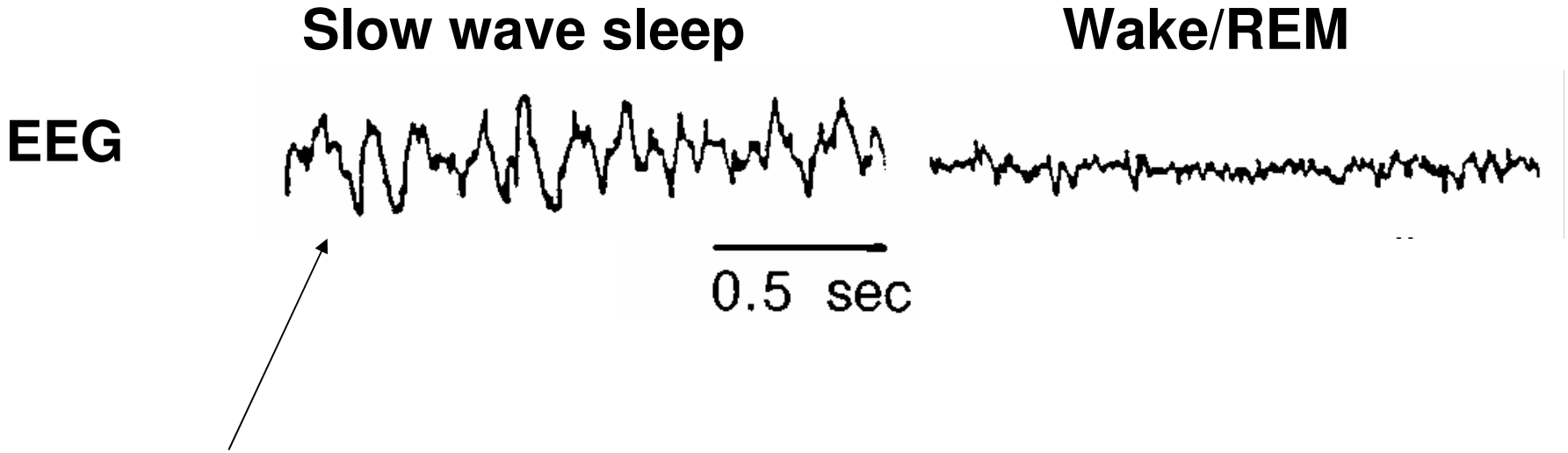
Major theories of schizophrenia

- NMDA hypofunction theory (NMDAR antagonists given to humans induce all major symptoms of the disease)
- Dopamine hyperfunction theory (D2 antagonists produce effective treatment of schizophrenia)
- Interneuron theory (postmortem tissue shows a reduction of GAD and parvalbumin in fast-spiking interneurons)

- **NEW THEORY THAT ENCOMPASSES THE OLD**:
- Delta oscillations theory. The interneurons abnormality greats hyperactivity that produces mild cognitive symptoms and produces a PREDISPOSITION for schizophrenia. Psychosis occurs rather suddenly when a loop involving the thalamus, hippocampus and VTA goes into a positive feedback state characterized by delta oscillations. Only a small part of the thalamus is involved (probably the nucleus reuniens) and this blocks the flow of corollary discharge from the mPFC to the temporal lobe. The loss of corollary discharge produces the deficits in sense of self that constitute a core symptom of the disease.

Delta frequency waves in slow wave sleep



Delta is synchronized over all cortical regions

McCarley et al, J. Neurophysiol. 1983, 50:798

Schizophr Res. 2008 Feb;99(1-3):225-37. Epub 2007 Dec 21._ Links

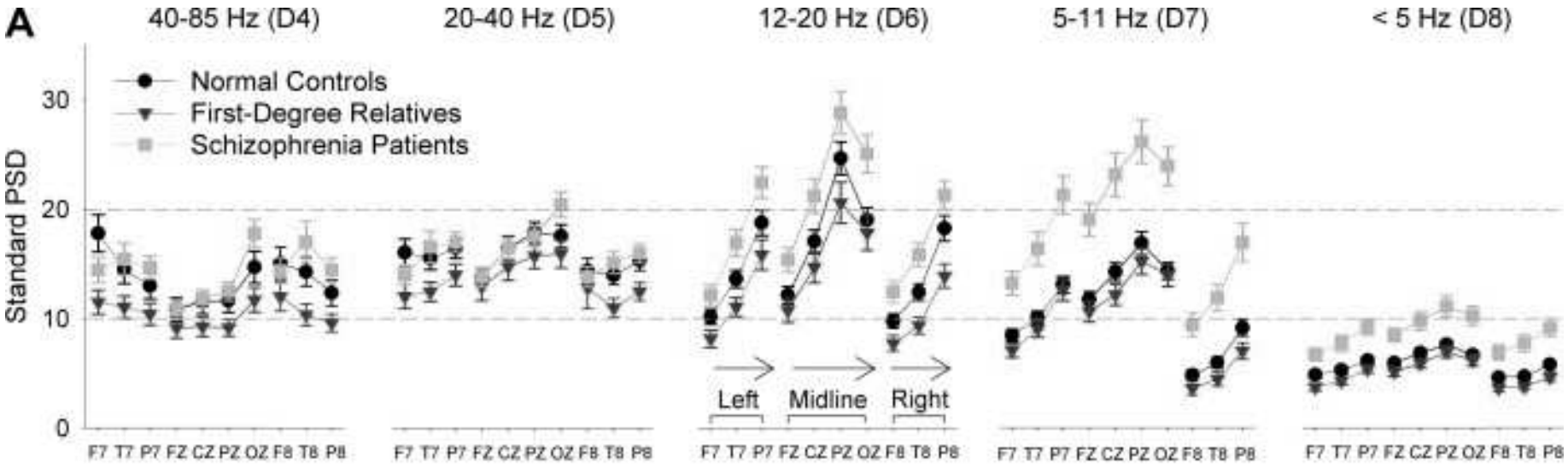
The status of spectral EEG abnormality as a diagnostic test for schizophrenia.

Boutros NN, **Arfken C**, **Galderisi S**, **Warrick J**, **Pratt G**, **Iacono W**.

OBJECTIVE: A literature review was conducted to ascertain whether or not EEG spectral abnormalities are consistent enough to warrant additional effort towards developing them into a clinical diagnostic test for schizophrenia. METHODS: **Fifty three** papers met criteria for inclusion into the review and 15 were included in a meta-analysis of the degree of significance of EEG deviations as compared to healthy controls. Studies were classified based on a 4-step approach based on guidelines for evaluating the clinical usefulness of a diagnostic test. RESULTS: **Our review and meta-analysis revealed that most of the abnormalities are replicated in the expected directions with the most consistent results related to the increased preponderance of slow rhythms in schizophrenia patients** This effect remained consistent in un-medicated patients.

A second meta-analysis, this time of studies using MEG instead of EEG, concludes that theta/delta is elevated in temporal lobe (Siekmeier PJ, Stufflebeam SM.)

Mismatch negativity and low frequency oscillations in **schizophrenia** families.
Elliot Hong L, Moran LV, Du X, O'Donnell P, Summerfelt A.
Clin Neurophysiol. 2012



Enhanced delta is NOT seen in their first degree relatives {Clementz, 1994 ; Sponheim, 2003 ;Venables, 2009}. Even in twins discordant for schizophrenia increased delta was not observed in the healthy twin {Stassen, 1999 ;Weisbrod, 2004}.

The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia

Hall, M.-H.[a] , Taylor, G.[a], Sham, P.[d], Schulze, K.[b], Rijsdijk, F.[c], Picchioni, M.[b], Toulopoulou, T.[b], Ettinger, U.[e], Bramon, E.[b], Murray, R.M.[b], Salisbury, D.F.[a]

Abstract

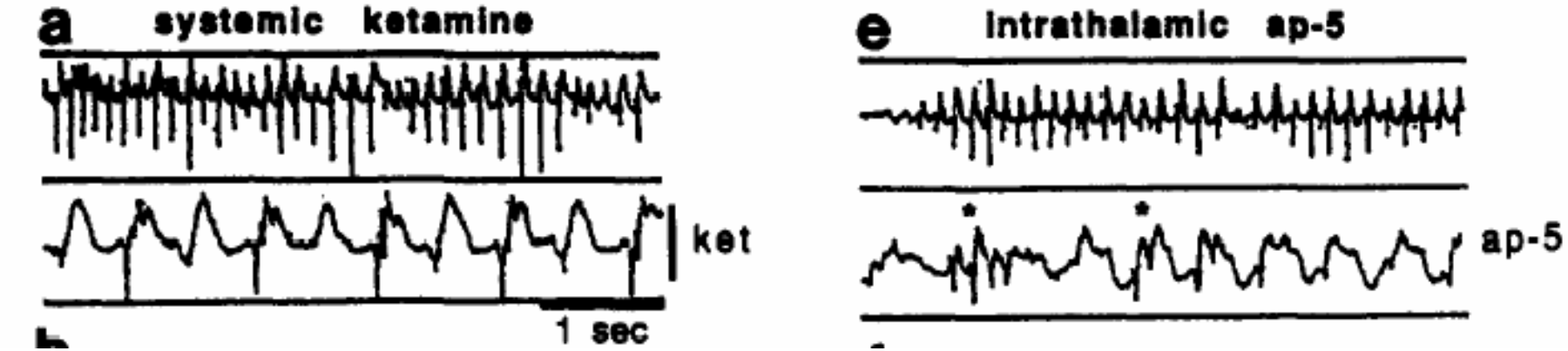
Background: Reduced power and phase locking of the early auditory gamma-band response (EAGBR) have been reported in schizophrenia, but findings are equivocal. Further, little is known about genetic (heritability) and environmental influences on the EAGBR or its potential as an endophenotype of schizophrenia. The present study used a twin design to examine whether EAGBR power and phase locking are heritable and reduced in schizophrenic patients and their unaffected co-twins and thus putative endophenotypes of schizophrenia. Methods: The study sample included a total of 194 individuals, consisting of 15 monozygotic [MZ] twin pairs concordant for schizophrenia, 9 MZ twin pairs discordant for schizophrenia, and 42 MZ and 31 dizygotic (DZ) control pairs. Evoked power and phase-locking factor of the EAGBR were computed on Morlet wavelet-transformed electroencephalogram responses to standard tones during an auditory oddball target detection task. Structural equation modeling was applied to estimate heritability and genetic and environmental correlations with schizophrenia for the EAGBR measures. Results: Both evoked power and phase-locking phenotypes were heritable traits (power: $h^2 = 0.65$; phase locking: $h^2 = 0.63$). Impaired EAGBR measures were significantly associated with schizophrenia. **Patients with schizophrenia and their unaffected identical co-twins exhibited significantly reduced EAGBR power compared with control subjects.** In each phenotype, shared genetic factors were likely the source of the observed associations with schizophrenia. Conclusions: Our results support EAGBR measures as putative endophenotypes of schizophrenia, likely reflecting an ubiquitous local cortical circuit deficit.

See also Venables, 2009

Delta oscillations appear in the frontal cortical EEG in response to NMDA antagonist

***another success for the NMDA hypofunction model

Buzsaki, 1988



Why does an antagonist of an excitatory amino acid stimulate oscillations?

