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THE ROLE OF THE HIPPOCAMPUS IN TRACE CONDITIONING.

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This is a preliminary review of new results on trace conditioning that attempts to integrate them into the framework of Vinogradova's (2001) Theta-Regulated Attention Theory.

Vinogradova's CA3 Comparator Hypothesis: Reply to Lisman (2006)

1. Lisman (2006) states that "this hypothesis poses a difficulty; even Vinogradova claims that septal responses are usually polymodal. If this is correct then a CA3 comparator could not use septal information to decide whether incoming information is novel or not" (p.37).

2. Lisman (1999) and Lisman et al (2005) proposed an alternative hypothesis - that the comparator is in CA1, and not in CA3, because CA3 stores temporal/permanent memories, and sends them to CA1 along with direct sensory information from entorhinal cortex.

3. Kryukov (2008) argues that Vinogradova's theory requires the CA3 comparator neither to be modality specific, nor to be storing any memory traces, but it allows for solving the novelty detection problem uniformly, for all signal modalities, because novelty detection is an emerging property of the whole PLL system, and not just a single part of it.

4. Vinogradova's theory backed by new data suggested new hypothesis to be proposed, that the hippocampus can function as a dual CA1-CA3 comparator and thus resolving many difficult problems in classical conditioning.

THETA-REGULATED ATTENTION THEORY - BASIC FEATURES

(Vinogradova, 2001)

- The theta rhythm and the septo-hippocampal system play a key role in the processes of selective perception, attention, and memory involving detection of novel and significant changes which should be recorded in memory.

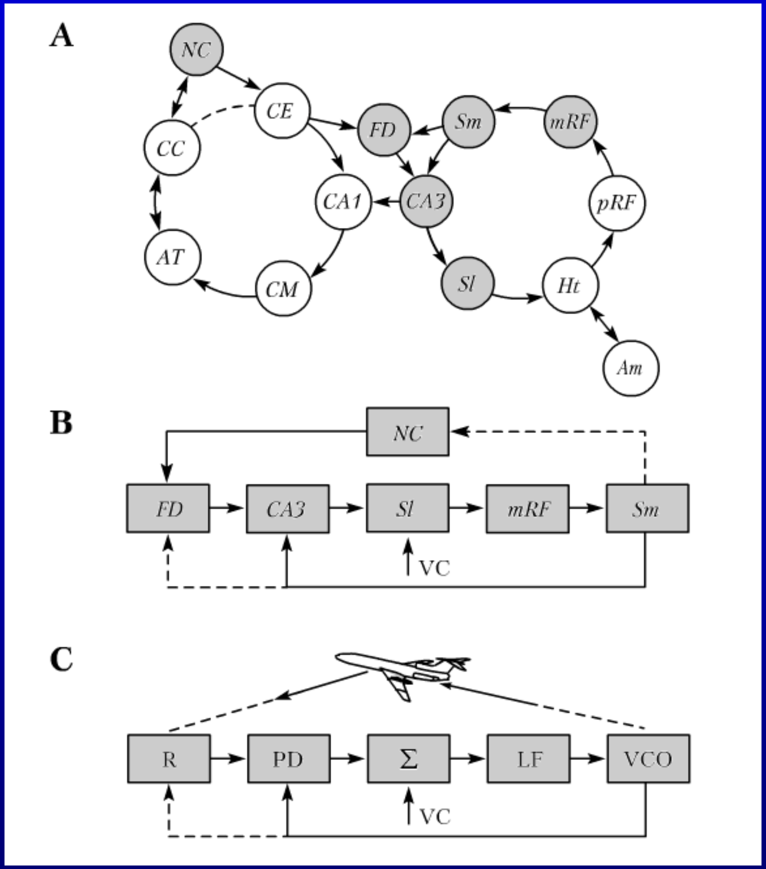
- The CA1 field-based information subsystem and the CA3 field-based regulatory subsystem jointly perform the functions of attention and initial recording of new memory traces.

- The CA3 field compares the two main inputs to the hippocampus – septal and cortical. Its output regulates the arousal and the theta-rhythm frequency, and monitors the information CA3-based subsystem.

- The CA1 field-based subsystem is circular or spiral delay line with variable times of delay and simultaneously is the main hippocampal output to the related cortical and subcortical structures.

THEORY OF THETA-REGULATED ATTENTION: RADAR ANALOGY

(Vinogradova, 1975; Kryukov, 1991)

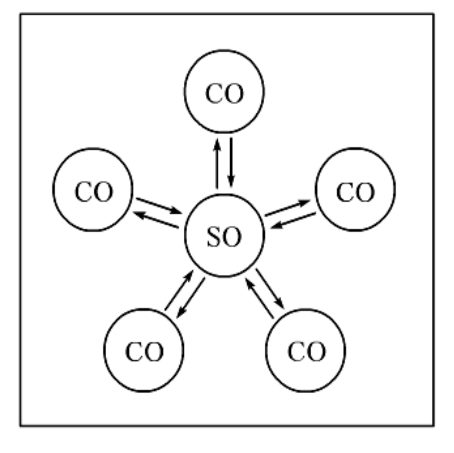


The main function of the hippocampus is to compare the new and existing traces. Via the feedback system, a mismatch signal will regulate the frequency of the theta rhythm, replaying the cortical traces and strengthening them on repetition.

