted out from a pool of neighboring cells recorded in area 18 of cats. Cell responses were tested with primary stimulus made of a sine-wave grating with optimal

parameters placed in the CRF, while a second grating was positioned in the receptive field of area 17. The second grating was thus in the periphery of the receptive field of area 18 cells. This supplementary grating was presented under two conditions: either it had the optimal parameters for the area 17 site or orthogonal orientation relative to area 18 cells. Thereafter, the same area 17 was GABA inactivated. Our findings suggest that neighboring cells from a single pool of units in area 18 react in different fashion, in spite of the fact that both cells belong to the same orientation domain.

2. Materials and methods:

2.1 Animal preparation

Adult cats (2.5-3.5 kg) premedicated with Atravel (acepromazine maleate, 1 mg/kg, i.m.) and atropine sulfate (0.04 mg/kg, i.m.) were anaesthetized with ketamine hydrochloride (25 mg/kg, i.m.) prior to catheterisation of the forelimb vein and tracheotomy. Xylocaine (lidocane hydrochloride, 2%) was injected at surgical sites, and xylocaine cream was applied to pressure points. Cats were placed in the stereotaxic apparatus, paralyzed with gallamine triethiodide (Flaxedil, initial dose 40 mg and 10 mg/kg/h during the experiment, i.v.) and artificially ventilated with a mixture of gases (N_2O/O_2, 70/30, supplemented with 0.5-1.0% halothane (Fluothane)) for the duration of the experiment. Flaxedil was delivered to the animal continuously in a mixture of 5% dextrose in lactated Ringer's solution. A heating pad was used to maintain the body temperature at 37.5^{0}C. The end-tidal CO_2 partial pressure was kept constant between 28-30 mm Hg by adjusting the rate and depth of respiration. Proper depth of anesthesia was ensured throughout the experiment by monitoring continuously EEG (electroencephalogram) power spectra and the ECG (electrocardiogram). The EEG was recorded by an epidural silver ball electrode that was

placed frontal to the recording sites. The antibacterial agent Tribrissen (24%, 30 mg/kg per day, s.c.) and the antibiotic Penlong (0.2 ml, i.m.) were administered to the animal. Pupils were dilated with atropine sulfate (1%) and the nictitating membranes were contracted with phenylephrine hydrochloride (2.5%). Plano contact lenses with no artificial pupil were placed on the cat's eyes to prevent the cornea from drying. The loci of the area centralis were inferred from the position of the blind spots, which were ophthalmoscopically back-projected onto a translucent screen.

2.2 Recording of area 18 and local inactivation of area 17

Electrical activity was obtained extracellularly from single unit (micropipette tip diameter: 1.5-3.0 μm) or from multiunit recordings (tip diameter: ~15 μm) in area 18 and multiunit activity (tip diameter: ~20 μm) in area 17. (Horsley-Clarke coordinates F=0.0~-6.0; L=0.0~6.0) Recording and injection electrodes in area 18 and area 17 respectively were separated by more than 3 mm. Cells of these two areas had non-overlapping receptive fields. After the microelectrodes were inserted, the cortex was covered with warm agar (3-4% in saline) and wax. The recording electrode was filled with a solution of sodium chloride

(0.9%), and the injection electrode was filled with GABA (0.1mM). The GABA solution was stained with 2% Chicago Sky Blue to verify subsequently the position of the pipette in histological sections. The injection electrode was inserted in the head of a nanoliter pump (WPI) that was modified to allow simultaneous recordings. The rate of injection was set to 20nl/min until the activity in area 17 became silenced, then reduced to 7nl/min during the time required to complete the experimental protocol. Previously we have shown that this rate of injection silences a tissue volume of 150-200 μm in diameter (Chabli et al., 1998).

2.3 Visual stimulation and data collection

Signals were amplified, displayed on an oscilloscope and played through an audio monitor. The action potentials were passed through a window discriminator and sent to a computer for peristimulus time histogram (PSTH) acquisition. The cells' receptive fields were determined using a hand-held projector with a narrow slit of light projected on a translucent screen placed 57 cm from the cat's eyes. During these preliminary tests, qualitative properties such as dimensions, orientation and directional selectivity, ocular dominance and velocity preference were noted. The quantitative evaluation of cellular response was achieved electronically with images generated on a cathode

ray screen (Mitsubishi Electronics, an effective display area of 380x285mm, with a refresh rate of 120 Hz) centered on the receptive field and synchronized with the data acquisition processes. Tests were carried out with moving bars and drifting sinusoidal gratings. Each stimulus condition usually consisted of a 4 to 5-s presentation for gratings or moving bars. During quantitative tests, visual stimuli were presented in randomized blocks of interleaved trials. Each stimulus was presented for 20~30 trials for PSTHs and for 100~150 trials for cross-correlograms (XCRGs), depending on strength of the firing rate. Spontaneous activity was tested with the same number of trials and under the same luminance as for tests. During the tests, cells were presented with one grating of optimal parameters located in the classical receptive fields of areas 17 or 18 neurons. With two gratings, optimal parameters were presented simultaneously in CRF of both visual areas. In the next step the same optimal parameters were presented in area 18 but with grating in area 17 having an orthogonal orientation relative to area 18. The tests were repeated during a local reversible inactivation of area 17 by GABA application.

2.4 Data analysis

Prior to injection of GABA, orientation tuning curves were obtained in both areas by presenting a bar at various orientations. PSTHs were analyzed in area 18 prior to, during and after area 17 depression. The XCRGs were computed from spike trains accumulated during data acquisition. XCRGs (bin width 1ms) were spanned intervals from -256 to +256 ms. XCRGs analysis was performed to reveal intercortical connections between two areas. The detectability index (DI) indicated if the peak of the XCRG was significant. This is a sign that there is a functional relationship between both units. DI more than 3 is considered to be significant (Melssen and Epping, 1987).

2.5 Spike sorting

Individual units were sorted out from multiunit activity by a spike separation method (DataWave Technologies). The algorithm uses Fast Fourier transform (FFT) and principal component analysis. Spike sorting is based on the assumption that action potentials from different cells have different amplitude and temporal characteristics and that these characteristics are stable during a single trial recording and across trials. Because spike separation was performed off-line attention was first paid to data acquisition. Tests of control recordings were made to insure that a time window of on-line unit

extraction was sufficient to fully reproduce spike waveforms off-line. During the recordings, the action potentials were detected by their voltage threshold and the unit extraction was centered on the peak of action potentials. Usually, three milliseconds of digitized voltages with a peak pre-time of 0.5-0.7 ms were sufficient to reproduce the shape of action potentials. The spike sorting procedure was performed automatically by the software using eight parameters such as amplitude (height) and width of peaks and valleys of the action potential, spike area and ratio of peaks. These principal component values formed clusters and Z-scores indicated the statistical significance of spike separation. Elliptical cluster boundaries were used. The result of cluster analysis as well as of isolated spikes was visually inspected by viewing the distance between clusters and the average of their waveforms in the chosen time window. As an additional control, a raster plot of activity with color coded isolated spikes and histograms of cross-correlation analysis between isolated spikes were checked for possible errors of spike separation. The software permitted manually adjusting parameters chosen for cluster analysis. It should be noted however that a spike separation procedure usually reduces the number of spikes of each particular neuron

because, in the case of simultaneous firing of cells recorded on the same channel, summation of their action potentials produces a waveform of irregular shape which may be assigned as "noise" by the software and thus is cut out of the activity. Also, reducing the number of spikes in isolated neurons is possible in the case of large variations in amplitude of action potentials of the same neuron as usually occurs when spikes arrive in bursts. Because there is typically a gradual decrease in amplitude of consecutive spikes in bursts, a misclassification is possible when the smaller action potentials are designated as another neuron (Eggermont, 2000). We however did not observe such a phenomenon in isolated spikes from our multiunit recordings. Usually, 3 to 4 neurons were reliably sorted out from the activity recorded by the same electrode and the isolated units differed in shape and amplitude.

2.6 Histology

At the end of the experiment, the animals were killed with an overdose of Nembutal. The saline in the recording electrode was replaced by saline+Chicago Sky Blue 4%. Then current was passed through this electrode (±25μv, 10~20 seconds) by a Grass D. C Constant Current Lesion Maker to mark the recording site. The brain was removed and prepared

for histology to confirm the location of the recording and injecting electrodes.

3. Results:

We recorded multiunit activities in area 18. Twenty pairs of cells were sorted out from these multiunit (40 neurons) recordings. Additionally in separate experiments, we recorded 15 single cells and measured their responses. Thus a total of 55 cells were subjected to the full protocol and were thoroughly analyzed. Finally, 17 other cells were recorded but the analyses could not be completed for various experimental reasons. Therefore, these cells were not analyzed. All cells but ten were tested under two stimulus conditions: one was a sine-wave grating with optimal orientation positioned in area 18, another one was two patches set at the optimal orientation for each area and the patch placed in area 17 was ninety degrees in relation to the preferred axis of orientation for the cell in area 18. This adds up to a total of 100 cases.

Cell groups were categorized in relation to the optimal orientation differences between areas 17 and 18. Hence the first group (iso-orientation group) contained units whose orientation disparity was less than 30 deg (0^0-30^0)(N=29). The next class (oblique difference) regrouped cells whose gap between orientations ranged from 31^0 to 60^0 (N=9). Finally the last group (orthogonal or cross-gap) had a

difference in orientation greater than 61 deg. (N=61). It is well documented that a remote patch, although when presented on its own fails to evoke a response, will modulate the strength of the evoked discharge induced from the excitatory zone of the receptive field (Hubel and Wiesel, 1965; Allman et al., 1985; Knierin and Van Essen, 1992; DeAnglis et al., 1994; Li and Li, 1994). It has been reported that when orientations of both patches differ less than 30 deg (iso-orientation configuration), the area 18 cell discharge may be increased or decreased. Similarly, an orthogonal configuration (cross-orientation difference) generates facilitation or decline of responses. Figure 1A illustrates the number of cases exhibiting each effect. Cross-orientation inhibition (32%) is the most frequently observed effect. Figure 1B displays the distance between receptive fields (center to center). It shows that in most cases there was no overlap between receptive fields of areas 17 and 18.

Single cell recordings

The typical example of figure 2 illustrates results for a complex type cell. This neuron of area 18 responded to the sine-wave grating in a pattern characteristic of this family of units which respond by increasing their firing rate in a sustained fashion. The response magnitudes are

shown in Fig.2B. If a second grating, whose orientation and direction are optimal for area 17, was positioned within the receptive field of the latter area, it failed to increase the firing rate of the area 18 cell (not shown). Optimal orientations for both areas are shown in Fig.2C. However, when both gratings are presented simultaneously, as shown in A (middle sketch) the response is considerably diminished (-68%, iso-condition, Fig.2B). A decrease of the same magnitude occurs if the area 17 patch is rotated to become orthogonal in relation to the optimal orientation of area 18 (-75%) (Fig.2A, upper row and B). Thus in this example, the supplementary target produces an inhibition regardless of its orientation (Fig.2A cont. row and B). Area 17 inactivation reduced the excitation of the area 18 cell. Furthermore, GABA injection abolished the interactions between both targets since no modification was observed when they were applied simultaneously. As shown in Figure 2B, the neuron discharged with the same magnitude for all conditions of stimulation during injection. In particular, the decline of the evoked response failed to occur in the presence of the peripheral target. After the arrest of GABA injection in area 17 (Fig.2 Rec. row and B) the higher response amplitude and the inhibition brought by the supplementary target were observed again. This result

suggests that the facilitation and inhibition of discharges depend upon area 17 or long horizontal connections that traverse area 17.

Responses of a simple cell of area 18 are illustrated in figure 3. Simple cells respond to sine wave gratings with a rhythmic pattern that corresponds to the temporal drift of the grating (Fig.3A upper row, cont.). The same paradigm was applied. Dual stimulation produced a robust facilitation when both sine-wave patches were oriented optimally for the respective sites (Fig.3A upper row). Rotating the area 17 patch by 90^0 produced the weakest discharge in area 18. The magnitudes of the responses were plotted in B (Fig.3). Injecting GABA in the same site of area 17 produced a significant reduction of responses when area 18 was stimulated in isolation (Fig.3B). Interestingly, the iso-orientation facilitatory effect was as robust as prior to injection (Fig.3A and B), whereas the cross condition did not change the magnitude of the control response. This result suggests that facilitation under iso-conditions is independent of area 17 whereas inhibition does depend upon area 17 since it is absent during inactivation.

Neighboring cells

In the following sections we describe data obtained through recordings of multiunit activities in order to examine the behavior of neighboring neurons since they were sorted out from a single pool of cells and all exhibited orientation preferences within ~20 deg. Units of each pair thus belonged to the same orientation domain. Fig.4A displays discharge magnitudes of multiunit responses. In the control condition, that is prior to area 17 inactivation, the presentation of two targets together produced less evoked firing in multiunit activity in area 18. The decline of this multiunit activity occurred for both conditions of stimulation, that is for the same and for orthogonal orientations of the sine-wave patch placed in area 17. GABA injection reduced the response when area 18 was stimulated singly. Adding the supplementary target had very little effect. From this pool of cells two neurons were isolated simultaneously, of which spike waveforms are shown in Fig.4B. Although these two units belonged to the same neuronal pool they reacted in opposite fashion when the remote target was applied. Sections C and D show that adding a sine-wave patch in area 17 produced a sharp decrease of the evoked response in cell A, whereas, the companion cell B increased its firing rate at the same

time, in reaction to the identical stimulus configuration. Orientation of the area 17 patch was then rotated to be orthogonal relative to the orientation of area 18 cells. This condition produced the same effect: cell A and cell B exhibited a fall and rise of their firing rates, respectively. Hence these two types of response modulations occur regardless of the orientation of the peripheral target.

Next, the site in area 17 was silenced with a GABA micro-injection. This inactivation results in a diminished excitation of both cells (Fig.4C, D, inj.) Furthermore, the modifications of area 18 responses induced by the presence of the second target are considerably weaker when compared to modifications observed prior to inactivation. This suggests that the changes brought by an additional target are processed at cortical levels through horizontal fibers.