Yuchun Zhang

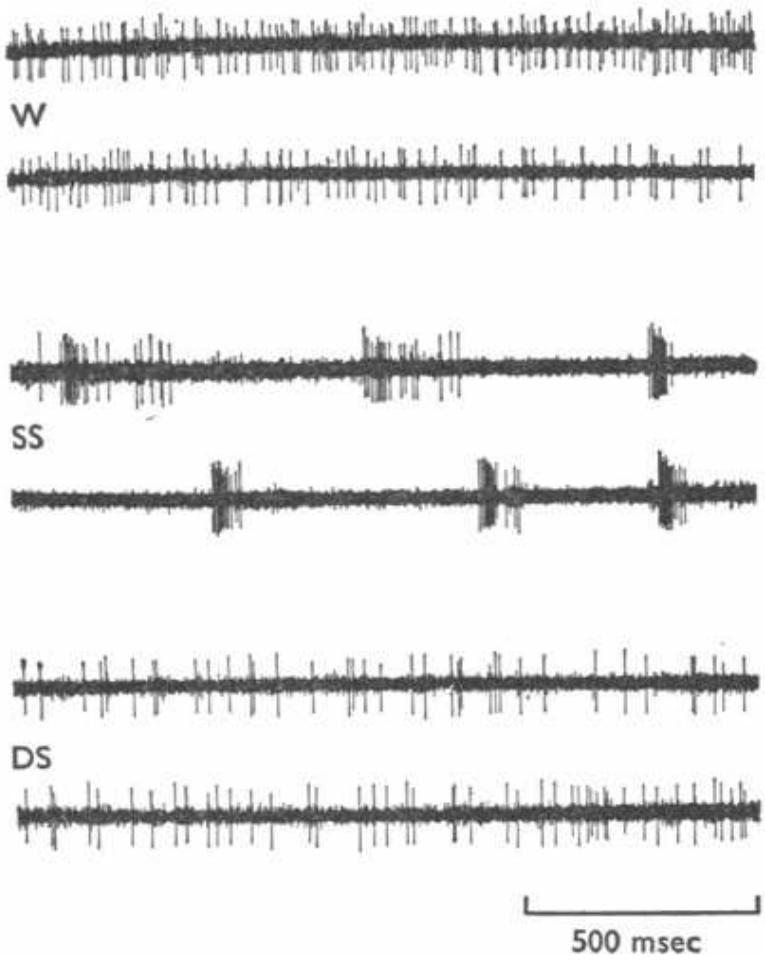
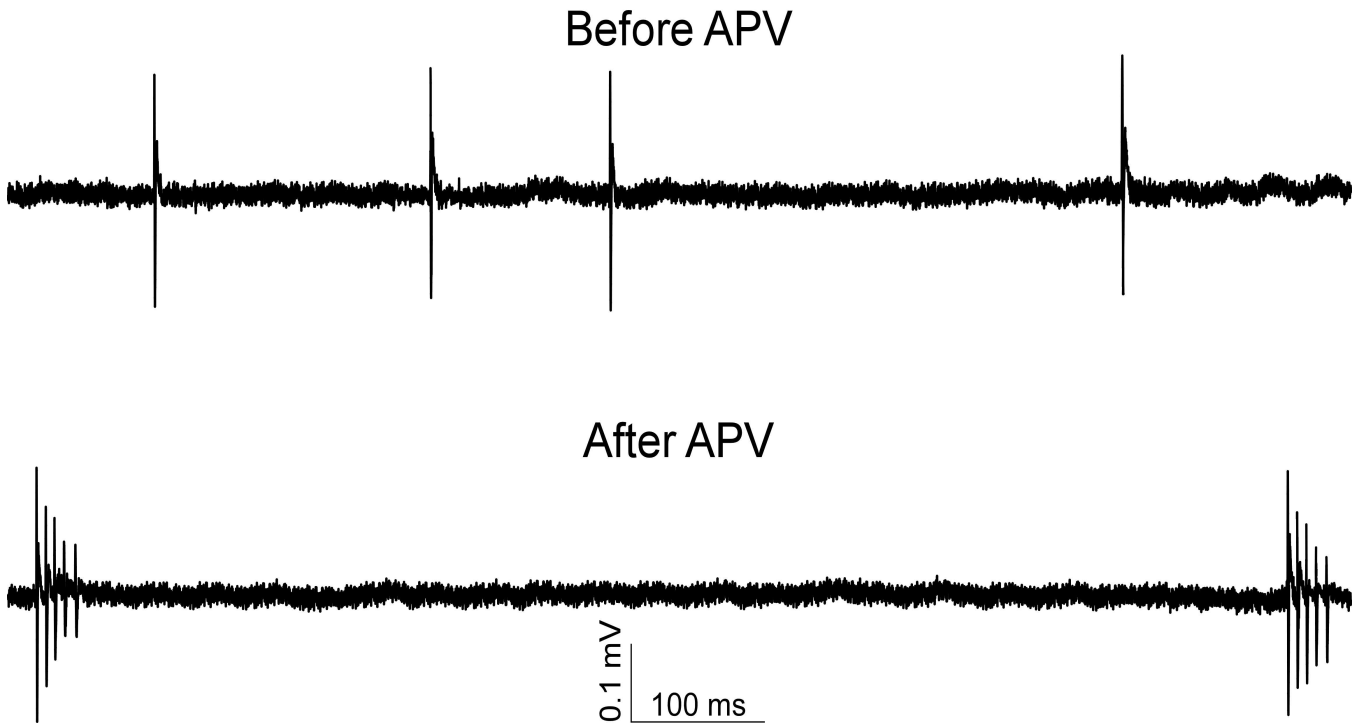


Fig. 1. Spontaneous activity of a neurone of nucleus reticularis thalami recorded during wakefulness (W), during sleep with synchronized e.e.g. (SS) and during sleep with desynchronized e.e.g. (DS).

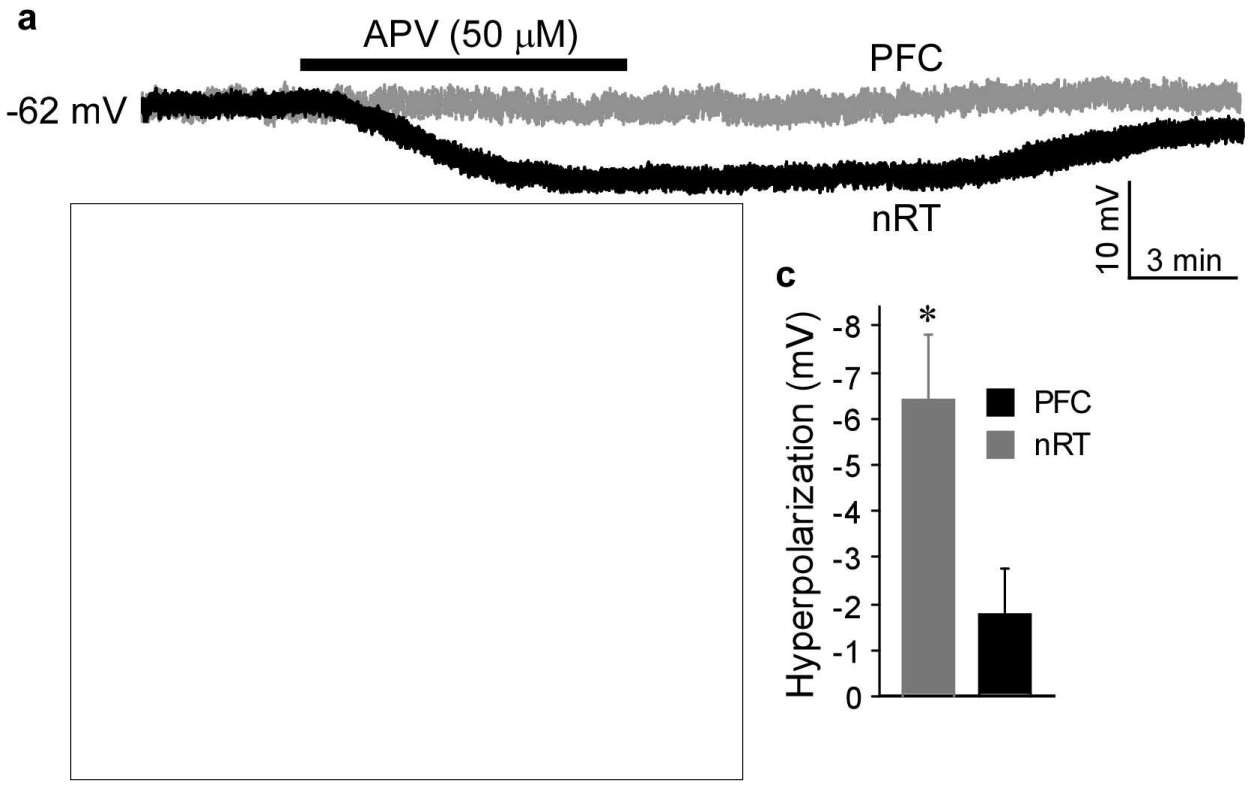
Delta frequency firing of nucleus reticularis cells during slow-wave sleep

Mukhametov et al, 1970

APV induces delta frequency bursting in isolated nRT (nucleus reticularis)



Blocking NMDAR hyperpolarizes neurons of thalamic reticular nucleus (nRT)

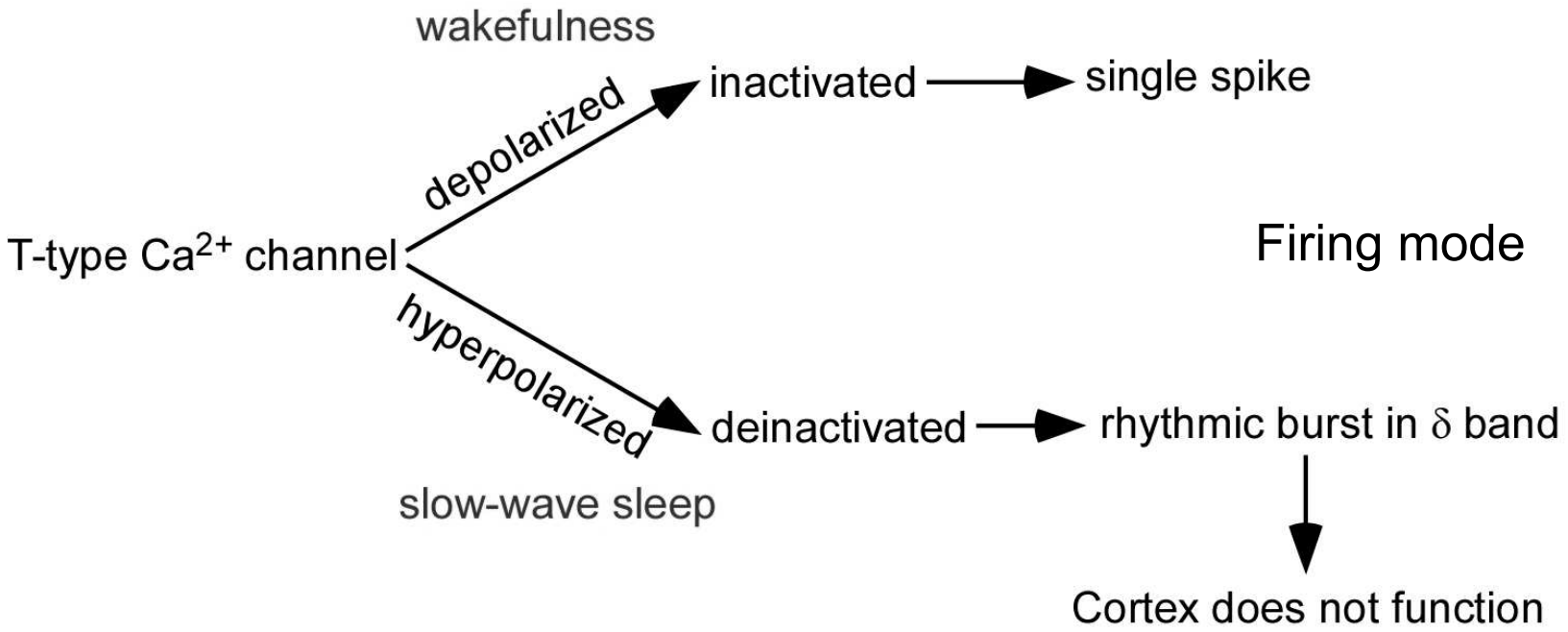


Rodolfo Llinas

Thalamocortical dysrhythmia:

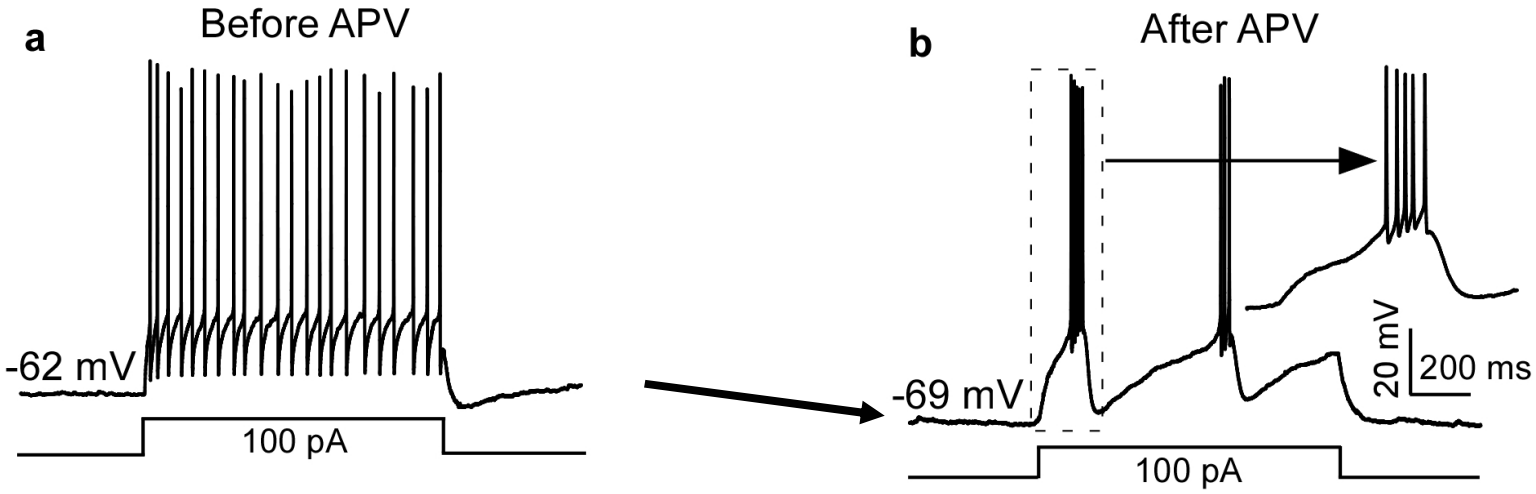
abnormal delta frequency oscillations in the awake state----

