



# Cognition and Cholinergic Function after Traumatic Brain Injury: *Lessons in TBI Translational Neuroscience*

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# Disclosures

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  - “A 12-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Preliminary Study to Determine the Efficacy and Safety of Donepezil Hydrochloride (E2020) in Patients with Persistent Mild to Moderate Memory Impairments Resulting from a Single Closed Head Injury,” Eisai Medical Research E2020-A001-209, Role: Consultant (study design), Site Principal Investigator, Project Period: 02/01/01 - 01/31/02
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  - “Rivastigmine Patch in Veterans with Cognitive Impairment following TBI” (RIVET), Department of Veterans Affairs, Office of R&D CX000239 (CCTA #0001), Role: Co-Investigator/Steering Committee Member, Project Period: 07/01/10 - 06/30/17
  - “Multicenter Evaluation of Memory Remediation after Traumatic Brain Injury with Donepezil,” DHHS/NIDILRR 90DP0060 (previously NIDRR H133A130047), Role: National Principal Investigator/Project Director, Project Period: 10/01/13 – 09/30/19
- All medications discussed are used “off-label” in persons with TBI
- Commercial support was not received for this activity
- I serve on the Medical Advisory Board for Alliance Family of Companies (aka Stratus Neuro), the clinical services of which are not relevant to the topic of this lecture
- I receive royalties from American Psychiatric Association Publishing, Inc., Cambridge University Press, Springer Publishing
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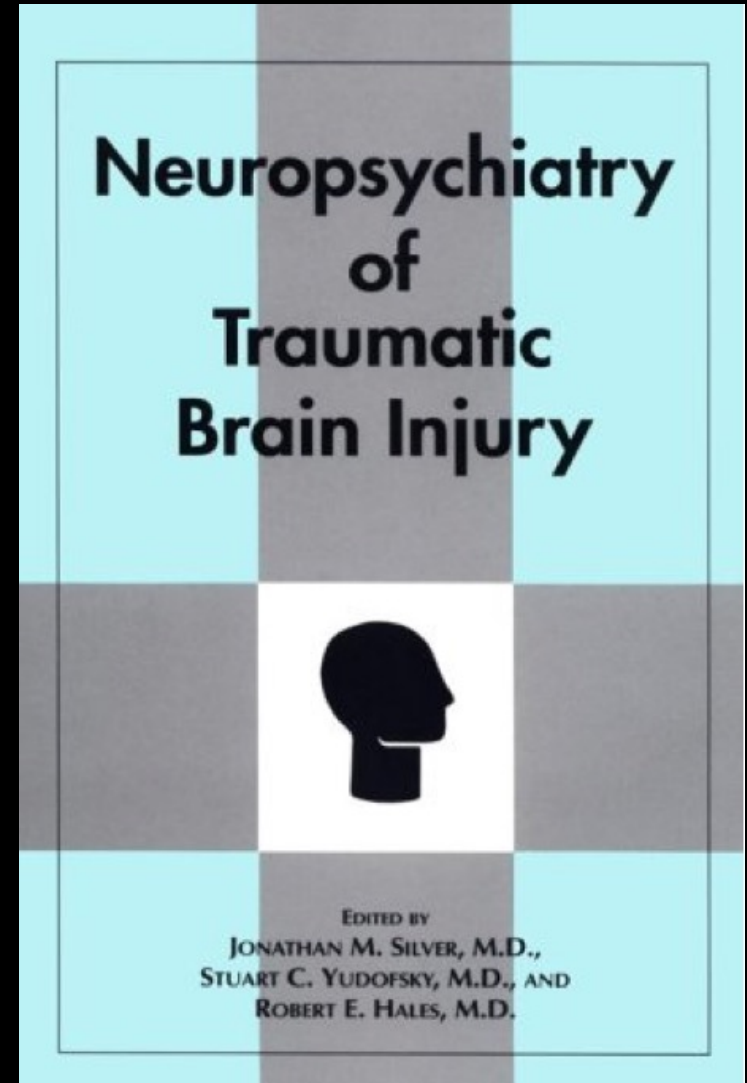
# Goals and Objectives

At the conclusion of this activity, participants will be able to:

- Explain the relationship between cognition and cholinergic function
- Describe cerebral cholinergic neuroanatomy and in health and after traumatic brain injury (TBI)
- Apply findings from clinical trials of cholinergic augmentation to the care of patients with cognitive impairments after TBI
- Consider the value of translational neuroscience in the service of advancing the care of persons with TBI

# UCH Neuropsychiatry Clinic: 1995-1996

- The evaluation and treatment of persons with TBI becomes an area of emphasis in this clinic
- Evaluation generally included:
  - clinical interview/history-taking
  - neurological examination
  - mental status (esp. cognitive) examination
  - neuroimaging (MRI)
  - EEG and/or other laboratory studies when indicated
  - neuropsychological evaluation



# Case Example 1

- A previously healthy 34-year old, right-handed woman sustained a mild TBI (PTA ~ 2 hours) in a motor vehicle accident 2 years prior to consultation. Her Glasgow Coma Score (GCS) = 15 in the ED. She was evaluated and released into the care of her spouse on the day of injury
- Following her TBI, she experienced impairment in attention and memory; she has been able to work part-time, and attributes her incomplete recovery of productivity to these problems
- Additionally, she developed problems with impulse control and affect regulation (brief paroxysms of crying and irritability)
- She was prescribed buspirone 10 mg twice daily by her psychiatrist to improve impulsivity and affective lability, which she describes as moderately effective

# Case Example 1

- On interview, she describes her attention problems as most evident in her difficulty completing tasks at both work and home, such as reading lengthy pieces of information or writing notes, learning new information such as names or telephone numbers, and following conversations. These problems are especially evident in (and made much worse by) noisy environments
- Neurological examination was normal
- MMSE score was 30/30 ( $Z = 1.1$ )
- On neuropsychological testing, she demonstrated mildly slow but errorless performance on the Trail Making Test – Part B and a few errors of omission on the Digit Vigilance task
- Magnetic resonance imaging of the brain (clinical study) was read as “normal for age”



# Case Example 2

- A 37-year old, previously healthy, right-handed man sustained a severe TBI (duration of PTA > 7 days) in a motor vehicle accident 15 years prior to this evaluation
- Although he made a substantial recovery subsequent to this TBI, he has experienced persistent and functionally limiting impairments of higher-level attention and of memory (new learning and recall) since his injury
- Additionally, he developed persistent motor deficits in his right hand and leg, recurrent migraine headaches, as well as intermittent auditory and visual perceptual impairments
- He is presently being treated with bupropion 100 mg per day and sertraline 200 mg per day to improve dysphoria and attentional impairments, which he describes as only partially helpful

# Case Example 2

- On interview, he describes difficulty sustaining attention to conversations easily, difficulty in learning new names of places or people, and problems keeping tracking of appointments and ongoing tasks in his apartment – these problems are markedly worse in noisy or busy environments
- MMSE = 30/30
- On neuropsychological testing, he demonstrated significantly slowed speed on tasks of timed attention, as well as a significant number of errors of omission on the Digit Vigilance task
- MRI demonstrated bilateral (left > right) anterior, ventral, and dorsal frontal and anterior temporal encephalomalacia and multiple areas of white matter injury, including in the left corticospinal tract



# Cases

- These patients were fairly typical of persons with TBI presenting in the late post-injury period to the UCH Neuropsychiatry Clinic:

Like many others across the continuum of injury severity, they complained of attention and memory problems as well as other TBI-related symptoms – and noted that their attention and memory problems were dramatically worse and functionally limiting in complex sensory environments

- Particularly among those at the milder end of the TBI severity continuum, “bedside” cognitive testing and formal neuropsychological assessments sometimes failed to demonstrate impairments concordant with their cognitive complaints – especially in relation to context-dependent problems with attention and memory

SCHIZO 00121

## Elementary neuronal dysfunctions in schizophrenia

Robert Freedman, Merilyne Waldo, Paula Bickford-Wimer and Herbert Nagamoto

*Center for Neurosciences and Schizophrenia, Denver Veterans Administration Hospital, University of Colorado Health Sciences Center, Denver, CO, U.S.A.*

(Received 19 February 1990, accepted 27 February 1990)

This paper describes an elementary deficit in sensory processing in people with schizophrenia. If paired sounds are presented to normal subjects, the response to the first sound, as measured by the P50 wave of the auditory-evoked potential, is much greater than the response to the second sound. The diminished response to the second sound is an example of a sensory gating mechanism that enables people to regulate their vigilance so that they can either detect all sounds in the environment or ignore most of them, in favor of narrowing the focus of their concentration. In schizophrenia, this mechanism is usually deficient; patients are in a state of hypervigilance and have diminished abilities to focus their attention. The deficiency appears to be genetically determined and to involve the brainstem control of sensory input to the hippocampus. Such sensory gating deficits may underlie more complex psychotic symptoms, such as hallucinations and delusions. Further studies of their neurobiology could lead to increased understanding of the pathophysiology of schizophrenia.

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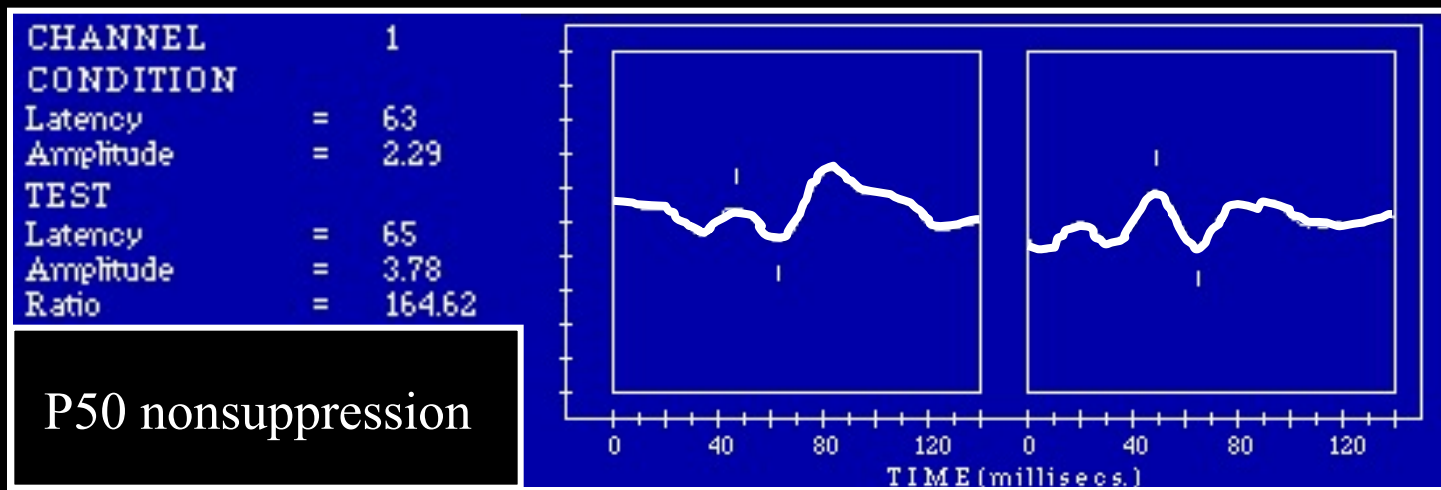
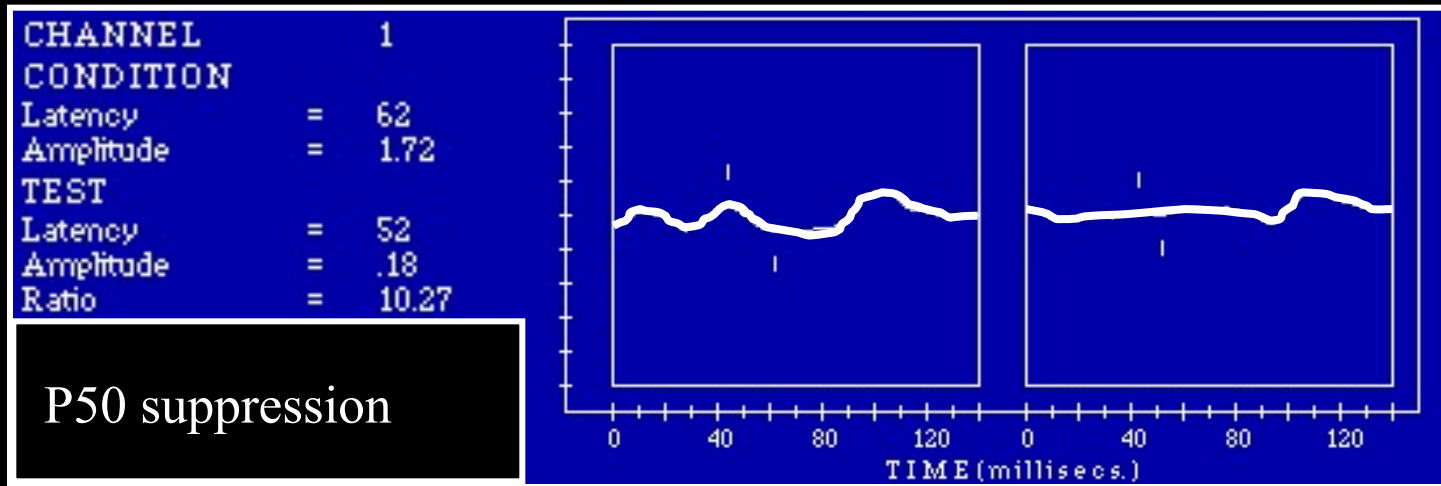
*Key words:* Sensory gating; Pathophysiology; (Schizophrenia)

