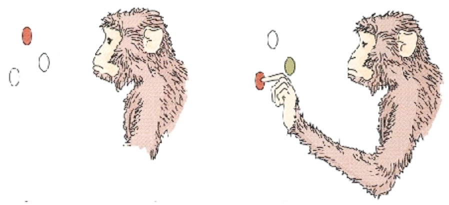
Sustained activity, Working Memory, Associative Memory

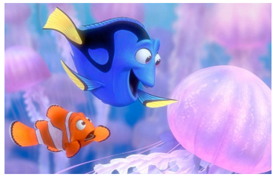
Readings:

C.Constandinis and XJ Wang, “a neural circuit basis for spatial working memory”, Neuroscientist, 2004

What is working memory ? (a.k.a. short-term memory)

- The ability to hold information over a time scale of seconds to minutes
- a critical component of cognitive functions (language, thoughts, planning etc..)





Delayed match-to sample task: remember ‘red’

http://news.bbc.co.uk/1/hi/health/4101431.stm

http://www.youtube.com/watch?v=M1Tui0Gbvq4&feature=related

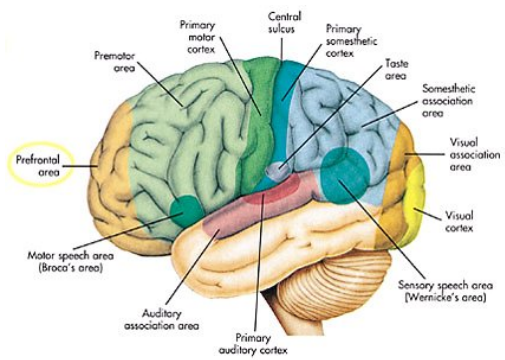
Test your working memory

http://www.ted.com/talks/peter_doolittle_how_your_working_memory_makes_sense_of_the_world.html

2:21-3:49

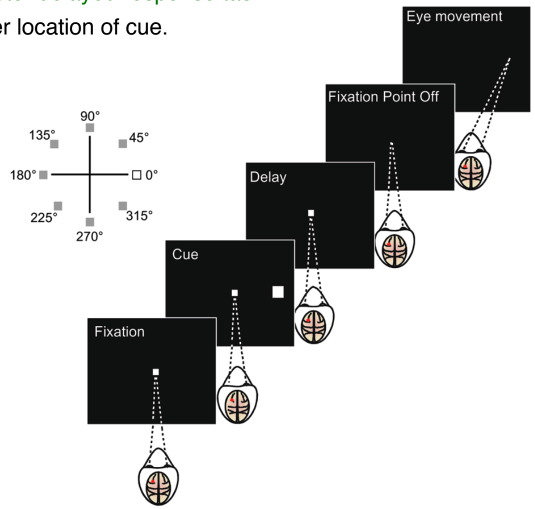
Sustained activity in PFC (1)

- Lesion and inactivation studies demonstrate crucial role of Prefrontal Cortex (PFC) in working memory, in particular dorsolateral PFC (PFdl).



Sustained activity in PFC (2)

Oculo-motor delayed response task:
remember location of cue.



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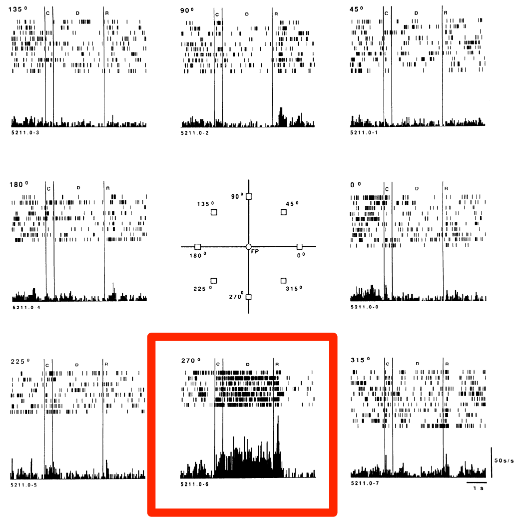
Sustained activity in PFC (2)



Funahashi et al, 1989

Working memory vs Long-term memory

• Long-term memory : molecular or structural changes

• Short-term/ working memory: Dynamic process that has not yielded to molecular characterisation: Sustained aka Delay Activity.

