

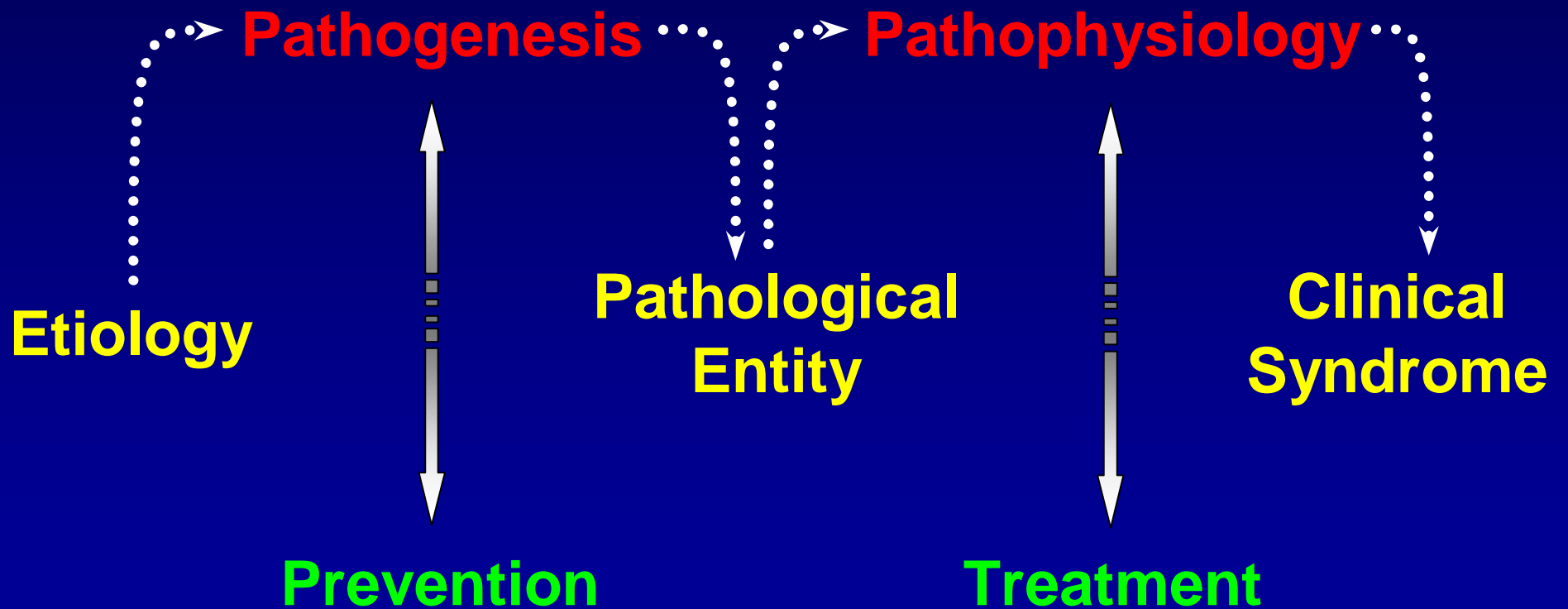
Biomarkers in Schizophrenia

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Disease Process in Schizophrenia



Biomarkers in the Context of Disease Process

- **Critical features of a biomarker**
 - **A direct consequence of the disease pathology**
 - **A proximal mediator of one or more components of the clinical syndrome**
 - **Measurable in the clinical setting**
 - **Detectable in the prodromal state**

Schizophrenia Affects Multiple Complex Brain Systems as Evidenced by the Range of Clinical Features

- **Positive symptoms:** Delusions, hallucinations, thought disorder
- **Negative symptoms:** Decreased motivation, diminished emotional expression
- **Cognitive deficits:** Impairments in attention, working memory, verbal fluency
- **Sensory abnormalities:** “Gating” disturbances
- **Sensorimotor abnormalities:** Eye tracking disturbances
- **Motor abnormalities:** Posturing, impaired coordination

