Brainwaves ("40 Hz") Research

The University of Birmingham

Introduction

Brainwaves -- or the "EEG" -- are electrical signals that can be recorded from the brain either directly or through the scalp. The kind of brainwave recorded depends on the behavior of the animal and is the visible evidence of the kind of neuronal (brain cell) processing necessary for that behavior.

We are working on fast brainwaves at about 40 cycles-per-second (Hz) which are known as the gamma band. Gamma rhythms appear to be involved in higher mental activity including **perception and consciousness**. It seems to be associated with consciousness (e.g., it disappears with general anesthesia).

Synchronous activity at about 40Hz appears to be involved in **binding** sensory inputs into the single, unitary object that we perceive. This process is so efficient that we are hardly aware that it goes on at all. **Recordings of neurons** in visual cortex show that synchronization at about 40 Hz links parts of the cortex excited by the same object and not those excited by different objects -- implicating in gamma rhythms in binding.

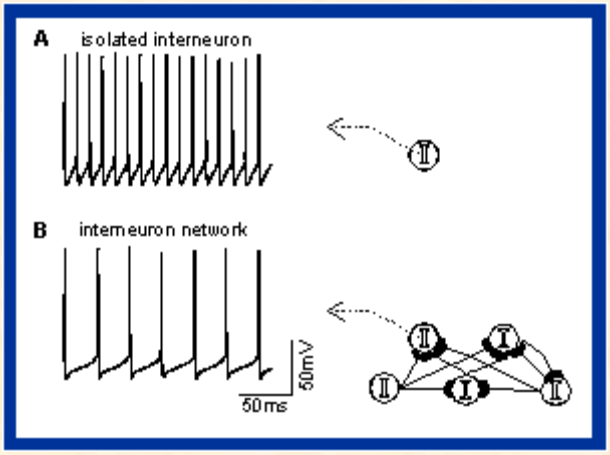
For instance, the color, shape, movement, and location of an object are processed in different parts of the visual cortex. And these features of an object need to be reunited into a single entity. This is known as the **binding problem**. And gamma rhythms are thought to provide a solution.

We have identified how the rhythm can be generated in small bits of cortex (see **Neuronal Networks for Gamma**). Recently we have identified how gamma rhythms may be synchronized in separate parts of the brain (ref **long-range synchronization of gamma**).

Neuronal Networks for Gamma

Several **mechanisms** have been put forward for gamma oscillations. We have found that the networks of inhibitory neurons can produce 40 Hz or gamma rhythms without the need for the much larger population of excitatory neurons (the pyramidal cells) because the rhythms survive drugs which block excitatory synaptic transmission. The essential idea is that when you drive inhibitory neurons so

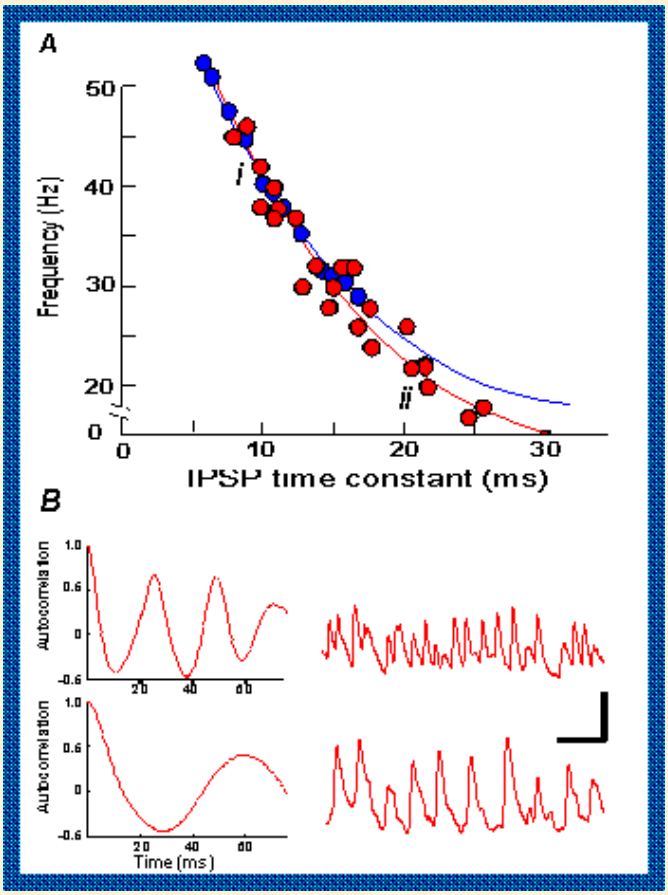
that they want to fire faster than around 40 times -a-second, the inhibitory synapses between these neurons prevent them firing faster than every 25 ms-or-so (the precise time is determined by the size and duration of the inhibitory synaptic potential). Because each inhibitory neurons connects to many others, these connections also synchronize the population of inhibitory neurons.



Jefferys, J.G.R., Traub, R.D., and Whittington, M.A. (1996) "Neuronal networks for induced '40 Hz' rhythms". *Trends in Neurosciences* 19, 202-208.

The rhythm depends on fast inhibitory synapses interconnecting the inhibitory neurons. It is driven by the steady activation of metabotropic glutamate receptors and at least in principal by other slow excitation of inhibitory cells. Slow inhibitory synapses using the GABA-B receptor depress the rhythm, which links with parallel pharmacological studies of behavior in Prof Bowery's Group in Pharmacology.

Experiments and realistic computer simulations together have shown that this model works. Slowing the inhibitory potentials (IPSPs) between inhibitory neurons slows the gamma rhythm as predicted. The experiments are mainly on hippocampus. This is a part of the cortex with a relatively simple anatomy, which makes it convenient for most of the studies outlined here.