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# Sensory Gating

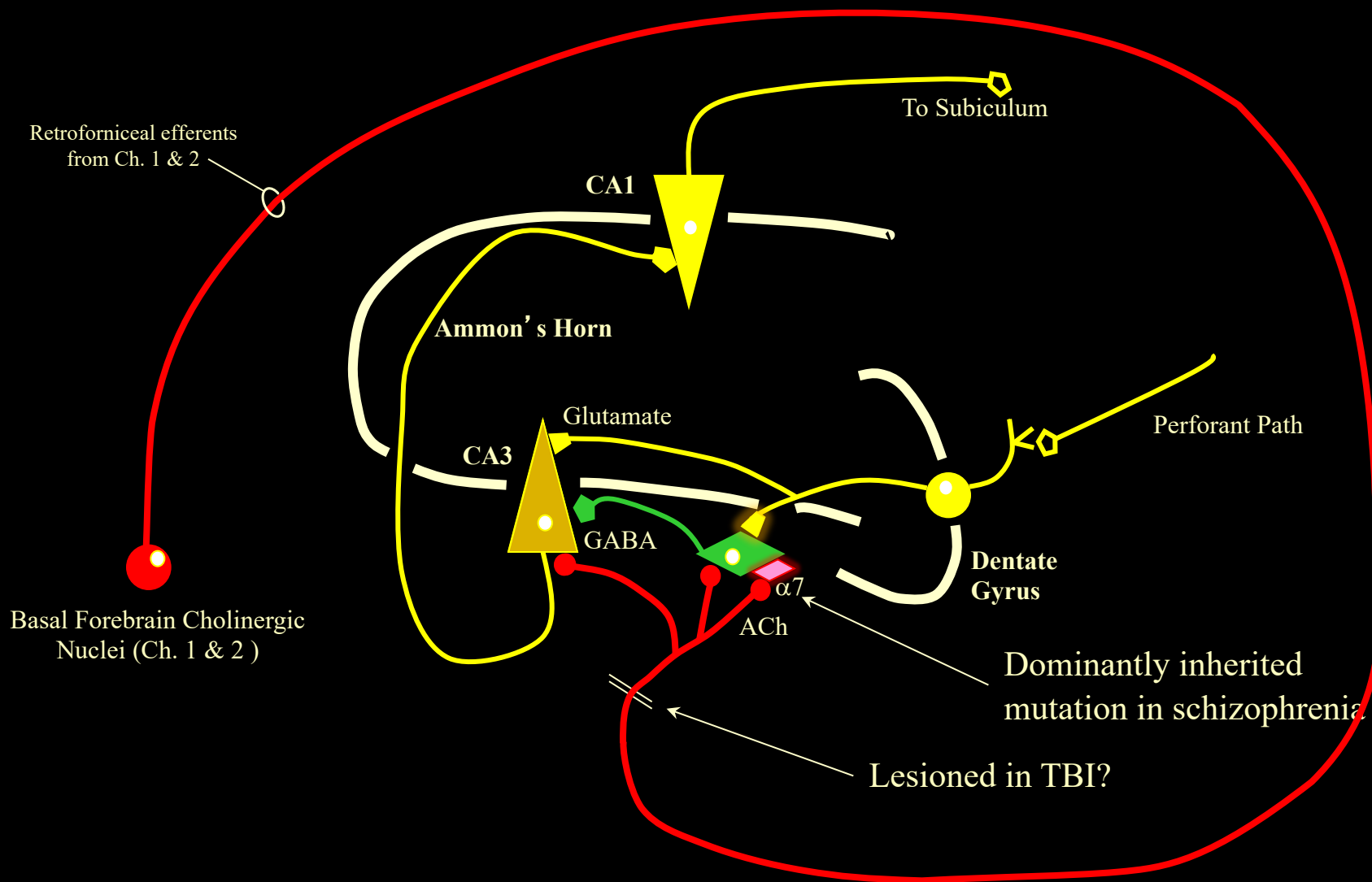
- A pre-conscious cortical function
- Facilitates “filtering” of highly processed multimodal stimuli received from heteromodal (particularly inferior parietal) cortex
  - hence, a pre-requisite to selective and sustained attention, working memory, memory, etc.
- Phenomenologically distinct from distractibility
- Cholinergically-mediated

# P50 Evoked Response to Paired Auditory Stimuli



(Freedman et al., 1994; Adler et al., 1993; Nagamoto et al., 1989; figure adapted from Arciniegas D et al.: Impaired auditory gating and P50 nonsuppression following traumatic brain injury. *J Neuropsychiatry Clin Neurosci.* 2000 Winter;12(1):77-85)

# Neurocircuitry of P50 ERP

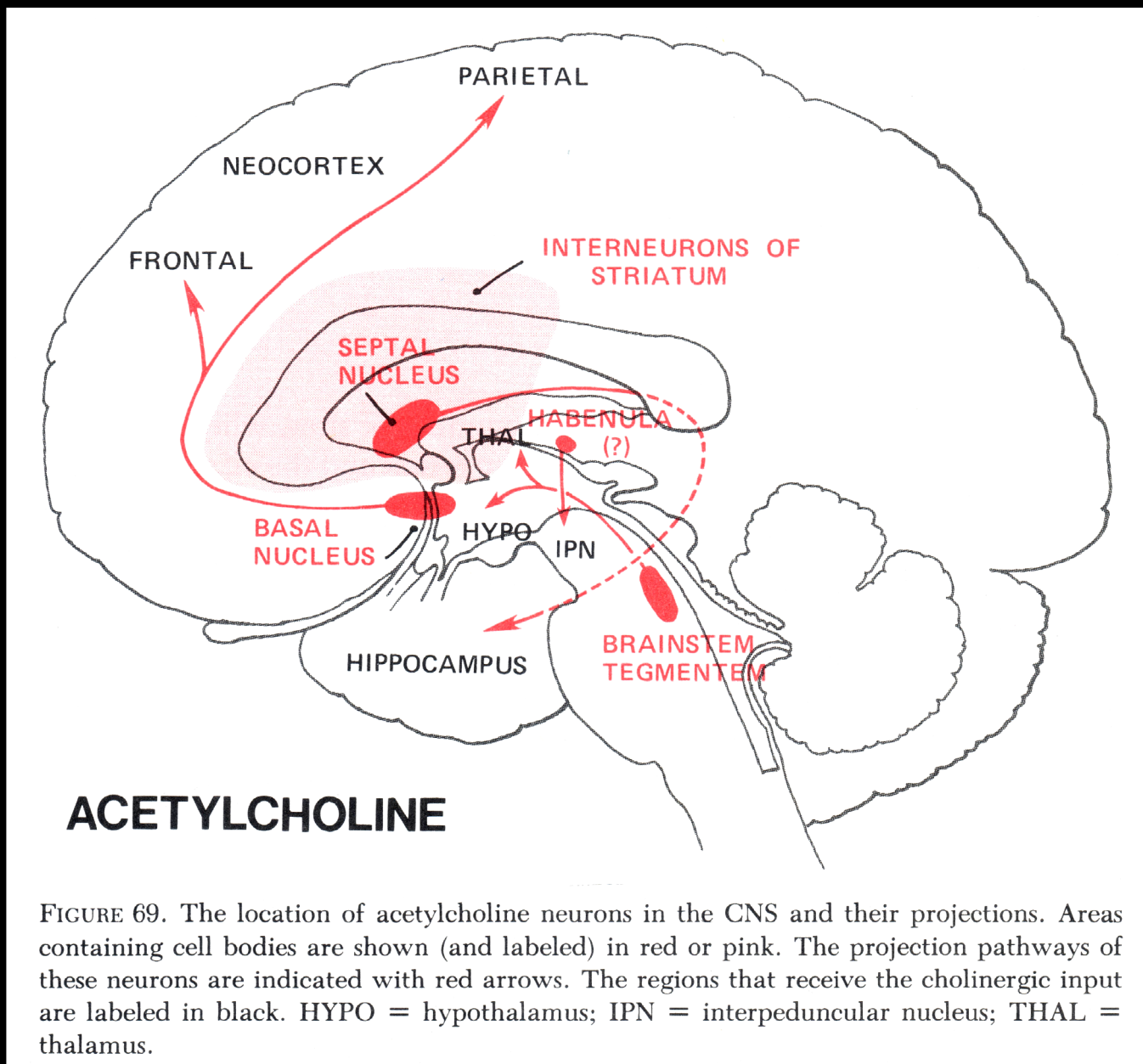


# Initial Questions

- Might the cognitive complaints offered by the patients in my clinic reflect, at least in part, impaired sensory gating?
- Has sensory gating impairment been demonstrated among persons with TBI?
- Is there any evidence of cholinergic dysfunction after TBI that might explain the development of impaired sensory gating (and/or impairments of other hippocampally-mediated cognitive functions) after TBI?
- If so, might augmentation of cerebral cholinergic function improve this problem and/or other aspects of cognition?



*Cerebral Cholinergic  
Structure and Function:  
A Brief Review*





**TABLE 1** *Cholinergic innervation of the human brain*

Cholinergic nucleus		Efferent pathway	Target structure(s)
Ch1	Septal nucleus	Fornix	Hippocampus
Ch2	Vertical limb of the diagonal band of Broca	Fornix	Hippocampus
Ch3	Horizontal limb of the diagonal band of Broca	Olfactory tract	Olfactory bulb
Ch4	Nucleus basalis of Meynert	Stria terminalis and ventral amygdalofugal pathway	Amygdala
		Medial pathway (within cingulum)	Medial orbitofrontal, subcallosal, cingulate, pericingulate, and retrosplenial cortices
		Lateral pathway Perisylvian division (within claustrum)	Insular and frontoparietal opercular cortices, superior temporal gyrus, and insula
		Capsular division (within medial aspect of the external capsule and ventral portion of the uncinate fasciculus)	Dorsal frontoparietal neocortex, middle and inferior temporal gyri, inferotemporal cortex, and parahippocampal gyrus; possible input to amygdala as well
Ch5	Pedunculopontine nucleus	Dorsal tegmental pathway of Shute and Lewis	Thalamus, cerebellum, globus pallidus, subthalamic nucleus, substantia nigra (pars compacta); medullary reticular formation and spinal cord; lesser contribution to striatum
Ch6	Laterodorsal tegmental nucleus	Dorsal tegmental pathway of Shute and Lewis	Thalamus, cerebellum, globus pallidus, subthalamic nucleus, substantia nigra (pars compacta); lesser contribution to striatum
Ch7	Medial habenula	Fasciculus retroflexus	Interpeduncular nucleus
Ch8	Parabigeminal nucleus		Superior colliculus; lesser contribution to the thalamus

Adapted from Arciniegas DB. Cholinergic dysfunction and cognitive impairment after traumatic brain injury. Part 1: The structure and function of cerebral cholinergic systems. *Journal of Head Trauma Rehabilitation* 26(1):98-101, 2011.

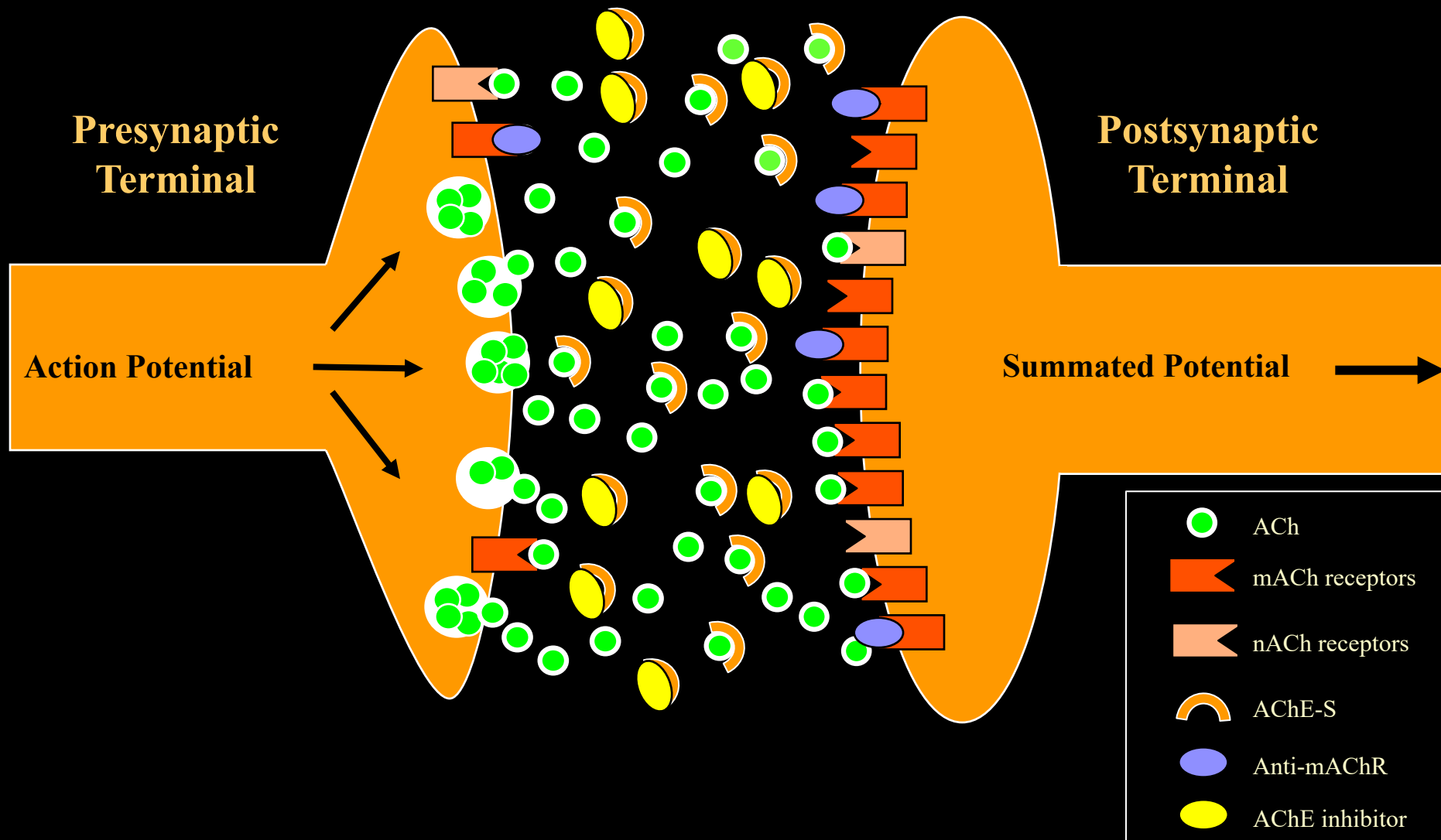
# Cholinergic Receptors

Muscarinic Receptors	Nicotinic Receptors
Predominant cholinergic receptor type in the CNS	Less abundant in the CNS than muscarinic receptors
All subtypes exhibit a slow response time (100-250 ms)	Comprised of $\alpha$ and $\beta$ subunits At least 7 forms of $\alpha$ and 3 forms of $\beta$ Many combinations possible
All are coupled to G proteins, linked to a variety of second messenger systems Phosphoinositol ( $M_1, M_3, M_5$ ) Coupling to cAMP ( $M_2, M_4$ )	Neuronal types are designated $\alpha$ -bungarotoxin sensitive or insensitive
Final effects are to open or close $K^+$ , $Ca^{2+}$ , or $Cl^-$ channels depending on the cell type on which the receptor is located	Final effects are to open $Na^+ > K^+ \gg Ca^{2+}$ channels depending on the cell type on which the receptor is located
Muscarinic receptors may facilitate excitation or inhibition depending on the type of ion channel that is activated	Nicotinic receptors tend to facilitate excitation of the neurons or engagement of second messenger systems