Sustained activity is very widespread

• Sustained activity is a widespread phenomenon

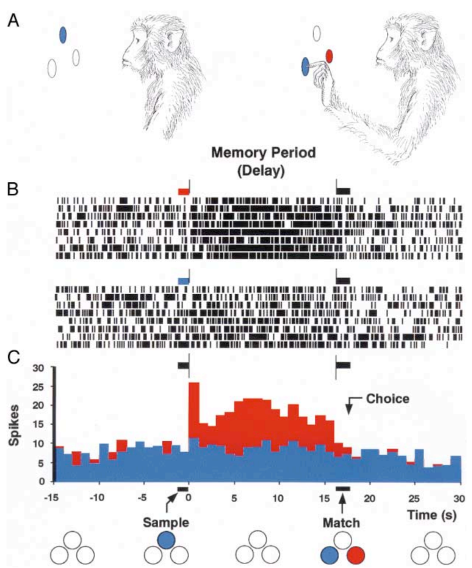
• LIP and PP also have neurons which direction-specific memory fields, similar to PFC.

• Also found in inferotemporal cortex (IT), Example of a discrete working memory.

• Memory related activity is also described in V3A, MT, V1, entorhinal cortex, Pre motor cortex, SMA, SC, basal ganglia...

• The distinct and cooperative roles of these areas remain unresolved.

Sustained activity in IT



Fuster and Jervey 1982

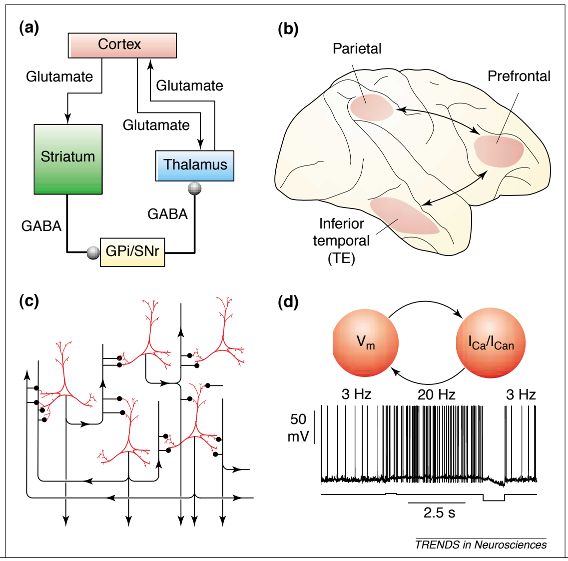
Working Memory and Sustained Activity

- A theory of working memory should answer:
- How it is initiated?
- Why does it persist ?
- What makes it specific?
- How does it end?

- Reason for capacity limit?
- Relationship with attention, long term memory?

- Mechanism : reverberations through connections (which?), or cellular?
- Lots of experimental and theoretical work to answer these questions, in PFC, HD, Oculo-motor system

How does a transient stimulus cause a lasting change in neural activity?



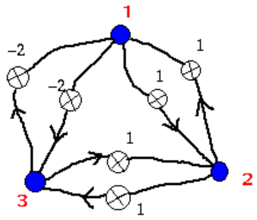
Attractor Paradigm for Persistent Activity

- Since the 1970s it has been proposed that delay activity patterns can be theoretically described by 'dynamical attractors' in recurrent neural networks.

Hopfield Networks

• A Hopfield net is a form of recurrent artificial neural network invented by John Hopfield (1982).
• Hopfield nets typically have binary (1/-1 or 1/0) threshold units:

$$s_i = \begin{cases} 1 & \text{if } \sum_j w_{ij} s_j > \theta_i, \\ -1 & \text{otherwise.} \end{cases}$$



weights in black
Nodes numbers in red

where s_j state of unit j, and θ_i is the threshold
The weights have to follow: $w_{ii}=0$, $w_{ij}=w_{ji}$

• Hopfield nets have a scalar value associated with each state of the network referred to as the "energy", E, of the network, where:

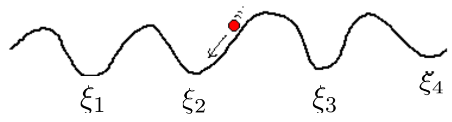
$$E = -\frac{1}{2}\sum_{i<j} w_{ij} s_i s_j + \sum_i \theta_i \; s_i$$

Hopfield Networks

• Running: at each step, pick a node at random and update (asynchronous update)
The energy is guaranteed to go down and the network to settle in local minima of the energy function.