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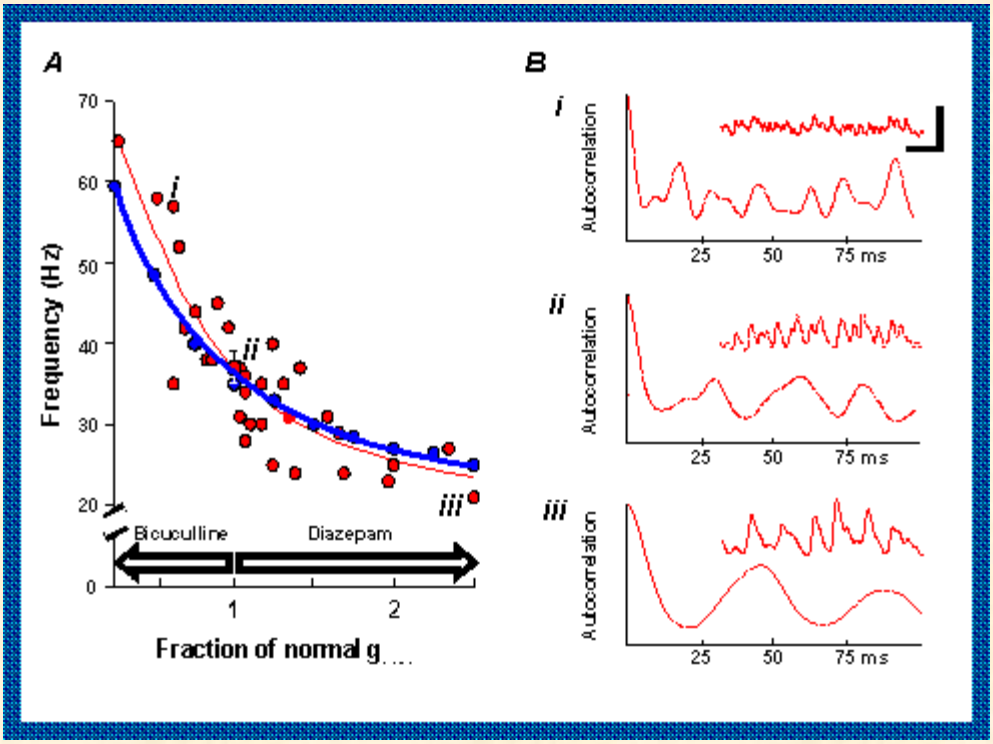
Simulations (**blue circles**) predicted and experiments (**red circles**) confirmed that:

1. Slowing the IPSP with barbiturates slows the oscillations.
2. Making the IPSPs smaller with the drug bicuculline speeds up the rhythm and making them bigger with diazepam slows it. The essential idea is that the smaller IPSPs take less time to return the membrane to threshold for the next round of excitation. Part B shows data for the parts of the graph labeled **i**, ii, or **iii**.



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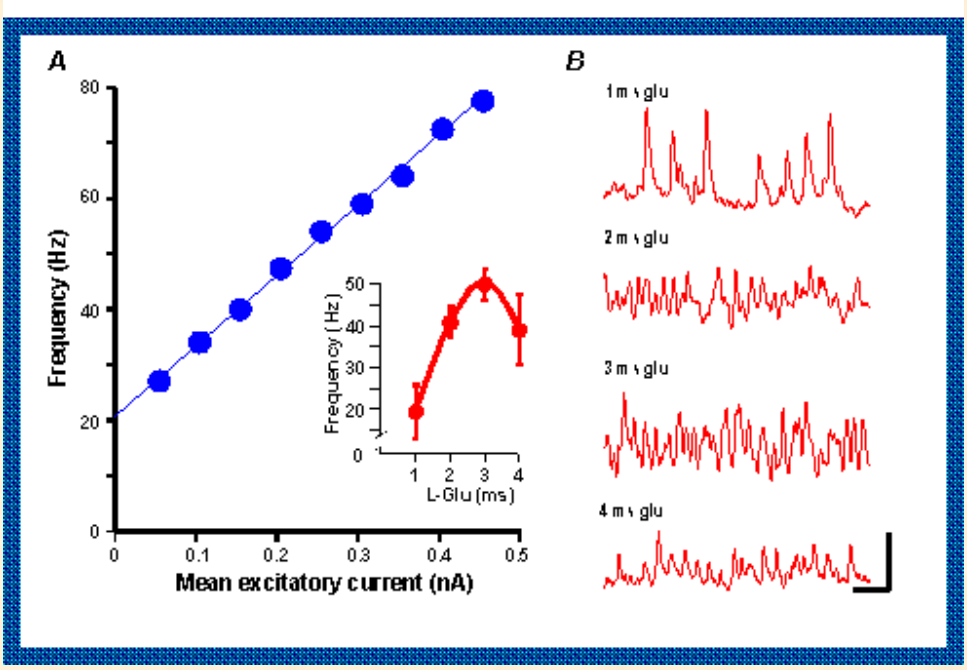
3. Making the tonic excitatory drive to the inhibitory neurons stronger speeds up the gamma rhythm