DOMINANT ARCHITECTURE OF "NEUROLOCATOR"

(Kryukov et al, 1990; Hegumen Theophan, 2004)

- The functional unit is a cortical oscillator (CO) composed of integrate-and-fire neurons in a network with local excitation links, recurrent inhibition and non-specific inputs from mRF.



- A septal oscillator (SO) serves as a coordinator ("orchestra conductor“) for cortical oscillators during information recording and replay. The two-way link is non-symmetrical, depending strongly on synchronization.

- Attention is switched from one CO group to another either by way of reset or through an automatic change of the SO frequency by a signal from the comparator output.

- Information is recorded in an ensemble of locally linked cortical oscillators whose lability is modified upon training in accordance with the phenomenon of the dominant *rhythm assimilation.*

KEY ASSUMPTIONS OF "NEUROLOCATOR"

(Kryukov et al, 1991)

- The model structure is similar to that of a standard phase-locked loop (PLL), and at the same time, is arranged much like the regulatory subsystem of the limbic system, with the septum acting as the central pacemaker and the CA3 field being a comparator (Vinogradova 1975, 2001).

- All COs serve as feature analyzers. They are inactive without specific inputs and fairly high arousal is essential for initiation of oscillations in the Θ/γ frequency range.

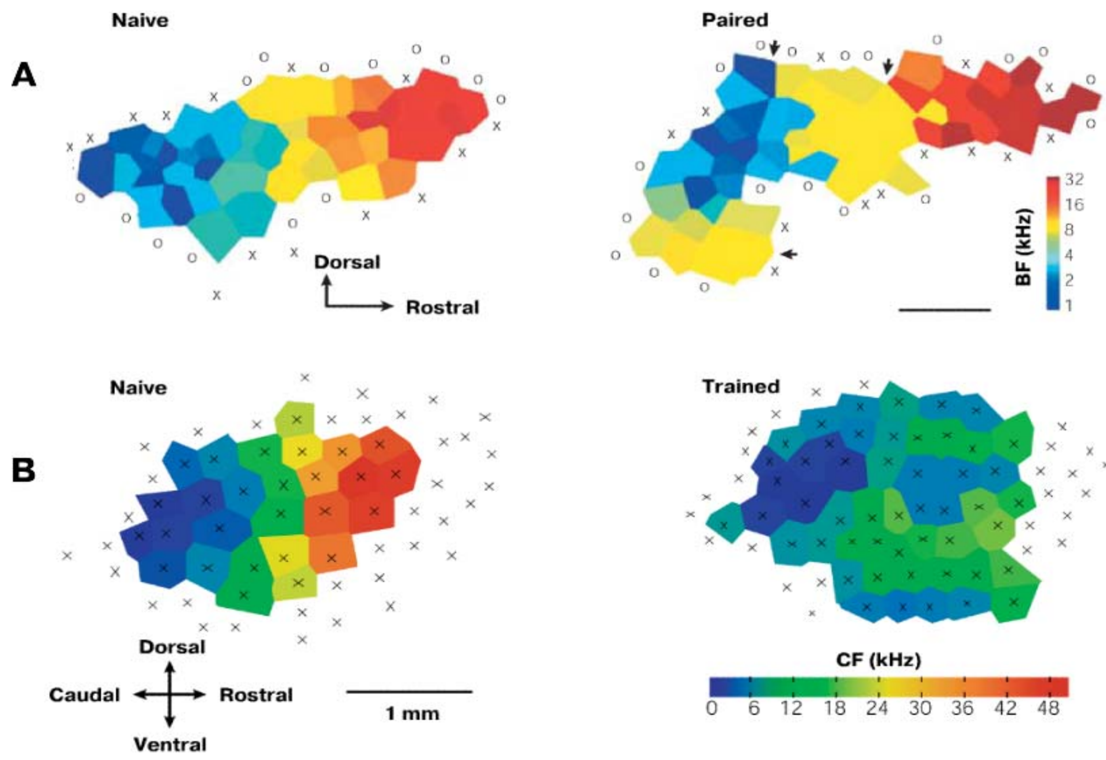
- Attention is an emergent feature of the system, which appears with an increase of arousal and manifests itself as transient synchronization of SO with a certain group of COs.

- Learning and consolidation rely on *space-frequency plasticity*, involving gradual changes in the natural frequency of COs towards the sync frequency in the learning process.