• Learning: the weights are set so as to 'shape' those local minima.
The network will learnt to converge to stored state even if it is given only part of the state:

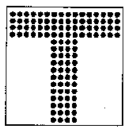
$$w_{ij} = \frac{1}{N}\sum_{k=1}^{k=N} \xi_i^k \xi_j^k$$



ξ_i =stored patterns

Associative memories

• The Hopfield network is an associative/content addressable memory. It can be used to recover from a distorted input the trained state that is most similar to that input. E.g., if we train a Hopfield net with 5 units so that the state (1, 0, 1, 0, 1) is an energy minimum, and we give the network the state (1, 0, 0, 0, 1) it will converge to (1, 0, 1, 0, 1).



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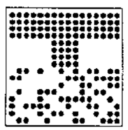
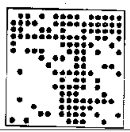


half of image corrupted by noise



20% corrupted by noise (whole image)

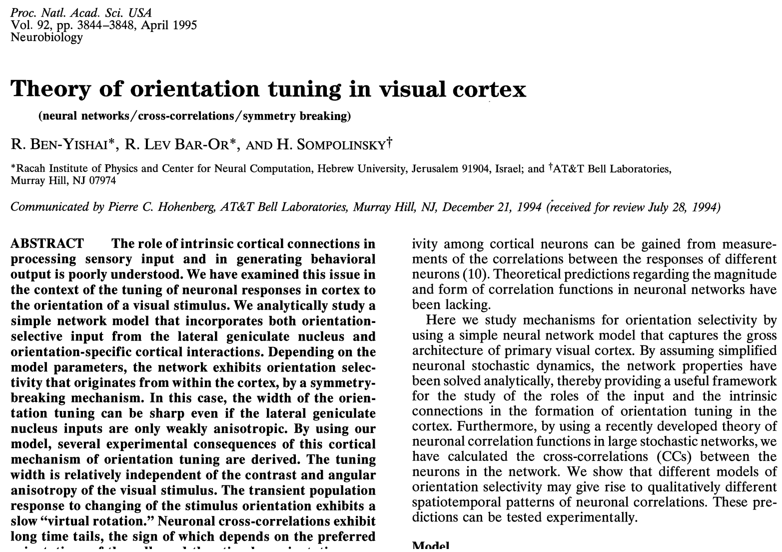
reminiscent of human memory?

Attractor paradigm for Persistent Activity

• Since the 1970s it has been proposed that delay activity patterns can be theoretically described by 'dynamical attractors', in recurrent neural networks.

• Recently, a great effort to build biophysically plausible model of sustained activity / attractor dynamics for memory.

The Ring Model (1)



Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 3844–3848, April 1995
Neurobiology

Theory of orientation tuning in visual cortex

(neural networks/cross-correlations/symmetry breaking)

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Communicated by Pierre C. Hohenberg, AT&T Bell Laboratories, Murray Hill, NJ, December 21, 1994 (received for review July 28, 1994)

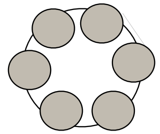
ABSTRACT The role of intrinsic cortical connections in processing sensory input and in generating behavioral output is poorly understood. We have examined this issue in the context of the tuning of neuronal responses in cortex to the orientation of a visual stimulus. We analytically study a simple network model that incorporates both orientation-selective input from the lateral geniculate nucleus and orientation-specific cortical interactions. Depending on the model parameters, the network exhibits orientation selectivity that originates from within the cortex, by a symmetry-breaking mechanism. In this case, the width of the orientation tuning can be sharp even if the lateral geniculate nucleus inputs are only weakly anisotropic. By using our model, several experimental consequences of this cortical mechanism of orientation tuning are derived. The tuning width is relatively independent of the contrast and angular anisotropy of the visual stimulus. The transient population response to changing of the stimulus orientation exhibits a slow "virtual rotation." Neuronal cross-correlations exhibit long time tails, the sign of which depends on the preferred

ivity among cortical neurons can be gained from measurements of the correlations between the responses of different neurons (10). Theoretical predictions regarding the magnitude and form of correlation functions in neuronal networks have been lacking.