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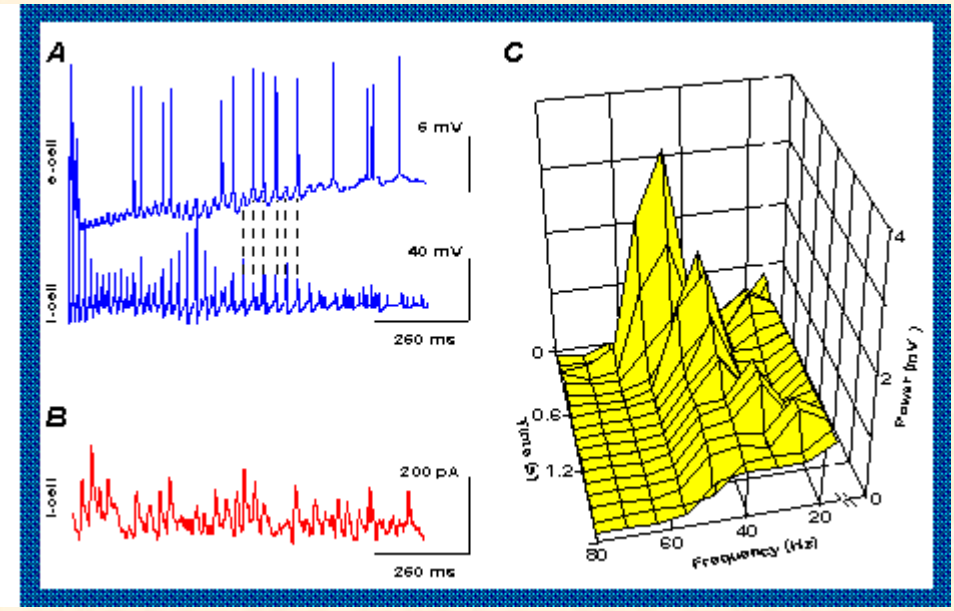
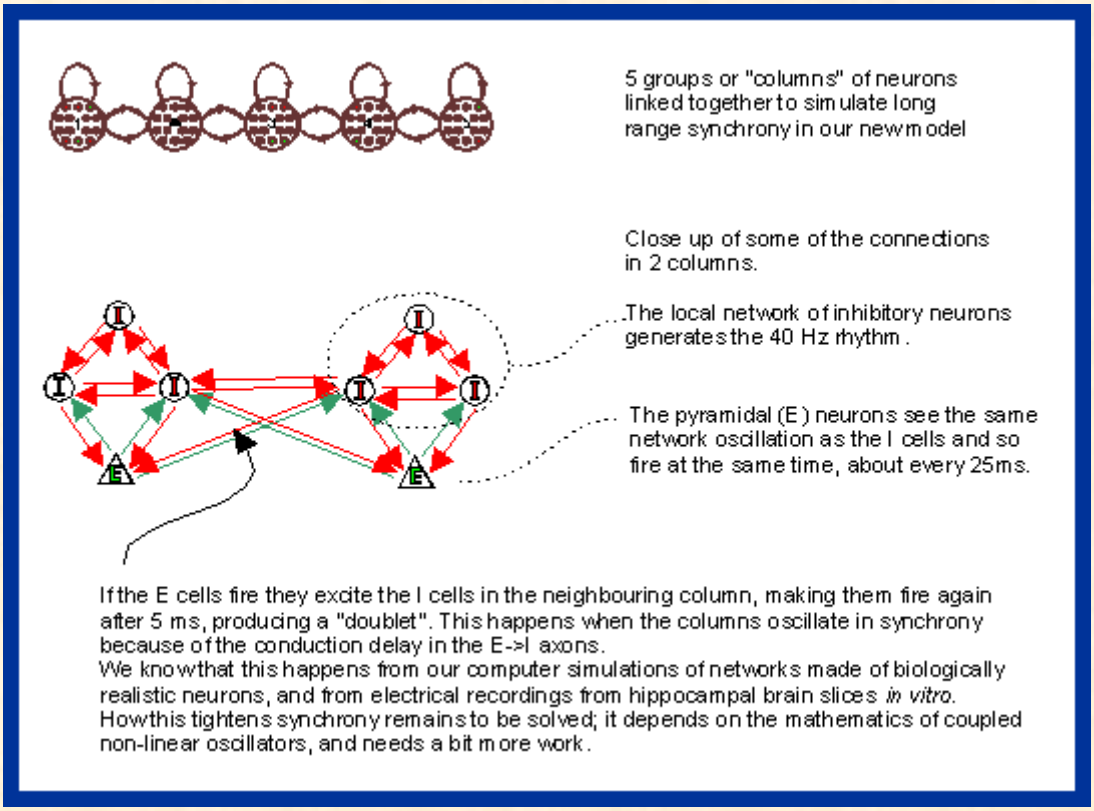
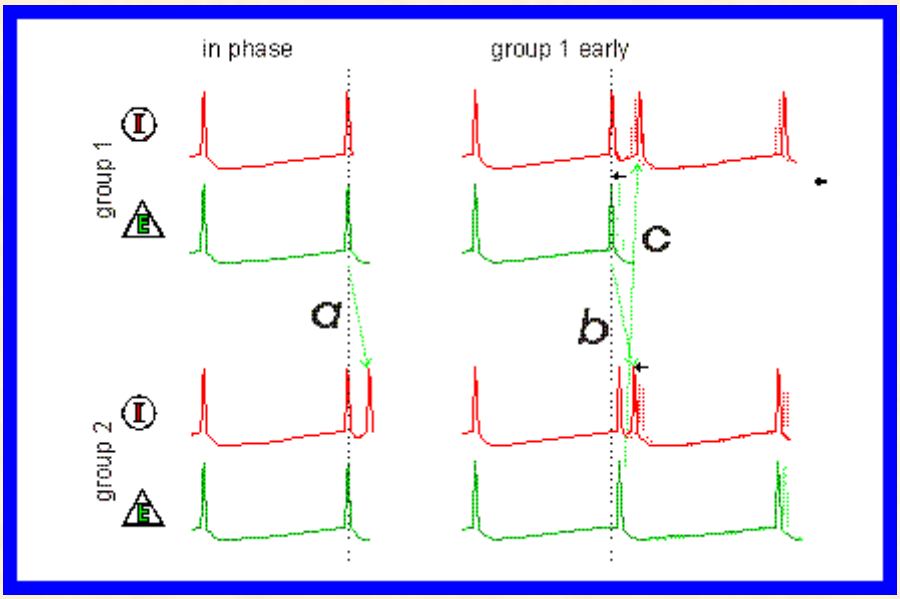
4. The excitatory drive can change so that the precise frequency of the oscillation may alter during each response.



The latest step forward was to see how this works over long distances faster than axons (nerve fibers) joining regions. (see **press release**)



Traub. R.D., Whittington. M.A., Stanford. I.M. and Jefferys. J.G.R. (1996) "A mechanism for generation of long-range synchronous fast oscillations in the cortex". *Nature* 382, 621-624



"in phase": If both groups are synchronous, then the Group 1 **E** cell spike takes (say) 5 ms to conduct **(a)** to Group 2 where it can trigger a second spike in the **I** cells (and likewise from Group 2 to 1 -- not shown here).

"Group 1 early": **E** cells are early in group 1 so the second spike of doublet it evokes in each Group 2 **I** cell is earlier **(b)** and next cycle is shorter than it would otherwise be. The second spike of the group 2 doublet may fall into the spike refractory period and disappear, and thus shorten the next cycle even more. When Group 1 is early, Group 2 must be late. So the second spike Group 2 **E** cells evoke in Group 1 **I** cells is late **(c)**, and the next cycle is longer. The end result is that the 2 groups tend to fall back in phase.

The computer simulations predicted that for this to work the system needed:

- each local network needs inhibitory connections (as before)
- local networks are connected together by connections to their inhibitory neurons from BOTH the **inhibitory neurons** and the **excitatory neurons** of their neighbors.