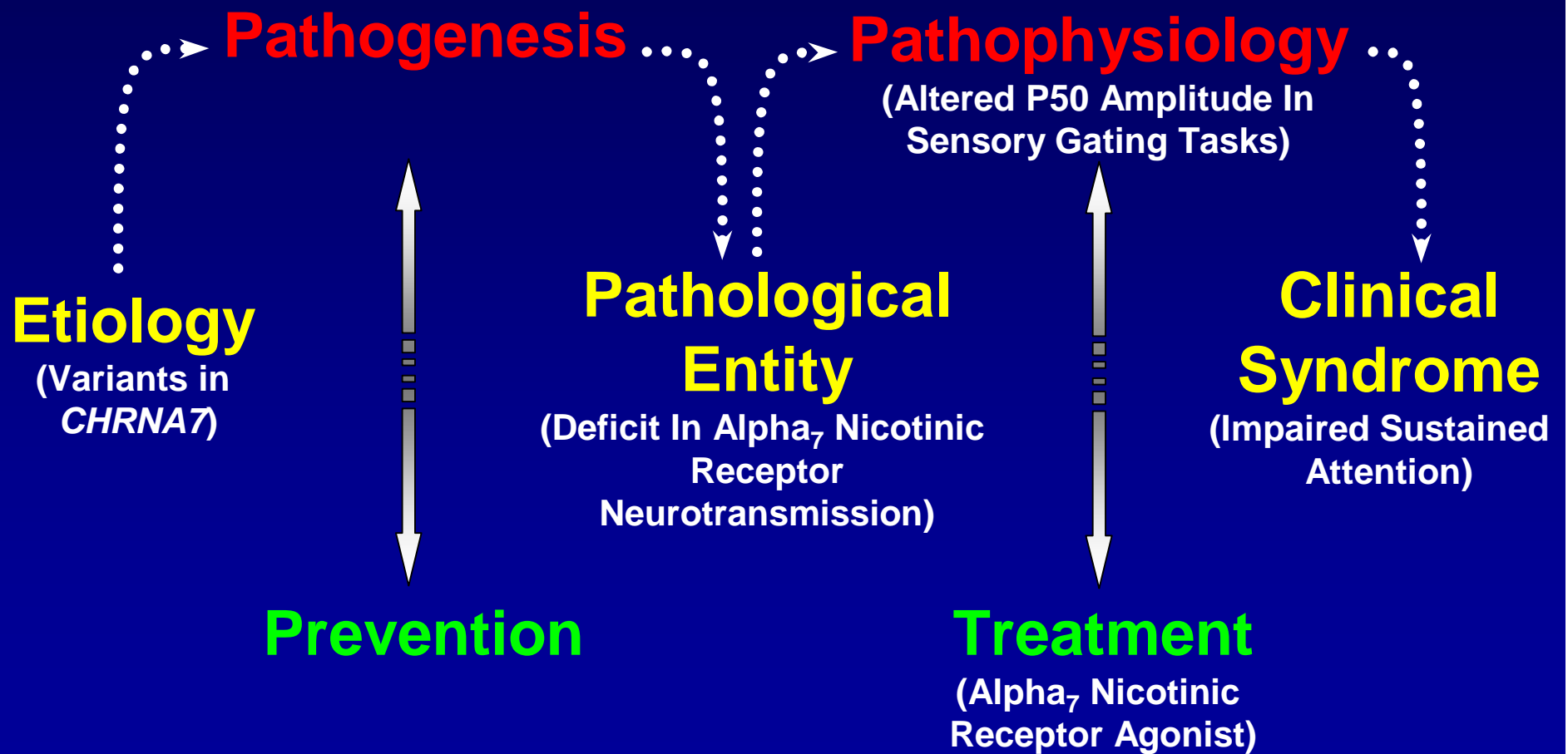
P50 Evoked Potential as a Biomarker of Impaired Attention

- **Fundamental deficit in schizophrenia is an inability to filter (gate) sensory stimuli, leading to deficits in sustained attention.**
- **When paired auditory stimuli are presented, the amplitude of the P50 component of the evoked response to the 2nd stimulus is normally reduced compared to the 1st stimulus.**
- **In schizophrenia, the P50 amplitude in response to the second stimulus is not reduced.**

P50 Evoked Potential as a Biomarker of Impaired Attention

- **In animals, cholinergic stimulation of alpha₇ nicotinic receptors on hippocampal interneurons is essential for the P50 reduction to the 2nd stimulus.**
- **Polymorphisms in *CHRNA7* are associated with the P50 abnormality in humans.**
- **Alpha₇ nicotinic receptor expression is reduced in schizophrenia.**