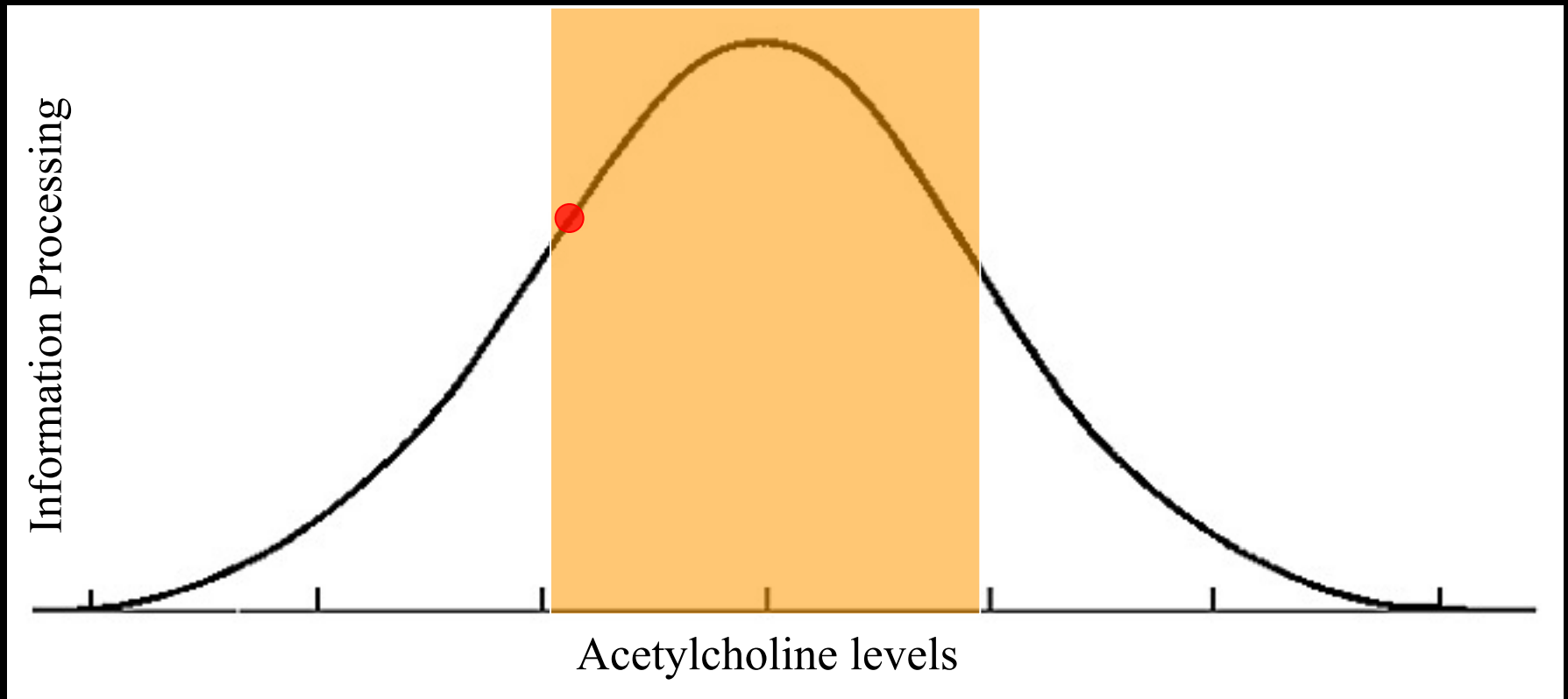
# Regulation of Cholinergic Neurotransmission

- Presynaptic feedback mechanisms at muscarinic and nicotinic receptors (autoreceptors)
- Modulation by other neurotransmitters via heteroreceptors located on acetylcholinergic neurons or at acetylcholinergic synapses
- Intrasympaptic metabolism (hydrolysis) by acetylcholinesterase
- Possibly intra- and extrasynaptic regulation via butyrylcholinesterase

# Regulation of Cholinergic Neurotransmission



# Acetylcholine and Information Processing



- Like glutamate and catecholamines, the relationship between acetylcholine and information processing systems is approximately Gaussian (both too little and too much compromise function)

# Role of Acetylcholine in the Central Nervous System

- Acetylcholine is a modulatory neurotransmitter
- Its principal effect in the CNS is to improve the efficiency of signaling effected by other neurotransmitters:
  - increases excitatory tone in reticulothalamic systems
  - improves information gating in the hippocampus and thalamus
  - increases the strength of signals co-processed with glutamate in the hippocampus so as to facilitate long-term potentiation
  - facilitates the effects of glutamate, GABA, dopamine, norepinephrine, and serotonin on information processing in frontal, temporal, parietal, and cerebellar areas

# Acetylcholine and Cognition

## Anatomy

- Reticular formation (Ch5-6)
- Entorhinal-hippocampal complex (Ch1, Ch2)
- Dorsal and lateral neocortex, including frontal-subcortical circuits (Ch4)

## Function

- Wakefulness and awareness
- Sensory gating
- Attention
- Working memory
- Explicit memory
- Sustained attention, working memory, language, visuospatial function, executive function, executive control of attention, memory, language, visuospatial function
- Comportment and social cognition
- Motivation



# *The Effects of Neurotrauma on Cerebral Cholinergic Function*



# TBI and Cholinergic Dysfunction

- The effects of TBI on cerebral cholinergic systems and the relationship between cholinergic dysfunction and posttraumatic cognitive impairments have the subject of scientific and clinical inquiry since the 1940s
- This area of research flourished in the 1980s and 1990s
  - research methods enabled characterization the short- and long-term consequences of neurotrauma on cerebral acetylcholine systems
  - methods by which to induce TBI in animals (controlled cortical impact, fluid percussion injury) were developed
  - all of these methods were paired with advances in measures of cognition, behavior, and motor function, enabling assessment of the cognitive consequences of experimental injury-induced cholinergic abnormalities

# Experimental Injury Studies

- Application of concussive forces in rats produces acute activation of central and forebrain cholinergic neurons
- Excessive cholinergic activation – especially of the brainstem Ch5-6, LDT-PPN, nuclear complex – impairs cerebral function and induces cataplexy (sudden loss of motor tone) characteristic of concussion with LOC
- These observations led Hayes et al. (1986) to propose the “pontine cholinergic system hypothesis” of concussion

# Experimental Injury Studies

- Pre-injury administration of cholinergic antagonists reduces cholinergic excitotoxicity as well as acute and chronic injury-induced memory impairments
- Among concussed rats, administration of scopolamine (a muscarinic antagonist) worsens posttraumatic memory impairments among animals with allowed to make a complete cognitive recovery – even at doses that are innocuous cognitively to uninjured animals
- In the absence of adequate pre-injury neuroprotection from cholinergically-mediated neuronal excitotoxicity, concussed animals develop chronic reductions in cholinergic function

# Loss of forebrain cholinergic neurons following fluid-percussion injury: implications for cognitive impairment in closed head injury

**RICHARD H. SCHMIDT, M.D., PH.D., AND M. SEAN GRADY, M.D.**

*Department of Neurological Surgery, University of Washington, Seattle, Washington*

✓ Disturbances in memory, concentration, and problem solving are common after even mild to moderate traumatic brain injury. Because these functions are mediated in part by forebrain cholinergic and catecholaminergic innervation, in this study the authors sought to determine if experimental concussive injury produces detectable morphological damage to these systems.

Fluid-percussion head injury, sufficient to cause a 13- to 14-minute loss of righting reflex, was produced in rats that had been anesthetized with halothane. Injury was delivered either at midline or 2 mm off midline and compared with appropriate sham-injured controls. After 11 to 15 days, the rat brains were stained in serial sections for choline acetyltransferase, tyrosine hydroxylase, dopamine  $\beta$ -hydroxylase, acetylcholinesterase, and nicotinamide adenine dinucleotide phosphate diaphorase. Cell counts were determined for the entire population of ventrobasal forebrain cholinergic cells. Midline injury produced a bilateral loss of cholinergic neurons averaging 36% in area Ch1 (medial septal nucleus), 45% in Ch2 (nucleus of the diagonal band of Broca), and 41% in Ch4 (nucleus basalis of Meynart), ( $p \leq 0.05$ ). Lateralized injury resulted in cholinergic neuron loss of similar magnitude ipsilaterally ( $p \leq 0.05$ ), but a smaller contralateral loss of between 11% and 28%. No loss of neurons was detected in the pontomesencephalic cholinergic groups Ch5 and Ch6. There was no visible effect of head injury on forebrain dopamine or noradrenergic innervation.

A significant and apparently selective loss of ventrobasal forebrain cholinergic neurons following brief concussive injury in rats is demonstrated in this study. This type of injury is known to produce significant disturbance in cognitive tasks linked to neocortical and hippocampal cholinergic function. It remains to be determined how this neuron loss occurs, whether it can be prevented with neuroprotective agents, how it affects innervation in target tissues, and whether it occurs in human victims of traumatic brain injury.

Schmidt RH, Grady MS. Loss of forebrain cholinergic neurons following fluid-percussion injury: implications for cognitive impairment in closed head injury. *Journal of Neurosurgery* 1995; 83:496-502.

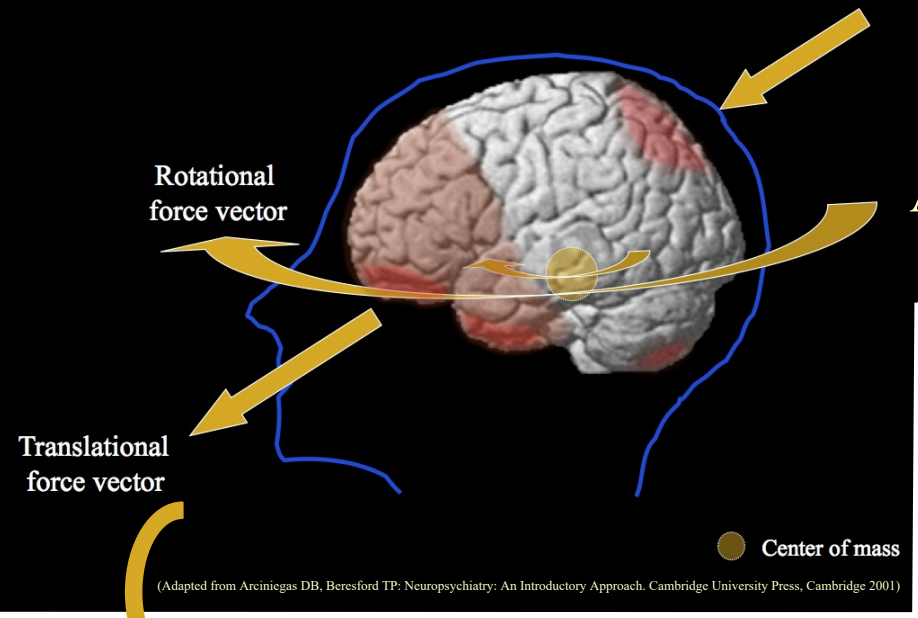
- Rats with experimentally induced midline injury suffered significant bilateral reductions in cholinergic neurons, including:
  - 36% reductions in area Ch1 (medial septal nucleus)
  - 44% reductions in area Ch2 (diagonal band of Broca)
  - 41% reductions in area Ch4 (nucleus basalis of Meynert)
- Lateralized injuries produced similarly severe losses of cholinergic neurons ipsilaterally (30-40%) and lesser losses contralaterally (11-28%)
- No losses of brainstem cholinergic neurons (Ch5-6)
- No losses of dopaminergic or noradrenergic neurons

# Experimental Injury Studies

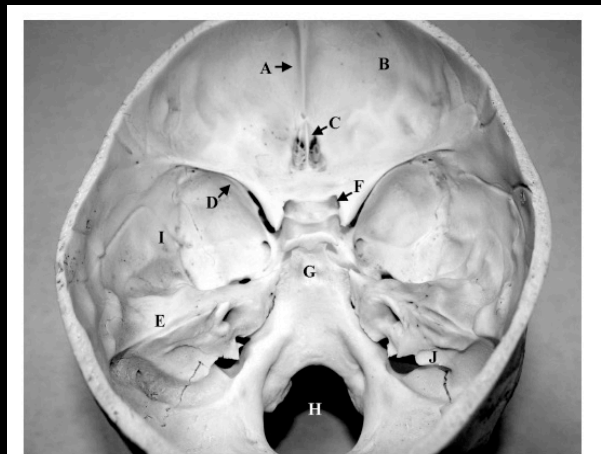
- Posttraumatic reductions in cholinergic function, both acute and long-term, appear to be due to:
  - reduced synthesis of acetylcholine
  - altered release of acetylcholine due to changes in ACh autoreceptor binding and signal transduction
  - injury to cholinergic projections
  - alteration in the numbers and function of pre- and post-synaptic muscarinic and nicotinic receptors
- Posttraumatic cognitive impairments are partially remediable via cholinergic augmentation