Group members and their research

John Jefferys	**http://www.brain.web-us.com/40hz/WW51.htm**
Enrico Bracci	**http://www.brain.web-us.com/40hz/WW51.htm**
Martin Vreugdenhil	**http://www.brain.web-us.com/40hz/WW51.htm**
Stephen Hack	**http://www.brain.web-us.com/40hz/WW70.htm**

Collaborators

Roger Traub - Professor of Mathematical Neuroscience, Neuroscience Unit, Department of Physiology, University of Birmingham, formerly IBM Research Division, Yorktown Heights, NY

Miles Whittington - Imperial College School of Medicine at St Mary's, London

Recent Publications

Whittington, M.A., Traub, R.D. and Jefferys, J.G.R. (1995). "Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation". *Nature* 373, 612-615

Traub R.D., Whittington M.A., Stanford I.M., and Jefferys J.G.R. (1996) "A mechanism for generation of long-range synchronous fast oscillations in the cortex". *Nature* 382, 621-624

Jefferys, J.G.R., Traub, R.D. and Whittington, M.A. (1996). "Neuronal networks for induced '40 Hz' rhythms". *Trends in Neurosciences* 19, 202-208

Traub, R.D., Whittington, M.A., Colling, S.B., Buzsáki, G., and Jefferys, J.G.R. "Analysis of gamma rhythms in the rat hippocampus in vitro and in vivo", *J.Physiol.(Lond.)*, 493 (1996) 471-484.

Whittington, M.A., Jefferys, J.G.R. and Traub, R.D. "Effects of intravenous anaesthetic agents on fast inhibitory oscillations in the rat hippocampus in vitro", *Br.J.Pharmacol*., 118 (1996) 1977-1986.

Whittington, M.A., Traub, R.D., Faulkner, H.J., Stanford, I.M., and Jefferys, J.G.R. "Recurrent EPSPs induced by synchronized fast cortical oscillations", *Proc.Natl.Acad.Sci.USA*, 94 (1997) 12198-12203.

Traub, R.D., Whittington, M.A., and Jefferys, J.G.R. "Gamma oscillation model predicts intensity coding by phase rather than frequency", *Neural Comput*., 9 (1997) 1251-1264.

Traub, R.D., Jefferys, J.G.R., and Whittington, M.A. "Simulation of gamma rhythms in networks of interneurons and pyramidal cells", *J.Comput.Neurosci*., 4 (1997) 141-150.

Whittington, M.A., Stanford, I.M., Colling, S.B., Jefferys, J.G.R., and Traub, R.D. "Spatiotemporal patterns of gamma-frequency oscillations tetanically induced in the rat hippocampal slice", *J.Physiol.(Lond.)*, 502 (1997) 591-607.

Colling, S.B., Stanford, I.M., Traub, R.D., and Jefferys, J.G.R. "Limbic gamma rhythms. I. Phase-locked oscillations in hippocampal CA1 and subiculum", *J.Neurophysiol*., (1998) (In Press)

Stanford, I.M., Traub, R.D., and Jefferys, J.G.R. "Limbic gamma rhythms. II. Synaptic and intrinsic mechanisms underlying spike doublets in oscillating subicular neurons", *J.Neurophysiol*., (1998) (In Press)

Addendum

A. Perception and Consciousness

Professor John Jefferys - Neuroscience Unit

Introduction

Fast, gamma rhythms range from 30-100 Hz and may vary in frequency during a response. The 20-100 Hz range that we consider here overlaps the beta band (15-30 Hz). But we will ignore the finer points of EEG classification here. The natural history and functional roles of synchronous gamma oscillations have been reviewed recently **[5, 10, 12, 22]**. Below is a potted history.

Gamma rhythms occur in humans and other mammals following sensory stimuli. They often occur in brief runs in these responses. "Induced rhythms" at 50-60 Hz were first described in olfactory bulb by Adrian **[1]**. They have since been found in: olfactory **[4]**, visual **[3a, 3b, 6, 7, 8, 11, 22]**, auditory **[13, 16]**, somatosensory **[2],** and motor cortex **[17, 19, 21]**. Gamma oscillations also occur in the **hippocampus** **[3, 24]** where the link with external sensory stimuli is less direct, but may still exist in the multimodal inputs it receives from higher order sensory cortices. Hippocampal gamma tends to occur during the theta (4-12 Hz) EEG that is a prominent feature of the hippocampus in vivo **[3, 23]**, especially during exploration.

In man, the auditory response includes brief "40 Hz transient responses" **[18, 25]** which increase when the subject pays attention and which disappear with loss of consciousness during anesthesia **[14]**. Repetitive auditory stimulation at ~40 Hz generates a large "40 Hz steady state response" **[9]**. MEG recordings in Man suggest that gamma rhythms can be very widespread **[20]** -- both during waking and dream states. Other MEG measurements in man suggest that gamma rhythms may be organized to sweep across the whole brain, perhaps providing "temporal binding .... into a single cognitive experience" **[15]**.

Bibliography

1. Adrian, E.D. "The electrical activity of the mammalian olfactory bulb", *Electroencephalogr. Clin. Neurophysiol.* 2 (1950) 377-388.

2. Bouyer, J.J., Montaron, M.F., Vahnee, J.M., Albert, M.P., and Rougeul, A. "Anatomical localization of cortical beta rhythms in cat", *Neuroscience*, 22 (1987) 863-869.

3. Bragin, A., Jand , G., N dasdy, Z., Hetke, J., Wise, K., and Buzs ki, G. "Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat", *J. Neurosci*. 15 (1995) 47-60.

3a. Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M., and Reitboeck, H.J. "Coherent oscillations: a mechanism of feature linking in the visual cortex? Multiple electrode and correlation analyses in the cat", *Biol. Cybern*. 60 (1988) 121-130.

3b. Eckhorn, R., Reitboeck, H.J., Arndt, M., and Dicke, P. "Feature linking via synchronization among distributed assemblies: simulations of results from cat visual cortex", *Neural Comput*. 2 (1990) 293-307.

4. Eeckman, F.H. and Freeman, W.J. "Correlations between unit firing and EEG in the rat olfactory system", *Brain Res. 528* (1990) 238-244.

5. Engel, A.K., K nig, P., Kreiter, A.K., Schillen, T.B., and Singer, W. "Temporal coding in the visual cortex: New vistas on integration in the nervous system", *Trends Neurosci*. 15 (1992) 218-226.

6. Engel, A.K., K nig, P., Kreiter, A.K., and Singer, W. "Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex", *Science*, 252 (1991) 1177-1179.

7. Engel, A.K., K nig, P., and Singer, W. "Direct physiological evidence for scene segmentation by temporal coding", *Proc. Natl. Acad. Sci. USA*, 88 (1991) 9136-9140.