role of resting potential and T-type Ca channels

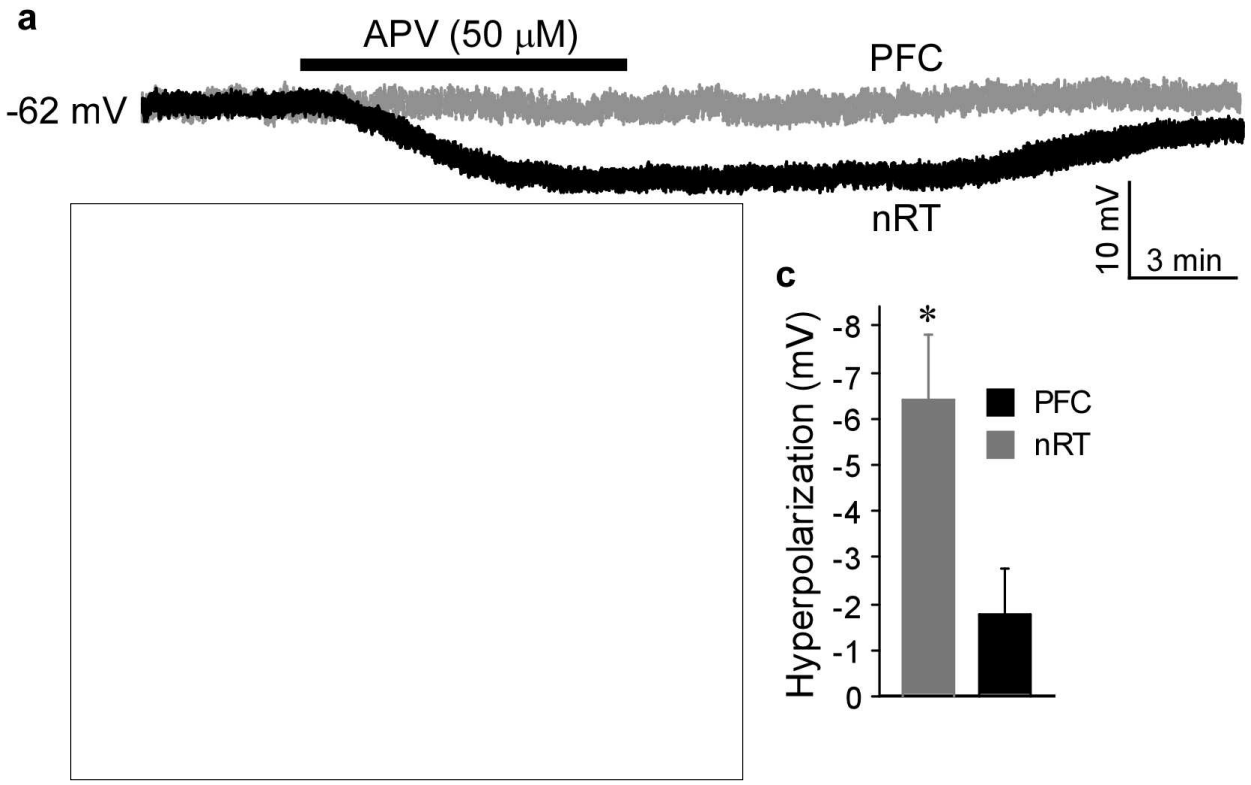


Llinas et al, 2005, TINS, 28:325

The hyperpolarization produced by blocking NMDAR changes firing mode in the nRT



Why does NMDAR antagonist hyperpolarize nRT neurons?

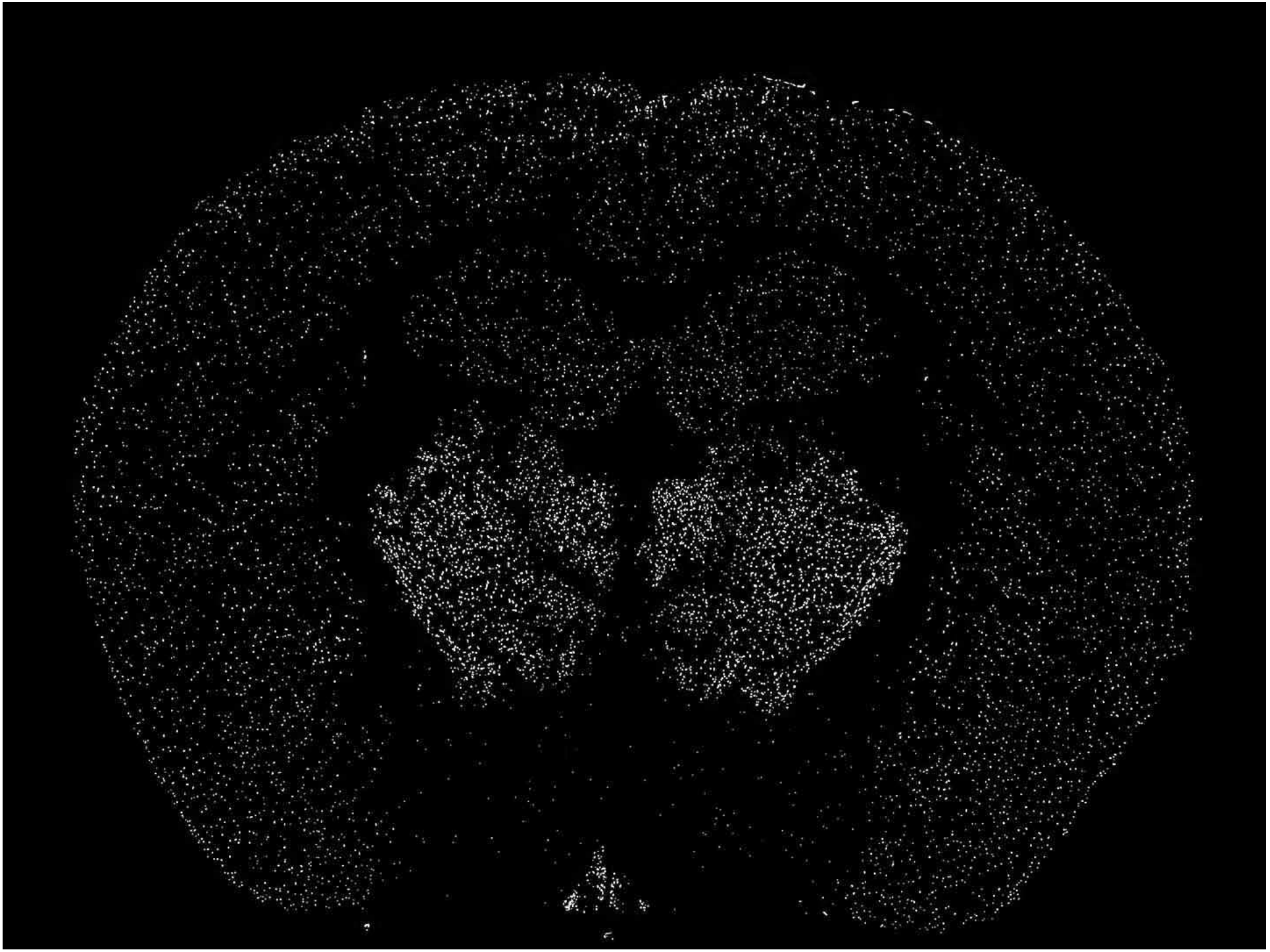


Science. 1989 Nov 10;246(4931):815-

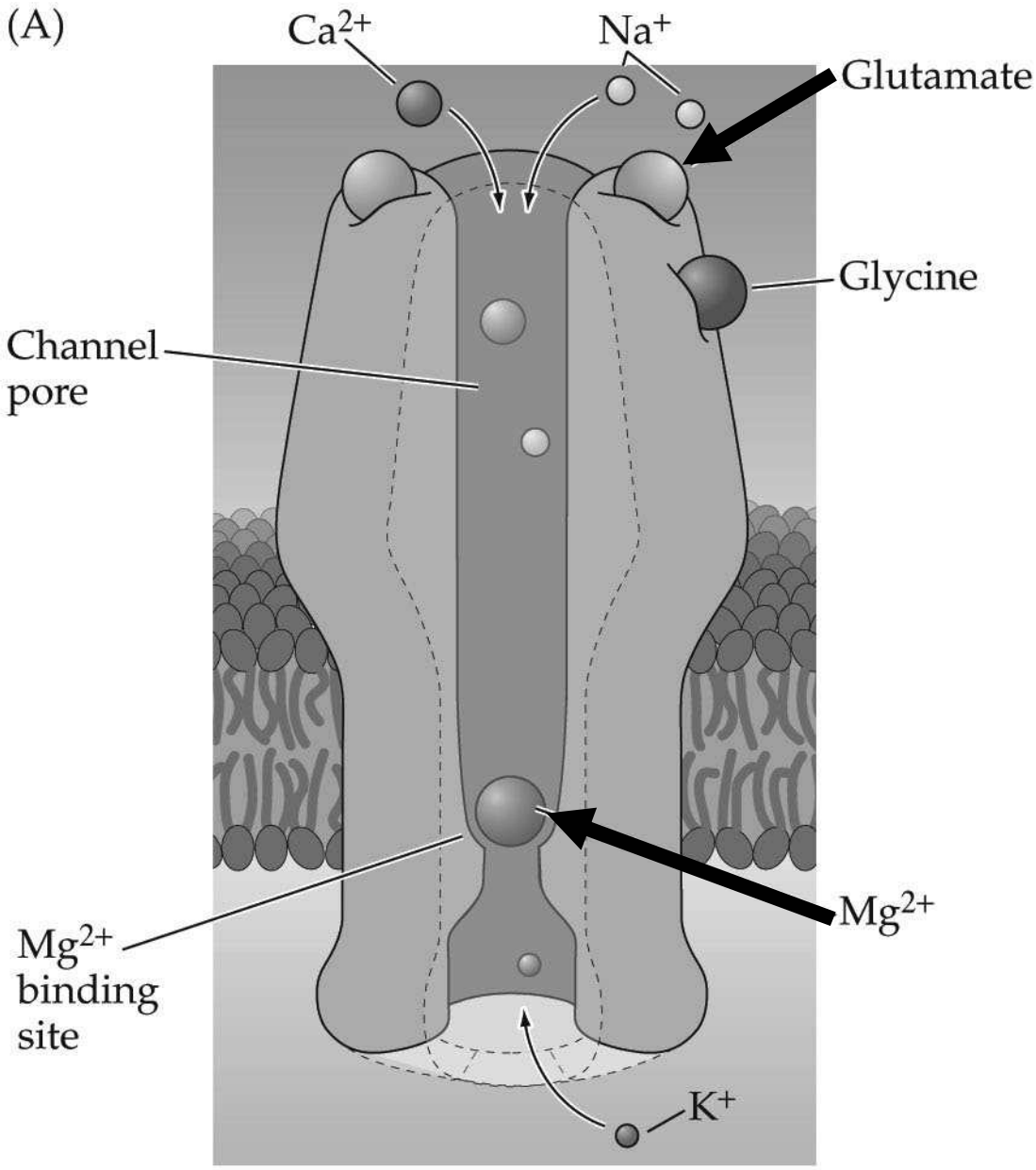
Tonic activation of NMDA receptors by ambient glutamate enhances excitability of neurons.

Sah P, **Hestrin S**, **Nicoll RA**.
Department of Pharmacology, University of California, San Francisco 94143.

Voltage clamp recordings and noise analysis from pyramidal cells in hippocampal slices indicate that N-methyl-D-aspartate (NMDA) receptors are tonically active. On the basis of the known concentration of glutamate in the extracellular fluid, this tonic action is likely caused by the ambient glutamate level. NMDA receptors are voltage-sensitive, thus background activation of these receptors imparts a regenerative electrical property to pyramidal cells, which facilitates the coupling between dendritic excitatory synaptic input and somatic action potential discharge in these neurons.