Thus, it is worth emphasizing that these two neurons which belong to the same orientation domain (optimal orientations cell A: 45^0, cell B: 67^0 see Fig.4F for orientation tuning curves) and exhibiting overlapping receptive fields (Fig.4E) behave in opposite fashion to the same experimental paradigm.

In all cases we attempted to disclose the presence of functional connections between pairs of neurons by cross-

correlating spike activity between sorted cells. One example is shown in Fig.5C. The oscillatory pattern of this cross-correlogram discloses an excitatory-inhibitory loop between both units (Perkel et al., 1967). The multiunit responses are illustrated in Fig.5A. The simultaneous presentation of two gratings of optimal orientation for areas 17 and 18 in their corresponding receptive field, enhanced the multi-unit activity in area 18 (Fig. 5A). When the orientation of the grating in area 17 was tilted to be vertical in relation to the orientation of the area 18 cells, the response of the cell in area 18 failed to change (Section A). In this case, the orientation disparity between neurons was 22^0, that is, in the iso-range (Fig.5G). Cells A and B are discriminated at the same time from this particular pool of neurons, of which spike waveforms are shown in Section B (Fig.5). The reaction of each cell to our experimental protocols is displayed in Figure 5D, E. Introducing a second grating of preferred orientation for the receptive field of area 17 cells lead to an iso-orientation inhibition in cell A, and at the same time, to an iso-orientation facilitation for cell B. As the area 17 grating was rotated 90^0 relative to the orientation of the area 18 cell, the B unit diminished its response amplitude,

whereas the nearby cell A maintained the same evoked discharge rate when area 18 was stimulated in isolation.

Inactivating area 17 by GABA injection resulted in a decline of the responses of cells A and B of area 18 when they were stimulated in isolation. For cell A adding a second target in iso-orientation condition slightly facilitated the response. The cross-orientation stimulus produced a weaker response. For cell B adding the second patch produced a sharp decline of activity regardless of orientation of the remote target.

Although these two neurons (cells A and B) belong to the same orientation domain and their receptive fields are superimposed (Fig.5F), they reacted differently.

In addition, it is interesting to note that response changes observed in single cells are quite different when compared to modifications measured in multiunit recordings (same pool). Out of 20 tested pairs 70% showed different behavior when submitted simultaneously to our paradigms and only in 30% of pairs did cells react in a similar fashion (Fig. 6).

Group data

In previous sections we have shown how individual cells reacted to our experimental conditions. Figure 7 displays the average changes of response magnitude in relation to

the optimal orientation difference between both areas. Prior to injection, a cross-orientation condition produced stronger facilitation (219%±40) than when iso-orientation was applied (150%±14) $P<0.06$. This latter trend was reversed during area 17 inactivation. Indeed, if the difference of orientation was in the iso-range (less than 30^0), the increase of discharges reached (282±66, $P<.05$). Also, the higher magnitude of changes when area 17 was inactivated suggests a release from inhibition or a subtraction of an additional excitatory input from area 17.

Figure 7B shows that inhibition is relatively independent of orientation disparities between areas, because the same level of inhibition was observed regardless of orientation differences between the two areas. Furthermore, area 17 inactivation did not modify the average decrease of responses, that is, the same level of inhibition was recorded when area 17 was injected with GABA, indicating that flanked stimuli exert their action through local or short-range connections. Finally, Figure 7C illustrates curves obtained with all cells grouped together with recovery from GABA application. It shows that effects were fully reversible.

4. Discussion:

The present investigation disclosed several new findings: which may be summarized as follows. Neighboring cells of area 18 with similar orientation preferences react in different fashion when a second sine-wave patch is applied in area 17, or in the far periphery of the receptive fields. Furthermore, inactivation of the same area 17 site also produces different reactions in neurons belonging to the same pool of cells. Facilitatory effects are dependent on differences of orientation between patches in areas 17 and 18. In contrast, inhibitory effects are of similar magnitudes regardless of the orientation disparity between the supplementary and the primary target. We also show that when area 17 is inactivated facilitation is more affected than inhibition, supporting the notion that the latter is carried by local circuitry. Data also suggest that neighboring cortical cells convey quite different neuronal information since they react in an unparallel fashion.

Although peripheral patches are mute since they fail to evoke neuronal impulses when presented in isolation, they do modulate central responses. The direction of the modulation of cell responses depends on various factors.

First, a facilitation of evoked discharges is associated with the dominant orientation of the stimulated or inactivated site. Cross-orientation conditions produce facilitation of significantly higher magnitude than increases obtained with iso-conditions. Depressing area 17 inverts these relationships. In contrast, decreases of responses appear to be independent of orientation differences between sites as the magnitude of the response decline is of the same strength regardless of the orientation difference. Interestingly the inactivation of area 17 fails to influence response decreases brought by dual stimuli conditions. This may be explained by the fact that inhibition may be mostly due to local connectivity and consequently long-range connections exert a lesser role in response declines.

In the cortex, visual response properties arise from complex cortical networks within which neurons exhibit functional relationships. It is well known that visual cortical neurons have CRF with well defined boundaries beyond which the targets are ineffective in exciting neurons. In contrast, stimuli falling within the bounds of CRF evoke excitatory responses. In addition, the central response diminishes when two gratings are presented simultaneously with the peripheral grating being at a

different orientation relative to the optimal orientation of the central core (DeAngelis et al., 1992). Within the limits of the receptive field, if this second grating is orthogonal to the central one, it produces a sharp suppression of excitation, which is called "cross-orientation inhibition" (Bonds 1989; Morrone et al., 1982). The modulation of the central discharge is also obtained if the supplementary grating is placed outside the edges of the CRF. At intracellular level, it has been demonstrated that remote targets may significantly alter membrane potential at sub-threshold levels for spike generation (Hirsch and Gilbert, 1991; Welikely et al., 1995). This modulation leads to a decrease of the central response when the remote stimulus is in an iso-orientation axis with respect to the preferred orientation of the receptive field (Dragoi and Sur, 2000; Walker et al., 2000). Conversely, the responses may be facilitated when the surround stimulus is in cross-orientation (Gilbert and Wiesel, 1990; Walker et al., 1999; Dragoi and Sur, 2000). In summary then, supplementary targets strongly impact on central responses through two neuronal circuits, namely short (within receptive field) or long (outside receptive fields) horizontal fibers (Bishop et al., 1971; Sillito, 1975; Eysel et al., 1990; Crook et al., 1991).

The neuronal circuitry of area 18 in cats is still far from being fully understood. Area 18 receives two main excitatory inputs, which are from geniculate and from long horizontal connections of area 17. Area 17 also receives feedback inputs from area 18 cells (Mignard and Malpeli, 1991). Both feed forward and feedback connections are mostly excitatory (Salin and Bullier, 1995). Long horizontal connections arise from pyramidal neurons, which send excitatory inputs to cells with the same orientation preference, but also can elicit suppressive effects via inhibitory interneurons (McGuire et al., 1991). Local inhibition networks play important roles within visual areas (Volgushev et al., 1993; Bullier et al., 1996). Inhibition is expected to arise from local inhibitory neurons. Some studies suggest that local inhibition within the cortex plays a modulatory role to generate orientation selectivity (Bishop et al., 1971; Sillito, 1975; Eysel et al., 1990; Crook et al., 1991). Several computation models attempted to demonstrate that lateral connections are not orientation specific in area 18 (Hata et al., 1991; Tamura et al., 1996). For instance, 53-59% of excitatory and 46-48% of inhibitory connections are mediated through iso-orientation fibers; the rest are connected via cross-orientation paths (Kisvàrday et al., 1997). Furthermore,

interneurons are presumed to mediate iso- and cross-orientation stimuli.

Local network

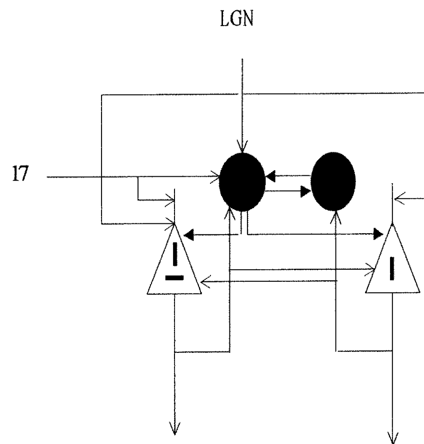

Fig. 8

The scheme depicted in Fig.8 summarizes push-pull mechanisms taking place between excitatory and inhibitory neurons as proposed by Dragoi and Sur (2000). The proposed circuit is slightly modified to take into consideration our data. In case of cell A (Fig.4C), the decay of responses due to the presence of the second targets were obtained via an inhibitory neuron, such as basket cells which are known to have a relatively broad tuning curve for orientation (Kisvàrday and Eysel, 1993). This inhibitory interneuron receives three inputs: one from area 17 (Bullier et al., 1984; Symonds and Rosenquist, 1984; Bullier et al., 1994), one from a nearby cell (Das and Gilbert, 1999), and

another from direct excitation of the LGN (Orban, 1984; Bullier, 1986). The facilitation obtained in cell B (Fig.4D) may be attributed to direct excitatory connections between pyramidal cells (Gilbert and Wiesel, 1979, 1983; Rockland and Lund, 1982; Martin and Whitteridge, 1984). Since depressing area 17 allows a relatively robust response one may assume that the input from other sources is prevailing. However the interactions between targets are very much reduced. In both cells, the changes of the magnitude of responses brought by the remote patch are smaller when compared to changes observed prior to GABA injection. Thus, although the neurons may receive a direct excitation from the LGN the relationships between targets are processed through cortico-cortical pathways. This push-pull mechanism allows the resulting net excitation or inhibition to shift in either direction depending on which contacts are more active. In our experiments, the second patch is positioned well outside the receptive field of the area 18 cell and it can either facilitate or inhibit the response. The former modulation appears to depend on the difference of orientation between sites. Interestingly, a cross-orientation configuration produces facilitation of higher magnitude than an iso-orientation arrangement. This latter relationship reverses when area 17 is inactivated.

Therefore, the target neuron appears to be contacted by cells having a broad spectrum of orientation preferences. Silencing area 17 cells, which is equivalent to removing one input, shifts the balance in favor of the remaining inputs.

By presenting simultaneously two stimuli we excite two sites in area 17 and 18. Hence neuronal interactions within area 18 may suffice to produce the observed modulation in our study. However, GABA injections failed to modify interactions between stimuli in only 17% of cases, thus suggesting a dominant contribution of the area 17. This may be so because the distance between receptive fields was superior to 2 deg in most cases. This distance may be too great to allow interactions carried exclusively through local area 18 circuits. It is also possible that local connections of area 18 are activated by area 17 efferent fibers.

Finally our results convey an additional message: brain imaging techniques occlude particular cellular activities.

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Figure 1

A: Summary of effects in relation to orientation disparities. Iso-F: Iso-orientation facilitation (<30^0); Cro-F: cross-orientation facilitation (>60^0); Iso-I: iso-orientation inhibition; Cro-I: cross-orientation inhibition; Obl-F: oblique-orientation facilitation; Obl-I: oblique-orientation inhibition (31^0~60^0); Unch: unchanged response. This histogram illustrates that cross-orientation inhibition is the most frequent occurrence. **B:** The distribution of inter-receptive field distance between areas 17 and 18 recording sites (N=35). Distance measured from center to center.

Figure 2

Modulation of responses of a complex cell. Single unit recordings. **A:** (upper row) Scheme of stimulus conditions. Opt. ori.: optimal orientation; orth.: orthogonal orientation; 17,18 refer to areas. Peristimulus time histogram (PSTH). Cont. row: Control, prior to GABA injection in area 17; Inj. row: Injection, during inactivation of area 17 with GABA; Rec. row: Recovery, after injection during recovery phase. Same for other figures. This example shows that dual stimulation of areas 17 and 18 produce a decline of cell discharges in area 18. This decline occurs when area 17 is presented with a grating whose orientation is optimal for area 17 and when this grating is rotated orthogonally in relation to area 18 neuron (Cont. row). The inactivation of area 17 decreases area 18 response and the interactions between both stimuli fail to occur (Inj. row). **B:** Response magnitude (Spikes/sec) (mean±SE). Bars are coded to correspond to stimulus conditions. **C:** Orientation tuning curves for areas 17 and 18. The arrow-heads point to optimal orientations. The orientation difference between these two areas is in iso-range. Insert: receptive field locations in relation to the area centralis (AC).

Figure 3

Modulation of responses of a simple cell. Single unit recordings. **A:** PSTH. Simultaneous stimulations of areas 17 and 18 enhance the response of the unit in area 18 when area 17 is excited with an optimal orientation grating. If area 17 is presented with a grating whose orientation is orthogonal to the area 18 cell, the evoked discharges of the area 18 cell are diminished (Cont. row). The inactivation of area 17 fails to modify the above influences (Inj. row). **B:** Response magnitude (spikes/sec) (mean±SE). Bars are coded to correspond to stimulus conditions. **C:** Orientation tuning curves for areas 17 and 18. The arrow-heads point to optimal orientations. The orientation difference between these two areas is in iso-range. Insert: receptive field locations in relation to the area centralis (AC).

Figure 4

Cells of the same pool react in opposite fashion. **A:** multiunit recordings. Response magnitude (spikes/sec) (mean±SE) bars are coded to correspond to stimulus conditions. The arrow-heads point to spontaneous activity levels. **B:** Spike waveforms are sorted out simultaneously from multiunit activities. They are labeled cells A and cell B. Z score=2.52. **C. D:** Plots of response magnitude for cell A and B. A supplementary grating stimulus in area 17 decreases the responses of cell A and increases the responses of cell B in area 18, regardless of the orientation of the patch in area 17. **E:** Receptive field locations in relation to the area centralis (AC). In area 18, receptive fields of cells A and B are superimposed. **F:** Orientation tuning curves for area 17, cells A and B. The arrow-heads point to optimal orientations. The optimal orientations for area 17, cell A and cell B are 22^0, 45^0 and 67^0 respectively. Cells A and B are in the same orientation domain.