8. Freeman, W.J. and van Dijk, B.W. "Spatial patterns of visual cortical fast EEG during conditioned reflex in a rhesus monkey", *Brain Res.* 422 (1987) 267-276.

9. Galambos, R., Makeig, S., and Talmachoff, P.J. "A 40-Hz auditory potential recorded from the human scalp", *Proc. Natl. Acad. Sci. USA*, 78 (1981) 2643-2647.

10. Gray, C.M. "Synchronous oscillations in neuronal systems: mechanisms and function", *J. Comput. Neurosci. 1* (1994) 11-38.

11. Gray, C.M., K nig, P., Engel, A.K., and Singer, W. "Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties", *Nature*, 338 (1989) 334-337.

12. Jefferys, J.G.R., Traub, R.D., and Whittington, M.A. "Neuronal networks for induced '40 Hz' rhythms", *Trends Neurosci*. 19 (1996) 202-208.

13. Keller, I., Madler, C., Schwender, D., and Poppel, E. "Analysis of oscillatory components in perioperative AEP-recordings: a nonparametric procedure for frequency measurement", *Clin. Electroencephalogr.* 21 (1990) 88-92.

14. Kulli, J. and Koch, C. "Does anesthesia cause loss of consciousness", *Trends Neurosci*. 14 (1991) 6-10.

15. Llin s, R. and Ribary, U. "Coherent 40-Hz oscillation characterizes dream state in humans", *Proc. Natl. Acad. Sci. USA*, 90 (1993) 2078-2081.

16. Madler, C., Keller, I., Schwender, D., and Poppel, E. "Sensory information processing during general anesthesia: effect of isoflurane on auditory evoked neuronal oscillations", *Br. J. Anaesth.* 66 (1991) 81-87.

17. Murthy, V.N. and Fetz, E.E. "Coherent 25-to-35 Hz oscillations in the sensorimotor cortex of awake behaving monkeys", *Proc. Natl. Acad. Sci. USA*, 89 (1992) 5670-5674.

18. Pantev, C., Makeig, S., Hoke, M., Galambos, R., Hampson, S., and Gallen, C. "Human auditory evoked gamma-band magnetic fields", *Proc. Natl. Acad. Sci. USA*, 88 (1991) 8996-9000.

19. Pfurtscheller, G., Flotzinger, D., and Neuper, C. "Differentiation between finger, toe and tongue movement in man based on 40 Hz EEG", *Electroencephalogr. Clin. Neurophysiol*. 90 (1994) 456-460.

20. Ribary, U., Ioannides, A.A., Singh, K.D., Hasson, R., Bolton, J.P.R., Lado, F., Mogilner, A., and Llin s, R. "Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans", *Proc. Natl. Acad. Sci. USA*, 88 (1991) 11037-11041.

21. Sanes, J.N. and Donoghue, J.P. "Oscillations in local field potentials of the primate motor cortex during voluntary movement", *Proc. Natl. Acad. Sci. USA*, 90 (1993) 4470-4474.

22. Singer, W. and Gray, C.M. "Visual feature integration and the temporal correlation hypothesis", *Annu. Rev. Neurosci*. 18 (1995) 555-586.

23. Soltesz, I. and Desch nes, M. "Low- and high-frequency membrane potential oscillations during theta activity in CA1 and CA3 pyramidal neurons of the rat hippocampus under ketamine-xylazine anesthesia", *J. Neurophysiol*. 70 (1993) 97-116.

24. Stumpf, C. "The fast component in the electrical activity of rabbit's hippocampus", *Electroencephalogr. Clin. Neurophysiol*. 18 (1965) 477-486.

25. Tiitinen, H., Sinkkonen, J., Reinikainen, K., Alho, K., Lavikainen, J., and Naatanen, R. "Selective attention enhances the auditory 40-Hz transient response in humans", *Nature*, 364 (1993) 59-60.

B. Binding

Professor John Jefferys - Neuroscience Unit

Introduction

Single unit recordings in vivo have revealed much about the events or features to which neurons respond. Individual neurons do not detect their preferred sensory features in isolation. They form part of neuronal networks whose emergent properties define the feature detection properties of the cortical column.

In the visual system, it used to be thought that successive hierarchies of neurons encoded progressively more complex features of objects. This scheme, however, is inflexible and inefficient. Conjunctions of more and more combinations of "low-level" features are needed to define progressively "higher level" features. It is difficult to see how such a scheme copes with the vast range of objects that we can recognize (the "combinatorial problem" **[7])** and with the many entirely unprecedented objects found in the modern World.

Frisbees, for instance, have no obvious precedent in the world in which our ancestors evolved. (While a recent visit to the Pitt Rivers Museum in Oxford revealed that circular quoits have a long history on the Indian subcontinent as a kind of throwing knife, they were made of metal and not brightly colored plastic!) Yet we are able effortlessly to distinguish a flying Frisbee against a complex background even though different and widely-separated cortical areas detect its shape, color, movement, etc.. And the same areas also detect the features of the background.

All this information then can be linked efficiently to the motor system to allow us to catch the Frisbee. A more plausible idea for how we accomplish such tasks is that transient "binding" functionally links the often discontinuous cortical networks needed to analyze the many features that make up real objects **[7]** and, conversely, "scene segmentation" functionally separates the networks encoding different objects from one another and from the background.

The problems of binding, segmentation and the role of synchronous oscillations were clearly identified by von der Malsburg **[9]** considering the "cocktail party effect" where we can to listen to one speaker despite the background babble. Much of the recent interest in gamma rhythms centers on the visual system **[1, 3, 4, 6, 7]**. Single and multi-unit discharges and local field potentials (**Fig. 1A**) can be synchronized at gamma frequencies between visual cortical areas separated by long distances, as long as those areas were stimulated by -- and selective for -- the same object. The repeated synchronized firing of neurons in different co-stimulated areas in principle provides a solution to the binding problem. This concept may generalize beyond the specific sensory cortices to association areas and the hippocampus, where information from different sensory modalities converge and may be bound into multimodal entities or perceptions.

The original models for binding and segmentation introduced the idea that neurons that oscillated together would work together **[9]**. Synchronisation matters more than tight bandwidth **[2, 7]**. Single episodes of neuronal synchronization might occur by chance. But repeated synchronization is much less likely to do so. At the cellular level, repeated synchronization could promote temporal summation at active synapses.