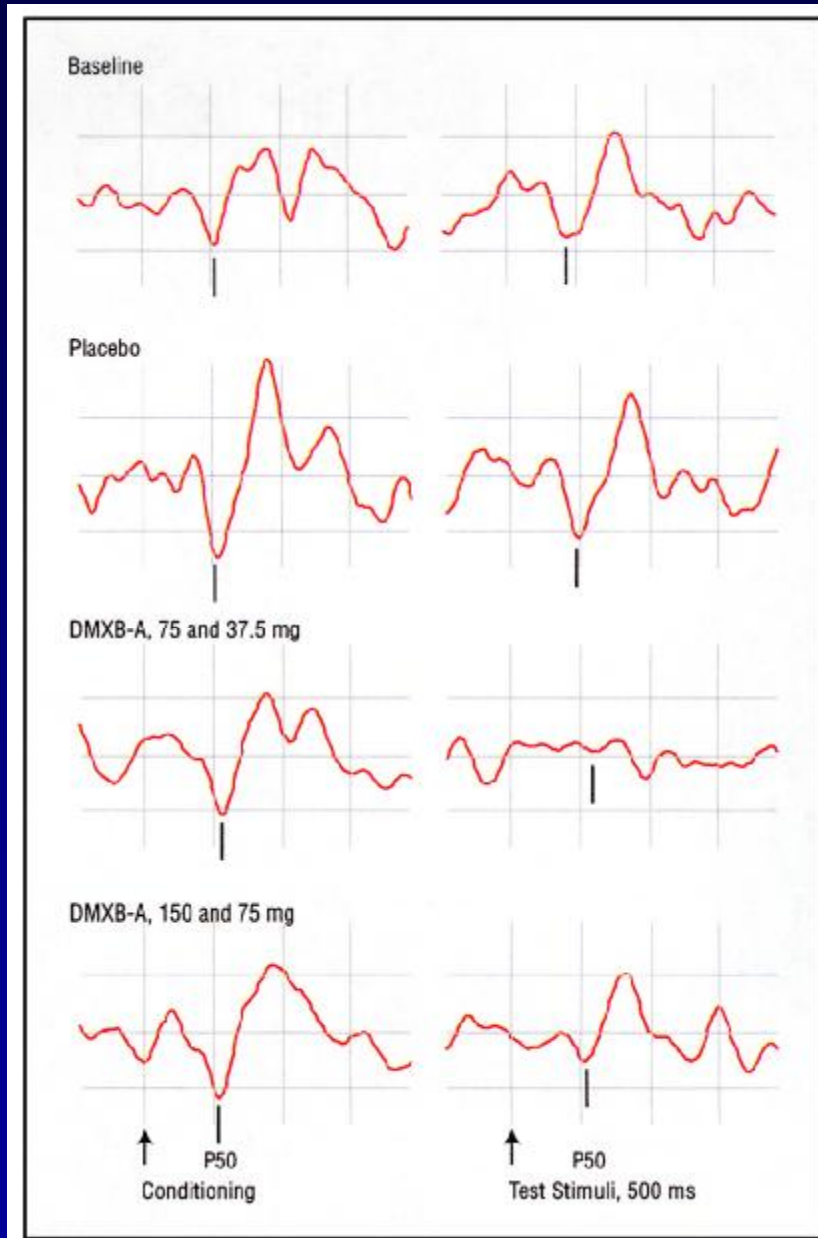
Disease Process in Schizophrenia



Proof-of-Concept Trial of an $\alpha 7$ Nicotinic Agonist in Schizophrenia

Ann Olincy, MD; Josette G. Harris, PhD; Lynn L. Johnson, PharmD; Vicki Pender, BS; Susan Kongs, BS; Diana Allensworth, BS; Jamey Ellis, BS; Gary O. Zerbe, PhD; Sherry Leonard, PhD; Karen E. Stevens, PhD; James O. Stevens, DVM, PhD; Laura Martin, MD; Lawrence E. Adler, MD; Ferenc Soti, PhD; William R. Kem, PhD; Robert Freedman, MD

Arch Gen Psychiatry 63:630, 2006



Representative Schizophrenia Subject

- DMXB-A, partial α_7 nicotinic agonist

- Assessed response to the acute administration of placebo and two doses of DMXB-A

- P50 inhibition improved consistent with activation of α_7 nicotinic receptors

- RBANS scores improved consistent with a beneficial effect on attention/cognition