Figure 5

Cells of the same pool react in different fashion. A: Multiunit recordings. Response magnitude (Spikes/sec) (mean±SE) bars are coded to correspond to stimulus conditions. The arrow-heads point to spontaneous activity levels. **B:** Spike waveforms are sorted out simultaneously from multiunit activities. They are labeled cells A and cell B. Z score=3.79. **C:** Cross-correlogram analysis between areas 17 and 18 spike trains. Note the oscillatory pattern typical of an excitation-inhibition loop with no or weak common input. **D. E:** Plots of response magnitude for cell A and B. The second grating in area 17 produces iso-orientation inhibition in cell A. At the same time it creates an iso-orientation facilitation and cross-orientation suppression in cell B. **F:** Receptive field positions in relation to the area centralis (AC). In area 18, receptive fields of cells A and B are superimposed. **G:** Orientation tuning curves for area 17, cells A and B. The arrow-heads point to the optimal orientations. The optimal orientations for area 17, cell A and cell B are 67^0, 67^0, 45^0 respectively. They are in iso-range.

Figure 6

Summary of the simultaneous reaction of 20 pairs of neighboring neurons. This histogram shows 70% of neurons react in different fashion, 30% in identical fashion to the same stimulus paradigm. Diff.: difference, Iden.: identical.

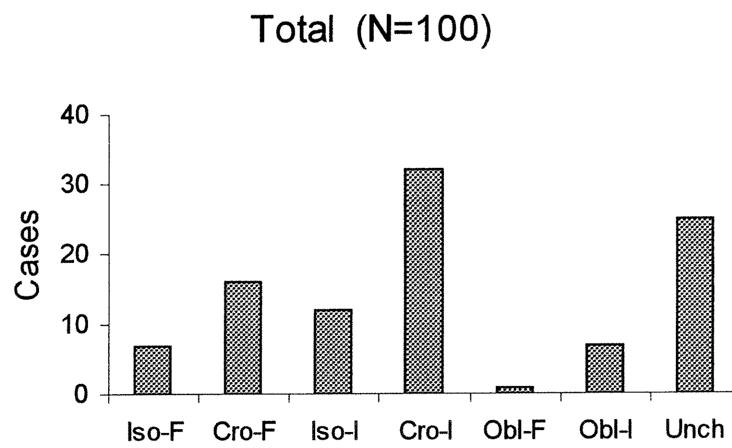
Figure 7

Relationship between response changes and orientation difference between areas 17 and 18. Cont.: prior to injection of GABA in area 17; Inj.: during inactivation of area 17; Rec.: after injection during recovery phase. **A:** Excitation: mean response changes. **B:** Inhibition: mean response changes. Inhibitory effects are orientation independent. **C:** Mean response changes. All cells grouped. (*$p<0.05$; **$p<0.06$). 100% is the magnitude of control response: cells in area 18 are stimulated in isolation.

Figure 8

The scheme of local population interactions between excitatory and inhibitory neurons in area 18. Filled circles: inhibitory neurons, white triangles: excitatory neurons. The bars inside cells indicate the optimal orientation for areas 17 and 18. 17: area 17, LGN: lateral geniculate nucleus.

A



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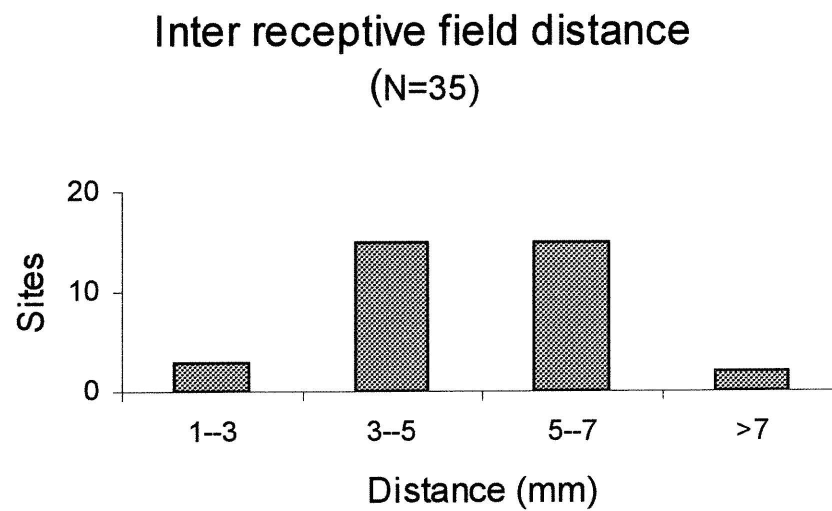
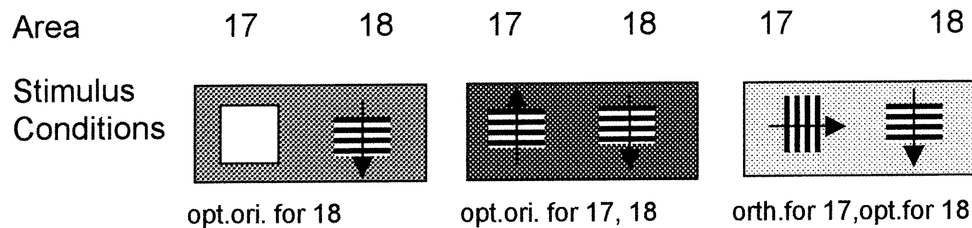
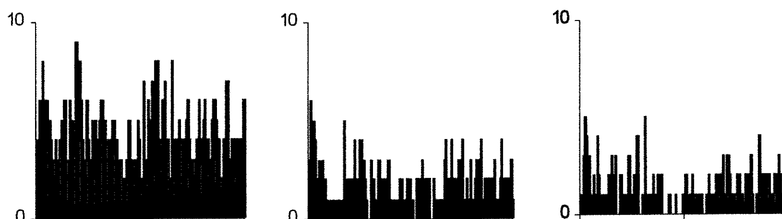
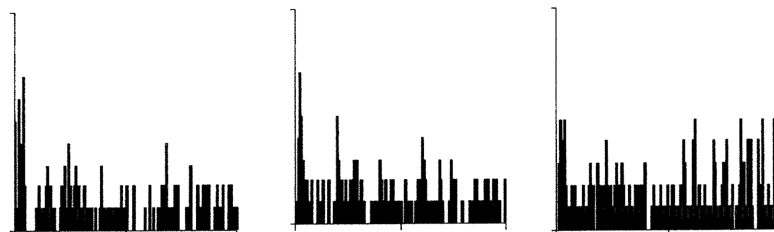
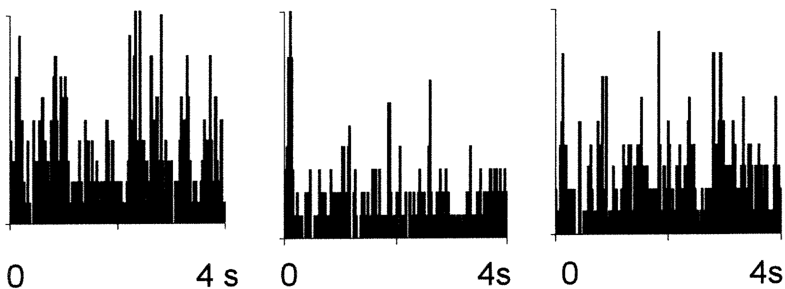


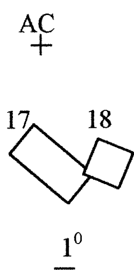
Fig. 1

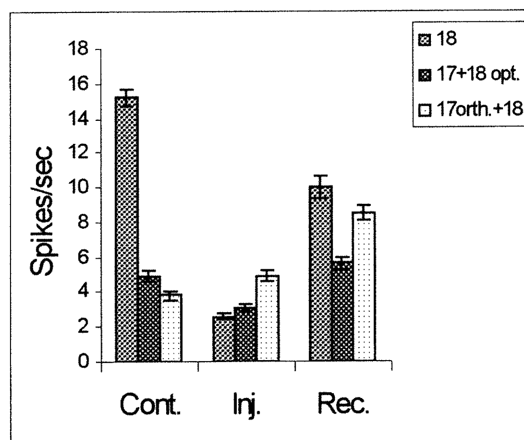












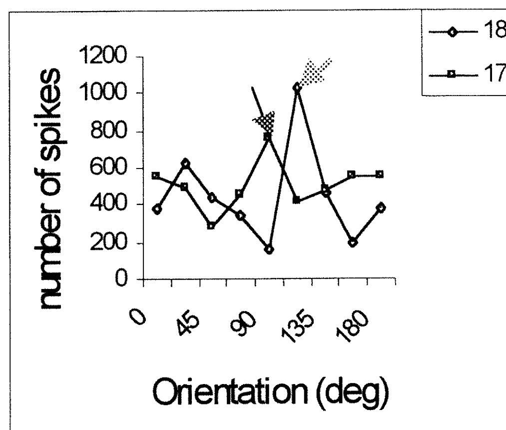
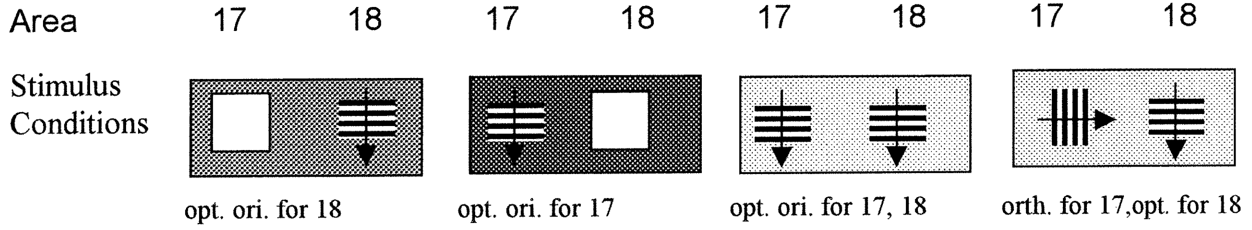
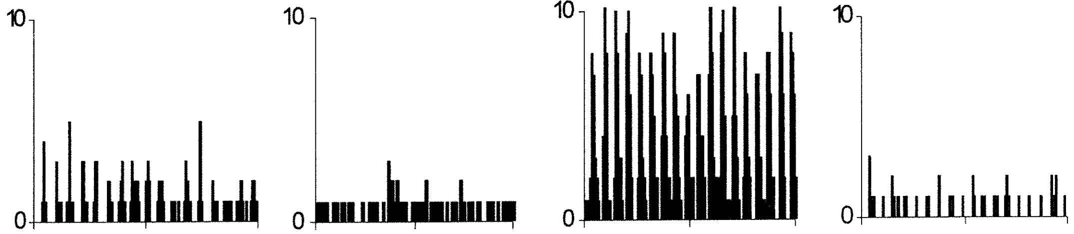


Fig. 2

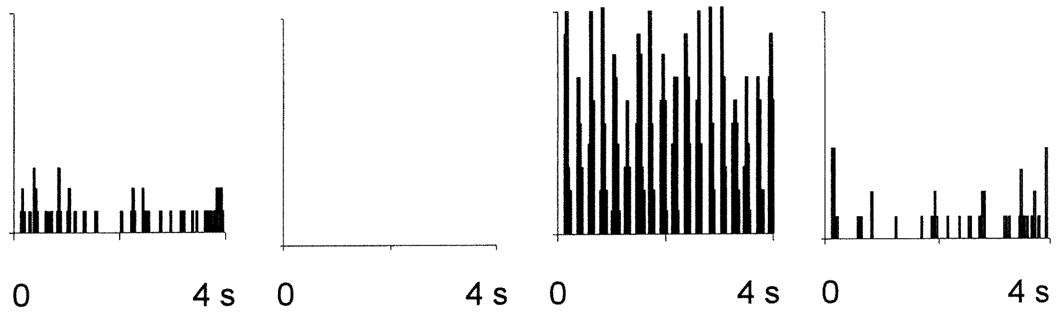
A



Cont.
Spikes/bin



Inj.



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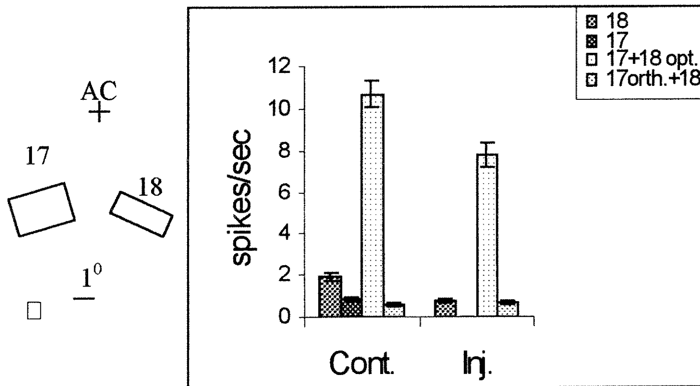

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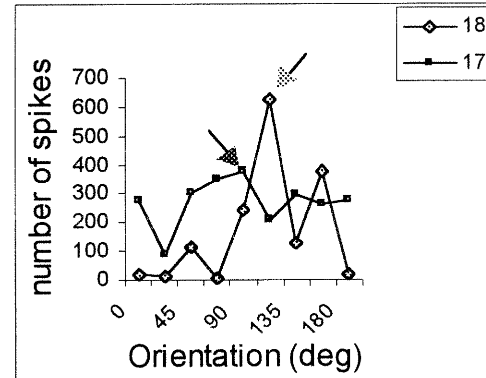