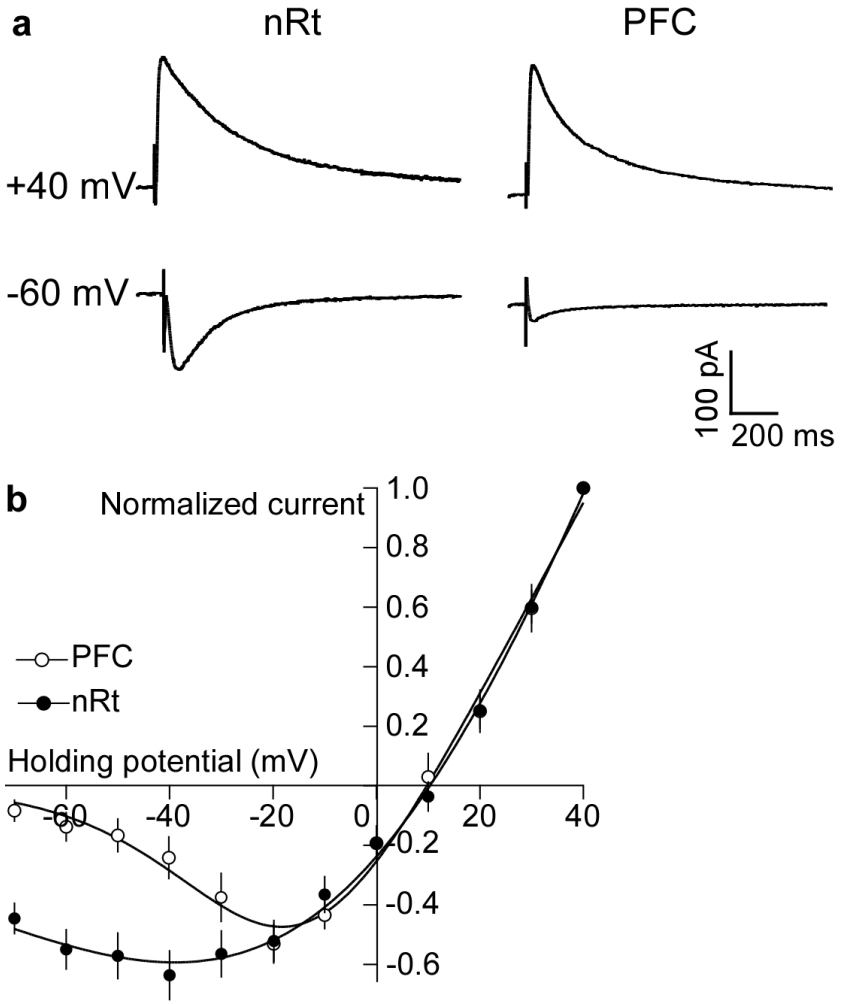


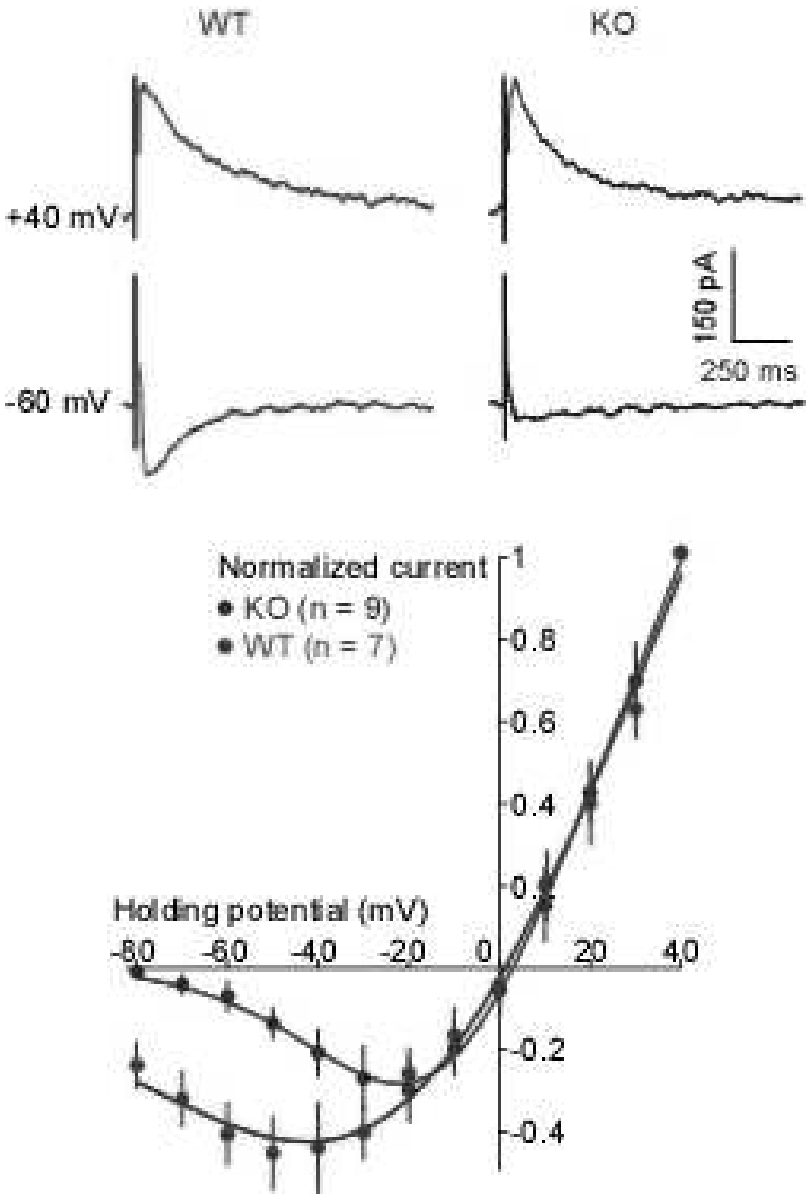
Ambient glutamate produces partial tonic activation of NMDARs, but with NR2A and NR2B, this has no effect on resting potential because the channels are blocked by Mg. Why is thalamus different?



***NEUROSCIENCE, Fourth Edition,* Figure 6.7 (Part 1)**

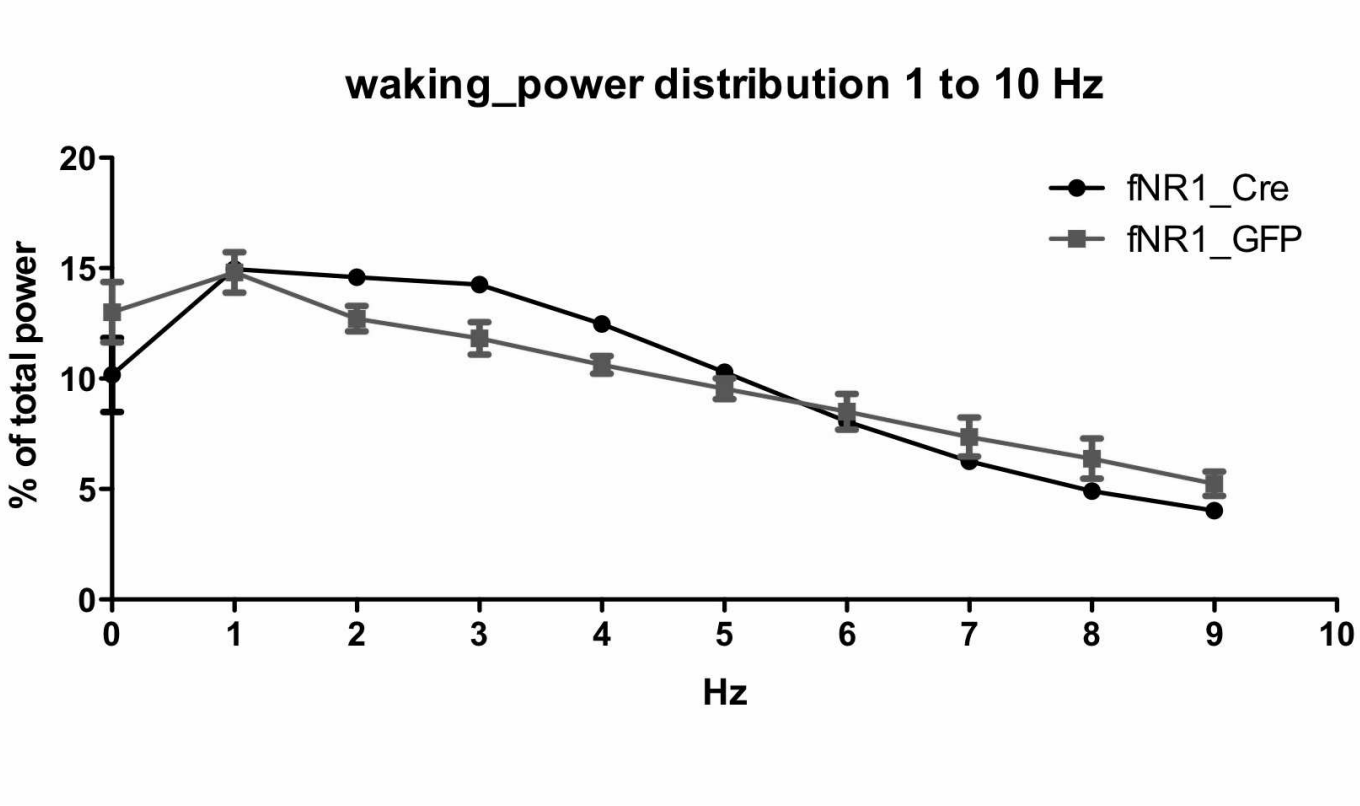
I-V curves of NMDAR in nRT cells shows weak Mg block (weak rectification) characteristic of NR2C





In the NR2C knockout mouse (Andres Buonanno), the weak rectification of the NMDAR response is eliminated

Virally mediated KO of NMDARs in the nRT increases the power of cortical delta oscillations

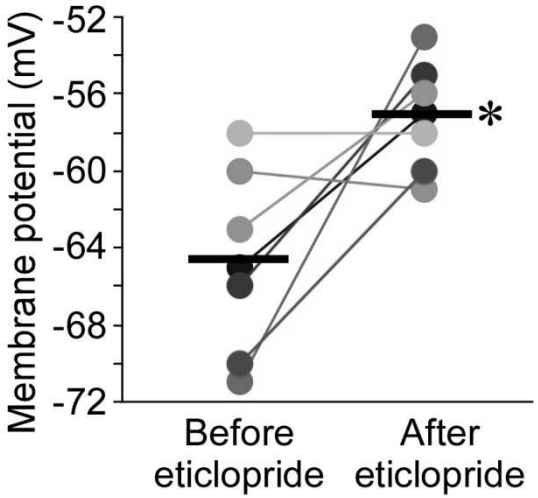


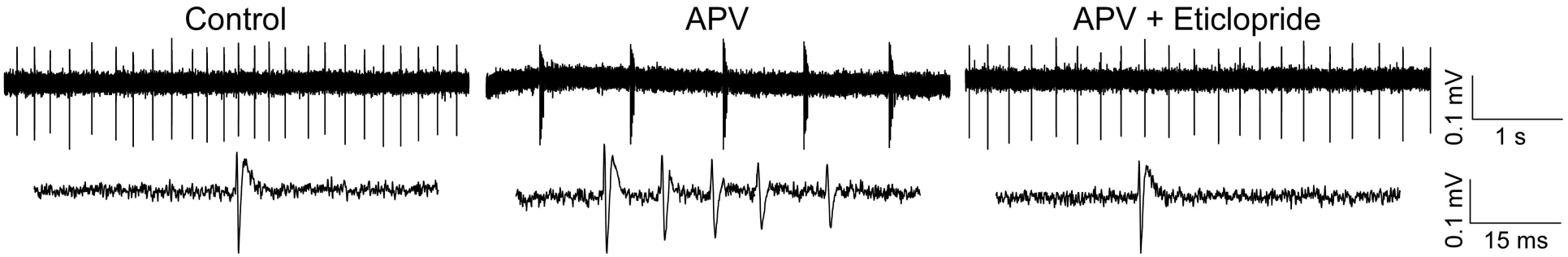
- **CONCLUSIONS:** The large hyperpolarization produced by NMDAR antagonist in the thalamus is due to the presence of a rare isoform, NR2C, which has weak Mg block. The hyperpolarization removes inactivation from T-type Ca channels and causes delta frequency bursting.

Major theories of schizophrenia

- NMDA hypofunction theory (NMDAR antagonists given to humans induce all major symptoms of the disease)
- Dopamine hyperfunction theory (D2 antagonists produce effective treatment of schizophrenia)
- Interneuron theory (postmortem tissue shows a reduction of GAD and parvalbumin in fast-spiking interneurons)

D2 antagonist depolarizes nRT and blocks the bursting produced by APV; this could be a basis for the efficacy of neuroleptics

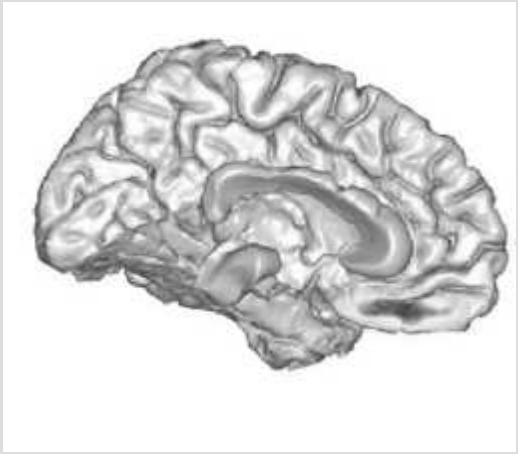




The input to the hippocampus is from the midline thalamic nucleus, the nucleus reuniens.

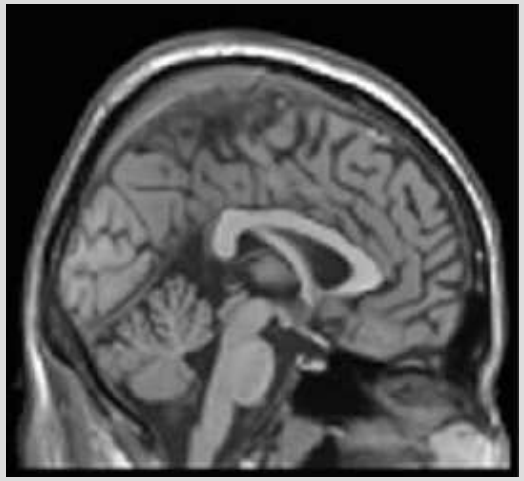
According to the thalamocortical dysrhythmia hypothesis, the nature of the disease is determined by which thalamic nuclei generate delta/theta oscillations.