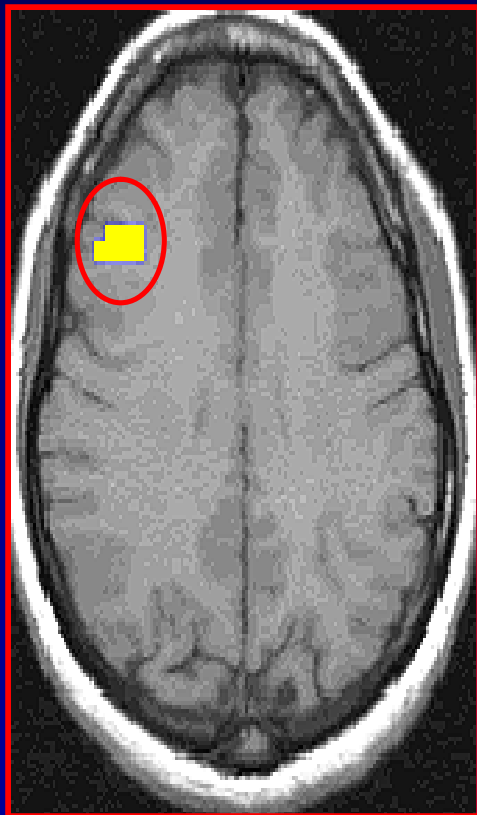
- P50 response may serve as a means for selecting subjects with impaired attention who are likely to benefit from therapy and for monitoring their response

Schizophrenia Affects Multiple Complex Brain Systems as Evidenced by the Range of Clinical Features

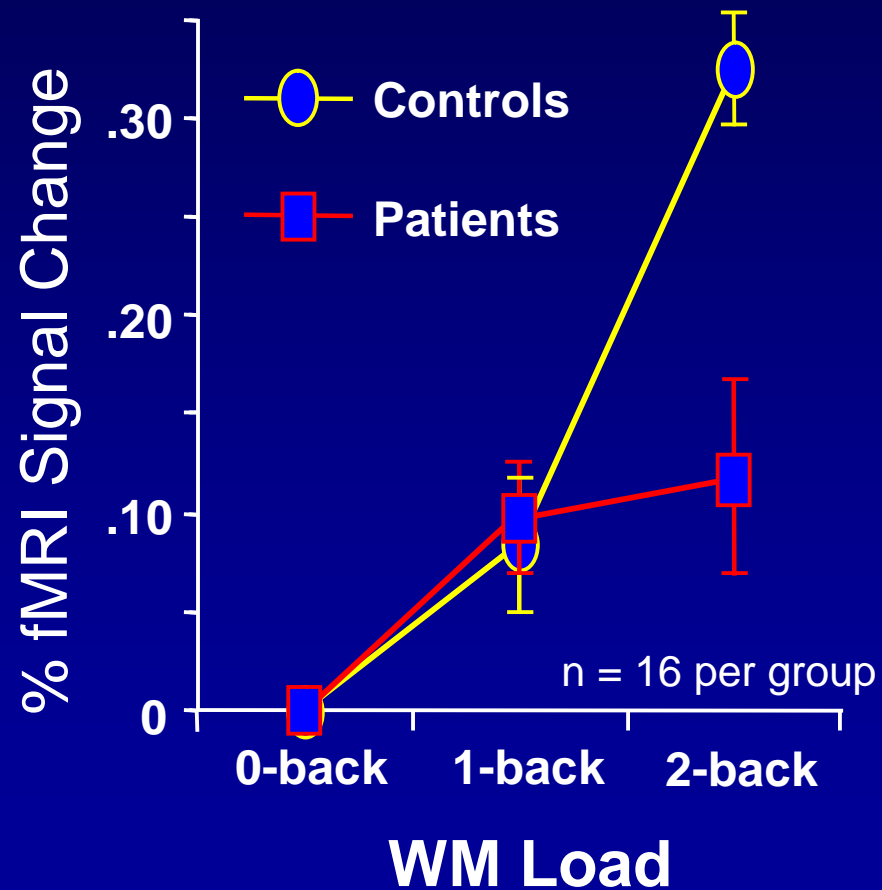
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DLPFC Activation as a Function of Working Memory Load in Schizophrenia