# Human Studies: Neurotransmitter Excitotoxicity

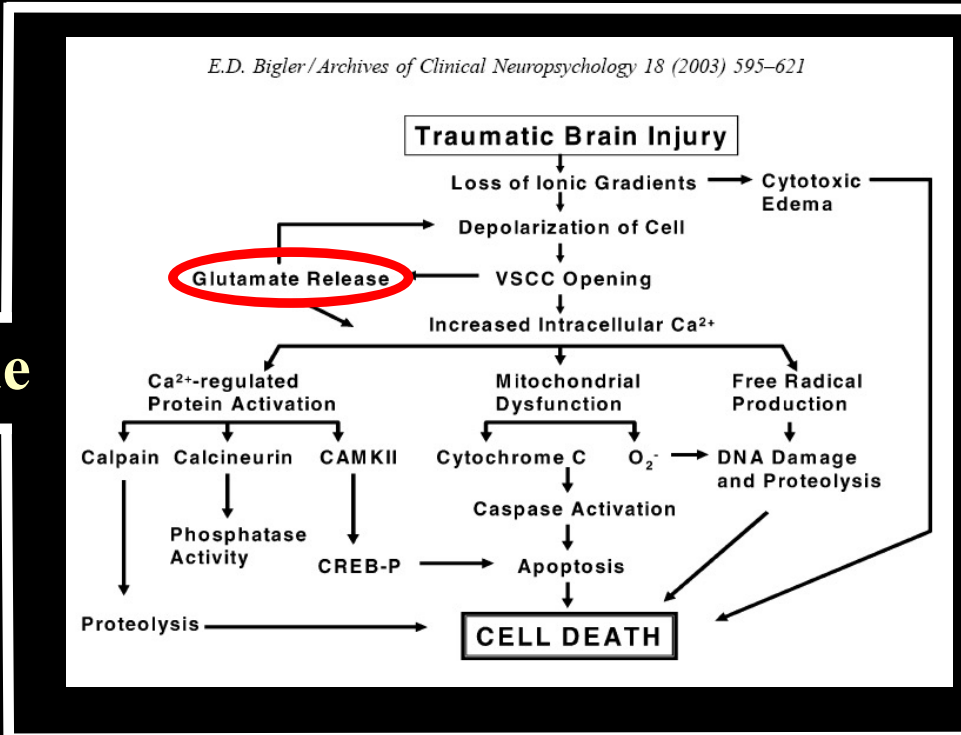
## Inertial Forces: Translation, Rotation, and Angular Acceleration Forces



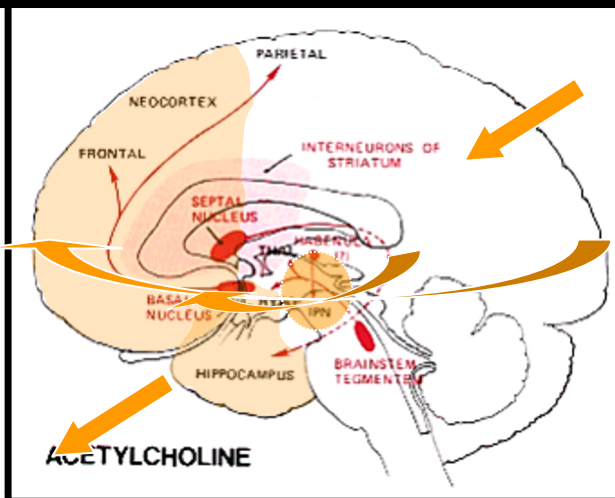
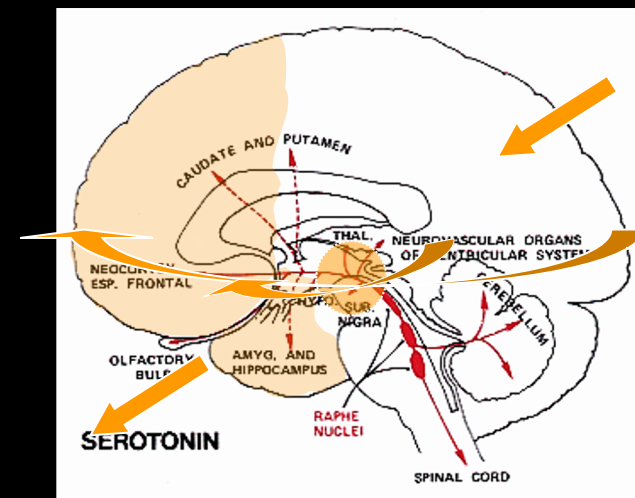
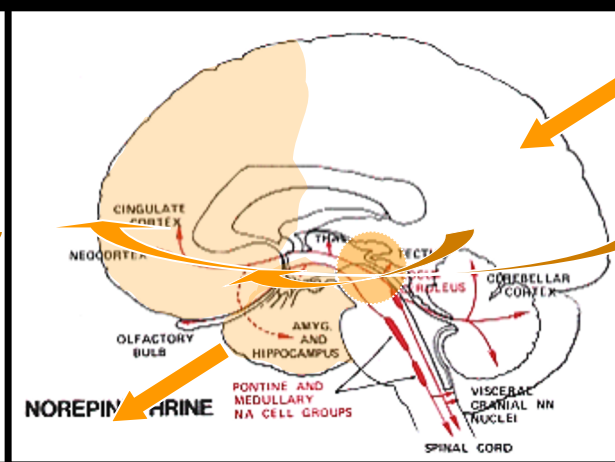
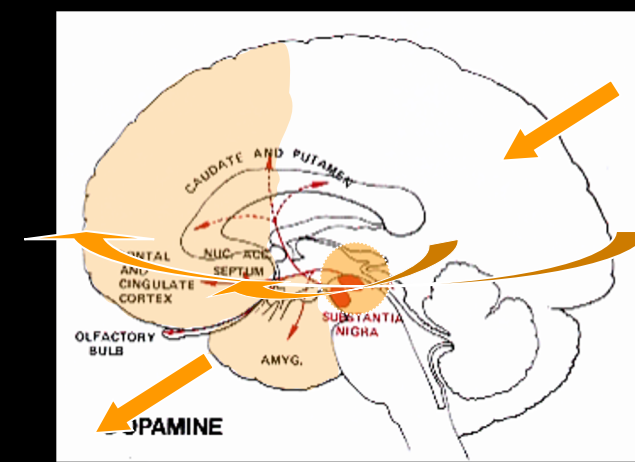
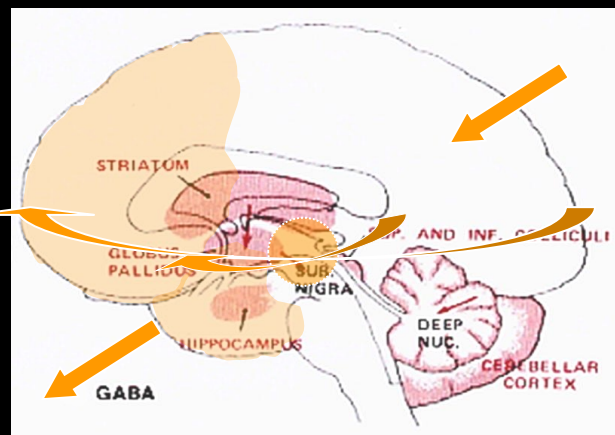
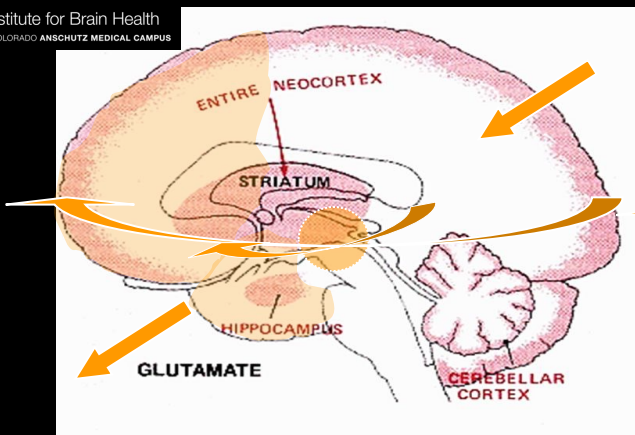
## Cytotoxic Cascade



E.D. Bigler / Archives of Clinical Neuropsychology 18 (2003) 595-621



## Contact Forces



Adapted from Gilman S, Newman SW: Manter and Gatz' s Essentials of Clinical Neuroanatomy and Neurophysiology. FA Davis Co., Philadelphia, 1987.

Biomechanical force illustrations adapted from Arciniegas DB, Beresford TP: Neuropsychiatry: An Introductory Approach. Cambridge University Press, Cambridge, 2001.

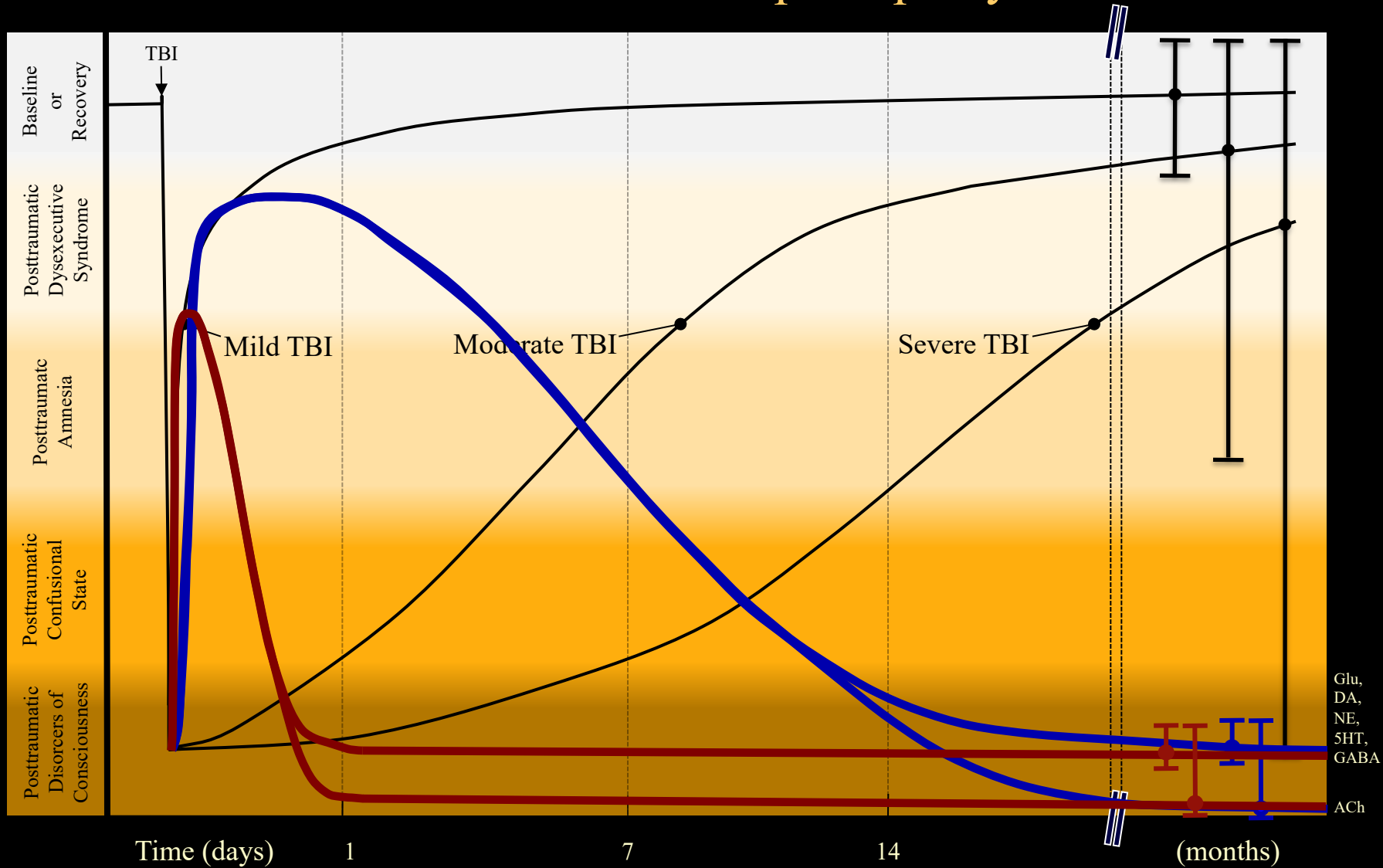


# Injury Factors: Neurochemistry

- Neurotransmitter “storm” at time of TBI
  - acute increases in glutamate,<sup>1-5</sup> dopamine,<sup>6,7</sup> norepinephrine,<sup>6,7</sup> serotonin,<sup>6-9</sup> and acetylcholine<sup>10</sup> are reported from CSF samples in the acute post-injury period among persons with severe TBI
  - these acute neurotransmitter excesses are associated with severe disturbances of brain function
  - among those who survive their injuries, cerebral glutamate, dopamine, norepinephrine, and serotonin levels appear to normalize in the days to weeks following TBI<sup>6;11-13</sup>