In Schizophrenia spectrum disorder there is a source of theta/delta in vmPFC



Front Hum Neurosci. 2011;5:69. Epub 2011 Jul 29.
Imaging of thalamocortical dysrhythmia in neuropsychiatry.
Schulman JJ, Cancro R, Lowe S, Lu F, Walton KD, Llinás RR.

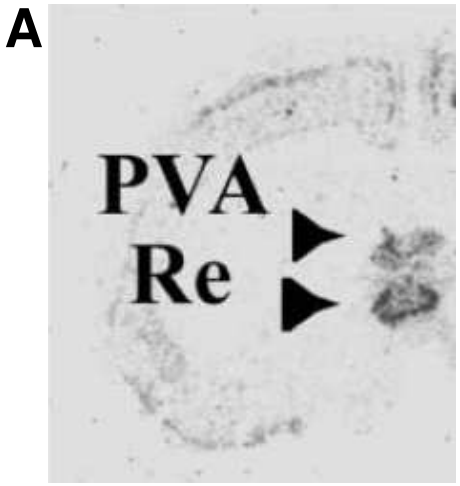
BOLD: ketamine produces decrease in metabolism in vmPFC (blue)

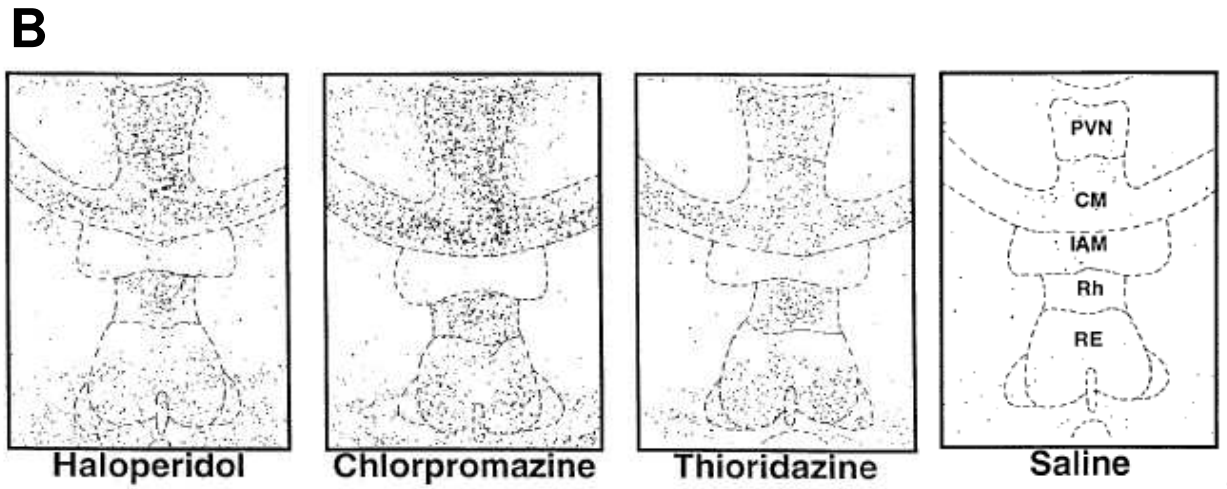


Increase in metabolism in thalamus and hippocampus.(not shown)

Glutamate and the neural basis of the subjective effects of **ketamine**: a pharmaco-magnetic resonance imaging study.
Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM.
Arch Gen Psychiatry. 2008 Feb;65(2):154-64

Hints of a special role for midline thalamic nuclei (including the nucleus reuniens)





Castran

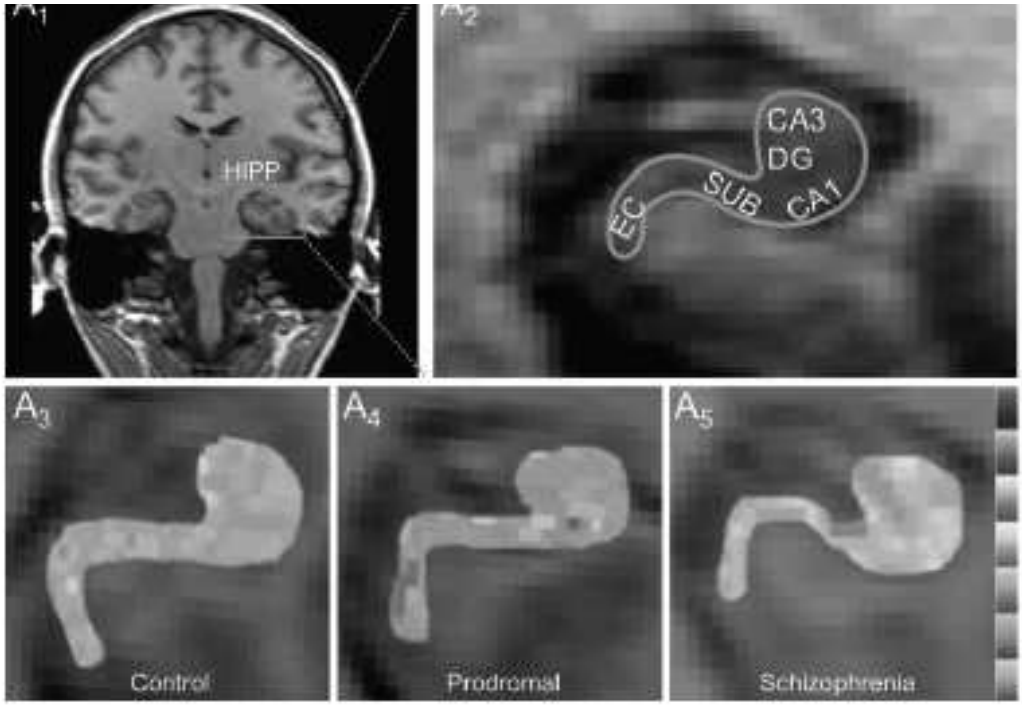
Bruce Cohen

NMDAR antagonist produces largest cFOS signal in midline nuclei

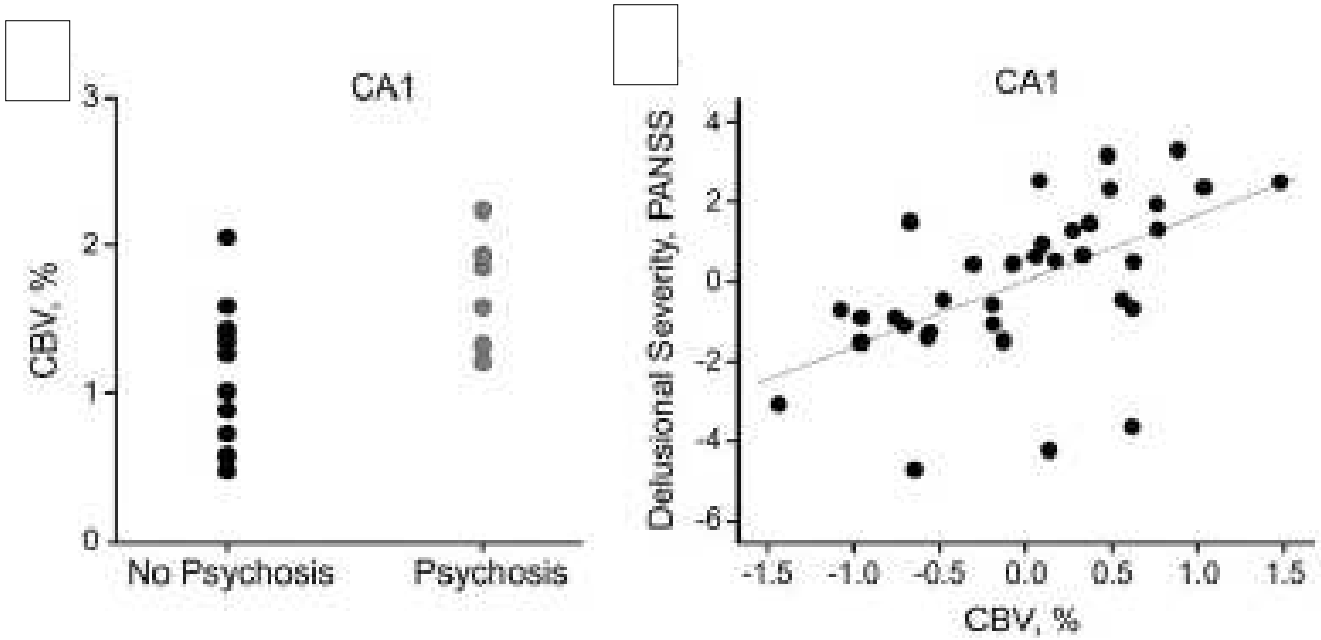
Neuroleptics excite local interneurons in midline thalamic nuclei

The midline thalamic nucleus, the nucleus reuniens, is the ONLY thalamic innervation of the hippocampus. The reuniens does not innervate the dentate or CA3, but does innervate CA1.

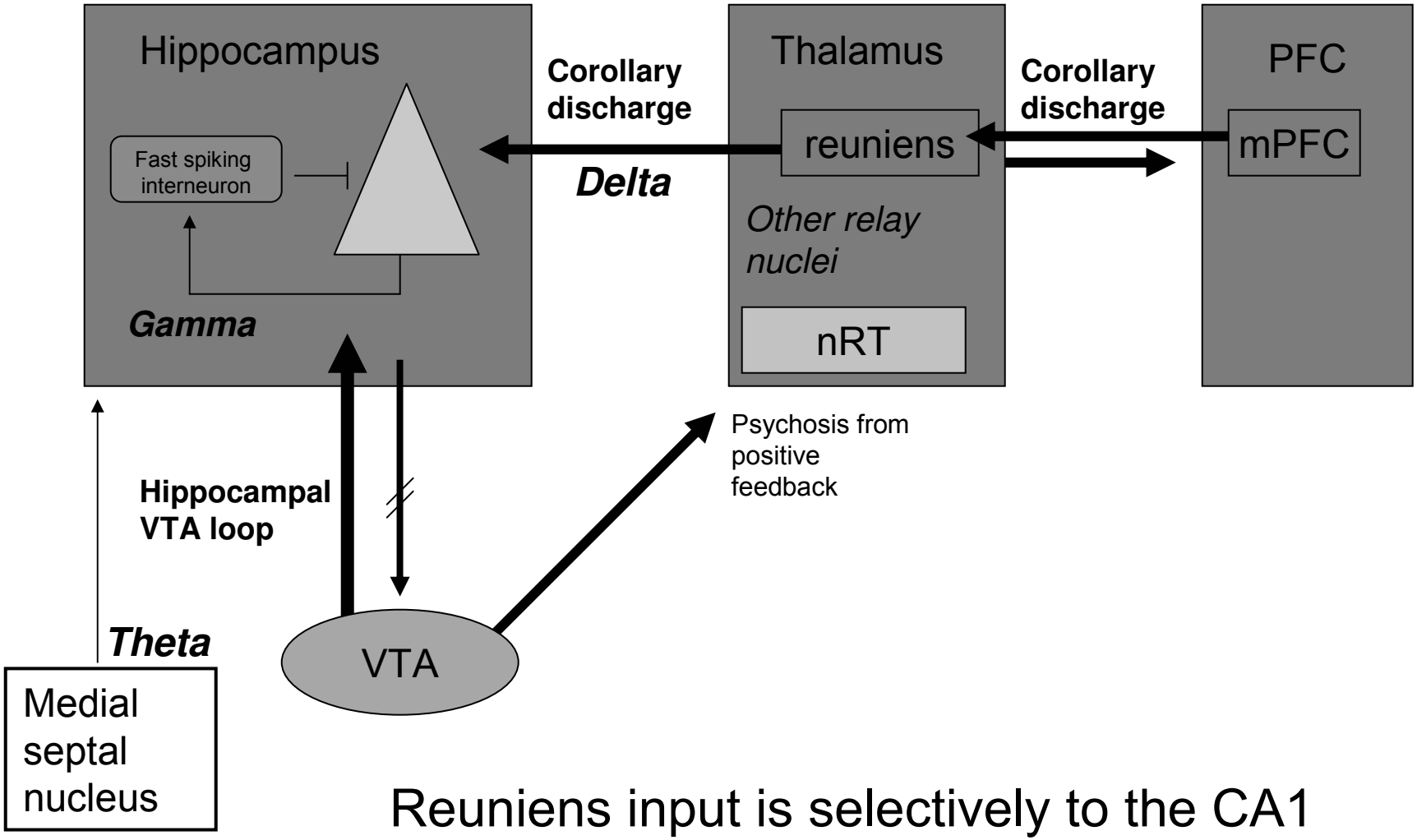
It is therefore of interest that in SZ, CA1 is selectively hyperactive (next slide).



How high-resolution basal-state functional imaging can guide the development of new pharmacotherapies for **schizophrenia**.
Gaisler-Salomon I, Schobel SA, Small SA, Rayport S. Schizophr Bull. 2009 Nov;35(6):1037-44.