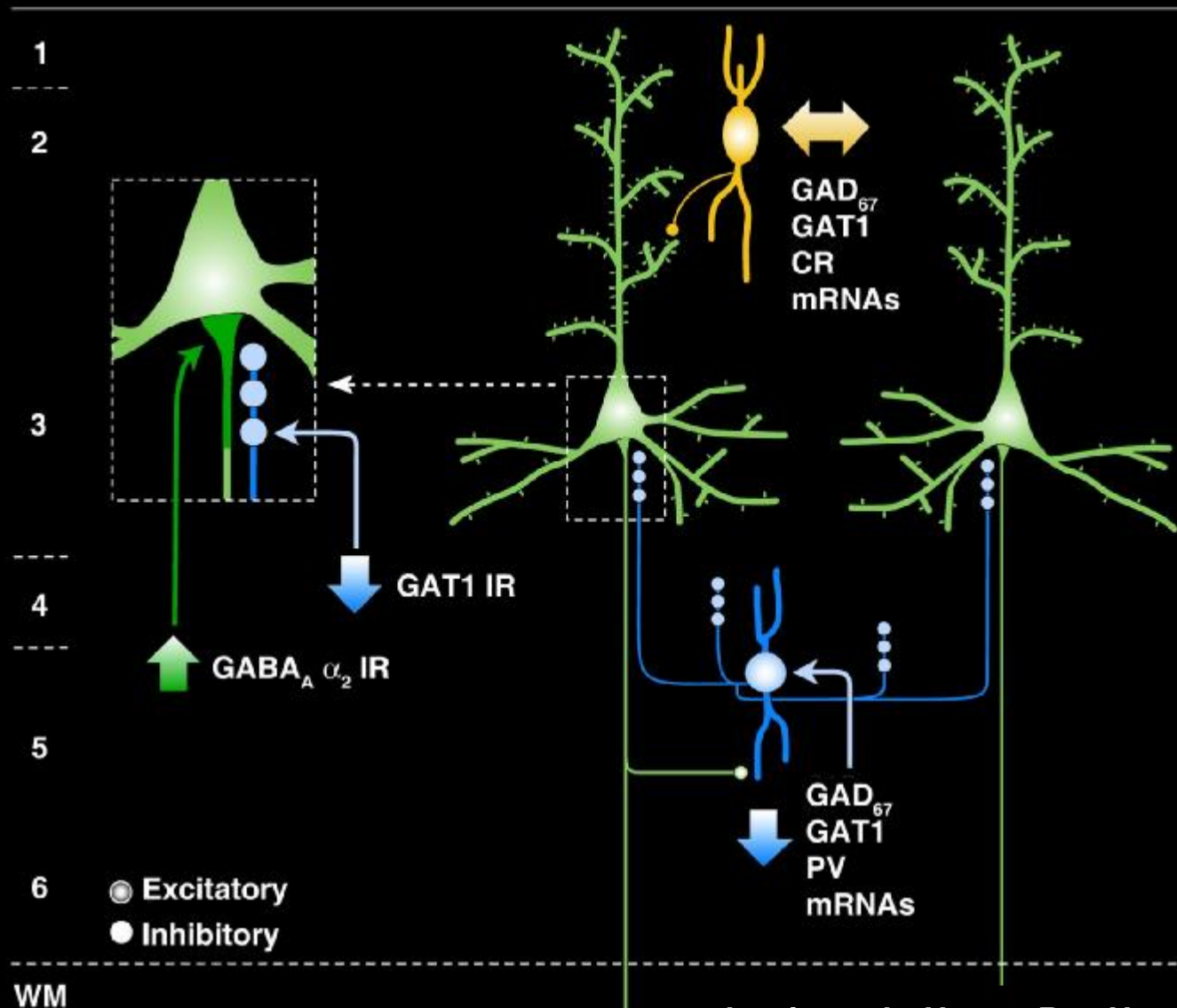
R DLPFC (BA46)



+28 mm



Selective Alterations in DLPFC GABA Neurotransmission May Contribute to Working Memory Deficits



Provisional Interpretation

- **Pathological entity**

- Reduced GAD₆₇ mRNA expression with decreased GABA synthesis in chandelier neurons

- **Compensatory changes**

- Decreased PV expression

- PV reduces the residual intra-terminal Ca²⁺ levels that contribute to the facilitation of GABA release during repetitive firing (*J Neurophys* 89:1414, 2003; *J Neurosci* 25:96, 2005)

- Reduced GAT1 expression

- Blockade of GABA re-uptake prolongs the duration of IPSCs when nearby synapses are activated synchronously (*J Neurosci* 23:2618, 2003)