# Course of Recovery after TBI: Acute Traumatic Encephalopathy

Stage of Acute Traumatic Encephalopathy



Glu,  
DA,  
NE,  
5HT,  
GABA  
ACh

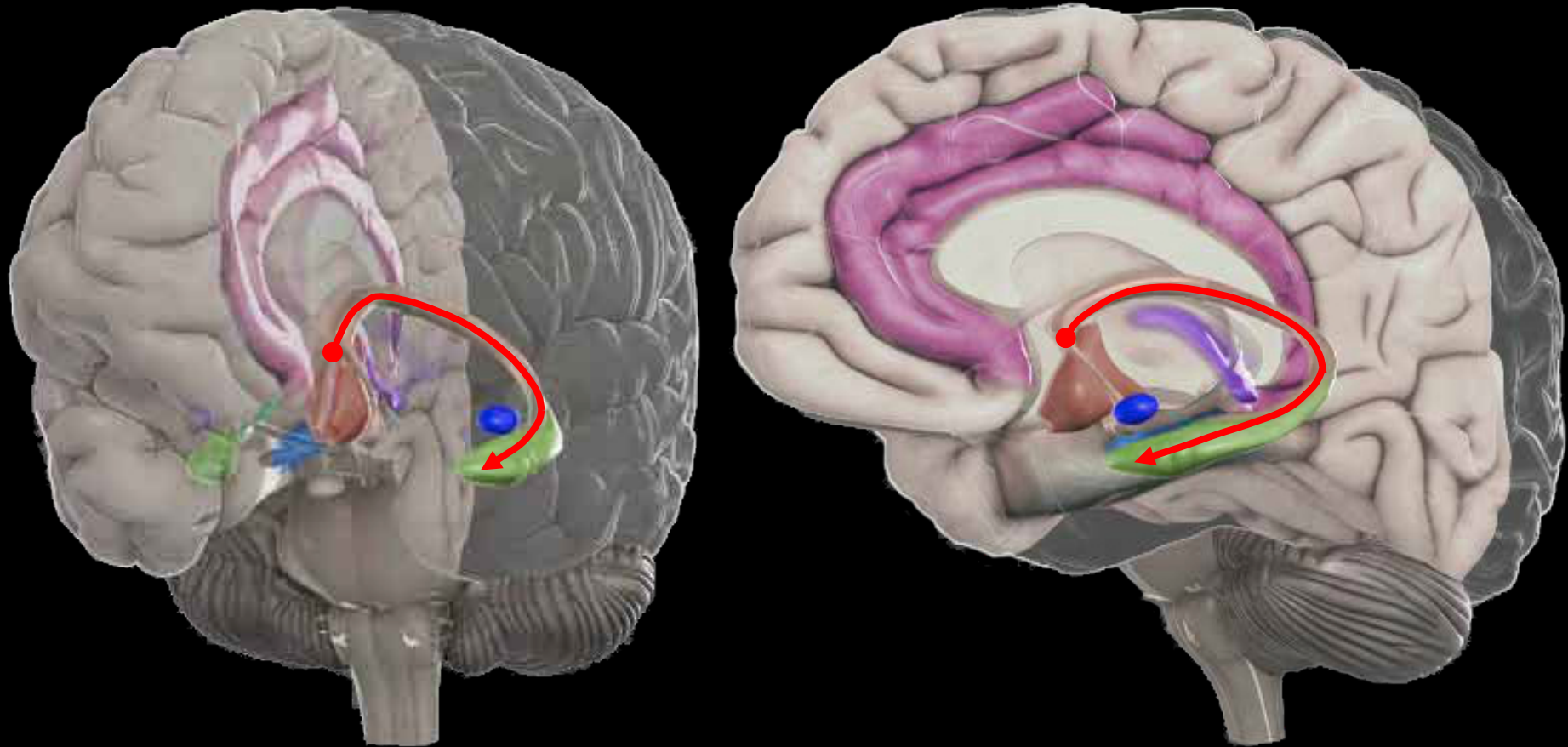
# Human Studies

- In the late 1990s and early 2000s, the Glasgow group performed several studies of TBI-induced alterations in cerebral cholinergic structure and function, which revealed:
  - reduced frontal, temporal, and parietal choline acetyltransferase (ChAT) within hours of TBI
  - bilateral reductions in ChAT persist for weeks after TBI
  - losses of Ch4 neurons (average of 40-50%) in 50-70% of persons with TBI examined at autopsy, with Ch4 neuronal losses greatest in those surviving longest
  - preservation of M1 and M2 receptors and of  $\alpha 4\beta 2$  and  $\alpha 7$  nicotinic receptors

# Human Studies

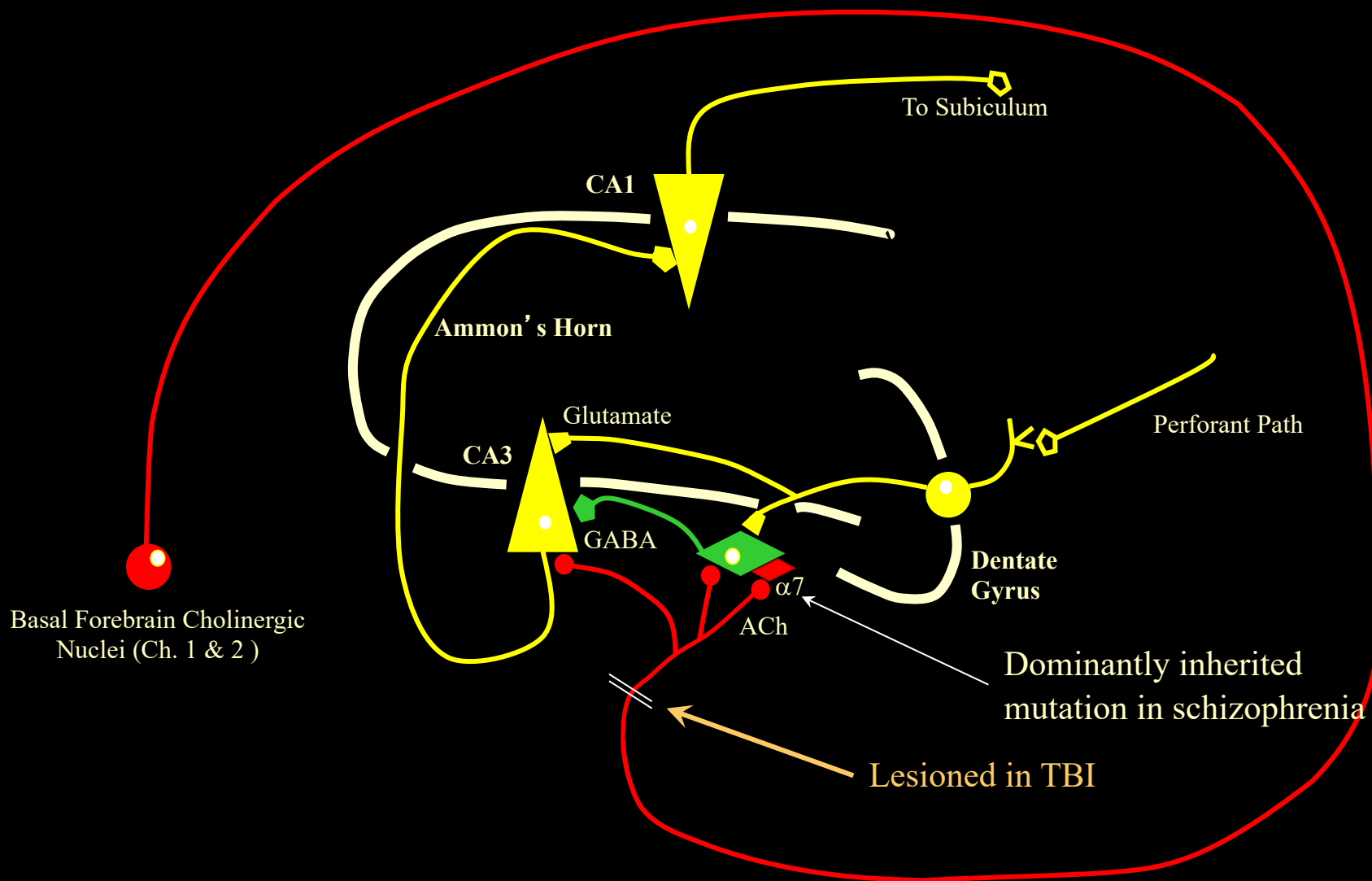
- Cholinergic projections from Ch1 and Ch2 (i.e., the septohippocampal pathway within the fornix) to the hippocampus are especially vulnerable to rotation-related shear-strain forces occurring during TBI in humans
- Acetylcholine is critically involved in the hippocampally-mediated, cholinergically-dependent process of declarative memory, and injury to the fornix is a common consequence of TBI - and one that is associated consistently with chronic posttraumatic memory deficits and other hippocampally-dependent cognitive processes

# Ch1-Ch2 to Septohippocampal Pathway



Near-coronal (left) and sagittal (right) views of the limbic system. Colors: pink – cingulate cortex; dark blue – amygdala; light blue – entorhinal cortex; green – hippocampus; tan – fornix and mammillary bodies; purple – epithalamus; brown – hypothalamus. Figure adapted from The G2C Brain, Cold Spring Harbor Laboratory (<http://www.g2conline.org/2022>).

# Neurocircuitry of P50 ERP





BRAIN INJURY, 1999, VOL. 13, NO. 1, 1-13

## Subject Review

Attention and memory dysfunction after traumatic brain injury: cholinergic mechanisms, sensory gating, and a hypothesis for further investigation

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(Received 5 July 1998; accepted 17 August 1998)

“Clinical and Electrophysiologic Investigation of Attention and Memory Dysfunction following Traumatic Brain Injury”

Department of Veterans Affairs, Veterans Health Administration, Office of R&D, Medical Research Service, Rehabilitation Research and Development, Research Career Development Award-1 (RR&D CDA-1)

PI: David B. Arciniegas, MD  
Co-I/Mentors: Martin L. Reite, MD, Lawrence E. Adler, MD, Christopher M. Filley, MD

Dates of Funding: 04/01/99 - 03/31/02

Project Description: This project investigated the electrophysiologic, neuroimaging, and neuropsychological bases of attention and memory dysfunction following traumatic brain injury.



# Subjects

- 18 - 60 years of age
- History of definable TBI: (non-penetrating, not requiring neurosurgical intervention, post-traumatic amnesia of at least 15 minutes, with or without loss of consciousness)
- TBI at least one year prior to study
- No neurologic, psychiatric, or substance problems prior to TBI
- No seizures following TBI
- Onset and persistence of symptoms consistent with impaired auditory gating following TBI
- No active mood, anxiety, or substance disorder at the time of recording
- Age and education adjusted MMSE  $\geq$  25th %-ile
- Glasgow Outcome Score  $\geq$  4



## Impaired Auditory Gating and P50 Nonsuppression Following Traumatic Brain Injury

David Arciniegas, M.D.  
Ann Olincy, M.D.  
Jeannie Topkoff, B.S.

Traumatic brain injury (TBI) can produce persistent attention and memory impairment that may in part be produced by impaired auditory sensory gating. The P50 evoked waveform response to paired auditory stimuli appears to be a useful measure of auditory gating. The first controlled measurement of the P50 ratio in TBI patients is described: when 20 patients with persistently symptomatic TBI were compared with 20 control subjects, the P50 ratio was significantly greater in the TBI group. The potential neurophysiologic and therapeutic implications of this finding in TBI patients who report symptoms consistent with impaired auditory gating are discussed.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2000; 12:77-85)

J Neuropsychiatry Clin Neurosci 12:1, Winter 2000

Traumatic brain injury (TBI) may produce persistently impaired auditory gating. This cholinergic-dependent, hippocampally mediated preattentive cognitive function that facilitates filtering of auditory stimuli may be indexed by the P50 evoked waveform to paired auditory stimuli. Abnormal P50 suppression post TBI is believed to result from injury to the hippocampus and/or its afferent cholinergic projections. This hypothesis was tested by comparing hippocampal and total brain volumes on MRI between ten P50-nonsuppressing TBI patients and ten normal control subjects matched for age, gender, and education. TBI subjects had highly significant bilateral hippocampal volume reductions, even when covaried for reductions in total brain volume. Degree of volume loss was not correlated with initial TBI severity. Findings support the hypothesis that hippocampal injury underlies P50 nonsuppression post TBI and suggest that such structural abnormalities may be observed even in "mildly" injured persons.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2001; 13:213-221)

J Neuropsychiatry Clin Neurosci 13:2, Spring 2001

## Reduced Hippocampal Volume in Association With P50 Nonsuppression Following Traumatic Brain Injury

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## The Cholinergic Hypothesis of Cognitive Impairment Caused by Traumatic Brain Injury

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Cognitive impairments are among the most common neuropsychiatric sequelae of traumatic brain injury at all levels of severity. Cerebral cholinergic neurons and their ascending projections are particularly vulnerable to acute and chronic traumatically mediated dysfunction. In light of the important role of acetylcholine in arousal, attention, memory, and other aspects of cognition, cerebral cholinergic systems contribute to and may also be a target for pharmacologic remediation among individuals with post-traumatic cognitive impairments. This article will review the evidence in support of this hypothesis. Evidence of relatively selective damage to cholinergic injury, the development of persistent anticholinergic sensitivity, and the effects of cholinergic augmentation on memory performance are presented first. Thereafter, neuropathologic, electrophysiologic, and pharmacologic evidence of cholinergic dysfunction after traumatic brain injury in humans is reviewed. Finally, future directions for investigation of the cholinergic hypothesis and possible clinical applications of this information are discussed.

### Introduction

Cognitive impairments are among the most common neuropsychiatric sequelae of traumatic brain injury (TBI) at all levels of severity, and typically include impairments of arousal, attention, memory, and executive functioning [1-4]. Although each of these domains of cognitive function may be disrupted by direct injury to cortical, subcortical, or brain stem elements of the distributed cerebral networks that support them, injury to the axons connecting these

elements or providing them with required for their function also automatic cognitive impairments [5,6].

The neurochemical bases of impairment are not completely understood, but dysfunction of glutamate, dopamine, norepinephrine, and acetylcholine (ACh) systems are contributors to such problems. Efference copy of these neurotransmitters or such alterations may contribute to cognitive impairment. In addition, other cognitive impairment may occur during the acute injury period. The evidence of these systems among persons with automatic cognitive impairments is an exception of that regarding the cerebral cholinergic hypothesis.