Space-frequency spatial plasticity of receptive fields (RF) in the auditory cortex of a rat (Weinberger, 2003)

A — tone + VTA stimulation

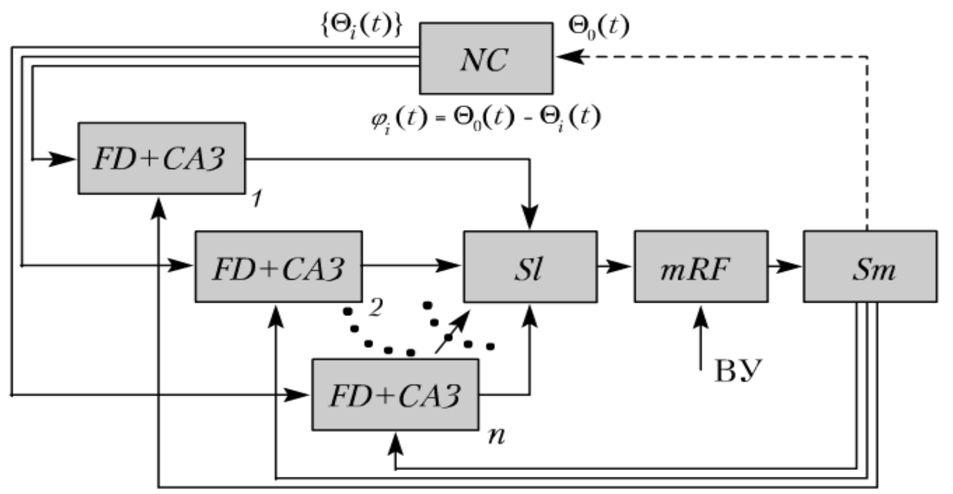
B — tone + water after lever pressing



"RF plasticity has major characteristics of associative memory. It is not only associative, but also it is highly specific, discriminative, rapidly acquired, retained at least for many weeks, develops consolidation over hours and days, and exhibits generality across a variety of training tasks". (Weinberger, 2003, p. 271)

THE BLOCK DIAGRAM AND BASIC EQUATION OF "NEUROLOCATOR"

(Kryukov, 1991)



$$\frac{d\varphi_i}{dt} = \Lambda_{0i} - \Big[\sum_{j=1}^{n} A_{0j}\, g(\varphi_j) + N_j(t)\Big] F(p), \quad (i = 1, \dots n) \qquad (1)$$

where φ_i — difference between oscillation phases of the septal and the ***i***-th cortical oscillators; Λ_{0i} — their frequency mismatch; $\boldsymbol{A_{oj}}$ — activity of neocortical oscillators corresponding to the ***j***-th lamella; **g(τ)** — nonlinear function of phase discriminator; $\boldsymbol{N_j(t)}$ — "white" noise of the ***j***-th lamella; ***n*** — total number of lamellas; ***F(p)*** — transfer function of the low-pass filter ***mRF.***

ATTENTION-RELATED FEATURES OF "NEUROLOCATOR"

- Attention is transient. It is impossible with either too low or too high arousal.
- Attention is controlled by changes in the frequency detuning (Λ_0) produced either automatically from the comparator output or volitionally from other brain structures.
- Attention is controlled automatically by codes of external signals at the theta rhythm frequency (spatial features) as well as at its own harmonic frequencies (non-spatial features), if less efficiently.
- Attention is normally unitary, but with a certain reduction in parameter of arousal it may be divided among 4-7 objects.

MEMORY-RELATED FEATURES OF "NEUROLOCATOR"

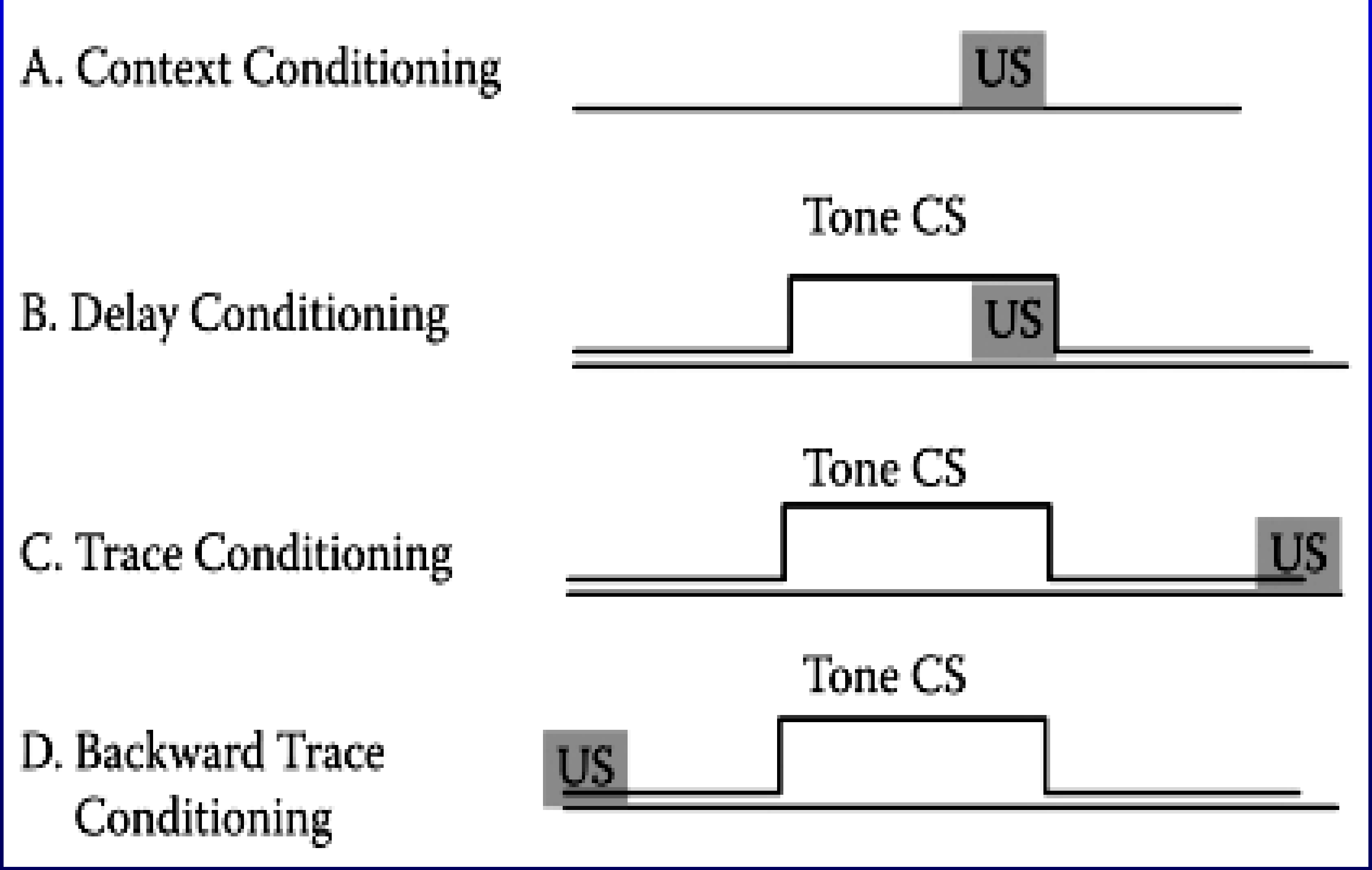
- Memory capacity is practically unlimited, as encoding by isolabile configurations (ensembles) allows the temporary recruiting of oscillators from other configurations.