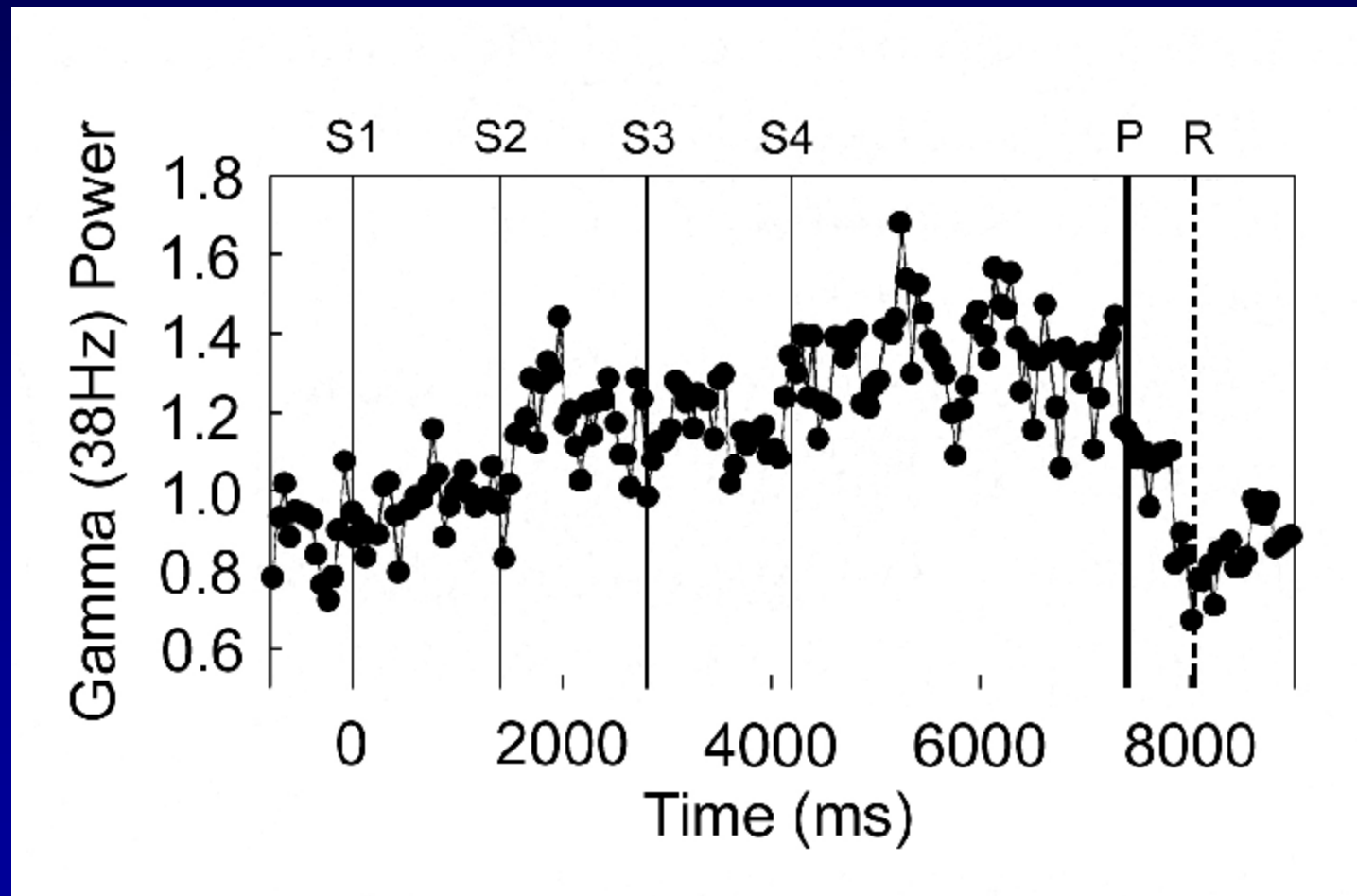
- Up-regulated post-synaptic receptors

- Increase the efficacy of released GABA at AIS

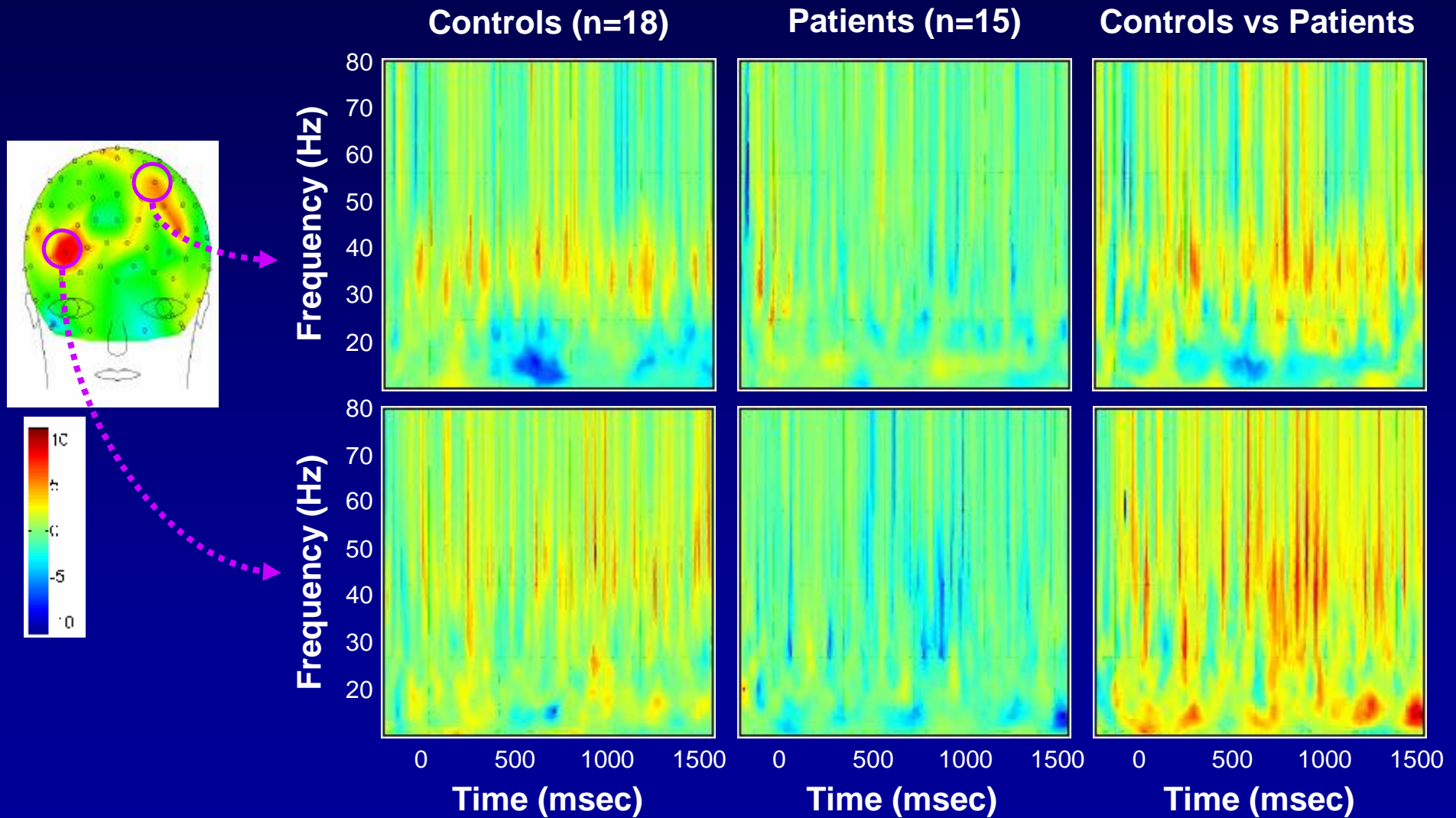
Functional Consequences of Reduced Chandelier Neuron Input to Pyramidal Neuron Axon Initial Segments

- **PV-positive GABA neurons and pyramidal neurons share common sources (e.g., thalamic afferents) of excitatory input (Melchitzky et al., *J Comp Neurol* 408:11, 1999).**
 - The resulting feed-forward, disynaptic inhibition limits the time window for the summation of excitatory inputs required to evoke pyramidal neuron firing (Pouille and Scanziani, *Science* 293:1159, 2001).
- **Each chandelier neuron targets multiple axon initial segments (Peters et al., *J Comp Neurol* 206:397, 1982).**
 - Thus, a given chandelier neuron can synchronize the activity of local populations of pyramidal neurons (Klausberger et al., *Nature* 421:844, 2003).
- **PV-positive, fast-spiking GABA neurons in the middle layers are linked via both chemical and electrical synapses.**
 - These networks oscillate in the gamma band (30-80 Hz) range (Tamas et al., *Nat Neurosci* 366, 2000).