Here we study mechanisms for orientation selectivity by using a simple neural network model that captures the gross architecture of primary visual cortex. By assuming simplified neuronal stochastic dynamics, the network properties have been solved analytically, thereby providing a useful framework for the study of the roles of the input and the intrinsic connections in the formation of orientation tuning in the cortex. Furthermore, by using a recently developed theory of neuronal correlation functions in large stochastic networks, we have calculated the cross-correlations (CCs) between the neurons in the network. We show that different models of orientation selectivity may give rise to qualitatively different spatiotemporal patterns of neuronal correlations. These predictions can be tested experimentally.

Model

The Ring Model (2)

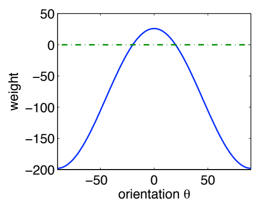


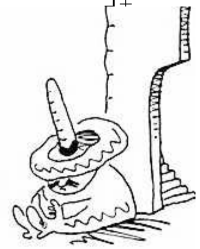
• N neurons, with preferred angle, θ_i ,evenly distributed between $-\pi/2$ and $\pi/2$

• Neurons receive thalamic inputs *h.*

+ recurrent connections, with excitatory weights between nearby cells and inhibitory weights between cells that are further apart (mexican-hat profile)

$$\tau_r \frac{dv(\theta)}{dt} = -v(\theta) + \left[h(\theta) + \int_{-\pi/2}^{\pi/2} \frac{d\theta'}{\pi} \left(-\lambda_0 + \lambda_1 \cos(2(\theta - \theta'))\right) v(\theta') \right]_+$$

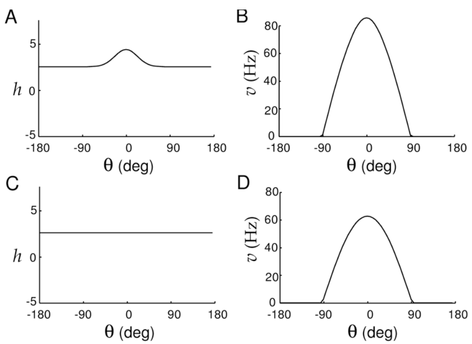




The Ring Model (5): Sustained Activity

• If recurrent connections are strong enough, the pattern of population activity once established can become independent of the structure of the input. It can persists when input is removed.

• A model of working memory ?



Network Mechanisms & Biophysical Models

• Anatomical organisation of PFC resembles a recurrent network

• Biophysical realistic computational modelling has shown that such recurrent networks can give rise to location-specific, persistent discharges

(Compte et al 2000, Gutkin et al 2000, Tegner et al 2002, Renart et al 2003a, Wang et al 2004)

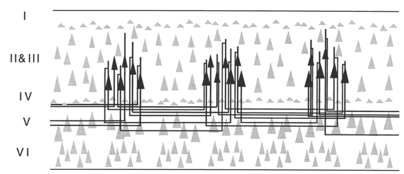


Fig. 4. Schematic diagram illustrating the pattern of connections between prefrontal neurons in the superficial layers. The figure summarizes results of anatomical tracer injection experiments and retrograde labeling. From Kritzer and Goldman-Rakic (1995), with permission.

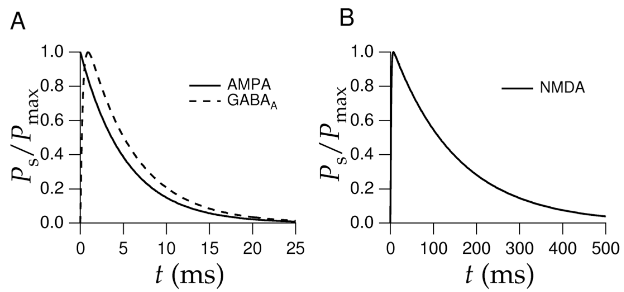
Network Mechanisms & Biophysical Models

- Modelling studies show that stability is an issue in such network.
- Strong recurrent inhibition is needed to prevent runaway excitation and maintain specificity
- Models are also challenged by accounting for spontaneous activity in addition to memory state
- Oscillations can destabilise the memory activity.