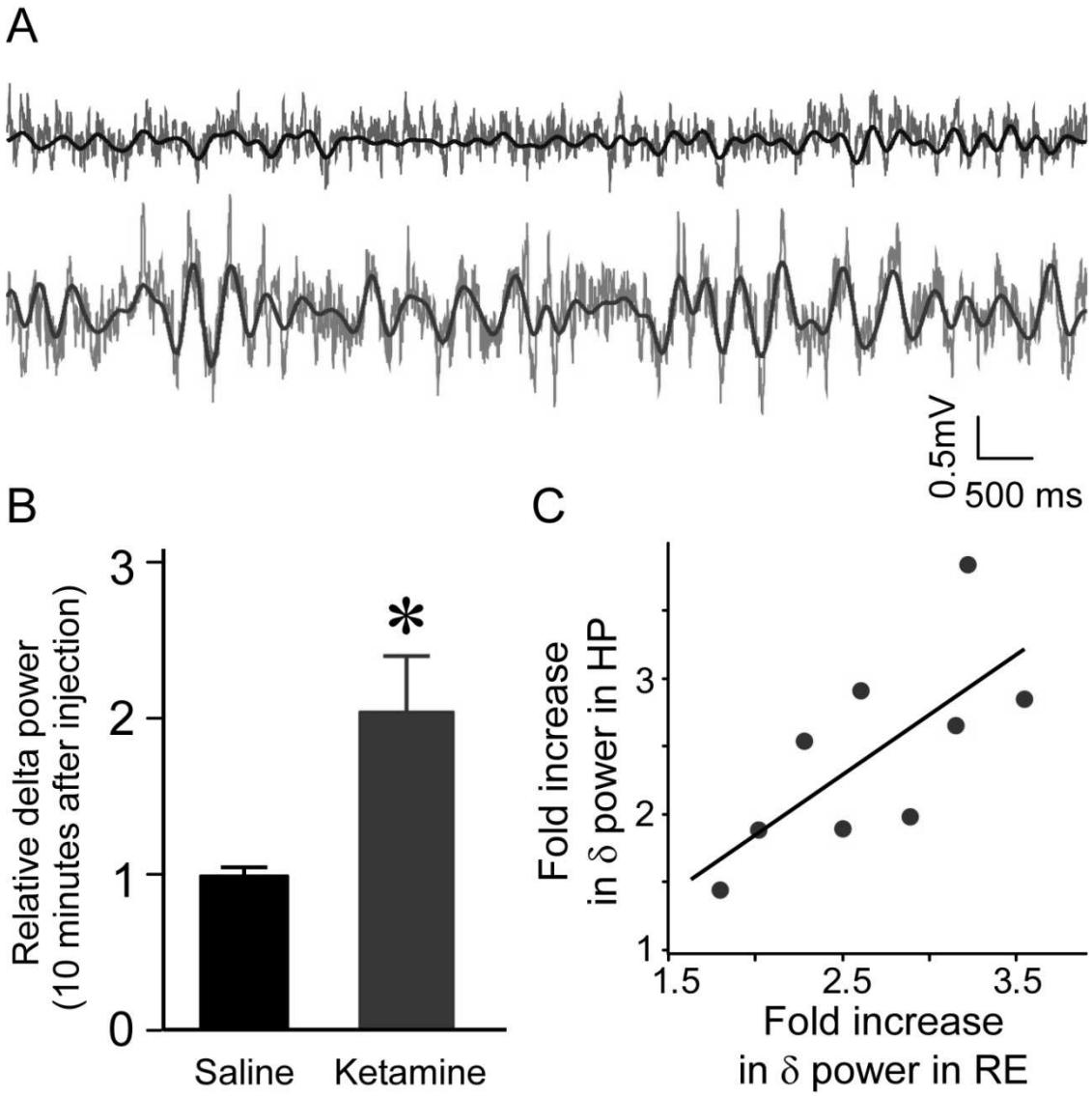
Neonatal damage to hippocampus produces hyperactivity and hyperdopaminergic state

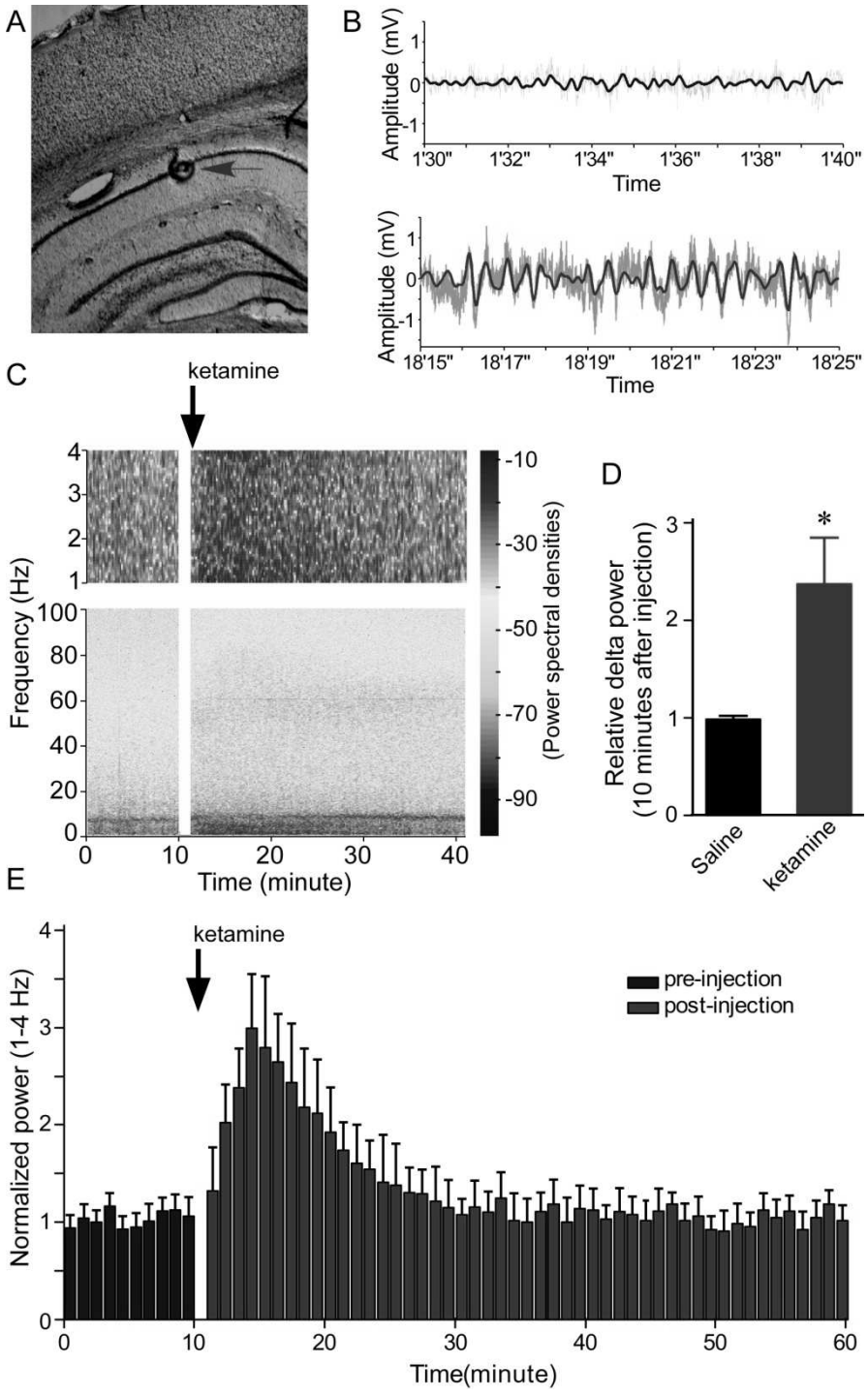


Reuniens input is selectively to the CA1 region of the hippocampus, the same region that shows hyperactivity in SZ

We wanted to test the hypothesis that the delta state in the reuniens could drive delta in CA1. We also wanted to know if the overall level of CA1 activity is increased. Such hyperactivity could drive the dopamine system, which, in turn, promotes delta in thalamus. We have previously proposed (Biol Psychiatry) that the thalamus-hippocampus-VTA loop could go into positive feedback.

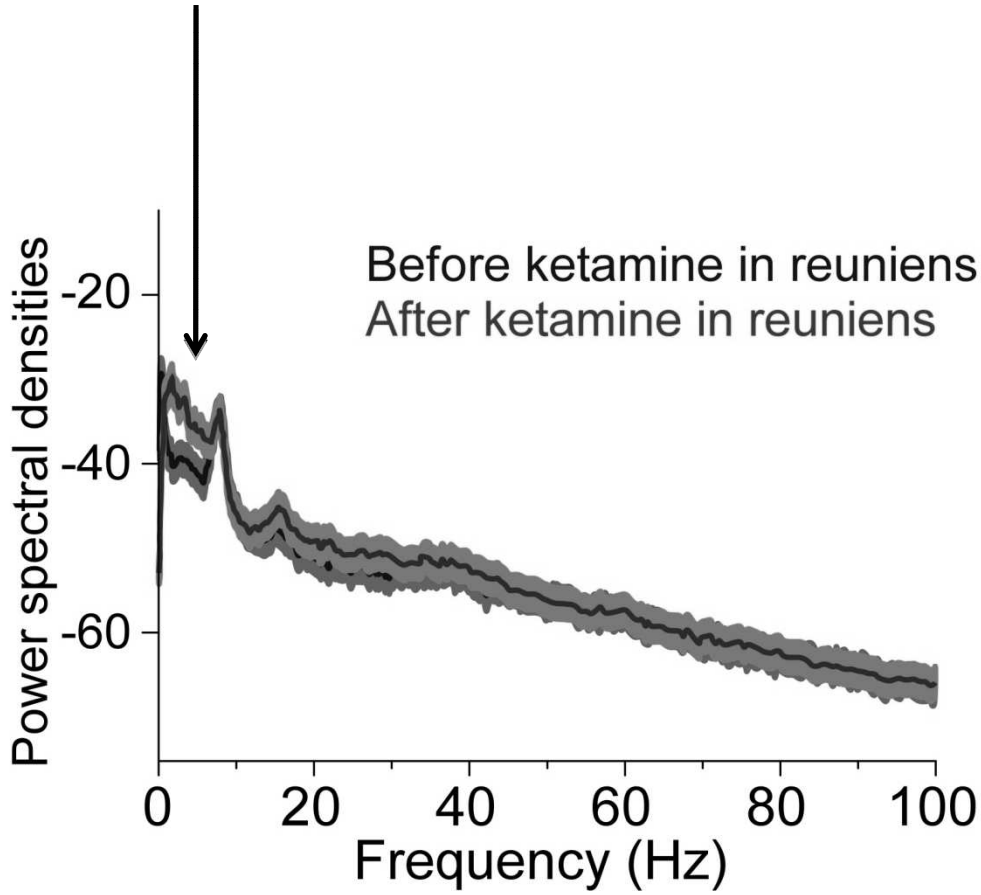
Systemic NMDAR antagonist (Ketamine) evokes delta oscillations in the nucleus reuniens



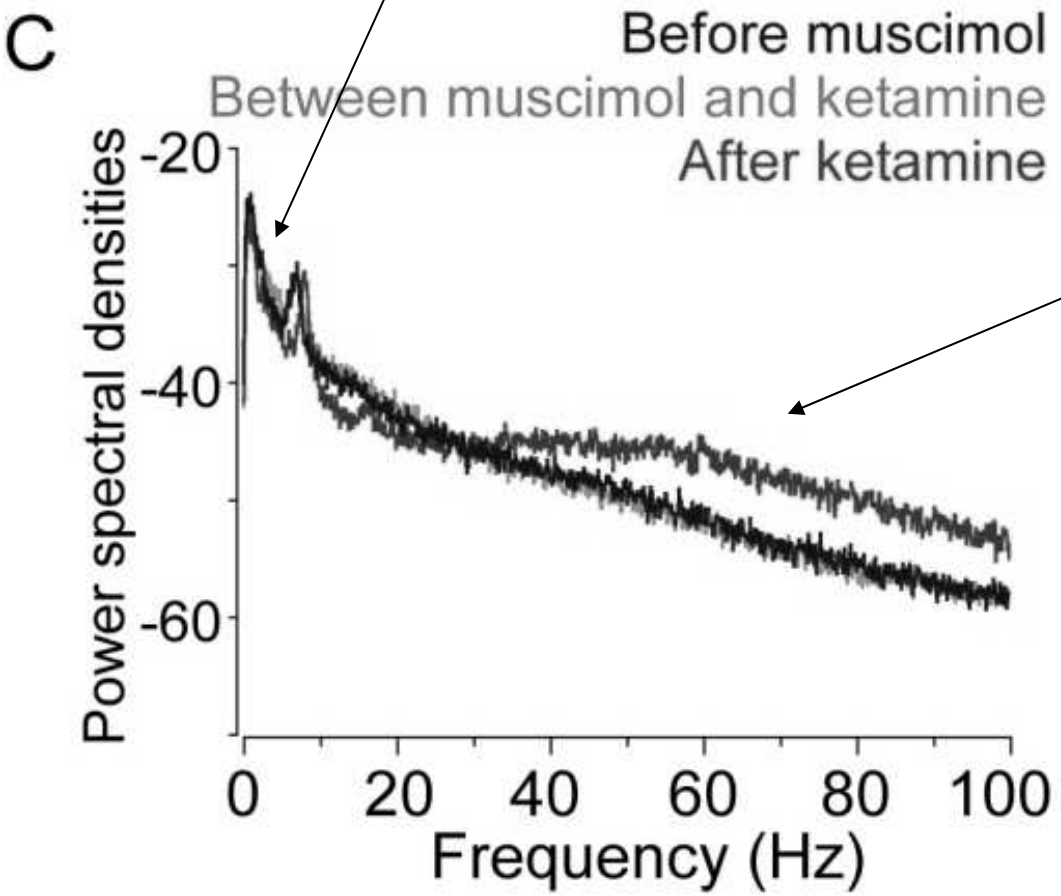


Systemic NMDAR antagonist (Ketamine; 50mg/kg) enhances delta power in the CA1 hippocampal region. **The firing rate and gamma power are also increased.**