The key point is that the gamma oscillation is not proposed to represent information itself, but rather to provide a temporal structure for correlations in the neurons that do encode specific information [2, 5, 7]. We speculate that the function of gamma rhythm is to provide a reference clock to control the firing of the excitatory neurons, which do most of the processing of the information in hippocampus and neocortex.

The general significance of this mechanism is controversial. Not everyone finds unit correlations in the gamma band. For instance, in some experiments on monkey visual cortex [8, 11]. This could be related to choices of stimuli and recording sites or to technical differences (gamma can occur in brief bursts, with considerable jitter in frequency [2], so it could conceivably be smudged out in averaged measurements on 0.5s runs of EEG or 20 cycles at 40 Hz [11]). However, the reasons for these discrepancies remain unresolved. Others conclude that while gamma rhythms may exist, they are simply an epiphenomenon. That is, they are just an irrelevant detail that falls out of the need to connect neurons in a particular way [10].

We believe that one key step to resolving these issues is to understand the cellular and network mechanisms that generate gamma rhythms, and to develop pharmacological tools that will allow us to probe their roles in vivo.

Bibliography

1. Engel, A.K., K nig, P., Kreiter, A.K., and Singer, W. "Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex", *Science*, 252 (1991) 1177-1179.
2. Engel, A.K., K nig, P., and Schillen, T.B. "Neural coding: Why does the cortex oscillate", *Curr. Biol.* 2 (1992) 332-334.
3. Engel, A.K., K nig, P.. and Singer, W. "Direct physiological evidence for scene segmentation by temporal coding", *Proc. Natl. Acad. Sci. USA*, 88 (1991) 9136-9140.
4. Freeman, W.J. and van Dijk, B.W. "Spatial patterns of visual cortical fast EEG during conditioned reflex in a rhesus monkey", *Brain Res.* 422 (1987) 267-276.
5. Gray, C.M., Engel, A.K., K nig, P. and Singer, W. "Synchronization of oscillatory neuronal responses in cat striate cortex: temporal properties", *Vis. Neurosci*. 8 (1992) 337-347.
6. Gray, C.M., K nig, P., Engel, A.K., and Singer, W. "Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties", *Nature*, 338 (1989) 334-337.
7. Singer, W. and Gray, C.M. "Visual feature integration and the temporal correlation hypothesis", *Annu. Rev. Neurosci*. 18 (1995) 555-586.
8. Tovee, M.J. and Rolls, E.T. "Oscillatory activity is not evident in the primate temporal visual cortex with static stimuli", *Neuroreport*, 3 (1992) 369-372.
9. von der Malsburg, C. and Schneider, W. "A neural cocktail-party processor", *Biol. Cybern*. 54 (1986) 29-40.
10. Wilson, M.A. and Bower, J.M. "Computer simulation of oscillatory behavior in primary visual cortex", *Neural Comput.* 3 (1991) 498-509.
11. Young, M.P., Tanaka, K., and Yamane, S. "On oscillating neuronal responses in the visual cortex of the monkey", *J. Neurophysiol*. 67 (1992) 1464-1474.

C. Recordings of Neurons

Introduction

Coherent rhythms may have other functions.

One idea is that they provide a timing reference for a neural code that depends on the phase relationship of individual neurons with the reference oscillation. The stronger the excitation to an individual neuron, the earlier in the cycle it will fire. Thus neurons that fire at similar phases in the rhythm will have received similar intensities of input which may be used, for instance, to lock their outputs together for more effective summation.

This hypothesis was proposed for hippocampal theta **[2]** and more recently for gamma **[1]**.

Bibliography

1. Hopfield, J.J. "Pattern recognition computation using action potential timing for stimulus representation", *Nature*, 376 (1995) 33-36.
2. O'Keefe, J. and Recce, M.L. "Phase relationship between hippocampal place units and the EEG theta rhythm", *Hippocampus*, 3 (1993) 317-330.

D. Brainwaves: synchronization of tetanically-evoked gamma - revised version

Introduction

Cortical oscillations at gamma (30-100 Hz) and beta (10-30 Hz) frequencies are implicated in cognitive tasks. Gamma and beta oscillations evoked in the hippocampal slice in vitro by tetanic stimulation can be synchronised with phase lags faster than the conduction delays expected from the distance between the stimulating electrodes. This led Traub to develop an innovative **model** based on networks of fast synapses using glutamate and GABA as their transmitters.

While this theoretical model is feasible on the basis of the known cellular and network properties of the hippocampus, and may well apply under some experimental circumstances, we now have doubts on its application to tetanically evoked gamma rhythms because of: (1) the **spatial extent** of the gamma focus means that the actual distance between the oscillating populations is much less than the distance between the two stimulating electrodes (typically ~1-2mm), and (2) **new evidence and ideas** on the mechanism of tetanically-evoked gamma rhythms.

One of our earlier publications illustrates the first problem (spatial extent) with a figure concerning the relationship between gamma rhythms in the CA1 region and those in the subiculum.

The stimulus (20 pulses at 100Hz delivered to the CA3 end of CA1) evokes population spikes at 31Hz (low gamma range) 0.4mm away. The point of this particular figure was to show that the gamma rhythm is projected to the subiculum (presumably via CA1 pyramidal neuron axons in the alveus). It also shows that, if a second stimulus delivered to the other end of CA1 (say at 1.0mm) evoked an oscillation in a similar area of tissue, then there would be no more than 0.2mm separating the oscillating areas -- much less than the apparent 1mm.

In fact. it now looks as though oscillating regions become synchronized if they fuse into one single oscillating focus.

E. Mechanisms

Introduction

Several theories exist for the generation of gamma oscillations in various parts of the brain. They all need further experimental testing. It is possible that gamma oscillations arise by different mechanisms in different parts of the brain and that several mechanisms combine in individual regions. The cartoons in the **Figure** are highly simplified representations of some of their components. We will consider the various mechanisms roughly in chronological order and indicate the main regions where they have been implicated immediately after their respective headings.

Feedback loops between excitatory and inhibitory neurons (olfactory bulb, piriform cortex, entorhinal cortex, primary visual cortex). Freeman and colleagues developed a model for induced rhythms in several olfactory structures, which proposed that the synchronous oscillation is generated by a feedback loop between excitatory and inhibitory neurons [2]. They proposed that some mutual connectivity was also required within the pools of both excitatory and inhibitory neurons to stabilize the oscillations. Ermentrout [3] has shown that mutual excitation amongst the excitatory neurons is necessary for stable oscillations to be generated by a recurrent inhibitory loop. However, our recent simulations suggest that other conditions may suffice for stable oscillations (R.D. Traub, unpublished).