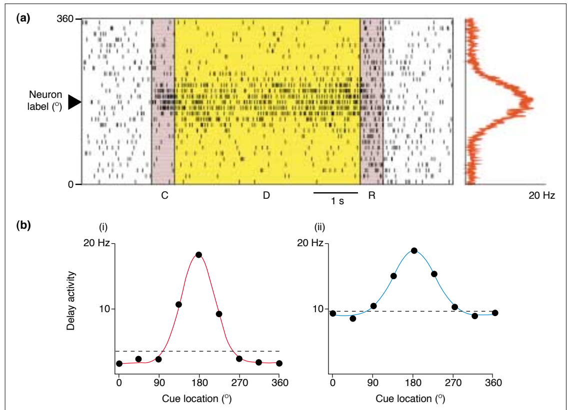
- Working memory is found to be particularly stable when excitatory reverberations are characterised by a fairly slow time course, e.g. when synaptic transmission is mediated by NMDA receptors (prediction)

Synaptic input

- Different synapses have different dynamics.
- Excitatory synapses: AMPA is fast, NMDA slow.
- Inhibitory synapses: GABAa are fast, GABAb slower.



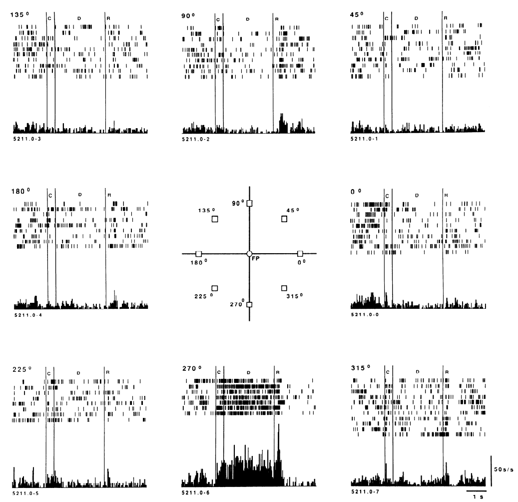
Network Mechanisms & Biophysical Models



[Compte, Brunel, Goldman-Rakic and Wang, 2000]

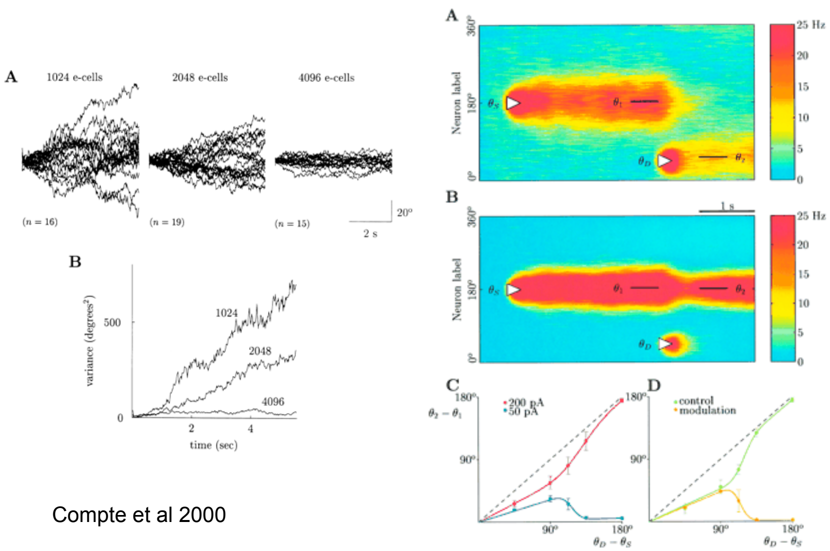
- Network of ~2500 integrate and fire neurons, mexican hat connectivity, NMDA excitation.
- Reproduce Funahashi et al 1989.
- Selectivity of memory field, temporal drifts, robustness to distractors.