Fig. 3

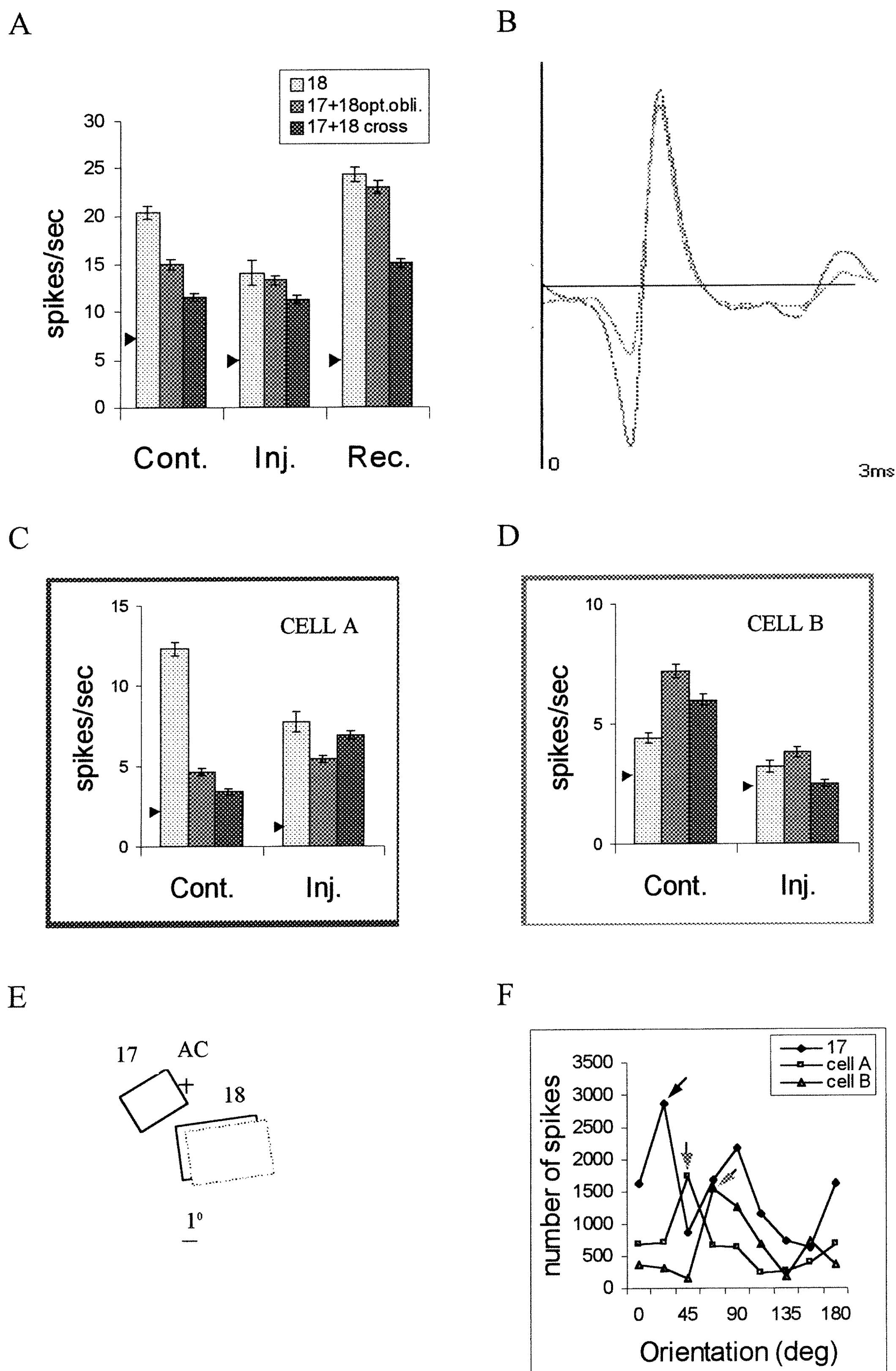
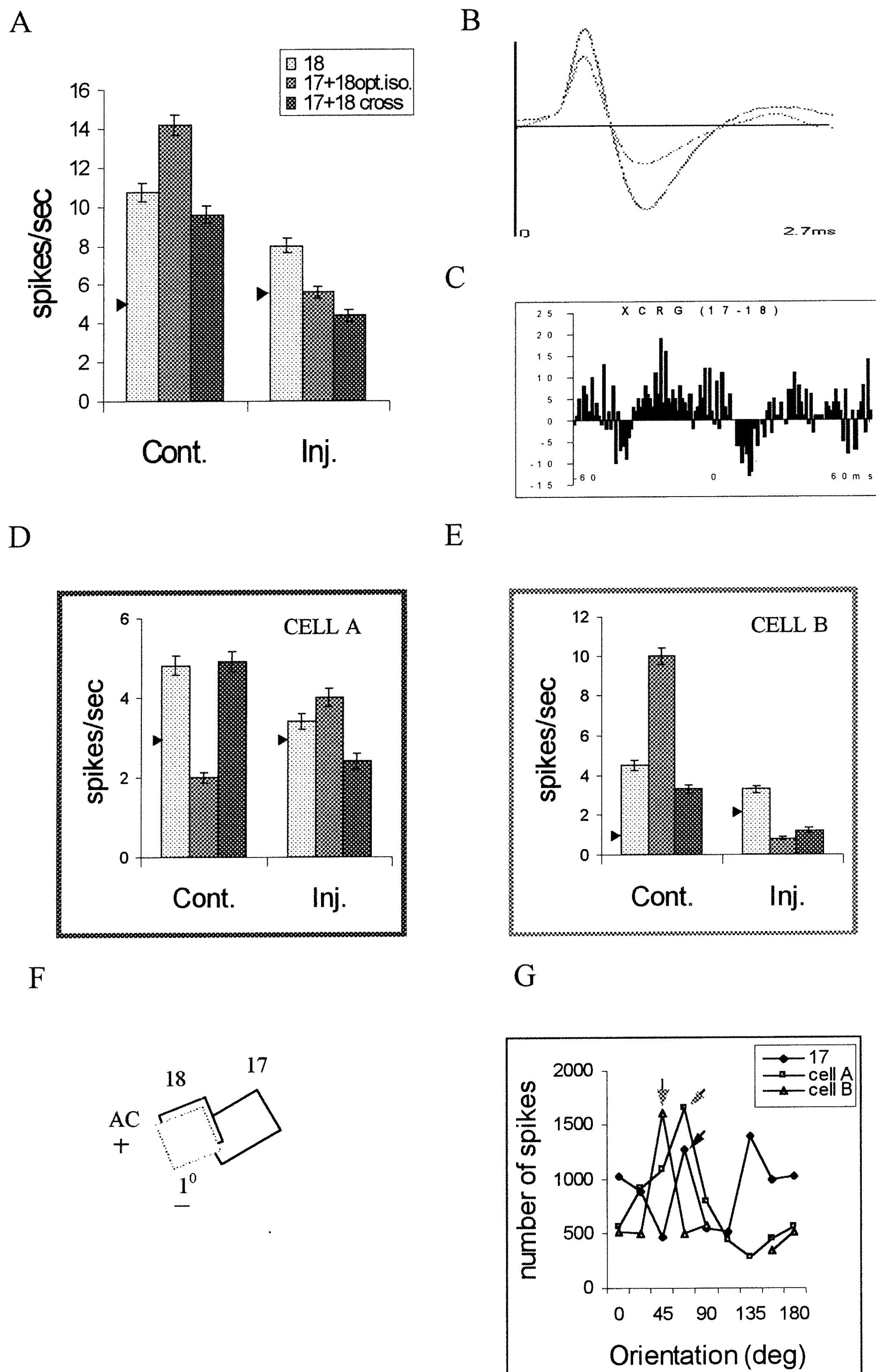


Fig. 4



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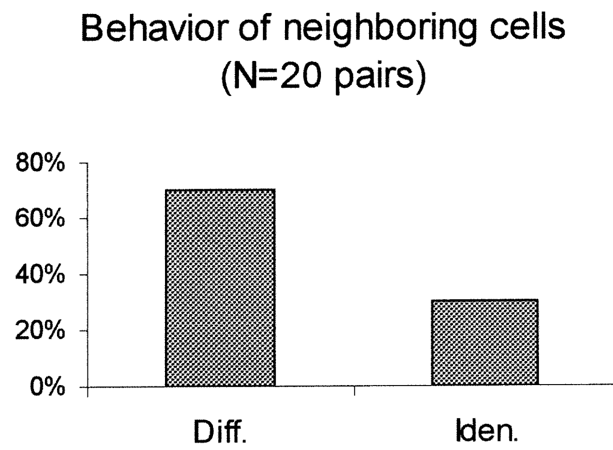
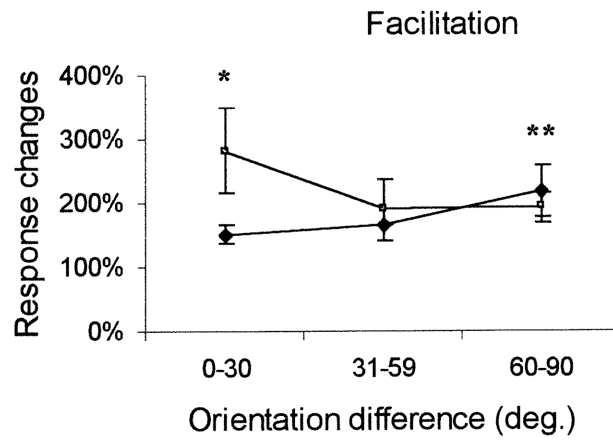
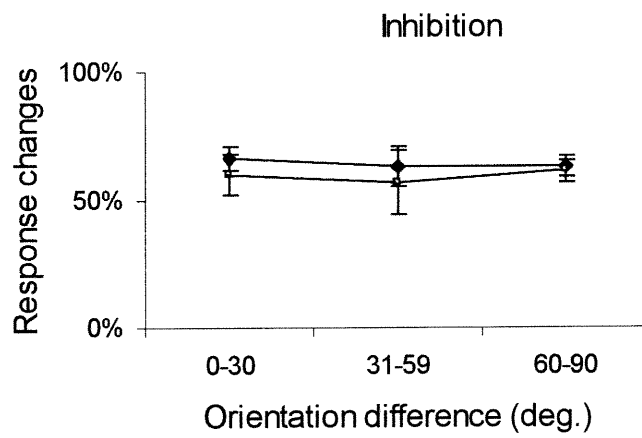


Fig. 6

A



B



C

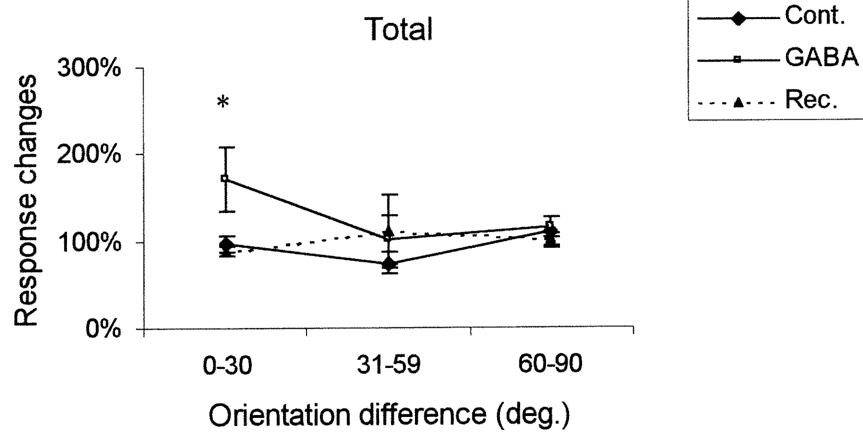


Fig. 7

General discussion

3-1. Receptive fields of the LGN and cortical neurons

In visual cortex, even though many neurons either simple or complex cells, receive their excitatory inputs from the lateral geniculate nucleus, which are largely insensitive to orientation, the response in the visual cortex is critically dependent on stimulus orientation. The main difference between cortical cells and LGN neurons is the shape of their receptive fields. Lateral geniculate neurons have concentric receptive fields, about one degree in diameter, with an antagonistic center-surround organization. Both ON-center and OFF-center geniculate cells respond well to small spots of light in the center of their receptive fields. Hubel and Wiesel (1962) have suggested that a simple cell field subregion is generated directly by excitatory inputs from a row of geniculate neurons. Thus subregions of cortical cell receptive fields are the projections of elongated receptive fields of several LGN neurons, and the width of the cortical receptive field subregion corresponds to the diameter of the geniculate receptive field centers. When the stimulus is oriented appropriately to fall simultaneously on all subregions of the cortical receptive field it produces a

strong response, but when the stimulus is improperly oriented, stimulating only a part of the receptive field, it evokes a weak response. In addition, an improperly oriented stimulus will not excite the cell because of the side-band inhibition.

3-2. Plasticity of cortical receptive fields

The modification of the receptive field properties can be termed "plasticity" or "dynamics". It is well documented that the development of the visual system is influenced by the visual experience during a critical period of postnatal life (Hubel and Wiesel, 1963, 1965). On the other hand, plasticity of adult primary visual cortex has been demonstrated. It has been reported that modifications in the orientation preference of cells occur when appropriate orientation is simultaneously presented outside the receptive field (Gilbert and Wiesel, 1990; Sillito et al., 1995; Sillito and Jones, 1996; Levitt and Lund, 1997), suggesting the influence of the regions surrounding the classical receptive field which may involve long-range horizontal connections. Dragoi and colleagues (2000) showed that orientation preference shifts following short-term and

long-term adaptation and cause a reorganization of orientation selective responses, suggesting that visual cortical neurons maintain a high level of discriminability for improving visual information (Coppola et al., 1998; Whitaker and McGraw, 2000). There is also evidence that changes in ON- and OFF- receptive field organization follow different pairings of current with visual stimuli (Shulz et al., 1993). Petter and Gilbert (1992) demonstrated that changes in receptive field size occur by conditioning with differing orientation stimuli. These modifications may be due to a form of synaptic plasticity or adaptation. In V1, the stimulation of silent regions outside the receptive field can modify a cell's sensitivity even in the absence of driving stimuli (Gilbert and Wiesel, 1992; Das and Gilbert, 1995). This illustrates an important role of contextual influences in perceptual cortical plasticity.

3-3. Measurement of classical receptive field size

Various methods were used to measure a classical receptive field size. The hand-plotting technique was performed by using a projector with a narrow light slip sweeping across the classical receptive field (CRF) (Hubel

and Wiesel, 1965; Barlow et al., 1967; Bishop and Henry, 1972). In my experiments, I used this method. This technique is a convenient and fast way to estimate the location and the dimensions of the CRF producing the smallest CRF size (the minimum receptive field) while the reverse correlation method yields detailed maps of the receptive field (Jones and Palmer, 1987a, b; DeAngelis et al., 1993, 1995a; Alonso et al., 1996; Ohzawa et al., 1996). In this method, the visual stimulus is a sequence of small bright and dark rectangular bars which flash randomly over the different locations in the receptive field of the recorded neurons covering the entire receptive field. This technique is very powerful for defining a slightly larger CRF.