Ketamine injection into the reuniens increases hippocampal delta

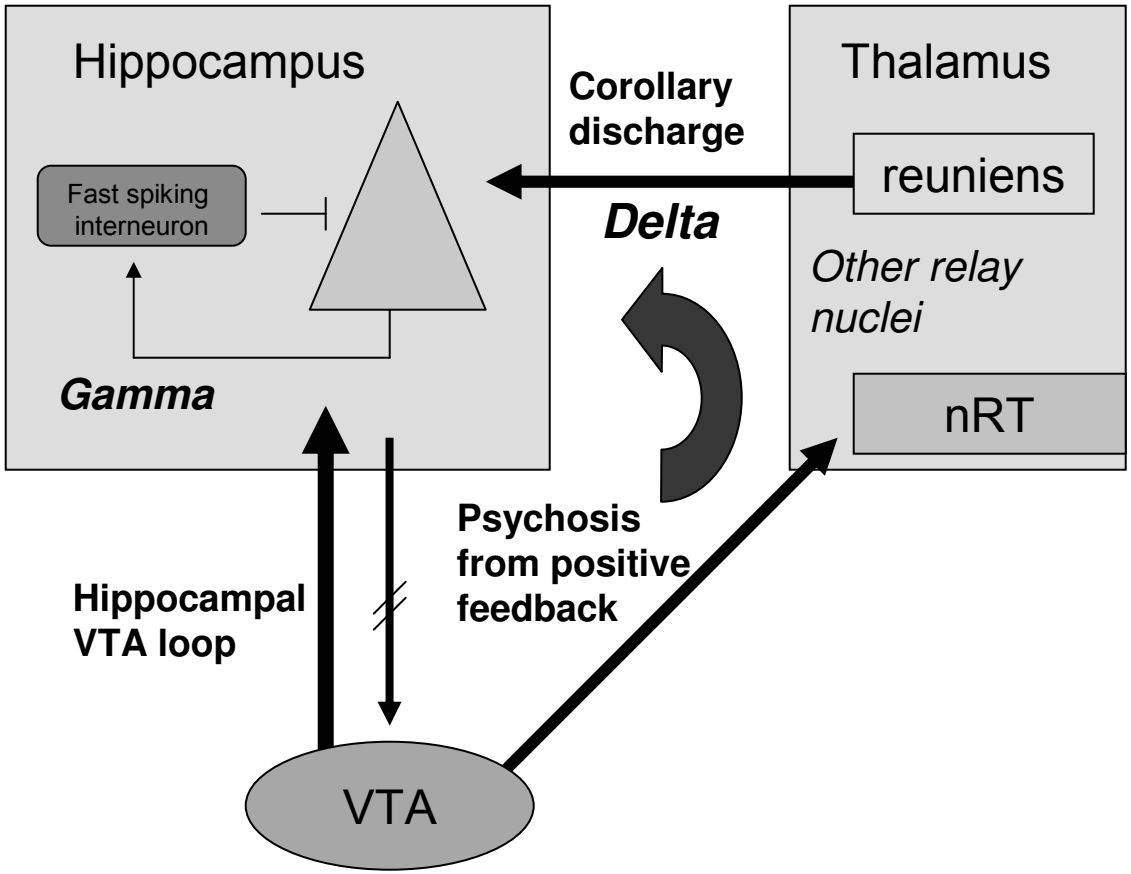


Muscimol injection into the reuniens blocks the enhancement of delta power by systemic ketamine



Ketamine-induced gamma is NOT blocked by muscimol

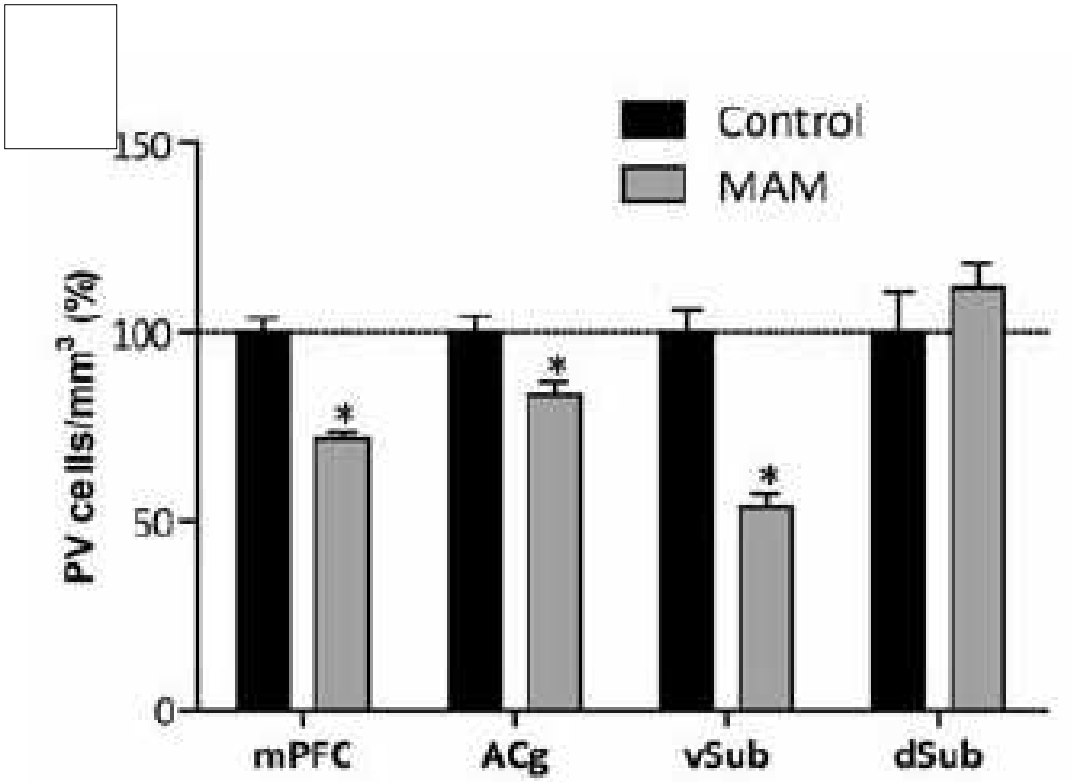
Neonatal damage to hippocampus produces hyperactivity, increased gamma and hyperdopaminergic state, making a PREDISPOSITION to psychosis



Model of psychotic break based: predisposition allows stress to trigger positive feedback in VTA-thalamic-hippocampal loop

A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia.

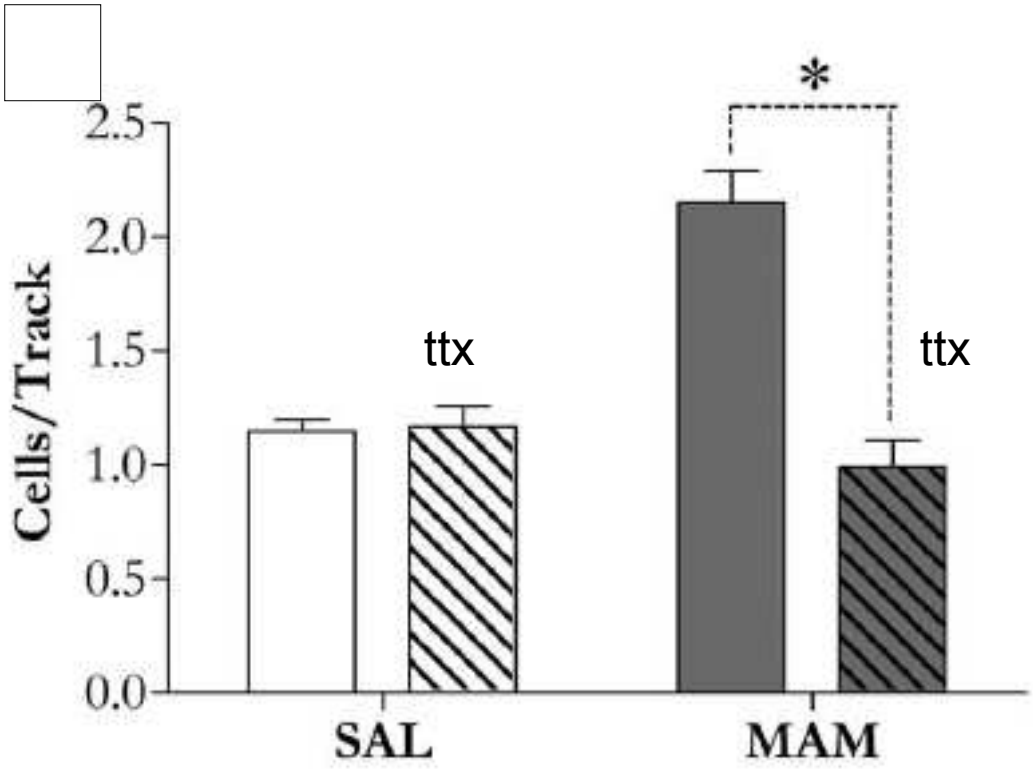
Lodge DJ, Behrens MM, Grace AA.
J Neurosci. 2009 Feb 25;29(8):2344-54.



Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia.

Lodge DJ, Grace AA.

J Neurosci. 2007 Oct 17;27(42):11424-30.

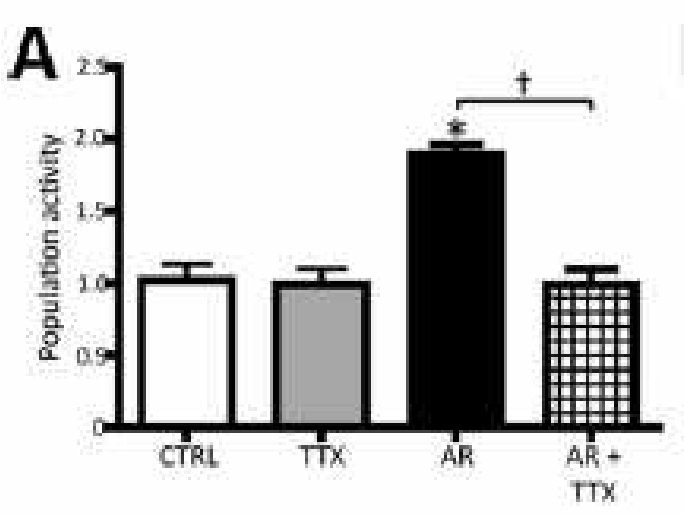


In MAM model, elevated dopamine actiivty is reduced by ttx injection into hippocampus

Aversive stimuli alter ventral tegmental area **dopamine** neuron activity via a common action in the ventral **hippocampus**.

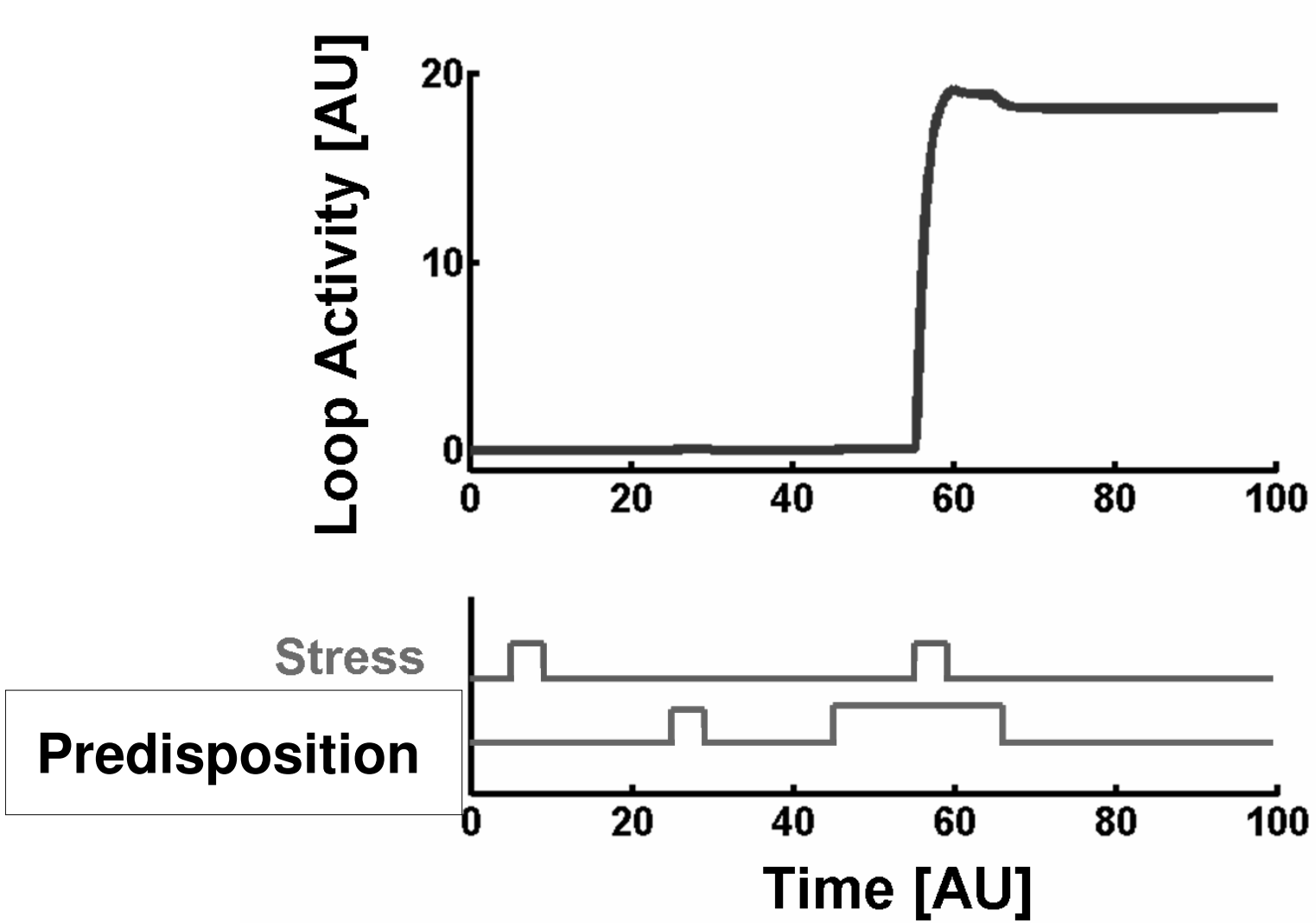
Valenti O, **Lodge** DJ, **Grace** AA.