Cerebral cholinergic neurons (Fig. 1) are particularly vulnerable to chronic traumatically mediated dysfunction [17,18\*,19\*]. In the acute period, cholinergic excess is followed by cerebral ACh levels [13]. In light of the important role of ACh in arousal, attention, memory, and other aspects of cognition [21-24], dysfunctional cholinergic systems may be a substantial contributor to cognitive impairments and also a target for pharmacologic remediation among persons with post-traumatic cognitive impairments [25\*,26].

In the service of providing direction to the cholinergic hypothesis of cognitive impairment caused by TBI, this article will report of this hypothesis. Studies of experimental injury models, in which there is relatively selective damage to cholinergic neurons, have shown that the effects of persistent anticholinergic agents on memory performance are mediated by the effects of cholinergic augmentation. These effects are presented first. Thereafter, electrophysiologic and pharmacologic evidence of cholinergic dysfunction after TBI in humans is reviewed. Finally, future directions for investigation of the cholinergic hypothesis and possible clinical applications of this information are discussed.



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## Applications of the P50 evoked response to the evaluation of cognitive impairments after traumatic brain injury

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Each year in the United States, at least 500,000 people experience a traumatic brain injury (TBI) that requires hospitalization [1]. The cost associated with TBI at all levels of severity exceeds \$48 billion per year [2,3]. Most TBIs result from motor vehicle accidents, falls, and assaults [2]. Severe TBI accounts for only 7% to 10% of TBIs [4-7], but frequently produces deficits that are pronounced and profound. Physical, cognitive, and emotional disturbances are common in patients with severe TBI [8-10], and intensive rehabilitation services are provided routinely in the treatment of these patients [11].

Mild and moderate TBIs occur more often than severe TBI, and the deficits produced by these injuries frequently are more subtle, recognized less often, and debated more contentiously than injuries resulting from severe TBI [4-7,12,13]. Nonetheless, the neuropsychiatric disturbances experienced by persistently symptomatic mild TBI survivors may produce significant disturbances in everyday function and are costly for these individuals, their families, and society in general [3,14-17].

Cognitive impairments are among the most common neuropsychiatric sequelae of TBI at any level of severity and typically include impairments of

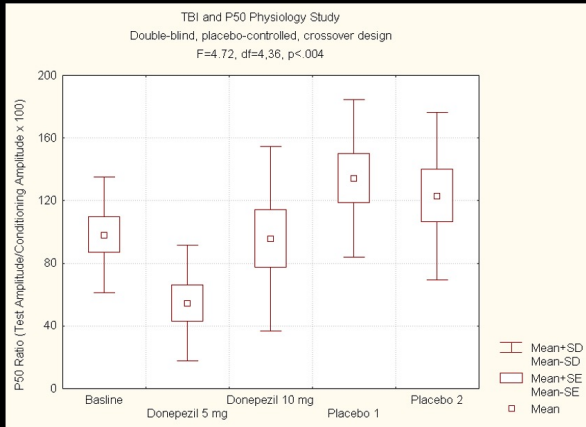
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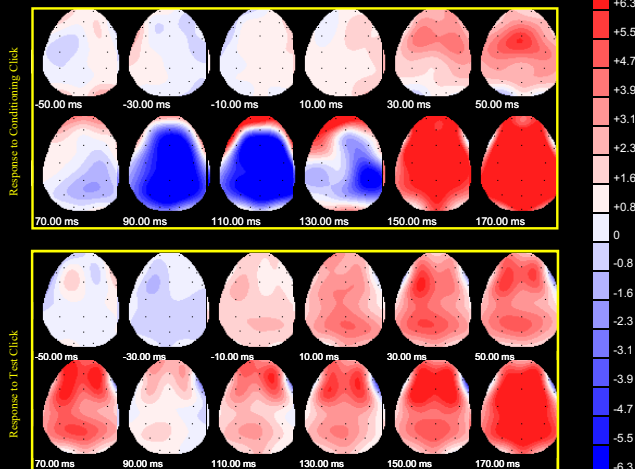
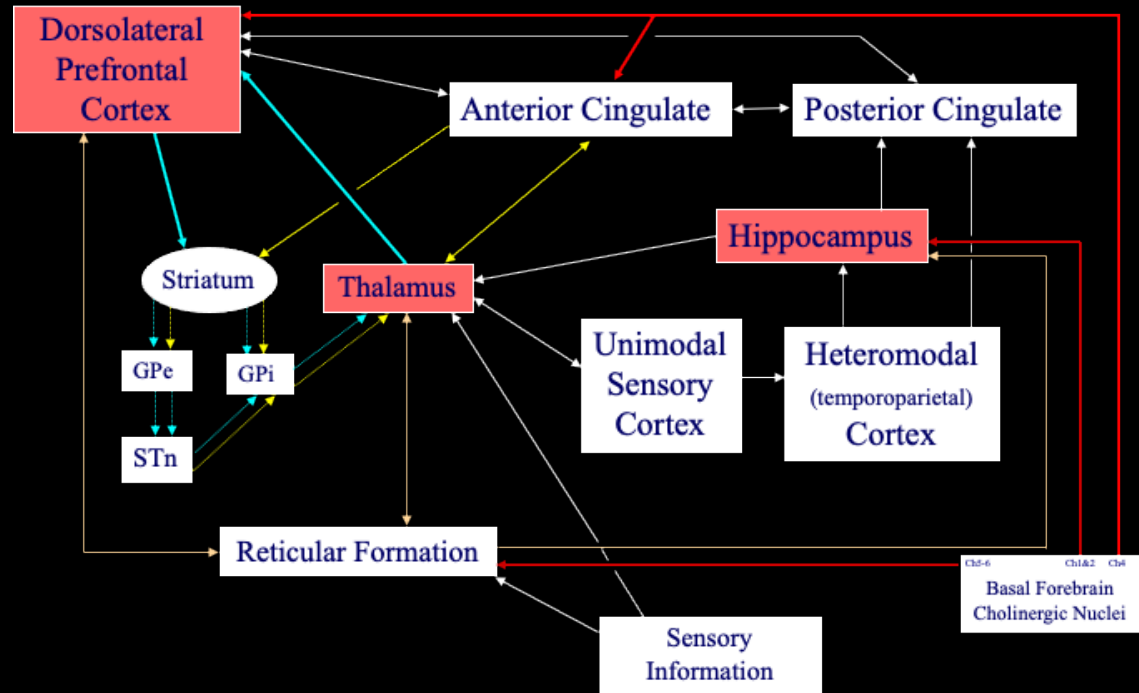
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# Proposed Model of Cholinergically-Dependent Network Nodes Contributing to Posttraumatic Cognitive Impairments



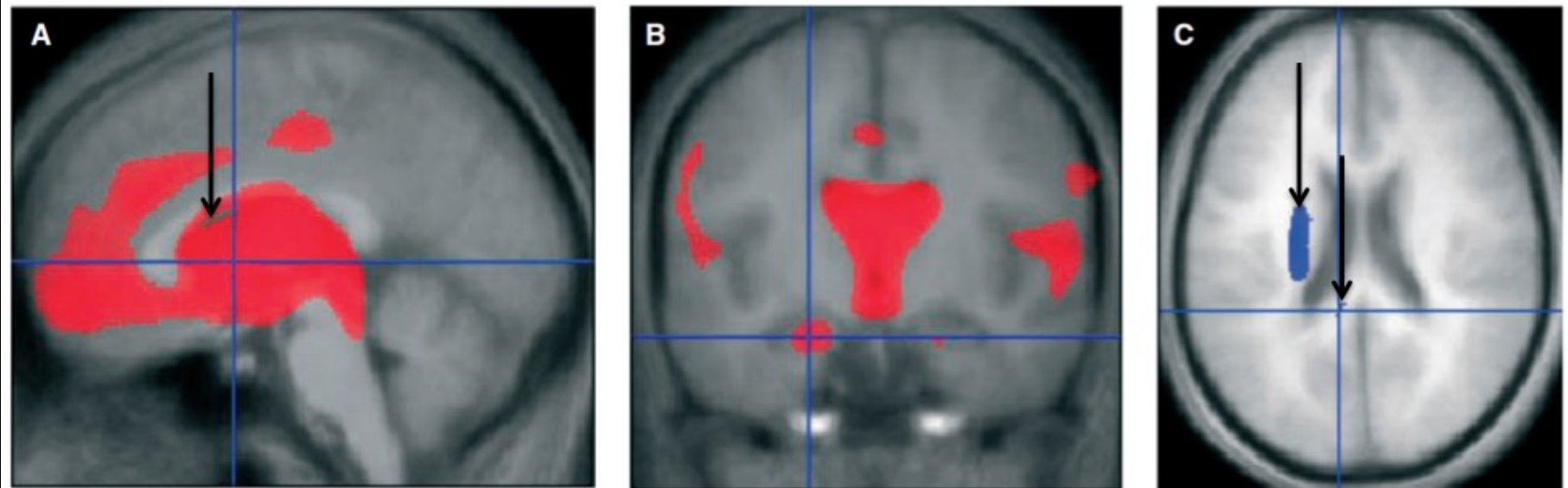
There was a significant effect of treatment condition on P50 ratio (F=4.7, df=4,36, p<.004), with relative normalization of P50 ratio during treatment with low-dose donepezil HCl but not high-dose donepezil HCl or placebo. Post-hoc analysis demonstrates a significant difference between donepezil HCl 5mg at all other conditions, but no difference between those other conditions. Cholinesterase inhibition using low-dose donepezil normalized P50 nonsuppression in 60% of subjects treated in this study. Responder rate changed to 30% during treatment with higher-dose donepezil. Arciniegas DB, Topkoff JL. Applications of the P50 evoked response to the evaluation of cognitive impairments following traumatic brain injury. *Physical Medicine and Rehabilitation Clinics of North America* 15:177-203, 2004.



# Human Studies

- Salmond and colleagues (2005) studied 31 individuals with moderate-to-severe TBI six or more months post-injury using neuropsychological metrics and voxel-based morphometric MRI of the brain
- The TBI group had impairments in processing speed, pattern and spatial recognition, and paired associate learning
- Their cognitive deficits correlated with:
  - gray matter reductions in Ch1, Ch2, Ch4, and Ch5-6
  - white matter density reductions in the septohippocampal pathway (Ch1 and Ch2 → hippocampus)
  - white matter density reductions in the medial and lateral capsular pathways (Ch4 → frontal and lateral temporal cortices)

# Salmond et al. (2005)



**Figure B.2.** Reductions in gray and white matter densities among persons with moderate-to-severe TBI and persistent posttraumatic cognitive impairments. Large area of altered signal in Panels A and B represent areas of decreased grey matter density. Dark areas in Panels A and C indicate areas of decreased white matter density (marked with arrows). In A, gray matter density reductions encompass the septal nuclei (Ch1 and Ch2) as well as the nucleus basalis of Meynert (Ch4), and reduction in the density of the septohippocampal pathway (fornix) is indicated with an arrow. In Panel C, reduced densities in the medial and lateral capsular pathways (Ch4 projections) also are visible. Adapted from Salmond CH, Chatfield DA, Menon DK, Pickard JD, Sahakian BJ. Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. *Brain* 128(Pt 1):189-200, 2005.

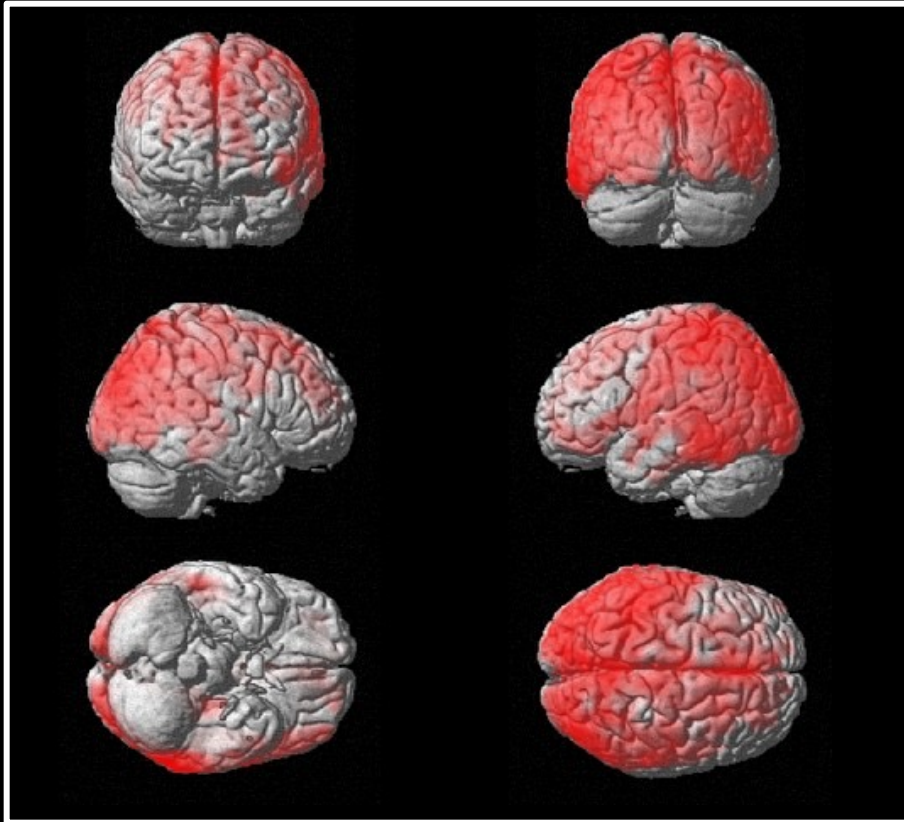
# Human Studies

- Salmond et al. (2006) subsequently studied 21 persons with moderate-to-severe TBI and a group of neurotypical comparators using neuropsychological assessments and two serial MRIs performed at least six months apart
- They observed stable and persistent impairments in memory, attention, and reaction time over the period of study (6-36 months post-injury)
- Gray and white matter reductions in the same locations and of similar severities as those in their prior study and remained stable from six to 36 months post-injury