- Lifetime of metastable memory traces is comparable with that of an organism, given an optimal number of the locally linked oscillators.

- Signals are quickly recorded owing to simultaneous reset excitation of all the oscillators encoding the stimulus.

- Many findings of psychophysical, neuropsychological, and neurophysiological research on memory may be easily explained by the well-know features of the PLL system.

What is Trace Conditioning?
It is one of the four basic conditioning paradigms, and the most difficult to model



WHY TRACE CONDITIONING IS IMPORTANT BUT DIFFICULT TO MODEL ?

- Requires intact hippocampus, mPFC, cerebellum, NC and interaction between them (Kalmbach et al, 2009).
- Requires attention, awareness and neurogenesis (Shors, 2004).
- Most simple example that can dissociate declarative memory from procedural one and provides means for studying awareness in animals Clark and Squire,1998) .
- Perhaps requires common neural code for cognition and action.
- Demonstrate full power of Theta-Regulated Attention Theory by Vinogradova (2001).
- In general: “Trace eyeblink conditioning may prove to be the Rosetta stone for identifying neuronal/synaptic mechanisms underlying declarative memory formation in the brain” (Christian and Thompson, 2003).

BASIC UNANSWERED QUESTIONS

1. "What does the hippocampus do during trace conditioning?" (Shors, 2004, p.252)

2. "How does the hippocampus 'know' what information must be processed and maintained for establishing a hippocampus-dependent trace memory versus that for the delay-type memory?" (Shors, 2004, p.252)