Sustained activity in PFC



Funahashi et al, 1989

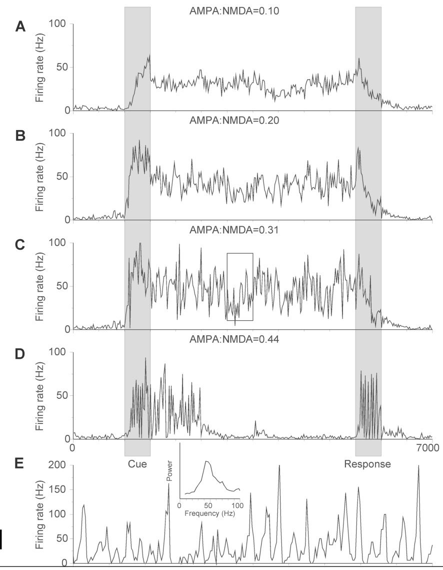
Biophysical Models -- drift and robustness to distractors.



Compte et al 2000

Network Mechanisms & Biophysical Models

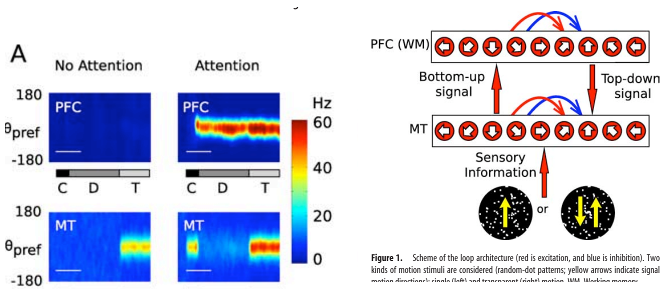
Fig. 6. Stability of persistent activity as a function of the AMPA:NMDA ratio at the recurrent excitatory synapses. *A–D*, Temporal course of the average firing rate across a subpopulation of cells selective to the presentated transient input, for different levels of the AMPA:NMDA ratio. As the ratio is increased, oscillations of a progressively larger amplitude develop during the delay period, which eventually destabilize the persistent activity state. *E*, Snapshot of the activity of the network in (*C*) between 3 and 3.5 seconds. *Top*, Average network activity. *Bottom*, Intracellular voltage trace of a single neuron. *Inset*, Power spectrum of the average activity of the network, showing a peak in the γ (40 Hz) frequency range. Persistent activity is stable even in the presence of synchronous oscillations. Adapted with permission from Renart, Brunel, and others (2003).



[Renart, Brunel, Wang , 2003]

Lots of interesting questions

- How are these attractors learnt?
- What is the relation with Attention?
- What is the relation with Long-term Memory ? (Is sustained activity helpful for storage of memory?) http://www.youtube.com/watch?v=k8Bgs8EarR0&feature=related



Ardid, Wang and Compte 2007

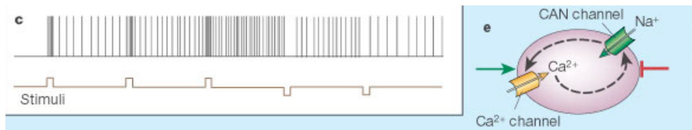
But cellular mechanisms should not be forgotten ...

[Egorov et al, Nature, 2002]

- Layer 5 of rat Entorhinal cortex *in vitro*, intracellular depolarisation + bath application of the ACh-receptor agonist leads to a Ca2+ -dependent plateau potential.
- leads to sustained firing at a constant rate > 13 min
- independent of synaptic transmission.
- activity level can be increased or decreased using repeated inputs.

see also [Lowenstein ... and Hausser, *Nat Neuro,* 2005, bistability in Purkinje neurons]

Could attractors be suited for remembering learned stimuli while such a system could help maintaining new stimuli?



Sustained Activity for Novel Inputs

- could be explained by cellular properties within the entorhinal and perirhinal cortex rather than recurrent interactions in PFC.

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Mechanisms underlying working memory for novel information

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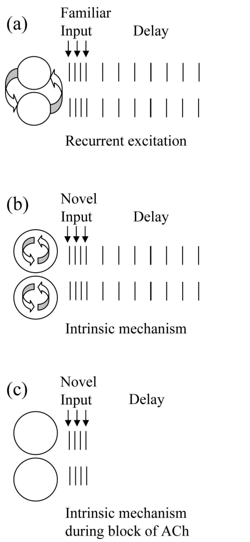
Abstract

We describe a theory that brain mechanisms underlying working memory for novel information include a buffer in parahippocampal cortices. Computational modelling indicates that mechanisms for maintaining novel information in working memory could differ from mechanisms for maintaining familiar information. Electrophysiological data suggest that the buffer for novel information depends on acetylcholine. Acetylcholine activates single-cell mechanisms that underlie persistent spiking of neurons in the absence of synaptic transmission, allowing maintenance of information without prior synaptic modification. fMRI studies and lesion studies suggest that parahippocampal regions mediate working memory for novel stimuli, and effects of cholinergic blockade impair this function. These intrinsic mechanisms in parahippocampal cortices provide an important alternative to theories of working memory based on recurrent synaptic excitation.