3-4. The classical receptive field and the surround

According to the conventional interpretation (Hartline, 1938), the classical receptive field was defined as the region in which appropriate stimuli can elicit an excitatory response from a cell; while surround was defined as the whole area "outside" the region determined as the classical receptive field. Thus, area 17 is in the

periphery of the receptive field of area 18 cells. If a "surround" stimulus evoked a response when presented alone, it was considered to be stimulating the classical receptive field but not the surround effect. Therefore, the suppressive surround is the most prominent effect although its strength varies substantially from cell to cell. Surround modulations were segregated into three groups, based on the position of the surround stimulus. Hubel and Wiesel (1965) have originally observed end-stop (end-stopping cell responds optimally to a length of the stimulus bar, thus the response decreases if the bar is extended beyond the length of the receptive field) only in complex cells but several other studies have shown that these properties applied to simple cells as well (Dreher, 1972; Rose, 1977; Kato et al., 1978; Orban et al., 1979a, b; Bolz and Gilbert, 1986; Knierim and Van Essen, 1992; DeAngelis et al., 1994; Li and Li, 1994), suggesting that there was virtually no difference in the strength of suppression between these two cell types (Walker et al., 2000). In general, end-stopping is thought to be expressed by cells in all cortical layers but it is more common in the upper layers (Camarda and Rizzolatti, 1976; Gilbert, 1977; Rose, 1977; Sillito, 1977; Kato et al., 1978; Leventhal and Hirsch, 1978; Bullier and Henry, 1979; Henry

et al., 1979; Sherk and LeVay, 1983). The majority of the studies investigated end-stopping only, in which bar stimuli were used. In contrast, others have studied the side-stop zone (side-stopping cell responds optimally to a width of the stimulus bar, thus the response decreases if the bar is extended beyond the width of the receptive field) (Glezer et al., 1973; Albus and Fries, 1980; De Valois et al., 1985; Born and Tootell, 1991; Knierim and Van Essen, 1992; DeAngelis et al., 1994; Li and Li, 1994) or used stimuli that encircle the classical receptive field (Blakemore and Tobin, 1972; Maffei and Fiorentini, 1976; Nelson and Frost, 1978; Knierim and Van Essen, 1992; Li and Li, 1994; Lamme, 1995; Sillito et al., 1995; Zipser et al., 1996; Sengpiel et al., 1997). Some studies, using sine-wave grating stimuli, have shown that suppression may arise from any region in the surround (Walker et al., 1999).

Traditionally, within the classical receptive field of visual neurons excitation is elicited by the visual stimulus with optimal parameters, such as orientation, direction, spatial frequency, contrast, velocity, and so on. Inhibition is easily demonstrated with orthogonal orientation (Morrone et al., 1982). Outside the classical receptive field, stimuli can modify the responses evoked from the receptive field, but stimuli presented in

isolation beyond the classical receptive field should not excite the cells (Hubel and Wiesel, 1965; Allman et al., 1985; Knierim and Van Essen, 1992; DeAngelis et al., 1994; Li and Li, 1994). There are a variety of influences on the orientation selectivity in the receptive field from the periphery. Several studies in cat (Blakemore and Tobin, 1972; Nelson and Frost, 1978; Orban et al., 1979; DeAngelis et al., 1994; Li and Li, 1994) and in monkey (Born and Tootell, 1991; Knierim and Van Essen, 1992) have shown that the response to a preferred orientation could be diminished by a peripheral stimulus and that this surround inhibition was maximal when stimuli were at the same orientation. However, it has been reported that stimulation beyond the receptive field causes inhibition independent of orientation (Bishop et al., 1973; Maffei and Fiorentini, 1976). Facilitation has also been reported for a wide variety of configurations and appears to be context dependent (Maffei and Fiorentini, 1976; Li and Li, 1994; Kapadia et al., 1995; Sillito et al., 1995; Rossi et al., 1996; Levitt and Lund, 1997; Polat et al., 1998). Some studies have demonstrated that contextual influences extend far beyond these local modulatory zones (Allman et al., 1990; Gilbert and Wiesel, 1992; Knierim and Van Essen, 1992; DeAngelis et al., 1994; Li and Li, 1994; Kapadia et

al., 1995; Sillito et al., 1995; Zipser et al., 1996). Contextual surround modulation has been interpreted as some psychophysical phenomenon such as the tilt illusion (Gilbert and Wiesel, 1990), perceptual pop-out (Kastner et al., 1997; Knierim and Van Essen, 1992; Nothdurft et al., 1999), and figure-ground segregation (Lammer, 1995, 1997; Zipser et al., 1996).

Areas outside the classical receptive field have been studied extensively. Surround modulatory effects are not always linked to the orientation stimuli but can also depend on a variety of stimulus parameters in the receptive field, including differences in direction, spatial frequency, velocity, contrast and so on. In my experiments, I just tested the orientation disparity between two receptive fields in areas 17 and 18. Thus the receptive field of area 17 was in the surround of the receptive field of area 18. Therefore, I focus on the orientation-dependent surround modulatory effects to the classical receptive field.

3-5. Surround facilitatory effect

Different orientations of the surround sine-wave gratings produce effects of different strength.

Facilitatory effects of surround stimulation occur only when central and peripheral gratings are iso-oriented (Maffei and Fiorentini, 1976). There is also evidence of this sort of disinhibition of surround stimulus expanded to remote area (Li and Li, 1994). My single unit recordings (Figure 3 in paper) show that when two gratings with the same orientation (90^0 optimal for both areas) were positioned in the receptive fields of areas 17 and 18 separately, a strong facilitation was elicited. This is consistent with the findings of Li and Li (1994). Some facilitatory effects require a very precise alignment of central and surround stimuli (Nelson and Frost, 1985; Gilbert and Wiesel, 1990), but according to other investigations a strong facilitation appears when the surround stimulus is oriented orthogonally to the receptive field excitation (Sillito et al., 1995). In monkey, responses of V1 neurons also tend to be stronger when a cross-orientation is presented in the surround (Knierim and Van Essen, 1992).

Another factor contributing to the iso-orientation facilitatory effect from the surround is the contrast for central and surround stimuli. Iso-orientation surround stimuli exhibit excitatory influences with low contrasts,

and inhibitory was with higher contrasts (Sengpiel et al., 1997).

3-6. Surround inhibitory effect

In addition to the surround facilitation described above, a surround inhibition is also observed. Several studies (Orban et al., 1979a, b; DeAngelis et al., 1994; Li and Li, 1994) have suggested that the end- and side-inhibitions appear when the stimulus is aligned with the stimulus in the receptive field. That is in agreement with data obtained by Sengpiel et al. (1997) where inhibitory surround effects were strong when the surround stimulus was oriented similarly to the optimal orientation of the receptive field and weak when surround stimuli were orthogonal to the optimal orientation in the receptive field center produce. These effects persist even when there is a relatively large gap between center and surround stimuli. The interacting region extends up to 8-12 cycles of sine-wave grating from the center (Polat and Sagi, 1993, 1994). The predominant modulatory effect of texture surround is suppression. Cross-orientation inhibition has been proposed as a key mechanism in the generation of

cortical orientation selectivity (Bishop et al., 1973; Sillito 1979; Morrone et al., 1982; Matsubara et al., 1987; Eysel et al., 1990; Born and Tootll, 1991; Crook and Eysel, 1992; Sillito et al., 1995). Figure 1A (in paper) shows that cross-orientation inhibition is much more frequent, in agreement with these studies. Some investigations showed that the inhibitory effect was virtually independent of surround orientation (Bishop et al., 1973; Maffei and Fiorentini, 1976; Segpiel et al., 1997). My result (paper Fig. 7B) is consistent with these studies. It shows that inhibition is relatively independent of orientation disparities between areas, because the same level of inhibition was observed regardless of orientation differences between the two areas.

Orientation inhibition resulting from within and outside the receptive field has somewhat different characteristics. If two gratings are presented simultaneously in the receptive field, the second grating with non-optimal orientation reduces the response to the optimal orientation stimulus alone (DeAngelis et al., 1992). While the second grating is presented with an orientation orthogonal to the optimal orientation in the receptive field, it causes cross-orientation inhibition (Petrov et al., 1980; Morrone et al., 1982; Bonds, 1989)

but it does not elicit a response on its own. Indeed, inhibitory effects from within the receptive field are roughly non-oriented (Bonds, 1989; DeAnglis et al., 1992).

Furthermore, cross-correlation analysis shows that the majority of pairs of neurons with inhibitory interactions have orientation preferences differing by 22-45^0 (Hata et al., 1988). Excitatory intracortical projections have a clustered appearance with similar orientation preference (Gilbert and Wiesel, 1983; Ts'o et al., 1986; Schwarz and Bolz, 1991). Inhibitory connections are largely diffuse (Albus et al., 1991; Albus and Wahle, 1994). Inhibitory inputs from outside the receptive field could play an important role in shaping neuronal responses in the visual cortex.

3-7. The origin of suppression

It was demonstrated that geniculate afferents make only excitatory synapses (Garey and Powell, 1971; Stone, 1972). In addition, Bonds (1989) did not find cross-orientation suppression in geniculo-cortical afferents, suggesting that suppression does occur within the visual cortex. There are

also anatomical and physiological supports for inhibitory neurons in layer IV (Kisvàrday et al., 1983, 1985; Martin et al., 1983; Martin, 1988; Somogyi et al., 1983, 1986). These results provide strong evidence that suppression mechanisms exist in visual cortex.

There is some evidence for the involvement of cortical inhibition in orientation tuning, which is mediated by the inhibitory transmitter GABA. When GABA inhibition was blocked by its antagonist bicuculline (Rose and Blakemore, 1974; Sillito, 1975, 1977, 1979; Wolf et al., 1986) or the input from a remote cortical site was inactivated with GABA (Eysel et al., 1990; Crook et al., 1991; Crook and Eysel, 1992), then both paradigms resulted in broadening or even loss of orientation tuning at the recording site.

3-8. Surround interaction

It has been shown that surround interactions may be an integral component of the receptive field organization throughout the visual pathway. Surround suppression is present in the LGN (Cleland et al., 1983; Jones et al., 1996). Additionally, a similar property was found in area

17, and the degree of suppression in LGN is slightly smaller than that in area 17 (Walker et al., 2000). Surround suppression has also been demonstrated for cells in the middle temporal (MT) area of the monkey (Raiguel et al., 1995; Xiao et al., 1995, 1997a,b).

Long-range horizontal connections in the striate cortex may account for surround modulation. These connections may extend up to 3-4 mm of cortex (Gilbert and Wiesel, 1989) and link neurons with similar orientation preferences (Ts'o et al., 1986; Ts'o and Gilbert, 1988; Bosking et al., 1997; Kisvàrday et al., 1997). Long-range horizontal connections are likely formed by pyramidal cells (Gilbert and Wiesel, 1979; 1983; Rockland and Lund, 1982; Martin and Whitteridge, 1984). They provide excitatory input directly on excitatory neurons and also terminate on inhibitory interneurons (McGuire et al., 1991) thus producing the specific suppressive effect. Also it was demonstrated that feedback from the high areas may contribute to surround modulation (Lamme et al., 1997), by virtue of the larger receptive fields of cells at higher stages of visual processing. One possibility to account for this is that excitatory and inhibitory interactions are present in the same neurons but are located at different parts of the receptive field (Kapadia et al., 2000).

3-9. Connections between excitatory and inhibitory neurons

The dynamic properties of the cortical network arise from specific cortical circuitry. Excitatory and inhibitory networks have a distinctively different relationship to orientation maps. Although excitatory patches occupy mainly iso-orientation locations, inhibitory connections are more common than excitatory connections with non-iso-orientation locations. There is no significant difference between the orientation topography of area 17 and 18 projections (Kisvàrday et al., 1997). The excitatory patch connects up to 3-4 mm and inhibitory patch connection is 1.5-2 mm and less specific for orientation selectivity (Mitchison and Crick, 1982; Ts'o et al., 1986; Gilbert and Wiesel, 1989). Both excitatory and inhibitory neurons make short-range intracortical connections, while only excitatory neurons make long-range connections. Each type of connection targets both excitatory and inhibitory postsynaptic neurons (Beaulieu and Somogyi, 1990; McGuire et al., 1991; Anderson et al., 1994a). Excitatory neurons project mainly to other excitatory neurons but about 20% of their synapses are connected to inhibitory interneurons. In addition, inhibitory interneurons project to excitatory neurons and

to other inhibitory interneurons as well (Kisvàrday et al., 1993; Sik et al., 1995; Thomson and Deuchars, 1997).

3-10. Short-range connections

Cortical cells have short-range excitatory and inhibitory connections within each hypercolumn (Fries et al., 1977; Nelson and Frost, 1981; Miller, 1992). Local connections provide strong excitation and inhibition to both pyramidal and inhibitory interneurons (Dalva and Katz, 1994). Anatomical studies also support the prevalence of excitatory connections (Anderson et al., 1994b). Several other observations also suggested that excitatory populations are interconnected by recurrent excitatory synapses (Martin, 1988; Peters and Payne, 1993), and inhibitory populations are interconnected by recurrent inhibitory synapses (Beaulieu and Somogyi, 1990; Kisvàrday et al., 1993; Sik et al., 1995). In addition, local excitatory neurons excite neighboring inhibitory cells, which in turn inhibit excitatory cells (Beaulieu and Somogyi, 1990; McGuire et al., 1991; Ahmed et al., 1994). Cross-correlation studies showed that cells with orientation preferences up to 40^0 difference shared a common

excitatory input (Toyama et al., 1981). In contrast, inhibitory connections arise from cells with broader distribution of orientation preferences than excitatory connections (Toyama et al., 1981; Michalski et al., 1983; Hata et al., 1988). The strength of inhibitory connections is up to 60^0 orientation difference between pre- and postsynaptic cells. There is also evidence that local inhibitory connections target neurons of all orientations (Dalva et al., 1995). In paper Figure 7B, area 17 inactivation did not modify the average decrease of responses, that is, the same level of inhibition was recorded when area 17 was injected with GABA, indicating that flanked stimuli exert their action through local or short-range connections.