Freeman et al [2] predicted that inhibitory cells should lag behind the excitatory by 0.25 cycle (6.5 ms at 40 Hz). Experimental support came from single unit and EEG recordings in vivo from olfactory bulb, anterior olfactory nucleus, prepiriform cortex, and entorhinal cortex [2]. The signals fell into 2 groups -- one set fired in phase with the gamma EEG, and one led or lagged by 0.25 cycle. Unfortunately, these measurements cannot identify the neurons in each group.

In contrast, hippocampal interneurons recorded during gamma fire in phase with pyramidal cells [1]. This is predicted by our inhibitory network model (see below) -- both when isolated from the excitatory network [13] and when connected with pyramidal cells (Traub et al, unpublished simulations). Why the hippocampal and superficially similar olfactory cortical circuitry should differ remains unclear [2].

Wilson and Bower made similar models of piriform cortex [14] and primary visual cortex [15]. The geometric structure of these models differed. But the essential idea in both was that the amplitude and frequency of coherent 30-60 Hz oscillations evoked by afferent volleys were determined or "tuned" by a fast feedback inhibitory loop (**Fig. A**). Essentially, if the stimulus is appropriate (not too strong), enough activity in the recurrent excitatory connections between pyramidal cells persists after recurrent inhibition wanes in order to re-excite the pyramidal cell population. In the case of the piriform cortex model, they showed that the time constant of inhibition "tuned" the frequency of the gamma rhythm, so that longer open times for the chloride channels resulted in slower rhythms (and also a loss of power).

In their model of the primary visual cortex, Wilson and Bower [15] note in passing that local mutual inhibition between the interneurons "...improved frequency locking and produced auto- and cross-correlations with more pronounced oscillatory characteristics". This differs from the central role of the same kinds of connections in the generation of gamma rhythms in the hippocampus where they were both necessary and sufficient [11, 13].

In the visual cortex model, horizontal pyramidal cell axons were essential for long-range (upwards of 1mm) cross correlations [15]. These had zero phase lag as long as the EPSPs they generated were not too strong. Stronger EPSPs result in phase lags consistent with axonal conduction delays, while weaker ones were reminiscent of other kinds of loosely-coupled oscillators. In both the visual cortex and the

piriform cortex versions of this model, gamma rhythms (a) arose from interactions between networks of excitatory neurons; (b) could depend on the conduction velocities of intrinsic cortical connections (**Fig. 2B**); and (c) were tuned by the time constants of excitatory and inhibitory synapses. We are not aware of any attempts to dissect these complex interactions experimentally. In particular, an investigation of the effects of conduction delays on cortical oscillations would be instructive.

Intrinsic oscillations in individual neurons (thalamus, neocortex; **Fig. 2**C). Neurons in many parts of the brain have the intrinsic capacity to oscillate at about 40 Hz. Several types of neuron in the thalamocortical system do so (e.g., reticular **[9]** and intralaminar **[10]** neurons). In the neocortex itself, intrinsic cellular oscillators include sparsely spiny layer 4 neurons **[6]**; about 20% of long axon projection neurons in layers 5 and 6 **[8]**; and "chattering cells" (that fire brief trains of action potentials at 200Hz about 40 times a second) recently reported in vivo **[7]**.

Slice studies revealed that 40 Hz oscillations in sparsely spiny neurons in frontal cortex are generated by voltage-dependent persistent sodium and delayed rectifier currents **[6]**. Other frontal cortex neurons use fast persistent sodium currents, leak and slow non-inactivating potassium currents to generate 4-20 Hz **[4]**. Models suggest that similar mechanisms can generate 40 Hz **[12]**. At least some cortical neurons with intrinsic oscillator mechanisms project to contralateral areas, and to the thalamus, providing routes for long-range synchronization of these oscillations **[8]**. The existence of cells with intrinsic oscillations at 40 Hz does not in itself explain the synchronization of local populations of neurons, but it is likely to pace population rhythms when the neurons are suitably coupled by chemical and/or electrical synapses **[5]**.

Bibliography

1. Bragin, A., Jand , G., N dasdy, Z., Hetke, J., Wise, K., and Buzs ki, G. "Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat", *J. Neurosci*. 15 (1995) 47-60.

2. Eeckman, F.H. and Freeman, W.J. "Correlations between unit firing and EEG in the rat olfactory system," *Brain Res*. 528 (1990) 238-244.

3. Ermentrout, G.B. "Phase-plane analysis of neural activity". In M.A. Arbib (Ed.) The Handbook of Brain Theory and Neural Networks, MIT Press, Cambridge, MA, 1995, pp. 732-738.

4. Gutfreund, Y., Yarom, Y., and Segev, I. "Sub-threshold oscillations and resonant frequency in guinea-pig cortical neurons: physiology and modeling", J. Physiol. (Lond.), 483 (1995) 621-640.

5. Llin s, R.R. "The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function", *Science*, 242 (1988) 1654-1664.

6. Llin s, R.R., Grace, A.A., and Yarom, Y. "In vitro neurons in mammalian cortical layer 4 exhibit intrinsic oscillatory activity in the 10-to-50 Hz frequency range" [published erratum appears in *Proc Natl Acad Sci. USA* 1991 Apr 15;88(8):3510], *Proc. Natl. Acad. Sci. USA*, 88 (1991) 897-901.

7. McCormick, D.A., Gray, C.M., and Wang, Z. "Chattering cells: a new physiological subtype which may contribute to 20-60 Hz oscillations in cat visual cortex", *Soc. Neurosci. Abstr*. 19 (1993) 869(Abstract)

8. Nu ez, A., Amzica, F. and Steriade, M. "Voltage-dependent fast (20-40 Hz) oscillations in long-axoned neocortical neurons", *Neuroscience*, 51 (1992) 7-10.

9. Pinault, D. and Desch nes, M. "Voltage-dependent 40-Hz oscillations in rat reticular thalamic neurons in vivo", *Neuroscience*, 51 (1992) 245-258.

10. Steriade, M., Curro Dossi, R. and Contreras, D. "Electrophysiological properties of intralaminar thalamocortical cells discharging rhythmic (approximately 40 HZ) spike-bursts at approximately 1000 HZ during waking and rapid eye movement sleep", *Neuroscience*, 56 (1993) 1-9.