J Neurosci. 2011 Mar 16;31(11):4280-9.



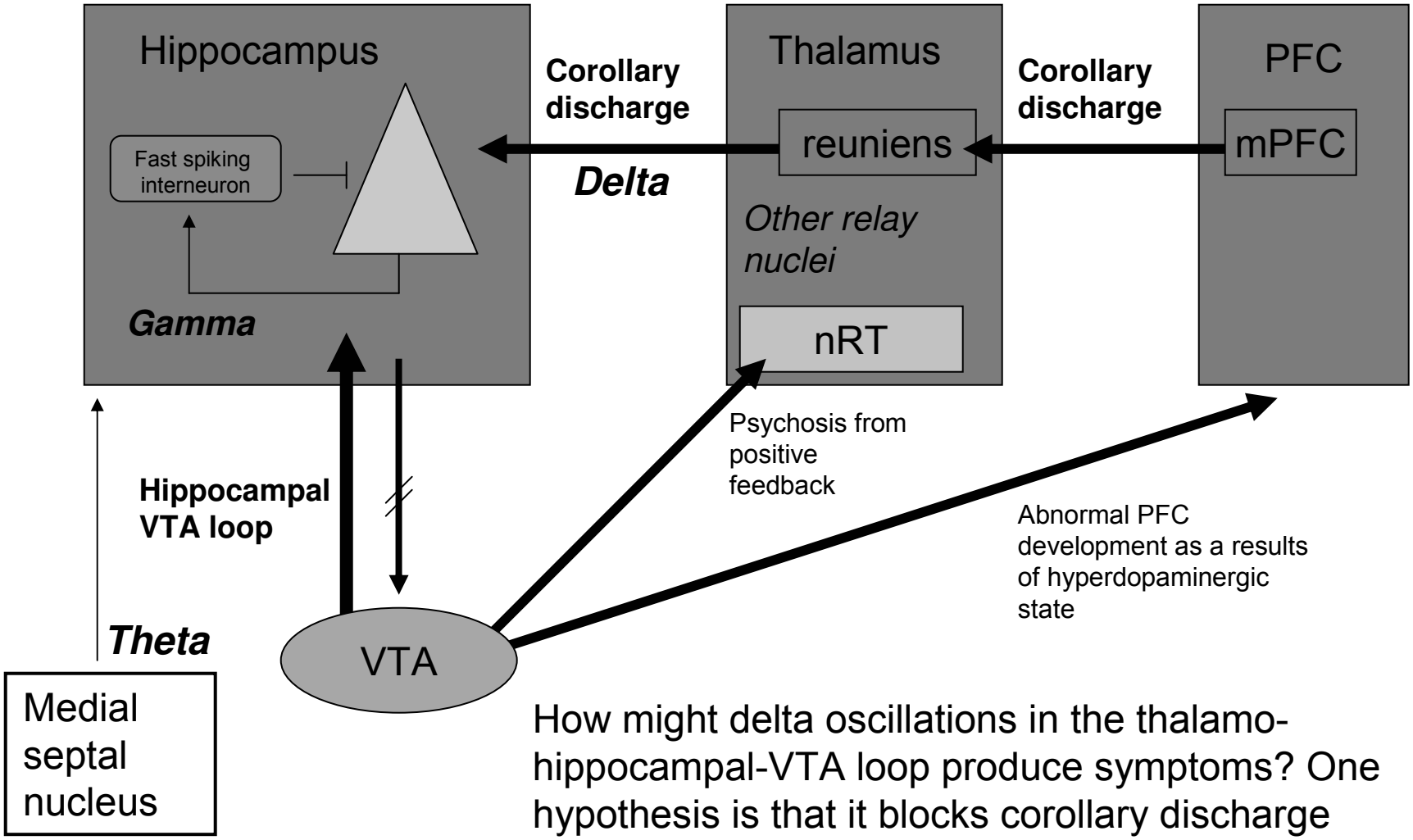
The effect of acute restraint (AR) is blocked by TTX injection into the ventral hippocampus.

Schizophrenia as a bistable system: Predisposition (such as NMDA hypofunction) or Stress by themselves are not sufficient to induce positive feedback, but together induce positive feedback (producing delta oscillations). This persists even after stress is removed. See article in Biological Psychiatry.



Buonanno, 2007; expression of NR2C develops in adolescence.

Neonatal damage to hippocampus produces hyperactivity and hyperdopaminergic state



How might delta oscillations in the thalamo-hippocampal-VTA loop produce symptoms? One hypothesis is that it blocks corollary discharge from the PFC from getting to the temporal lobe (via the reuniens pathway).

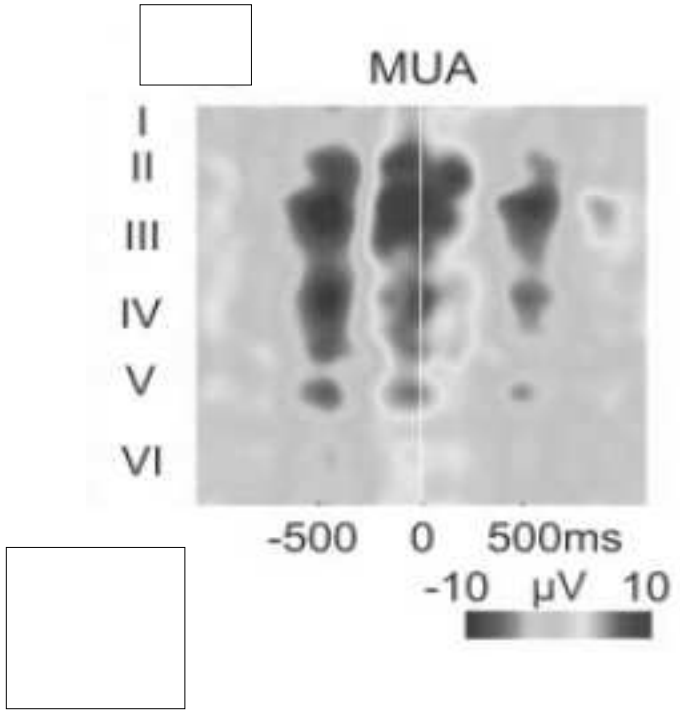
Schneider's first-rank symptoms of schizophrenia are symptoms which, if present, are strongly suggestive of schizophrenia.

The first-rank symptoms of schizophrenia include:

auditory hallucinations:
- hearing thoughts spoken aloud
- hearing voices referring to himself / herself, made in the third person
- auditory hallucinations in the form of a commentary

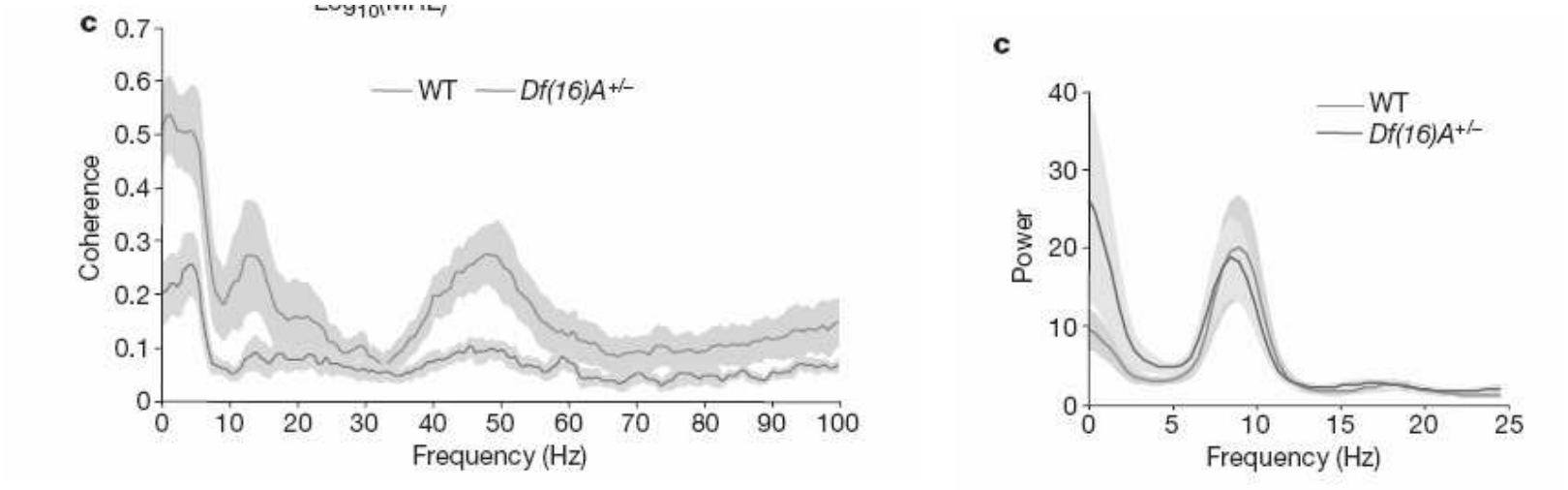
thought withdrawal, insertion and interruption
thought broadcasting
somatic hallucinations
delusional perception
feelings or actions experienced as made or influenced by external agents

During delta, there are substantial periods during each cycle when no firing occurs. For this reason, regions in which delta occurs may be minimally functional, yield "disconnection".



Brain. 2010 Sep;133(9):2814-29. Epub 2010 Jul 23.
Laminar analysis of slow wave activity in humans.
Csercsa R, Dombovári B, Fabó D, Wittner L, Eross L, Entz L, Sólyom A, Rásonyi G, Szucs A, Kelemen A, Jakus R, Juhos V, Grand L, Magony A, Halász P, Freund TF, Maglóczky Z, Cash SS, Papp L, Karmos G, Halgren E, Ulbert I.

Mouse model of human chromosome 22 microdeletion shows enhanced delta in the PFC and reduced frontal-temporal synchronization in the theta/delta band.



Nature. 2010 Apr 1;464(7289):763-7.
Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia.
Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA.

Hypothesis (Predisposition and Psychotic Break):

Schizophrenia is a dysrhythmia originating in the thalamus that results in sleep-like delta frequency oscillations in the awake state (Llinas). These oscillations occur only in *subregions* of the thalamocortical system (vmPFC/midline thalamus, hippocampus).

The abnormal oscillations can be/ mimicked by block of NR2C type of NMDAR in the gabaergic neurons of the nucleus reticularis of the thalamus.

The delta oscillations induced by NMDAR antagonist require D2 action.

Delta oscillations in the nucleus reuniens of the thalamus transmits delta to the hippocampus and vmPFC, where they interfere with 1) hipppocampal memory processes and 2) the information flow from the mPFC to the temporal lobe required for a sense of self.

There is an interneuron endophenotype that results in gamma frequency abnormalities and disinhibition. This makes a predisposition for the psychotic break. The break occurs when the thalamic-hippocampal-VTA loop goes into positive feedback and the delta oscillations are increased.

Genetic influences and prenatal insults produce interneuron abnormality and gamma abnormality, thereby creating predisposition for SZ by bringing the thalam-hippocampal-VTA loop closer to the threshold for positive feedback.

Stress raises dopamine further. This hyperpolarizes the nRT cells and pushes the loop over the threshold for positive feedback, creating delta oscillations in midline thalamus, hippocampus and mPFC. This is the "psychotic break".

Delta oscillations in the midline thalamus interfere with the corollary discharge normally passed from mvPFC to the temporal lobe, thereby contributing to the first rank symptoms of the disease.

END