# Östberg et al. (2011)

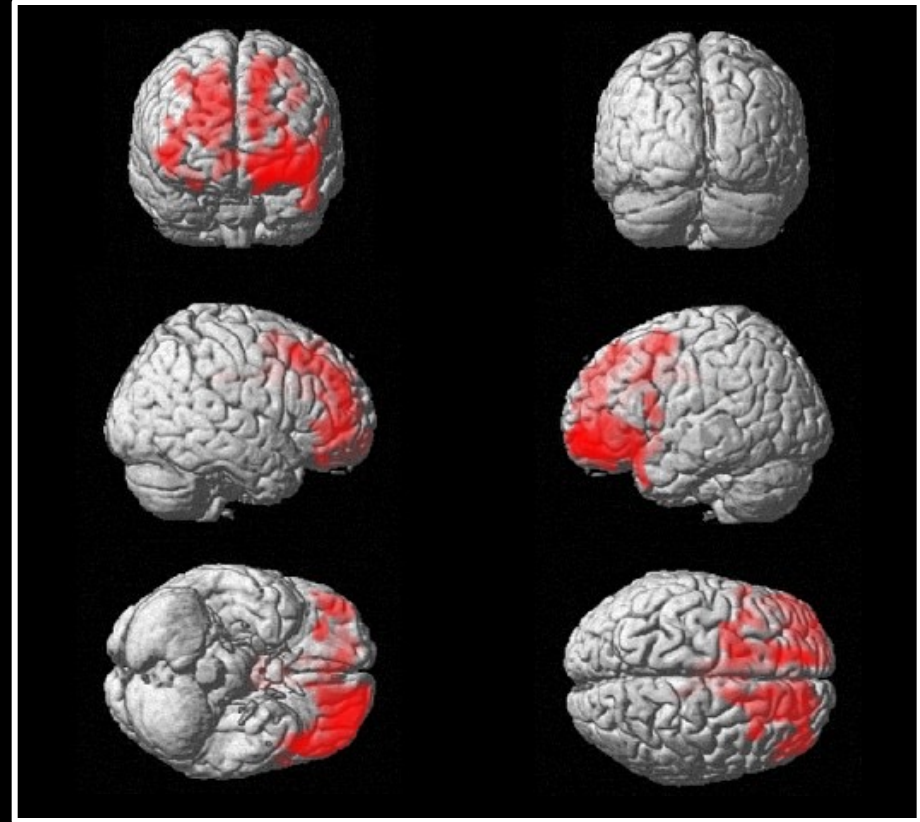
- Evaluated the integrity of the cerebral cholinergic system using  $^{11}\text{C}$ -MP4A PET (an ACh analog with high AChE specificity)
- Studied 17 participants with TBI and persistent postconcussive symptoms (attention deficit, memory impairment, diminished initiation, and fatigue) and 12 neurotypical comparators
- Observed widespread areas of decreased cortical acetylcholinesterase in a pattern consistent with those in the post-mortem studies of the Glasgow group (i.e., Dewar and Graham [1996], Murdoch et al. [1998, 2002])

## Östberg et al. (2011)



- Diffuse deficits in neocortical AChE among participants with TBI (vs. healthy uninjured comparators)

## Tenovuo et al. (2010)



- Focal deficits of AChE (a proxy for low levels of ACh) in frontal ROIs predict response to rivastigmine (an AChEI) among persons with TBI

# Injury Factors: Neurochemistry

- Persistent damage in and dysfunction of areas with dense glutamate and acetylcholine inputs
- Chronic primary cortical cholinergic dysfunction
  - damage to cerebral cholinergic nuclei<sup>1-3</sup>
  - loss of cholinergic afferents<sup>3,4</sup>
  - dysfunction of cholinergically-dependent information processing circuits<sup>5-8</sup>
- Possible chronic primary or secondary dysfunction in serotonin-, dopamine-, norepinephrine-dependent neuropsychiatric functions<sup>9</sup>



# *The Cholinergic Hypothesis of Cognitive Impairment due to TBI*

- Acetylcholine is necessary for normal cognition
- TBI results in cortical cholinergic deficits
- TBI-induced cortical cholinergic deficits contribute to posttraumatic cognitive impairments
- Augmentation of cortical cholinergic function may remediate posttraumatic cognitive impairments

# 27\* Peer-Reviewed Reports Describing AChEIs for Posttraumatic Cognitive Impairments

- **Physostigmine**
  - single-site double-blind placebo-controlled (2), open-label case series (1), single case (1) w/double-blind (1)
- **Donepezil**
  - Multicenter RCT (1), two-site double-blind placebo-controlled trial (1), single-site double-blind placebo-controlled trial (3), open-label case series (8), retrospective cohort design (1), single-case reports (2)
- **Rivastigmine**
  - multicenter RCT (1) with open-label extension (1), multicenter RCT (1), single-site double-blind placebo-controlled (1), open-label case series (1)
- **Galantamine**
  - open-label case series (1), open-label case reports (2), double-blind placebo-controlled trial (1)



# First Multicenter RCT of Donepezil for Persistent Posttraumatic Cognitive Impairments

- 1998: initial subject review and preliminary findings presented to Pfizer, Inc. (US distributor of donepezil)
  - development of multi-center RCT initiated
- 1999: Eisai, Inc. (manufacturer of donepezil) assumes control of project
  - used protocol based on previously conducted Alzheimer’s disease RCTs
  - engaged several well-known TBI clinicians and researchers as advisors – however, they largely ignored advice provided by their TBI advisors
  - used only a few well-established TBI clinical/research sites but many sites that participated in Eisai, Inc.’s Alzheimer’s disease RCTs (their “established investigators”)

# Donepezil RCT (cont.)

- 2000: Eisai, Inc. launches their 12-week multicenter RCT of Aricept™ (donepezil HCl) for persistent mild-to-moderate memory impairments after a single TBI launched
  - repeated changes in protocol undertaken as a result of (TBI consultant-anticipated) study design and execution problems
  - use of “ADAS-Cog-TBI,” concurrent medication restrictions, exclusions due to neuropsychiatric comorbidities, and substantial caregiver requirements present problems for study execution
  - study sites are under-funded
  - subjects unable to be recruited (7 subjects across 27 sites)
  - study terminated by Eisai, Inc. in early 2002

# Lessons from the Donepezil RCT

- Designing and conducting multicenter RCTs of medications for the treatment of neurobehavioral sequelae of TBI studies require investigators, consultants, and study sites with expertise and experience in the study of the neurobehavioral sequelae of TBI
- When entering a new area of research, it is prudent for sponsors to heed the reviews and advice offered by consultants with experience and expertise in the area under study (i.e., TBI)
- Alzheimer's disease clinical trials cannot be applied without modification to the study of treatments for the cognitive and non-cognitive neuropsychiatric sequelae of TB



# Multicenter Rivastigmine RCT

Articles

## Effects of rivastigmine on cognitive function in patients with traumatic brain injury

J.M. Silver, MD; B. Koumaras, BA; M. Chen, PhD; D. Mirski, MD; S.G. Potkin, MD; P. Reyes, MD; D. Warden, MD; P.D. Harvey, PhD; D. Arciniegas, MD; D.I. Katz, MD; and I. Gunay, MD

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**Abstract—Objective:** To compare the efficacy and safety of rivastigmine (3 to 6 mg/day) vs placebo over 12 weeks in patients with traumatic brain injury and persistent cognitive impairment. **Methods:** This prospective, randomized, double-blind, placebo-controlled study was conducted in 157 patients at least 12 months after injury. The primary efficacy measures were the Cambridge Neuropsychological Test Automated Battery (CANTAB) Rapid Visual Information Processing (RVIP) A' subtest and the Hopkins Verbal Learning Test (HVLT). The primary efficacy outcome was the proportion of patients who demonstrated 1.0 SD or greater improvement from baseline at week 12 on CANTAB RVIP A' or HVLT. **Results:** The percentage of responders at week 12 on either the CANTAB RVIP A' or HVLT was 48.7% for rivastigmine and 49.3% for placebo ( $p = 0.940$ ). Furthermore, for the overall study population, there were no significant differences for any of the secondary efficacy variables. In a subgroup of patients with moderate to severe memory impairment ( $n = 81$ ), defined as 25% impairment or greater on HVLT at baseline, rivastigmine was significantly better than placebo for a number of measures, including the proportion of HVLT responders and CANTAB RVIP mean latency. **Conclusions:** Rivastigmine was safe and well tolerated in patients with traumatic brain injury with cognitive deficits. Rivastigmine shows promising results in the subgroup of patients with traumatic brain injury with moderate to severe memory deficits.

# Multicenter Rivastigmine RCT

**Table 1** Demographic and baseline characteristics of the patients

Demographic characteristic	Rivastigmine (n = 80)	Placebo (n = 77)	p Value
Sex, n (%)			
Male	53 (66.3)	53 (68.8)	0.731
Female	27 (33.8)	24 (31.2)	
Race, n (%)			
White	71 (88.8)	69 (89.6)	0.458
Black	5 (6.3)	3 (3.9)	
Other	4 (5.0)	5 (6.5)	
Age, y			
Mean ± SD	37.0 ± 11.1	37.1 ± 9.8	0.975
Median (range)	37.5 (18–54)	38 (19–55)	
Time since most recent brain injury, months			
Mean ± SD	79.9 ± 78.7	103.4 ± 85.1	0.074
Median (range)	50.6 (12–365.6)	81.7 (13–392)	
Patient loss of consciousness, n (%)			
Yes	68 (85.0)	67 (87.0)	0.598
No	7 (8.8)	5 (6.5)	
Unknown	5 (6.3)	5 (6.5)	
Duration of loss of consciousness, days			
Mean ± SD	23.3 ± 32.8	22.5 ± 23.0	0.881
Score of best Glasgow Coma Scale within first 24 hours	n = 40	n = 36	
Mean ± SD	6.3 ± 3.0	6.8 ± 4.0	0.555
Median (range)	6.0 (3.0–15.0)	5.5 (3.0–15.0)	

**Table 1** Demographic and baseline characteristics of the patients

Demographic characteristic	Rivastigmine (n = 80)	Placebo (n = 77)	p Value
Patient loss of memory, n (%)			
Yes	65 (81.3)	69 (89.6)	0.928
No	5 (6.3)	5 (6.5)	
Unknown	10 (12.5)	3 (3.9)	
Duration of post-traumatic amnesia, days			
Mean ± SD	50 ± 71.4	71.4 ± 100.5	0.245
Alteration in mental state, n (%)			
Yes	73 (91.3)	72 (93.5)	0.672
No	3 (3.8)	2 (2.6)	
Unknown	4 (5.0)	3 (3.9)	
WAIS-III vocabulary score			
Mean ± SD	10.1 ± 2.8	9.7 ± 2.8	0.374
Median (range)	10.0 (4.0–16.0)	10.0 (5.0–18.0)	
WAIS-III information score			
Mean ± SD	10.0 ± 3.0	9.9 ± 2.9	0.892
Median (range)	10.0 (5.0–17.0)	10.0 (5.0–18.0)	
WAIS-III summed information and vocabulary			
Mean ± SD	20.2 ± 5.4	19.7 ± 5.2	0.588
Median (range)	20.0 (9.0–32.0)	20.0 (11.0–33.0)	

WAIS = Wechsler Adult Intelligence Scale.

# Multicenter Rivastigmine RCT

- Overall study group (n=157) composed of persons with either impaired attention, impaired memory, or both
  - no treatment effect
- Based on our prior argument regarding high probability acetylcholinesterase-responsive target symptoms, post-hoc comparison of the memory impaired subgroup (n=81) was performed
  - rivastigmine 3-6 mg daily improved memory and speed of processing
  - numeric (but not significant) improvement on measures of attention, executive function, mood, QoL, and on CGI – study was underpowered to test efficacy on these outcomes





# Rivastigmine Open-Label Extension Study

## Long-term effects of rivastigmine capsules in patients with traumatic brain injury

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STEVEN G. POTKIN<sup>3</sup>, PATRICIO F. REYES<sup>4</sup>, PHILIP D. HARVEY<sup>5</sup>,  
DOUGLAS I. KATZ<sup>6,7</sup>, IBRAHIM GUNAY<sup>2</sup>, & DAVID B. ARCINIEGAS<sup>8,9</sup>

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### Abstract

**Objective:** To investigate the safety, tolerability and efficacy of rivastigmine capsules (3–12 mg/day) in a 26-week, multi-centre, open-label extension of a double-blind study.

**Methods:** Patients with traumatic brain injury (TBI) and persistent cognitive impairment who had received rivastigmine (3–6 mg/day) or placebo for 12 weeks could enter the extension study and receive rivastigmine ( $\leq 12$  mg/day). Patients were assessed using a range of cognitive tests including the Hopkins Verbal Learning Test (HVLT) and the Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing (CANTAB RVIP) A' sub-test. Safety measures included monitoring of adverse events.

**Results:** In the extension study ( $n = 127$ ), the mean duration of rivastigmine treatment was 23.8 weeks and the mean final dosage was 7.9 mg/day. Approximately 40% of patients were responders ( $\geq 1.0$  SD improvement from baseline) on CANTAB RVIP A' or HVLT total score at week 38 or endpoint. Statistically significant changes from week 12 at week 38 were observed for CANTAB-RVIP A' and HVLT-total word recall for the sub-group of ex-placebo patients with greater severity of initial impairment. The safety profile of rivastigmine capsules was consistent with the label.