3-11. Long-range connections

Long-range horizontal connections link cells across distinct regions and spread over four hypercolumns (~1 mm, Hubel and Wiesel, 1962) in the visual field (Gilbert and Wiesel, 1979; Rockland and Lund, 1982; Livingston and Hubel, 1984; Martin and Whitteridge, 1984). Long-range

horizontal connections are excitatory and originate from pyramidal cells in the surround (Gilbert and Wiesel, 1989). These cells contact other pyramidal cells and nearby inhibitory cells as well (Kisvàrday et al., 1986; McGuire et al., 1991). Long-range excitatory neurons link target neurons with orientation preferences similar to their own (Rockland and Lund, 1982; Gilbert and Wiesel, 1989; Katz and Callaway, 1990; Das and Gilbert, 1995; Weliky et al., 1995; Toth et al., 1996).

The fundamental feature of neural circuitry in the visual cortex is the existence of recurrent excitatory and inhibitory connections via excitatory neurons and inhibitory interneurons. Cells in the receptive field obtain inputs from feedforward afferents and inputs from outside the receptive field through long-range intercortical connections. The surround modulation of cortical responses can be explained by alterations of the balance between local excitation and inhibition. Iso-oriented surround stimulation increases the firing rate of local inhibitory cells which in turn further suppresses their postsynaptic pyramidal cells, whereas cross-oriented stimuli in the surround have the opposite effect (Dragoi and Sur, 2000). Therefore, the cortical neurons integrate diverse inputs to produce outputs. The output of a cell can

be created by excitatory, by inhibitory, or by a combination of both mechanisms (Volgushev et al., 1993).

3-12. Interneurons

Inhibition in the cortex has been known to balance the effect of excitation (Sillito 1975b; Toth et al., 1997). In visual cortex, it is suggested that inhibition could play a crucial role in shaping of receptive field properties, such as orientation and direction selectivity (Blomfield, 1974; Koch and Poggio, 1985; Crook et al., 1997; 1998). More recently, Tsodyks et al. (1997) have suggested that interneuron-interneuron connections play a role in the hippocampus.

The interactions between targets may rest on the cortical local dynamic connections between excitatory and inhibitory interneuron that propagate neuronal activity to target cells. It is suggested that the inhibition arises from interneurons with geniculate-like, non-oriented receptive fields (Hegelund, 1981). For instance, in paper Fig. 4C, the decay of response due to the presence of the second targets were obtained via inhibitory interneuron, regardless of the orientation of the patch in area 17.

Moreover, intracellular recordings (Tucker and Katz, 1998) have demonstrated that inhibitory connections arise from cells with a broader range of orientation preference than excitatory connections. It implies that the inhibition could generate orientation selectivity by suppressing responses to either iso- or cross-orientation stimuli. It is thought to be mediated by basket cells which can transmit iso-orientation $\pm(0^0\sim30^0)$, oblique $\pm(30^0\sim60^0)$ and cross-orientation $\pm(60^0\sim90^0)$ inhibition (Kisvàrday et al., 1993). Another inhibitory component could arise from orientation biased interneurons. These cells are relatively well orientation tuned, thus causing the response suppression of the recipient neuron. Specifically, when two gratings are applied in iso- or cross-orientation arrangements in areas 17 and 18, the neuronal responses are modulated through alteration of the balance between local excitatory and inhibitory cells, that is iso- or cross-orientation inhibition (Dragoi and Sur, 2000).

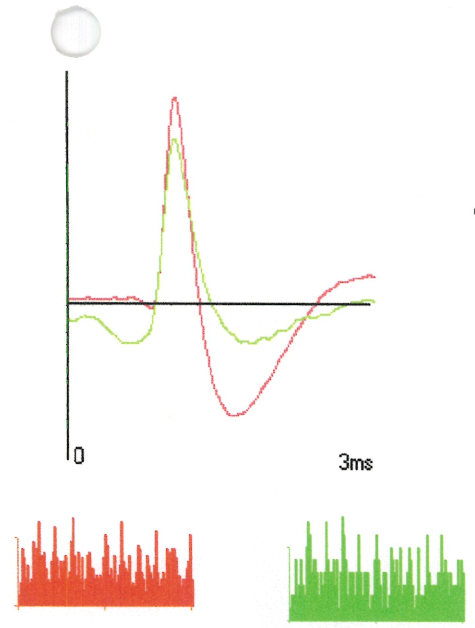
3-13. Connections in area 18

Area 18 is believed to have a complex connection network that is difficult to interpret by simple network

rules. Area 18 of cat's visual cortex receives two major inputs: one originates in the lateral geniculate nucleus (Orban, 1984; Bullier, 1986; Spitzer and Hochstein, 1988), the other from area 17 fibers (Symondsand and Rosenquist, 1984; Bullier et al., 1984; Bullier et al., 1994). Furthermore, area 18 cells also receive additional local recurrent inputs from nearby cortical cells. Cross-correlation analysis showed that neighboring neurons have strong physiological connections with each other, largely independent of relative orientation preferences. Therefore, different neurons in the same orientation column would show different degrees of their response properties (Das and Gilbert, 1999). This is consistent with our results that neighboring neurons react in a different fashion to the same stimulus configuration. These types of results cannot be obtained by brain imaging techniques.

Appendix

In the following appendix, I will illustrate the scheme of the experiment, other examples and statistics which I did not show in the paper, because of space limitation. In addition, they may help future research in Lab of Dr. Molotchnikoff.



Spike sorting

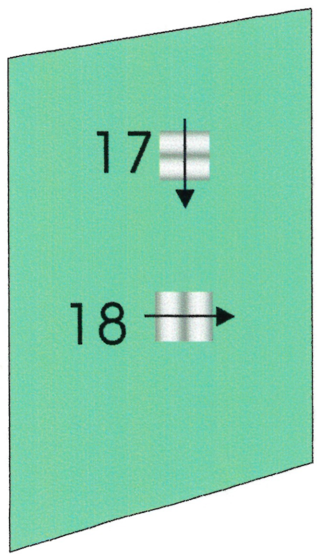
Recording in 18

Pump

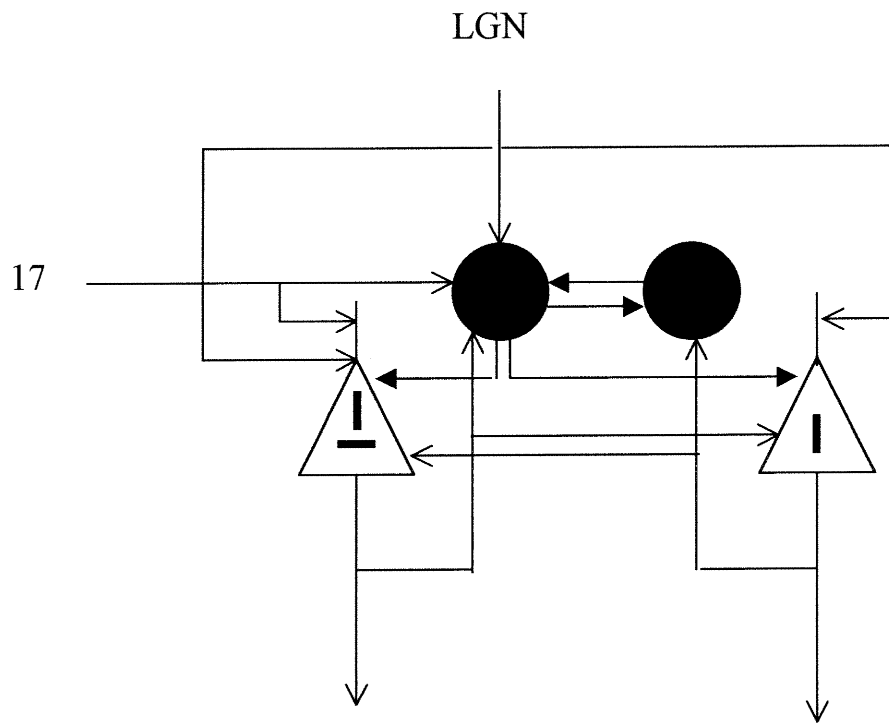
GABA 0.1 mM
in saline +
Chicago Sky
Blue 2%

18
19
17

Recording in 17



Scheme of the experiment



Scheme of local population interactions between excitatory and inhibitory neurons

Filled circles: inhibitory neurons;
white circles: excitatory neurons;
Bars inside cells indicate the optimal orientation difference between areas 17 and 18.

Fig. 2

Figure 3:

Modulation of responses of a complex cell. Single unit recordings. **A:** (upper row) Scheme of stimulus conditions. Opt. ori.: optimal orientation; orth.: orthogonal orientation; 17,18 refer to areas. Peristimulus time histogram (PSTH). Cont. row: Control, prior to GABA injection in area 17; Inj. row: Injection, during inactivation of area 17 with GABA; Rec. row: Recovery, after injection during recovery phase. Same for other figures. This example shows that dual stimulation paradigm does not change significantly response in area 18 when both areas are stimulated with optimal gratings (Cont. row). The inactivation of area 17 almost abolishes the evoked discharges in area 18, however a further decline of response occurs when the area 17 stimulus is added (Inj. row). **B:** Response magnitude (Spikes/sec) (mean±SE). Bars are coded to correspond to stimulus conditions. **C:** Orientation tuning curves for areas 17 and 18. The arrow-heads point to optimal orientations. The orientation difference between these two areas is in cross-range. **D:** Cross-correlogram analysis between areas 17 and 18 spike trains, showing that activity of both units in areas 17 and 18 is synchronized.

Insert: receptive field locations in relation to the area centralis (AC).

In this figure, responses in area 17 are illustrated in right column.

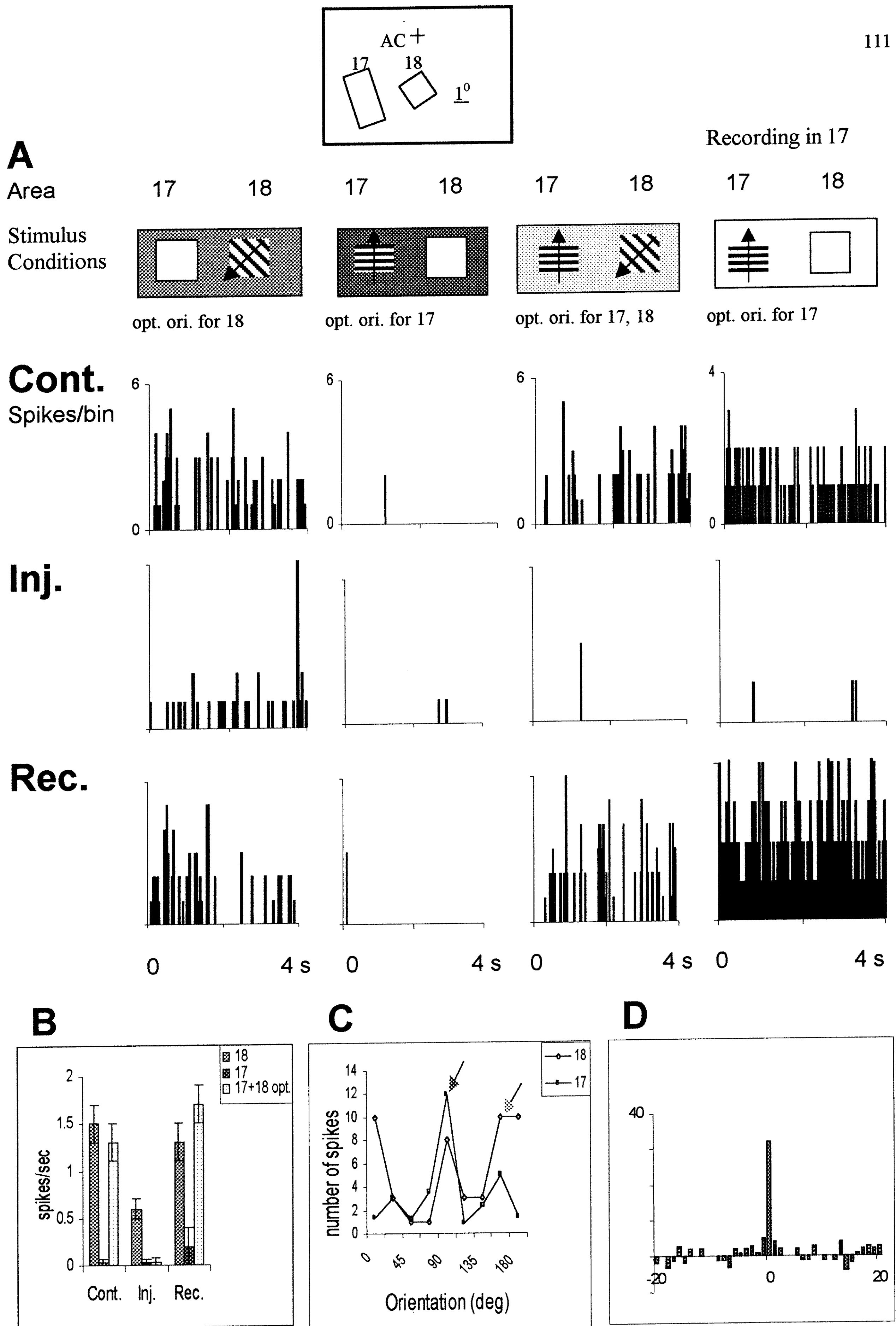
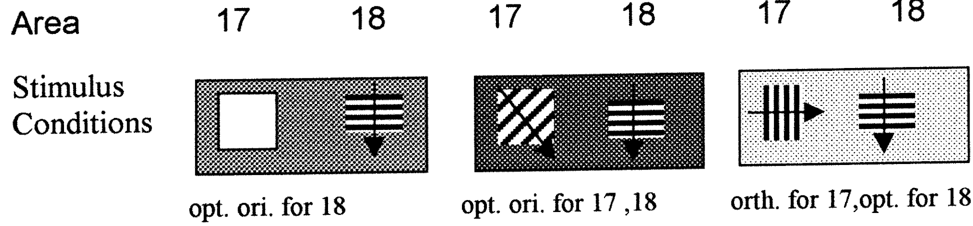


Fig. 3

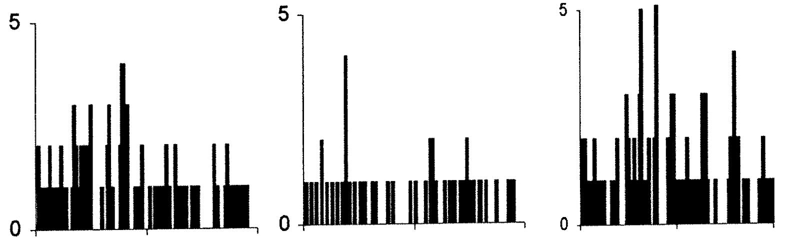
Figure 4:

Modulation of responses of a complex cell. Single unit recordings. **A:** PSTH. Simultaneous stimulations of areas 17 and 18 at their optimal orientations induces a decline of evoked response of the neuron in area 18. When area 17 is stimulated with a grating whose orientation is orthogonal to the preferred orientation of area 18 cell, the response of the cell in area 18 is unmodified (Cont. row). The injection of GABA in area 17 reduces evoked discharges of the unit in area 18 and diminishes the response modifications induced by simultaneous stimulation of area 17 (Inj. row). **B:** Response magnitude (spikes/sec) (mean±SE). Bars are coded to correspond to stimulus conditions. **C:** Orientation tuning curves for areas 17 and 18. The arrow-heads point to optimal orientations. The orientation difference between these two areas is in oblique-range.