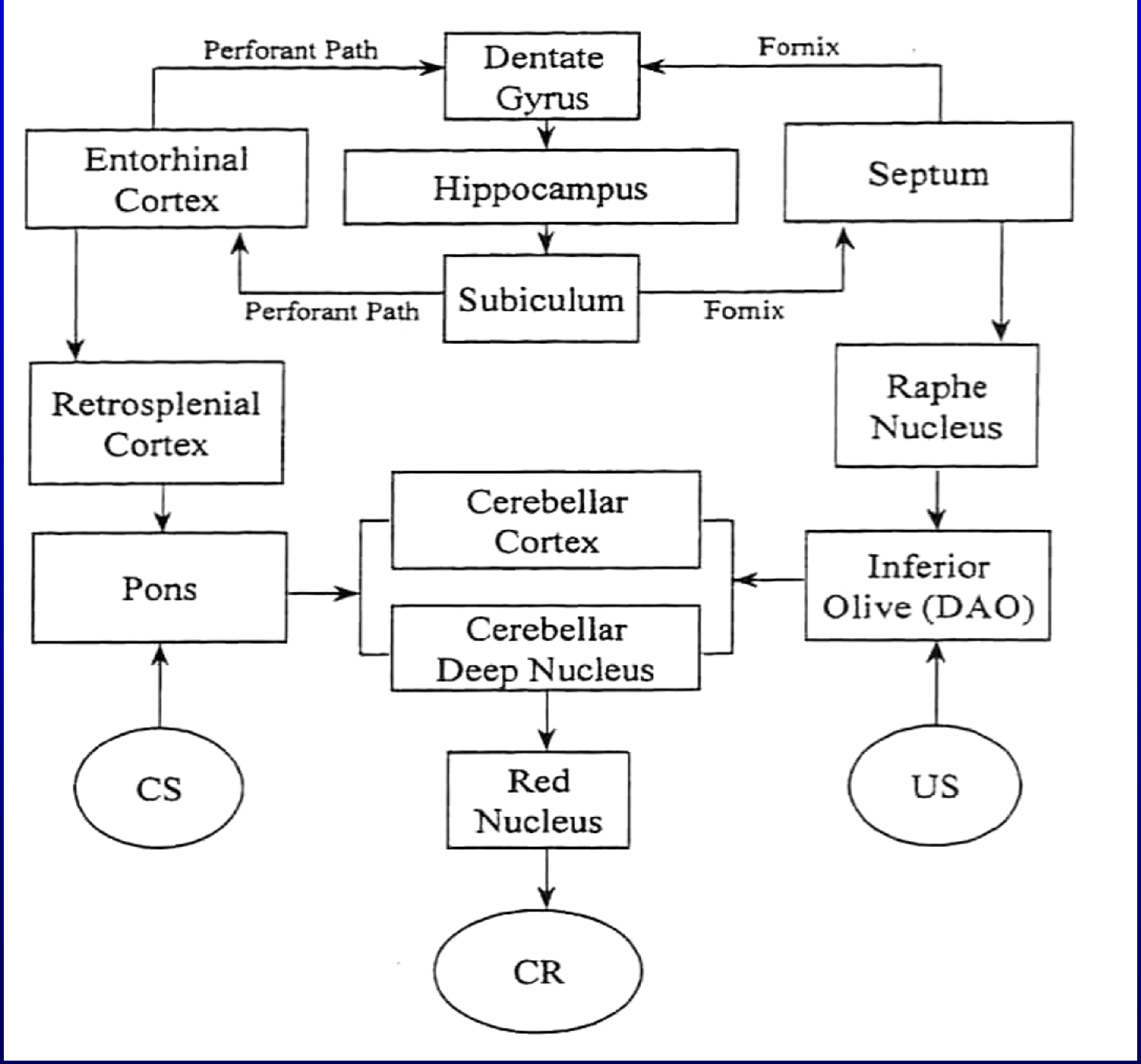
3. "A major unanswered question concerns the relation between the cerebellum and hippocampus in eyeblink conditioning" (Christian and Thompson, 2003, p.4)."How are the cerebellar, hippocampal, and cortical systems functionally interconnected?" (p.11)

4. "How awareness influence this form of learning, and the nature of hippocampal involvement in such an interaction? This is a most interesting and important current area of research "(Christian and Thompson, 2003, p.6).

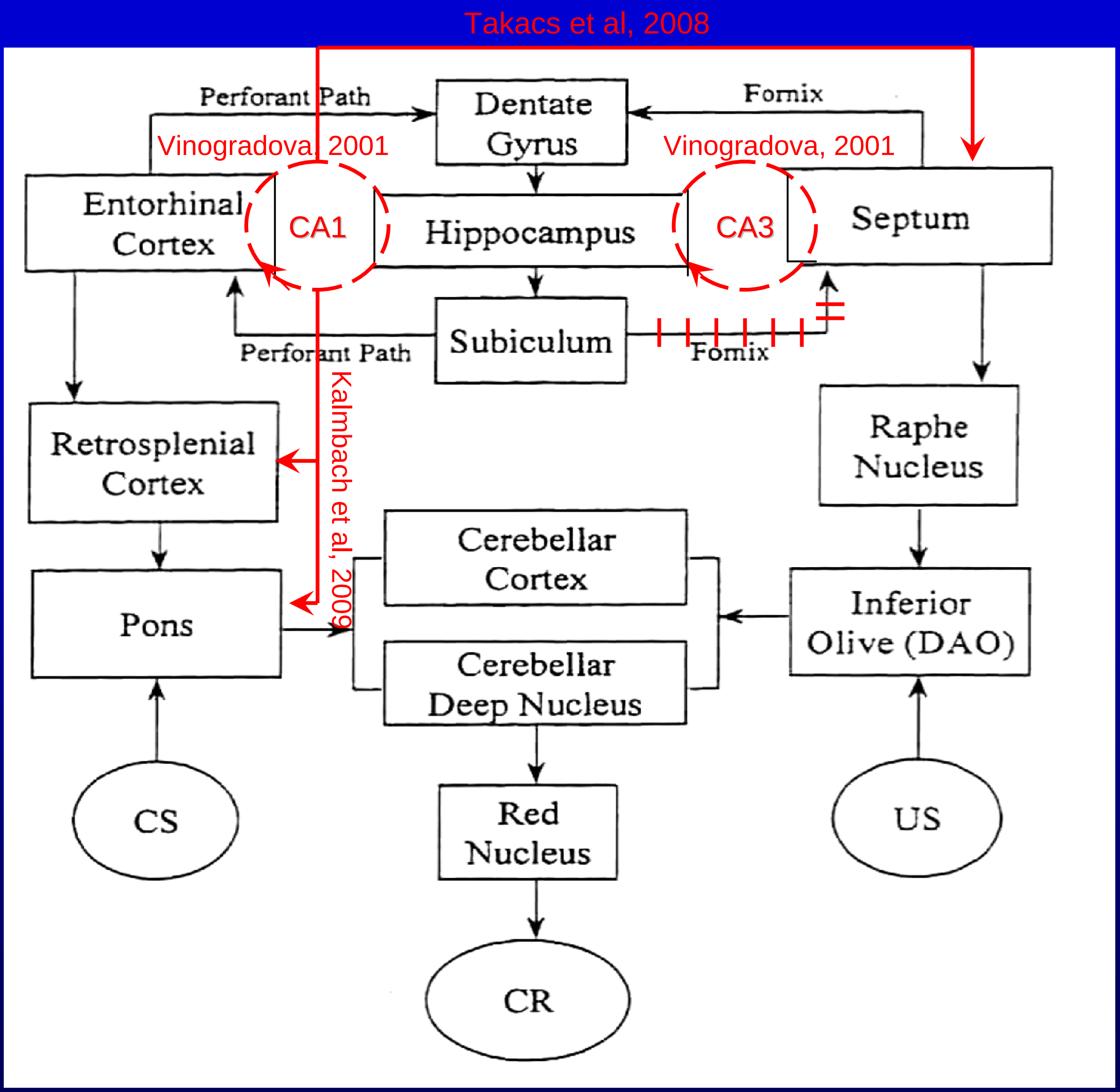
5. "Where is the trace in trace conditioning?" (Woodruff-Pak and Disterhoft, 2008, p.105) In the hippocampus, cerebellar, PFC, or in the neocortex ?