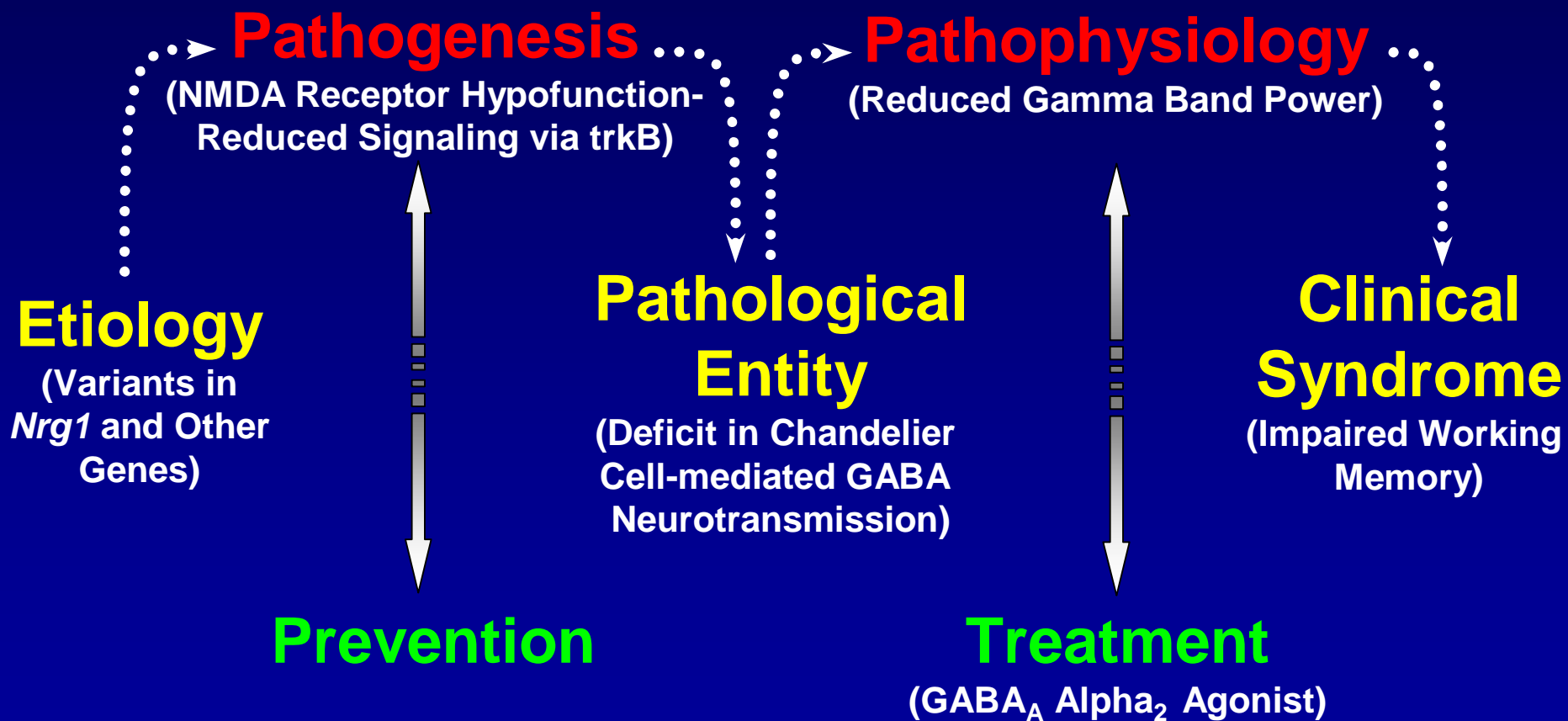
DLPFC Gamma Band Power Increases with Working Memory Load in Humans



Prefrontal Gamma Synchrony, Induced in a Cognitive Control Task, is Reduced in Patients with Schizophrenia



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- **Critical features of a biomarker**
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 - Measurable in the clinical setting
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- **Electrophysiological measures that reflect the emergent properties of *identified neurobiological mechanisms* offer promise as biomarkers**
 - In clinical trials of novel compounds
 - In identifying both prodromal and symptomatic individuals likely to benefit from such compounds

Biomarkers in the Context of Disease Process

- **Future promise**
 - **Ongoing advances in understanding the cell types and local circuits that generate oscillations of specific frequencies**
 - **More refined and biologically-informed cognitive paradigms to induce oscillations**
 - **Improved source resolution of scalp potentials**

Implications for Improving Working Memory Dysfunction in Schizophrenia

- Goal: Activate **selectively** GABA_A receptors containing the alpha₂ subunit **only** when GABA is normally released from chandelier neuron axon terminals.
 - Tonic activation of these receptors or increased firing rate of chandelier neurons would disrupt the synchronization of pyramidal cell activity.
- Agonists with “benzodiazepine-like” properties (i.e., positive allosteric modulators), and selectivity for GABA_A receptors containing the alpha₂ subunit, would preserve the critical timing of inhibition provided by chandelier cell inputs.
 - Available benzodiazepines activate GABA_A receptors containing alpha₁ and alpha₅ subunits which mediate sedation and alterations in hippocampal function, respectively.
- The up-regulated state of GABA_A alpha₂ receptors at axon initial segments may improve the specificity of drug targeting.