Link with disease (schizophrenia)

- Working Memory deficits core of cognitive deficits in Scz
- Schizophrenia associated with reduced function of NMDA receptor (and ketamine blocks NMDA).
- Instability of attractor states, shallower basins of attraction
- spontaneous attractors: positive symptoms?

Review

A computational neuroscience approach to schizophrenia and its onset

Edmund T. Rolls[a,*], Gustavo Deco[b,c]

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ABSTRACT

Computational neurosci
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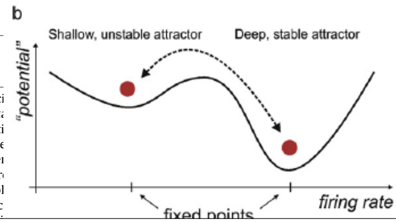


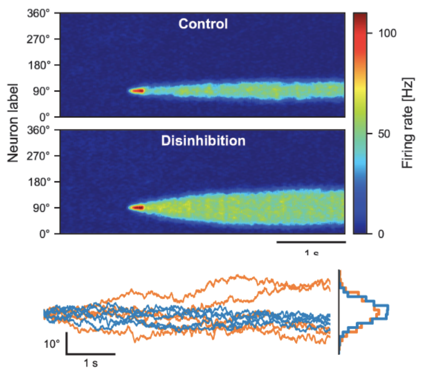
Link with disease (schizophrenia)

Cerebral Cortex Advance Access published November 29, 2012

Cerebral Cortex
doi:10.1093/cercor/bhs370

Linking Microcircuit Dysfunction to Cognitive Impairment: Effects of Disinhibition Associated with Schizophrenia in a Cortical Working Memory Model

John D. Murray[1,2], Alan Anticevic[3,4,5], Mark Gancsos[3], Megan Ichinose[3], Philip R. Corlett[3,5], John H. Krystal[3,4,5,6,7] and Xiao-Jing Wang[2,8]



- Desinhibition via perturbation of NMDA receptors on Inhib cells.
- broadens selectivity, increases drift and vulnerability to distractors

Ageing and working memory

LETTER

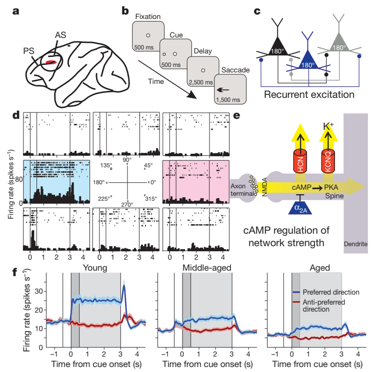
doi:10.1038/nature10243

210 | NATURE | VOL 476 | 11 AUGUST 2011

Neuronal basis of age-related working memory decline

Min Wang[1], Nao J. Gamo[1], Yang Yang[1], Lu E. Jin[1], Xiao-Jing Wang[1], Mark Laubach[1,2], James A. Mazer[1], Daeyeol Lee[1] & Amy F. T. Arnsten[1]

Many of the cognitive deficits of normal ageing (forgetfulness, distractibility, inflexibility and impaired executive functions) involve prefrontal cortex (PFC) dysfunction[1–4]. The PFC guides behaviour and thought using working memory[5], which are essential functions in the information age. Many PFC neurons hold information in working memory through excitatory networks that can maintain persistent neuronal firing in the absence of external stimulation[6]. This fragile process is highly dependent on the neurochemical environment[7]. For example, elevated cyclic-AMP signalling reduces persistent firing by opening HCN and KCNQ potassium channels[8,9]. It is not known if molecular changes associated with normal ageing alter the physiological properties of PFC neurons during working memory, as there have been no *in vivo* recordings, to our knowledge, from PFC neurons of aged monkeys. Here we characterize the first recordings of this kind, revealing a marked loss of PFC persistent firing with advancing age that can be rescued by restoring an optimal neurochemical environment. Recordings showed an age-related decline in the firing rate of DELAY neurons, whereas the firing of CUE neurons remained unchanged with age. The memory-related firing of aged DELAY neurons was partially restored to more youthful levels by inhibiting cAMP signalling, or by blocking HCN or KCNQ channels. These findings reveal the cellular basis of age-related cognitive decline in dorsolateral PFC, and demonstrate that physiological integrity can be rescued by addressing the molecular needs of PFC circuits.