Highly simplified schematic drawing of the trace EBC

(Green and Woodruff-Pak, 2000)



PROPOSED MODIFICATION BASED ON NEW DATA



THEORY OF THETA-REGULATED ATTENTION: RADAR ANALOGY

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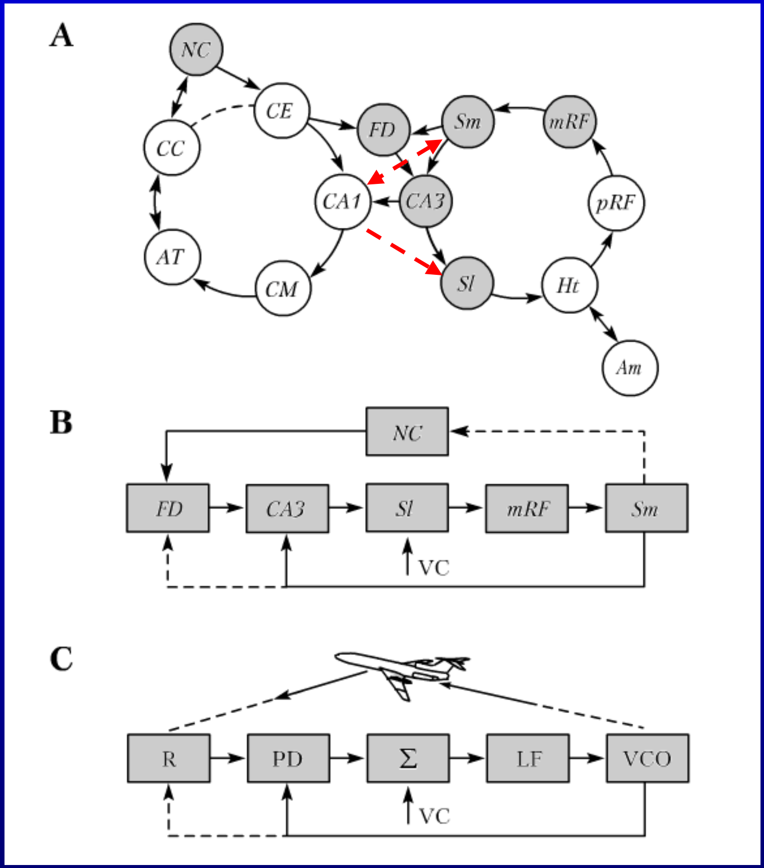
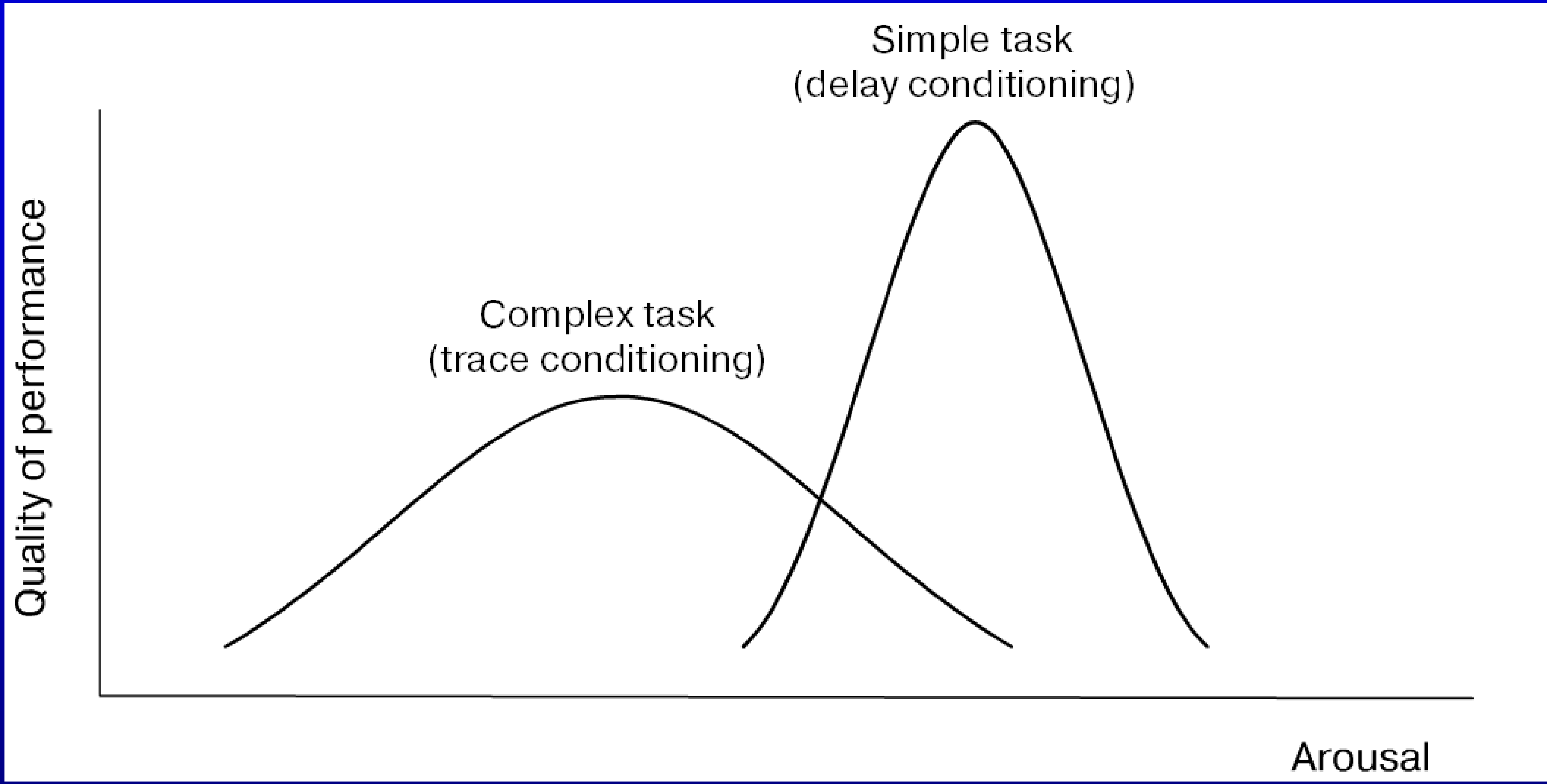