Insert: receptive field locations in relation to the area centralis (AC).



Cont.
Spikes/bin



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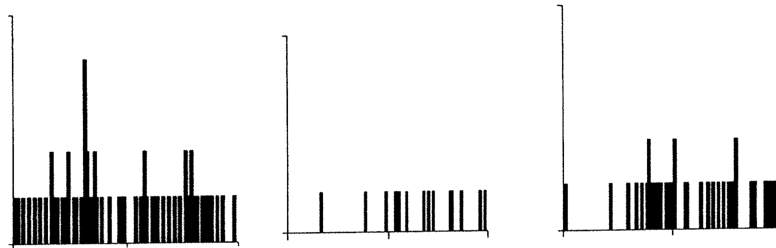
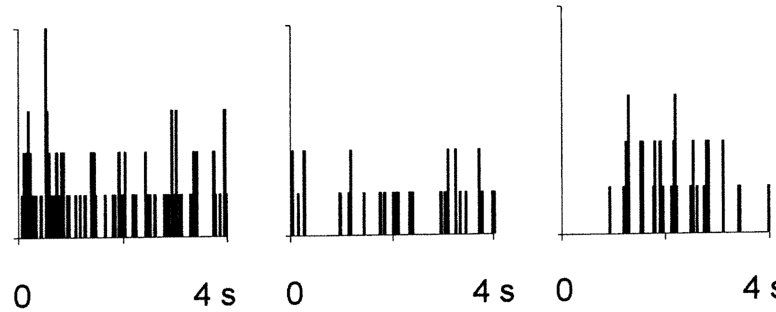
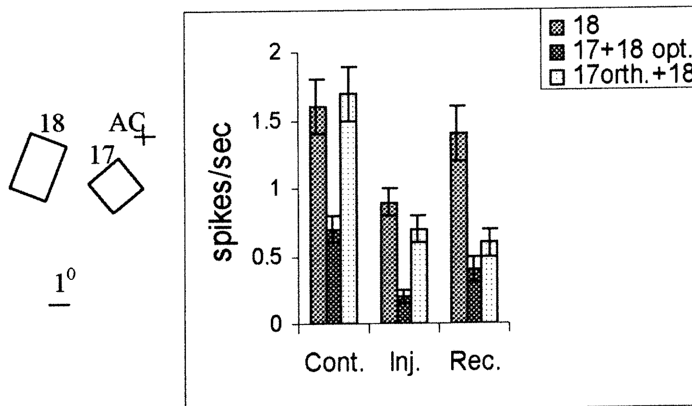


Rec.





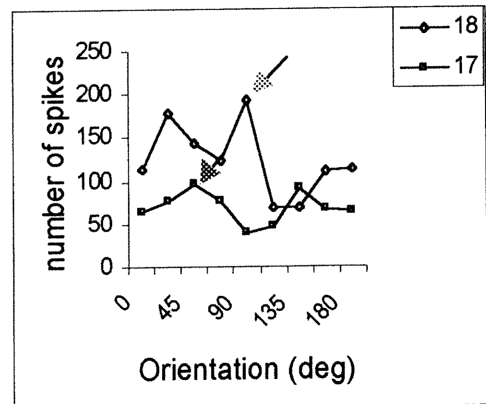
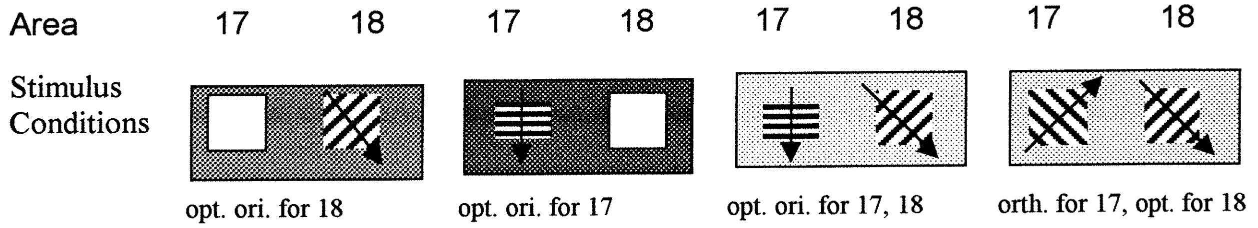


Fig. 4

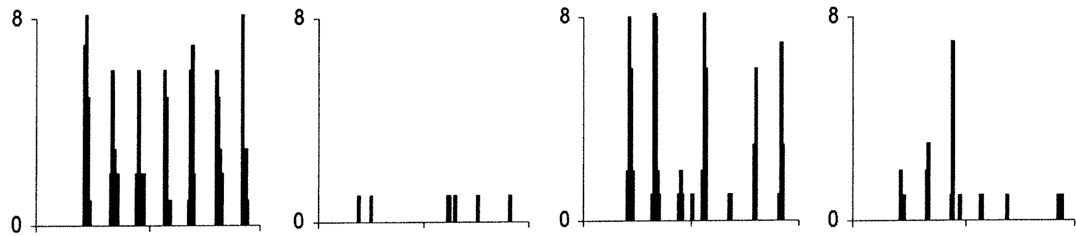
Figure 5:

Modulation of responses of a simple cell. Single unit recordings. **A:** PSTH. The response of area 18 is decreased when area 17 is stimulated with a grating whose orientation is orthogonal to the optimal orientation of area 18 cell (Cont. row). The activation of area 17 abolishes the response of this simple cell of area 18 to its own optimal stimulus (Inj. row). Interestingly, the area 18 neuron exhibits a response when both areas are simultaneously stimulated. **B:** Response magnitude (spikes/sec) (mean±SE). Bars are coded to correspond to stimulus conditions. **C:** Orientation tuning curves for areas 17 and 18. The arrow-heads point to optimal orientations. The orientation difference between these two areas is in iso-range.

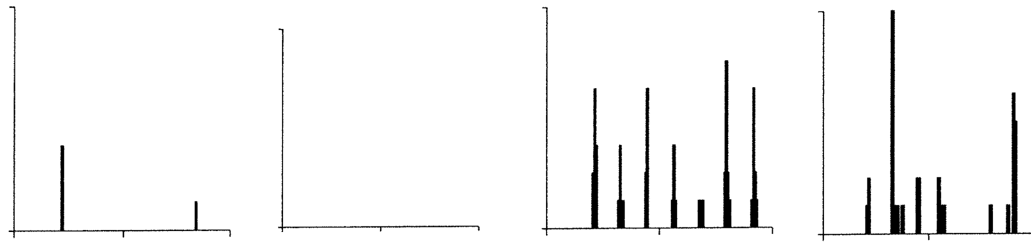
Insert: receptive field locations in relation to the area centralis (AC).



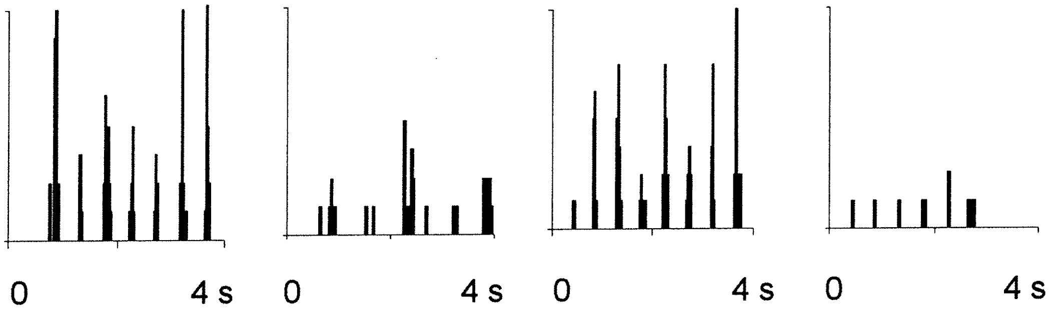
Cont.
Spikes/bin

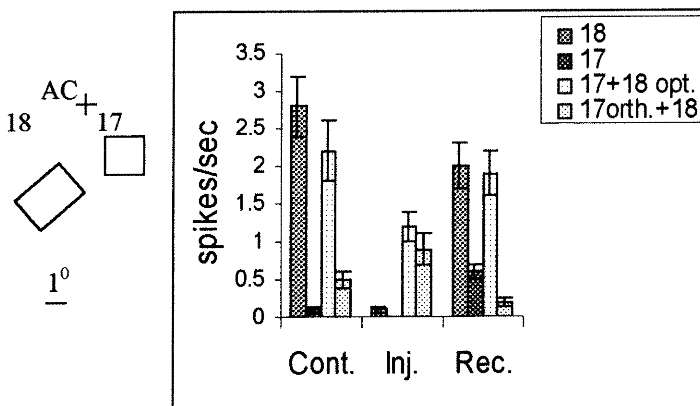


Inj.



Rec.





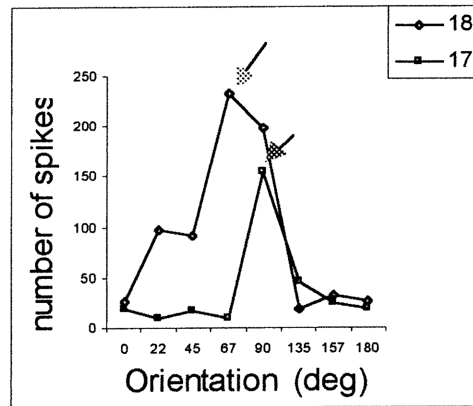


Fig. 5

Figure 6

Cells of the same pool react in identical fashion. **A:** multi-unit recordings. Response magnitude (spikes/sec) (mean±SE) bars are coded to correspond to stimulus conditions. The arrow-heads point to spontaneous activity levels. **B:** Spike waveforms are sorted out simultaneously from multi-unit activities. They are labeled cell A and cell B. Z score=3.72. **C. D:** Plots of response magnitude for cell A and B. A supplementary grating stimulus in area 17 decreases the responses of cell A and cell B as well, regardless of its orientation of the patch in area 17. The schematic local population interactions between excitatory and inhibitory neurons (Section C and D bottom). Filled circles: inhibitory neurons, white circles: excitatory neurons. The bars inside cells indicate the optimal orientation difference between these two areas, in this case is 0^0. The bold lines display involved paths.

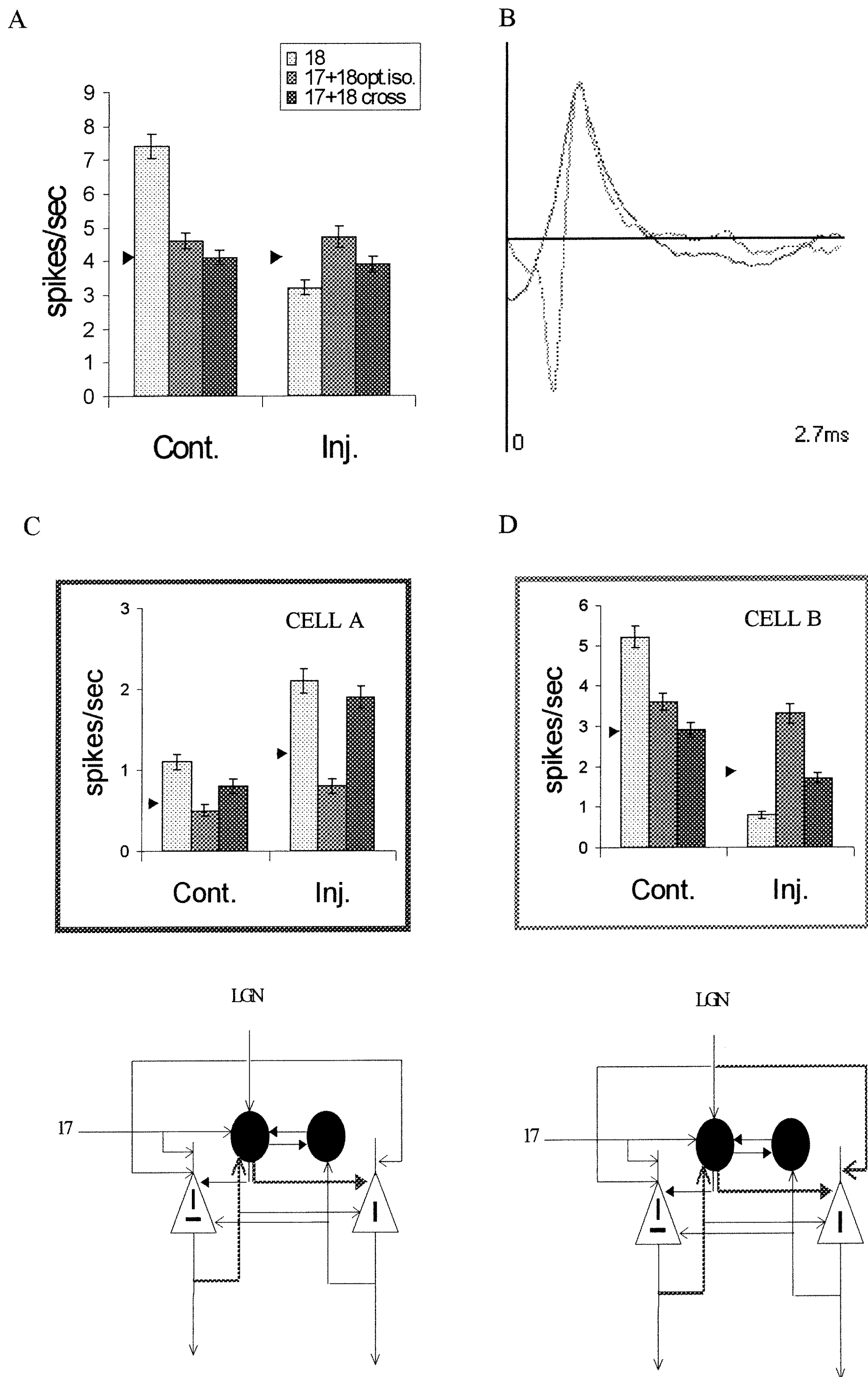


Fig. 6

Cells of same poll react in identical fashion

A diminished response in multi-unit activities in area 18 occurs when a second target is added (Section A). This second sine-wave patch is in the receptive field of area 17 cells and also in the periphery of the receptive field of area 18 cells. The preferred orientation for two areas is 67^0. When the orientation of area 17 cells is orthogonal relative to area 18 cells, the response remains the identical fashion. Single unit cell A and cell B are discriminated at the same time from this population of cells, whose selected spike waveforms are illustrated in Section B, response magnitudes are shown in Section C and D respectively. The supplementary grating either iso- or cross-orientation produces a reduced response in cell A and cell B as in multi-unit firing.