Trends in Cognitive Sciences 14 (2010) 365–375

Opinion

Cell PRESS

Dynamic Network Connectivity: A new form of neuroplasticity

Amy F.T. Arnsten, Constantinos D. Paspalas, Nao J. Gamo, Yang Yang and Min Wang

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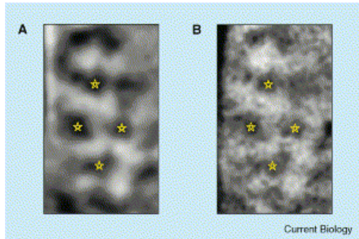
Prefrontal cortical (PFC) working memory functions depend on pyramidal cell networks that interconnect on dendritic spines. Recent research has revealed that the strength of PFC network connections can be rapidly and reversibly increased or decreased by molecular signaling events within slender, elongated spines: a process we term Dynamic Network Connectivity (DNC). This newly discovered form of neuroplasticity provides great flexibility in mental state, but also confers vulnerability and limits mental capacity. A remarkable number of genetic and/or environmental insults to DNC signaling cascades are associated with cognitive disorders such as schizophrenia and age-related cognitive decline. These insults can dysregulate network connections and erode higher cognitive abilities, leading to symptoms such as forgetfulness, susceptibility to interference, and disorganized thought and behavior.

- Strength of PFC connections are rapidly and reversibly modulated by molecular signaling events (e.g. cAMP gates potassium channels, ACh, NE, DA)
- to accommodate the state of arousal and cognitive or physiological demands
- Link with ageing and disorders

A related problem: spontaneous activity

- Where does it come from?
- How is it maintained? How does it 'move'?
- Are these 'attractor states'?
- Is it structured?
- Why is it there? (any functional advantages?)
- Is it noise?
- Is it the brain trying to 'predict' the input?



evoked (horizontal orientation) spontaneous (one frame)

Arieli et al 1997; Tsodyks et al, 1999; Fiser et al, Nature, 2004

Conclusions

- Attractor Networks as (main) model of working memory / sustained activity
- Effort to provide biologically plausible spiking models, comparable to recordings in PFC
- currently, interesting link with disease and ageing
  -- working memory impairments as instability of attractor states e.g. due to deficits in NMDA, changes in E/I balance.
- Spontaneous activity as a similar problem.

Lots of open questions and even the classical models are questioned ..

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Current Opinion in Neurobiology

Working models of working memory

Omri Barak[1] and Misha Tsodyks[2]

Working memory is a system that maintains and manipulates information for several seconds during the planning and execution of many cognitive tasks. Traditionally, it was believed that the neuronal underpinning of working memory is stationary persistent firing of selective neuronal populations. Recent advances introduced new ideas regarding possible mechanisms of working memory, such as short-term synaptic facilitation, precise tuning of recurrent excitation and inhibition, and intrinsic network dynamics. These ideas are motivated by computational considerations and careful analysis of experimental data. Taken together, they may indicate the plethora of different processes underlying working memory in the brain.

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activity related to storing a fixed item is not stationary, and there is a large heterogeneity in the firing profiles of different neurons [3,4,5*,6]. From the computational side, the network activity representing a memorized item should exhibit a sufficient degree of stability to ensure memory retainment. This requirement is especially challenging for storing continuous variables, such as orientation or spatial position of a visual cue, because of an inevitable drift along the variable's representation. Furthermore, integrating the various data-driven challenges in a self-consistent manner is often a non-trivial computational problem.

To cope with these challenges, various models incorporate different amounts of biophysical detail – highlighting the contribution of model elements to the various challenges (Figure 1, right). In the current review, we will briefly present the classic models of working memory, and proceed to highlight several recent attempts at addressing the different challenges. The focus of this review is on