The main function of the hippocampus is to compare the new and existing traces. Via the feedback system, a mismatch signal will regulate the frequency of the theta rhythm, replaying the cortical traces and strengthening them on repetition.

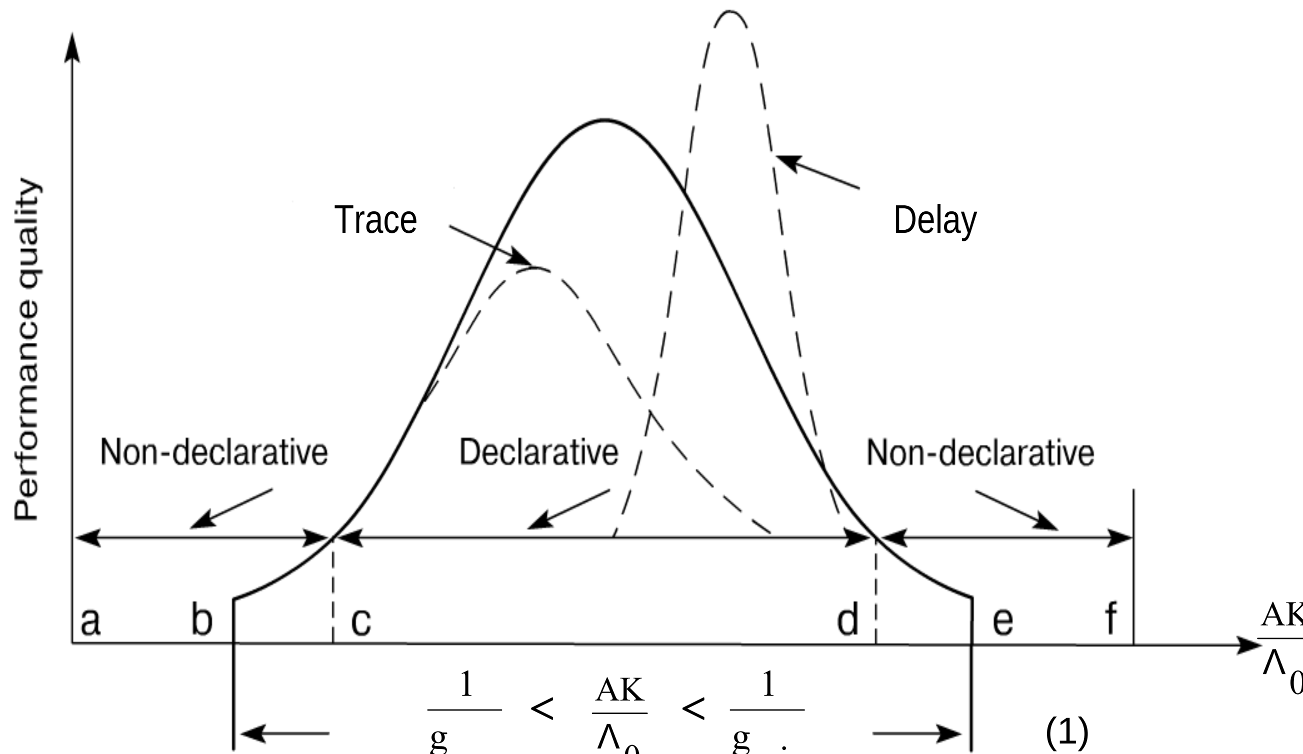
The Law of Yerkes – Dodson and Trace/Delay Dissociation