The following phase, these two different stimulus conditions create a reversed effect by GABA injection in the same site of area 17. They enhance the discharging rate compared with initial stimulation in area 18 cells. The introduction of the patch in area 17 during the silencing of area 17 produces an iso-inhibition of cell A response while cross-stimuli does not modify its firing rate. Iso and cross orientation facilitation in cell B response while

area 17 is silenced may disclose a strong input by adding a second target in the visual field. The second target activates thalam-cortical path which facilitate cortical firing rate.

Although cell A (67^0) and cell B (67^0) share the same orientation domain and the receptive field, react in identical fashion, but they involve in different pathways. The pathway scheme is described in Section C and D (bottom). Iso-orientation and cross-orientation inhibition produce by inhibitory interneuron in cell A as well as in cell B. However, cell B reveals excitatory input from LGN or elsewhere by depressing area 17. The output of the neuron depends upon the weigh of the various inputs.

Figure 7

Cells of the same pool react in different fashion. **A:** Multi-unit recordings. Response magnitude (Spikes/sec) (mean±SE) bars are coded to correspond to stimulus conditions. The arrow-heads point to spontaneous activity levels. **B:** Spike waveforms are sorted out simultaneously from multi-unit activities. They are labeled cell A and cell B. Z score=4.80. **C:** Cross-correlogram analysis between areas 17 and 18 spike trains. PSTHs are showed in Section C (bottom). They are complex and simple cell type. **D. E:** Plots of response magnitude for cell A and B. A second grating stimulated in area 17 produces iso-orientation facilitation and cross-orientation inhibition in cell A. However, dual stimuli fail to modify the response of cell B. The symbols are the same as Figure 6. The optimal orientation disparity between these two areas is 0^0 (iso-range).

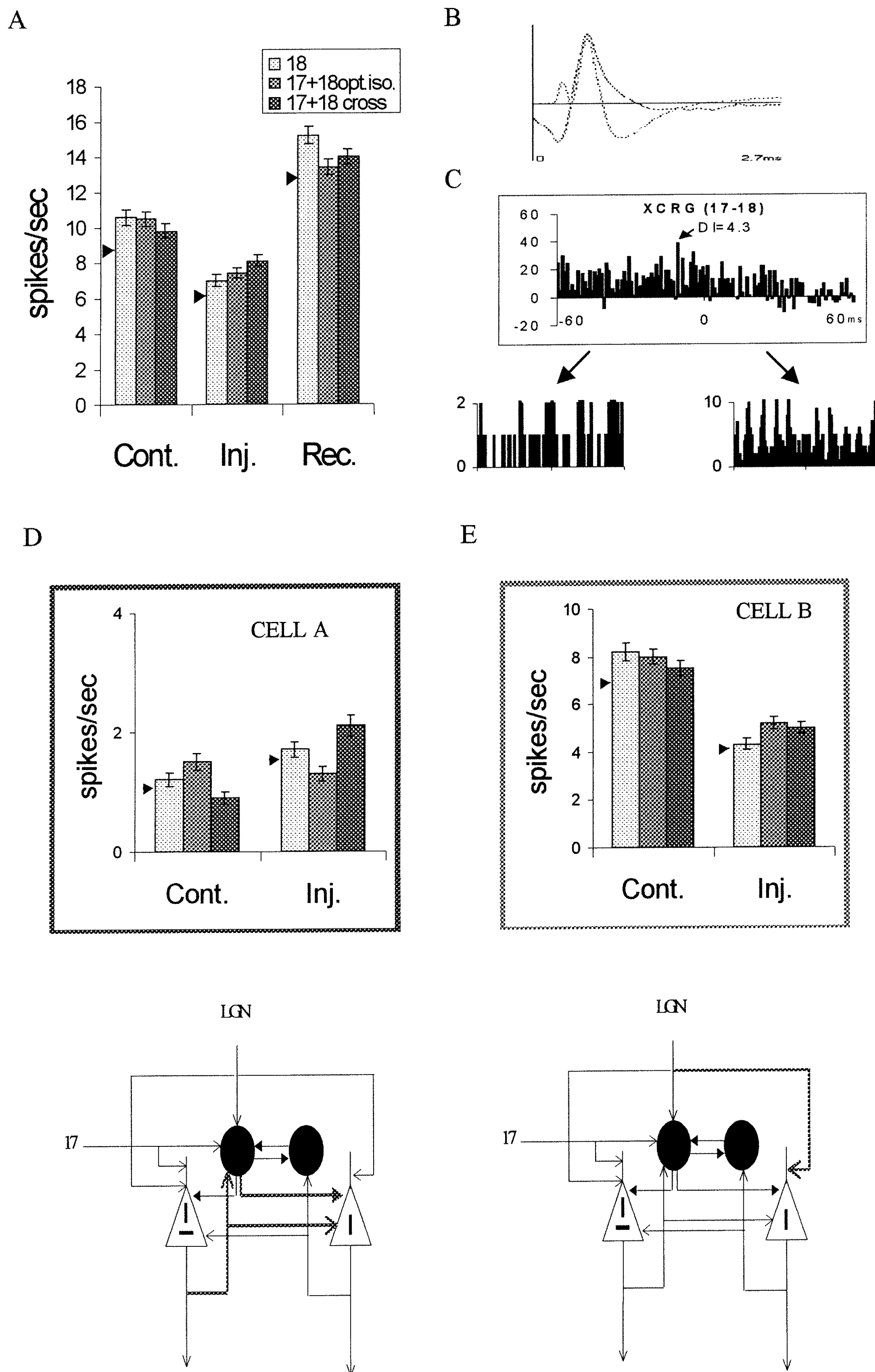


Fig. 7

Cells of the same pool react in different fashion

The application of sine-wave gratings presented together in the receptive fields of areas 17 and 18 either in iso-orientation or cross-orientation, fails to modify the firing rates of area 18 cells when compared to the stimulus in the receptive field of area 18 alone (Section A). The optimal orientation is 157^0 for both areas. Their sorted out single cell spike waveforms are depicted in Section B. PSTHs are shown in Section C (bottom). They are complex cell (cell A) and simple cell type (cell B), according to the classified criteria (Hubel and Wiesel, 1965) and also ratio of AC/DC response rate (Skottun et al., 1991).

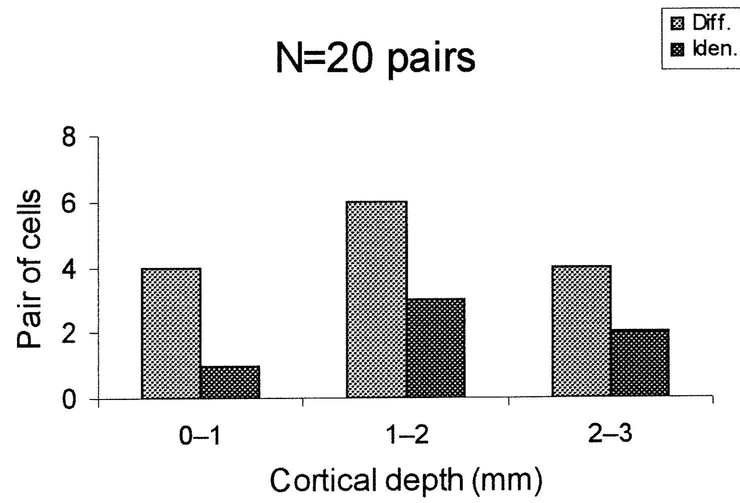
The presentation of two gratings of preferred orientation in the receptive fields of areas 17 and 18, excites the response in cell A, while no significant change occurs in cell B. When the orientation of area 17 is vertical relative to the orientation of area 18 cell inhibits the response in cell A, the companion cell B maintains the response magnitude as the control presentation.

The second processing, GABA micro-injection at the same site of area 17 decreases the responses to one grating of optimal orientation presented in area 18 solely in cell B if compared with prior to inactivation. A adding grating stimulus in area 17 increases the response of cell B, regardless of its orientation of the patch in area 17. However, the decline of response occurs to iso-orientation presentation in cell A, while cross-orientation stimulation enhances the response.

There is a peak shifted to the left in the cross-correlogram (Section C), whose DI is of 4.3. This is an above significant threshold (Melssen and Epping, 1987). The lag 11ms indicates that area 18 population fired before area 17 population. This is towards unmasking the feedback circuitry and computation between two areas.

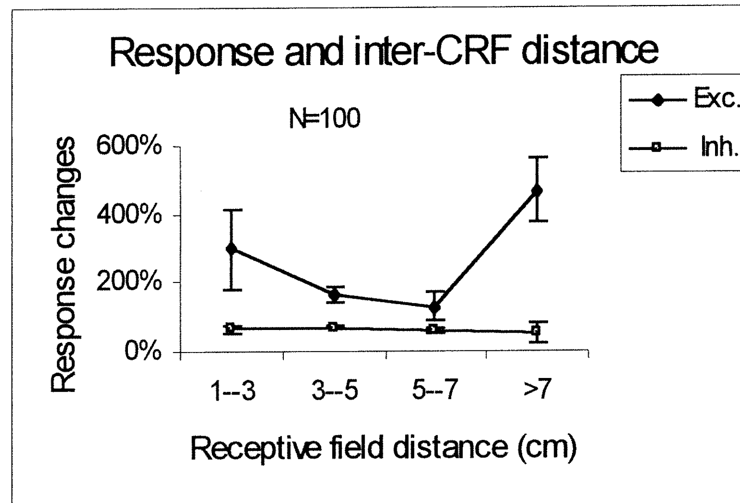
Do nearby cells (cell A:0^0 and cell B:-22^0) which are attributed to the same orientation domain and have receptive field superimposed that correspond to the same response reaction? The answer is no. They react in different fashion and classified to complex cell and simple cell types. For cell A, iso-orientation facilitation processes directly to target cell, while cross-orientation inhibition produces through inter-inhibitory neuron (Section D bottom). This response fashion is turned to be

opposite by depressing area 17. That is iso-orientation inhibition and cross-orientation facilitation. This result suggests that cell A arises input directly from area 17 or through interneuron to target cell. The discharge rate of cell B doesn't change when adding a second grating in receptive field of area 17, suggesting that cell B derives directly input from LGN (Section E bottom).



Diff : different
Iden : Identical

Fig. 8



Exc : excitation
Inh : Inhibition

Fig. 9

Table I

SURVEY: 20 PAIRS OF CELLS

		BEFORE		INJECTION	
PAIRS		CROSS	OPTIMAL	CROSS	OPTIMAL
YJ1	a	+	=	-	+
	b	-	=	-	-
Yk1	a	=	-	-	-
	b	+	+	+	+
Yk2	a	-	+ +	-	=
	b	+	=	+	-
Yk4	a	-	=	-	-
	b	+	+	+	+
YL1	a	-	-	+	-
	b	-	-	-	-
YM1	a		+ +		+ +
	b		=		-
YN2	a	+	=	+	+
	b	-	=	+	+
YN3	a	-		-	
	b	-		=	
YO2	a	-	=	-	-
	b	-	-	+	+
YO3	a	=	-	-	+
	b	-	+	-	-
YP1	a	= -		+	+
	b	=	=	=	=
YP2	a	+	-	+	+
	b	-	-	-	-
YQ1	a	-	-	+	+
	b	+	=	-	-
YQ2	a	-		-	
	b	-		+	
YR1	a	-	-	=	-
	b	-	-	+	+
YR2	a	-	+	+	-
	b	=	=	+	+
YS1	a	-	-	-	-
	b	-	-	+	-
YS2	a	-	-	=	-
	b	+	+	-	=
YT1	a	+	=	+	+
	b	+	=	+	+
YT2	a	=	+	=	-
	b	-	=	=	+

CROSS: ORIENTATION BETWEEN AREAS 17 & 18 >60 deg
OPTIMAL: OPTIMAL ORIENTATION IN EACH AREA
'+' : INCREASE; '-' : DECREASE; '=' : UNCHANGED

Table II: Summary of recorded cells

<table>
<tr><td colspan="2">Cats: 20</td><td>Single unit</td><td>Multi-unit</td></tr>
<tr><td colspan="2">Sites</td><td>15</td><td>20</td></tr>
<tr><td rowspan="2">Stimuli</td><td>opt.17,18</td><td>15</td><td>40</td></tr>
<tr><td>orth.17,18</td><td>11</td><td>34</td></tr>
<tr><td colspan="2">Cases</td><td>26</td><td>74</td></tr>
<tr><td colspan="4">Total: 100</td></tr>
</table>

Opt.: optimal orientation
Orth.: orthogonal orientation
17,18: area 17, area 18

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