11. Traub, R.D., Whittington, M.A., Colling, S.B., Buzski, G., and Jefferys, J.G.R. "Analysis of gamma rhythms in the rat hippocampus in vitro and in vivo", *J. Physiol. (Lond.)*, 493 (1996) 471-484.

12. Wang, X.-J. "Ionic basis for intrinsic 40 Hz neuronal oscillations", *Neuroreport*, 5 (1993) 221-224.

13. Whittington, M.A., Traub, R.D., and Jefferys, J.G.R. "Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation", *Nature*, 373 (1995) 612-615.

14. Wilson, M. and Bower, J.M. "Cortical oscillations and temporal interactions in a computer simulation of piriform cortex", *J. Neurophysiol*. 67 (1992) 981-995.

15. Wilson, M.A. and Bower, J.M. "Computer simulation of oscillatory behavior in primary visual cortex," *Neural Comput*. 3 (1991) 498-509.

F. Latest Press Release

Professor John Jefferys - Neuroscience Unit

New Research Clarifies Human Understanding
Provides A Solution to the Elusive "Binding" Problem

Birmingham, October 1996 -- It is one of the great and enduring scientific mysteries. How the 3 pounds of protoplasm -- the nerve cells and molecules that make up the brain -- generate the state that we call **consciousness**.

Now, an Anglo-American team of scientists from the University of Birmingham, IBM Research Center at Yorktown Heights New York and Imperial College School of Medicine at St. Mary's may have provided a major step in establishing a cellular basis for consciousness. In the October 17, 1996 issue of the international journal *Nature*, they report a potential solution to a famous quandary known as the "**binding problem**" -- how the brain "binds" together activity from spatially separated areas into a single coherent picture.

The research suggests new experimental approaches to studying the mind-body problem, while at a practical level it has implications for dementing and psychiatric illnesses such as schizophrenia that somehow disrupt the process of useful thought.

For years, researchers have suspected that the binding task is accomplished by nerve cells in distinct areas of the brain communicating between themselves by oscillating in phase like 2 different chorus lines kicking to the same beat even though they're dancing in different theatres. These oscillations have been detected in everything from the olfactory bulb of rabbits to the visual cortex of cats and even conscious humans. IBM, Birmingham, and Saint Mary's researchers now believe they have explained not only how the oscillations come about but also how the oscillatory rhythm is communicated from one area of the brain to another. These 2 findings are critical to understanding how the complex electric signals of large numbers of nerve cells generate awareness -- and perhaps even consciousness.

At the heart of the binding problem is how the brain processes its perception of objects. "The brain uses widely distributed parallel processing mechanisms, that are best understood in the case of vision," explains John Jefferys, Professor of Neuroscience in Birmingham. "Most people have no difficulty identifying objects such as a tennis ball flying through the air. The way our brains link the different areas that process color, shape, and motion so that we see the ball as a single object is so effective that we simply are not aware of the complex computations involved".

As long ago as the 1950s, researchers observed a distinct 40 cycles-per-second (Hertz) rhythm in the brains of animals while they were discriminating between smells or visual stimuli. In 1989, Gray and Singer in Germany detected the rhythm in the visual cortex of cats and noticed that not only were these oscillations tightly synchronized over a large part of the brain, but they also appeared strongest when the cat was looking at a single object and weakest or non-existent when the cat was looking at different and unrelated objects. No less a biological luminary than the Nobel Laureate Francis Crick has suggested that this synchronized firing of nerve cells was used by the brain not only as a means of focusing attention but also as the general mechanism of consciousness.

But how were these 40 Hertz oscillations generated? More than 30 years later in the February 16, 1995 issue of *Nature*, Miles Whittington, Roger Traub, and John Jefferys reported that the oscillations seem to emerge naturally from a network of neurons known as interneurons (or inhibitory neurons) that work to suppress and control the firing rate of the bulk of the brain's neurons (which are known as

pyramidal cells). What's more, the researchers showed that repetitive stimulation to the interneuron network would prompt the elicit 40 Hertz oscillations. This finding arose from laboratory work on fresh hippocampal brain tissue done by Jefferys and Whittington and computer simulations of networks of neurons constructed on an IBM SP supercomputer by Traub (a research staff member at IBM in New York).

Their proposal is that the inhibitory network receives a steady or slow excitatory drive which makes it oscillate. And that provides a clock which determines when pyramidal cells can fire. The fact that the inhibitory network can -- by itself -- sustain this oscillatory rhythm, separates the synchronizing control (or "clock") from the specific neuronal processing of information the "central processing unit". If the role of these so-called gamma rhythms is indeed to mediate binding, then mechanisms must exist for the selective coupling of areas involved in processing common entities.

In their latest *Nature* paper, Traub, Whittington, Stanford, and Jefferys report that they may have found this coupling mechanism. They show how these 40 Hertz oscillations can achieve a tight synchronization across different areas of the brain, thus providing a possible solution to the famous binding problem. In the latest work, Traub added pyramidal cells to his computer simulation of the network of inhibitory cells. With the pyramidal cells included, Traub found that the interneurons began firing twice in quick succession (in "doublets", as Traub calls it).

This "double beat" then serves as the time keeper that keeps neurons synchronized over long distances. The time lag of the second beat matches up with how long it takes a signal to travel to the next ensemble of neurons that are paying attention to the same object. And that beat keeps the oscillation synchronized. Not only do the doublets seem to explain the tight synchronization needed by the binding problem using "very simple circuitry,'" says Traub, but the model also led to 3 firm predictions about the oscillations in live cells that could be tested in the laboratory. When Whittington, Stanford, and Jefferys tested the predictions in the lab, the results on all 3 predictions matched the model exactly.

"This is how theoretical and experimental science should work together. Roger Traub's computer models are built firmly on real experimental data and make predictions that can be tested by experiment" says Jefferys. "In this case, it has worked out better than we dared hope".

For more information on this visit our web sites at

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http://www.research.ibm.com

Research Team members:-

Prof John Jefferys, Professor of Neuroscience, University of Birmingham
Dr Ian Stanford, Research Associate, University of Birmingham
Dr Miles Whittington, Lecturer, Imperial College School of Medicine at St Mary's (London)
Prof Roger Traub, Staff member, IBM Research Center, Yorktown Heights, New York and Columbia University Medical Center, New York.

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