1. The quality of any task performance varies as inverse U-shaped function of arousal.
2. The optimal arousal, corresponding to the best performance, is relatively low for complex tasks.
3. Given increased arousal, attention is focused on the main aspect of the situation at the sacrifice of other aspects, and the curve width is reduced.

"NEUROLOCATOR" EXPLAINS TWO DOUBLE DISSOCIATIONS

It is impossible to draw a clear line of demarcation between trace and delay conditioning, but there is a basic difference between declarative and non-declarative memory.



$$\frac{1}{g_{max}} < \frac{AK}{\Lambda_0} < \frac{1}{g_{min}} \qquad (1)$$

a-f — theta rhythm interval

b-e — normal phase sync interval

c-d — "consciousness" interval

$$\frac{d\varphi}{dt} = \Lambda_0 - A_\varphi K g(\varphi) \qquad (2)$$

$$A_\varphi = CS^t + US^t + CS^{t-\varphi} US^t \qquad (3)$$

The main trace CR effects are explained by the "neurolocator" model

- Intact septo-hippocampal system, mPFC, NC, cerebellum are critical for trace CR (Kalmbach et al, 2009) .
- There exists an optimal set of stimulus timing and intensity parameters for trace conditioning that makes it a difficult task in a non-optimal regime.
- Attention (Han et al,2003) and awareness (Clark and Squire, 1998; Weike et al 2007; Knight et al, 2006) are required.
- Theta is critically important for all basic trace effects, but especially for the following
  - (a) Neocortical gamma activity is coordinated by the hippocampal theta (Sirota et al, 2008)
  - (b) Attention and awareness are theta-contingent (Klimesch et al, 2001; Doesburg et al, 2009)
  - (c) Theta-contingent learning is several times faster (Griffin et al, 2004)
- Time intervals are learned before the expression of trace CR, not otherwise (Drew et al, 2005).

THE MAIN MODEL PREDICTIONS

- While the site of permanent storage of trace EBCR has not been determined as of yet (Woodruff-Pak and Disterhoft, 2008), the model predicts that the neocortex acts as a permanent repository of learned responses acquired by forebrain regions, with the hippocampus including.

- Despite the prevailing view that striatum serves as the ‘core timer’ (Meck et al, 2008), the model predicts that medial septum serves as a global pacemaker and (jointly with septo-hippocampal system) as a ‘core timer’ of variable speed and times.

- Depending on the kind of the task requirement, or paradigms, the hippocampus can function as theta phase comparator (CA3), or as a time comparator (CA1), or both, acting on a common septal theta oscillator to change the frequency of the oscillations.

- Due to a circular, or spiral, mode of neural reverberation in a CA1 based subsystem, the multipeak responses in a trace conditioning are possible most probably with equidistant times between the peaks.

CONCLUSIONS

- The trace conditioning requires an intact hippocampus, because of the novelty of complex stimulation, and the considerable difficulty of task requirements.
- For model solving such problem the unique timing mechanism is required so that after learning CS-US association system can predict the time of appearance of US without the eventual US. The latest new data suggest that such mechanism partially can be found in hippocampal CA1-based subsystem working as a delay line with variable delay times.
- The main message of our discussion is that the "Neurolocator" model, based on the hippocampal theory by Vinogradova (2001), can account not only for various effects of LTM (Kryukov, 2008), but also for trace conditioning as well.
- Simultaneously, the CA1 field comparator, much like CA3 field comparator, can compare the septal and cortical inputs, and thereby regulate arousal and the theta frequency, and monitor the information subsystem mPFC and cerebellum integrated.
- As a result, the uniform explanation of many conditioning effects becomes possible, so that it resolves most of the trace conditioning problems.
- The model "Neurolocator" appended with such CA1-based subsystem reveals grate explanatory strength and predictive power of Vinogradova's (2001) Theta- Regulated Attention Theory.

THANK YOU FOR YOUR 'THETA-REGULATED ATTENTION'.