**Conclusions:** Treatment with rivastigmine for up to 38 weeks was safe in patients with TBI and cognitive impairment.

**Keywords:** traumatic brain injury, open-label extension, rivastigmine, safety, efficacy

*Brain Injury*, February 2009; 23(2): 123–132

- 127 subjects from RCT enter the 26-week OLE study
  - 62 from placebo group
  - 65 from rivastigmine group
- Treatment with rivastigmine ( $\leq 12$  mg/day)
  - mean dose 7.9 mg/day
- Identical evaluation protocol to RCT

# Rivastigmine Open-Label Extension Study

- At low dose (rivastigmine 3-6 mg daily)
  - approximately 50% of subjects responded to treatment
  - posttraumatic memory impairment was the best primary target for cholinergic augmentation
- At higher doses (rivastigmine  $\geq$  6 mg/day)
  - approximately 40% of subjects responded to treatment
  - cognitive benefits of cholinergic augmentation were broader, and included improvements in attention, speed of processing, memory, and executive function



# MEMRI-TBI-D Study

[Study Details](#)

[Tabular View](#)

[No Results Posted](#)

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[? How to Read a Study Record](#)

## Study Description

Go to

### Brief Summary:

This is a four-site, randomized, parallel design, double-blind, placebo-controlled, 10-week trial of donepezil 10 mg daily for verbal memory problems among adults with TBI in the subacute or chronic recovery period. The study will recruit 160 persons with TBI and functionally important memory problems during a four-year period of open recruitment.

The study aims are:

1. To evaluate the effects of treatment with donepezil on verbal memory as assessed by the Hopkins Verbal Learning Test-Revised Total Trial 1-3;
2. To evaluate the effects of treatment with donepezil on memory-related activities as measured by the Everyday Memory Questionnaire;
3. To evaluate the effects of donepezil on attention, processing speed, neuropsychiatric symptoms, community participation, quality of life, and caregiver experiences.

<a href="#">Condition or disease</a>	<a href="#">Intervention/treatment</a>	<a href="#">Phase</a>
Traumatic Brain Injury	Drug: Donepezil	Phase 3
Memory Deficits	Drug: Placebo	

▶ Show detailed description

## Study Design

Go to

[Study Type](#) : Interventional (Clinical Trial)

[Estimated Enrollment](#) : 160 participants

[Allocation](#): Randomized

[Intervention Model](#): Parallel Assignment

[Masking](#): Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

[Primary Purpose](#): Treatment

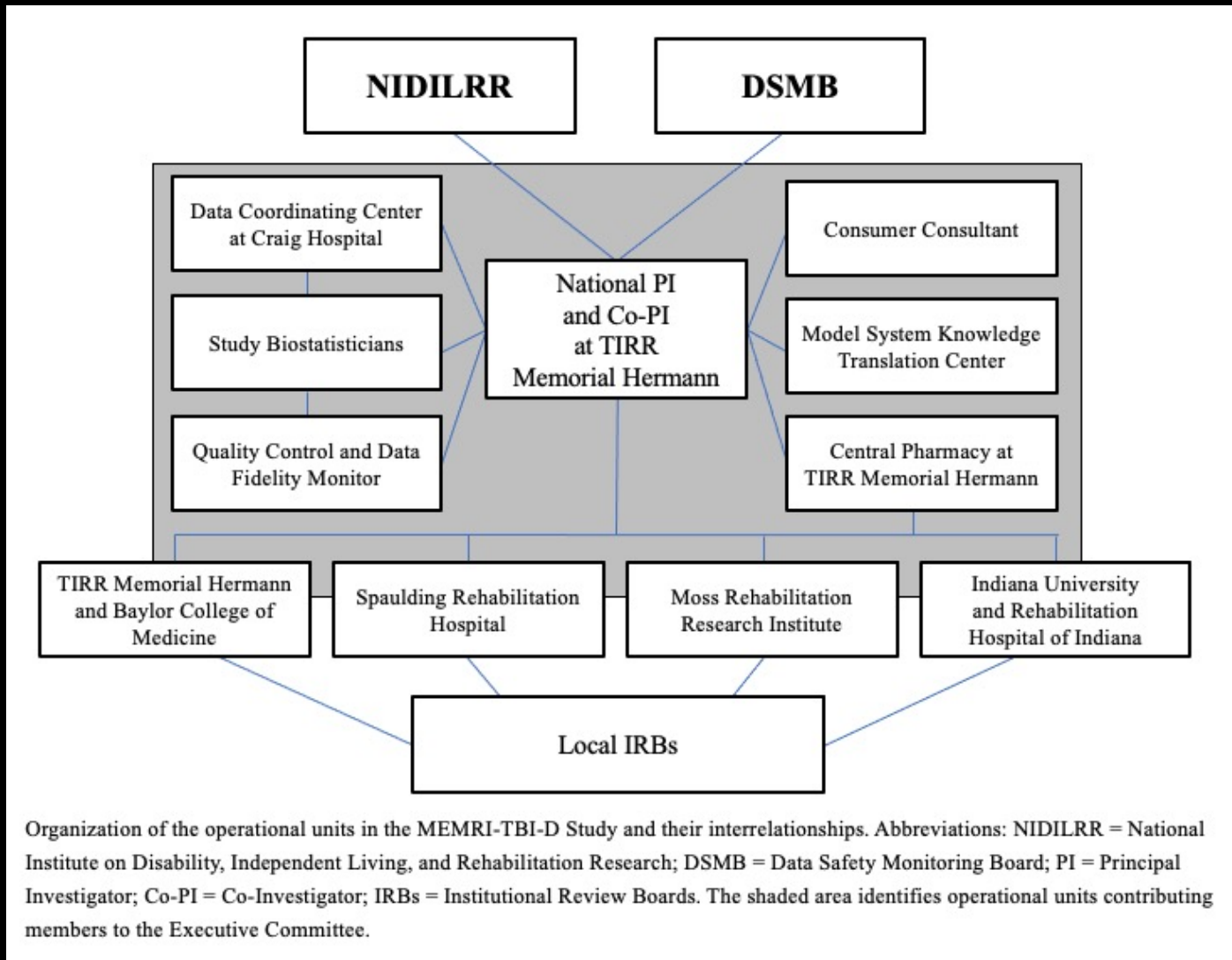
[Official Title](#): Four-site, Randomized, Parallel Design, Double-blind, Placebo-controlled, 10-week Trial of Donepezil 10 mg Daily for Verbal Memory Problems Among Adults With TBI in the Subacute or Chronic Recovery Period

[Actual Study Start Date](#) : October 1, 2013

[Actual Primary Completion Date](#) : January 13, 2020

[Estimated Study Completion Date](#) : August 2, 2020

# MEMRI-TBI-D Study



# Meta-Analysis of AChEIs on Verbal Memory Deficits after TBI

- The systematic review entailed a PubMed search following the strategy described in Arciniegas and Silver (2006)
- Initial abstract review identified and excluded review articles, pre-clinical (i.e., non-human) studies, and studies focused on or including conditions other than TBI
- Remaining articles were included if:
  - (1) TBI diagnoses were documented unequivocally
  - (2) TBI-related verbal memory impairments were present at study entry
  - (3) an AChEI was used to treat verbal memory impairments
  - (4) valid and reliable verbal memory measures were employed prior to and at the end of AChEI treatment
  - (5) placebo-treated comparison subjects and/or active-treatment comparators were included
  - (6) results reported enabled effect size estimations

# Meta-Analysis of AChEIs on Verbal Memory Deficits after TBI

Report	Design	TBI Severity	TSI (mos.)	Sample Size	Medication	Outcome Measure	Relevant Obs.	Cohen's <i>d</i>
Levin et al. (1986)	Single-site, double-blind, placebo-controlled, crossover	m-sTBI	1-12	16	Physostigmine	SRT-LTS	32	-0.01
Cardenas et al. (1994)	Single-site, double-blind, placebo- and active-comparator controlled, three-condition crossover	m-sTBI	≥ 3	36	Physostigmine	SRT-LTS	72	1.30
Zhang et al. (2004)	Two-site, randomized, double-blind, placebo-controlled, crossover	mTBI, m-sTBI	2-24	18	Donepezil	WMS-III AII	18	4.84
Silver et al. (2006)	Multicenter, randomized, double-blind, placebo-controlled	mTBI, m-sTBI	≥ 12	81	Rivastigmine	HVLT-R Total Trials 1-3	81	0.50
Kim et al. (2009)	Single-site, randomized, active comparator	m-sTBI	1-12	26	Donepezil	WMS	26	1.06

**Table B.2.** Effect sizes (Cohen's *d*) associated with acetylcholinesterase inhibitor treatment of memory impairments among persons with traumatic brain injuries (TBI) in the subacute and chronic recovery periods. **Abbreviations:** TSI=time since injury; mos.=months; Rel. Obs.=number of relevant observations; mTBI=mild TBI; m-sTBI=moderate-to-severe TBI; SRT-LTS= Selective Reminding Test-Long Term Storage; WMS = Wechsler Memory Scale; WMS-III = Wechsler Memory Scale – III; AII = Auditory Immediate Index; HVLT-R = Hopkins Verbal Learning Test-Revised.

Five studies, representing 229 drug-comparator observations, met criteria for inclusion in this meta-analysis. **Weighted mean Cohen's *d* = 0.83 (95% CI: 0.56-1.10)**

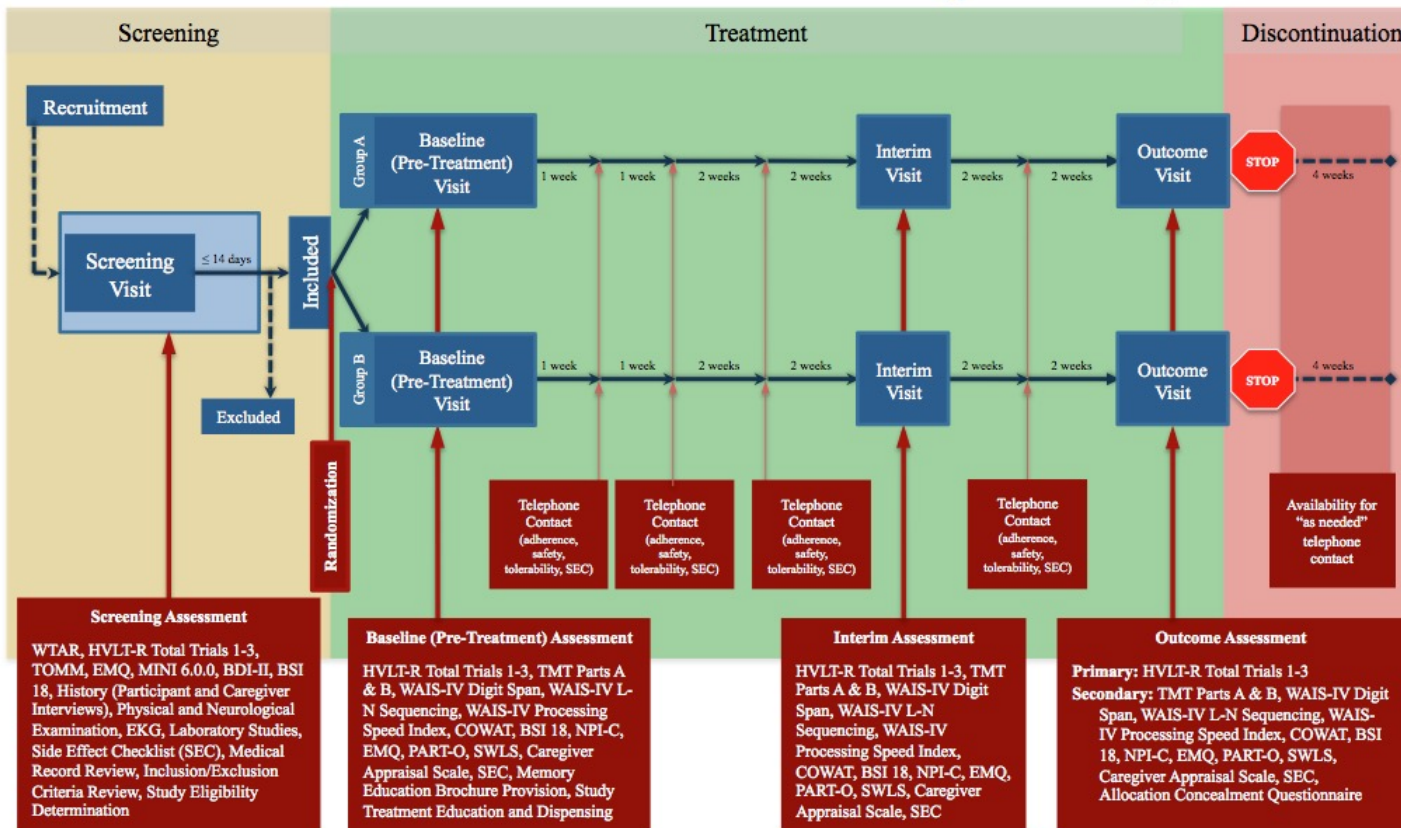
# AChEI Tolerability in TBI

- Across the 24 studies evaluated for inclusion in our meta-analysis, **743** persons with TBI received AChEI treatment
  - gastrointestinal (nausea, diarrhea) and urinary (frequency) side effects are common; headache, dizziness, fatigue, arthralgias/myalgias, and behavioral symptoms (anxiety, sleep disturbance) are observed but less common
  - in the largest and most assiduously performed RCT of any of these agents (Silver et al. 2006), the frequency of treatment-related adverse events not differ between rivastigmine and placebo
  - there were zero observed or suspected adverse effects on cardiac function or cardiac conduction parameters in this cohort of 743 persons with TBI
  - all adverse event-related discontinuation rate in this sample of 743 persons with TBI is 13.8% (103/743)

# MEMRI-TBI-D Study



## The MEMRI-TBI-D Study Design



**Figure B.3 - Revised.** Flow diagram of the Multicenter Evaluation of Memory Remediation after Traumatic Brain Injury with Donepezil Study (MEMRI-TBI-D Study). The flow of participants through the study occurs in three phases: Screening, Treatment, and Discontinuation. Assessments performed during each phase and the timelines for their performance are described in association with the flow arrows through each. Group A is allocated to donepezil, Group B is allocated to placebo.



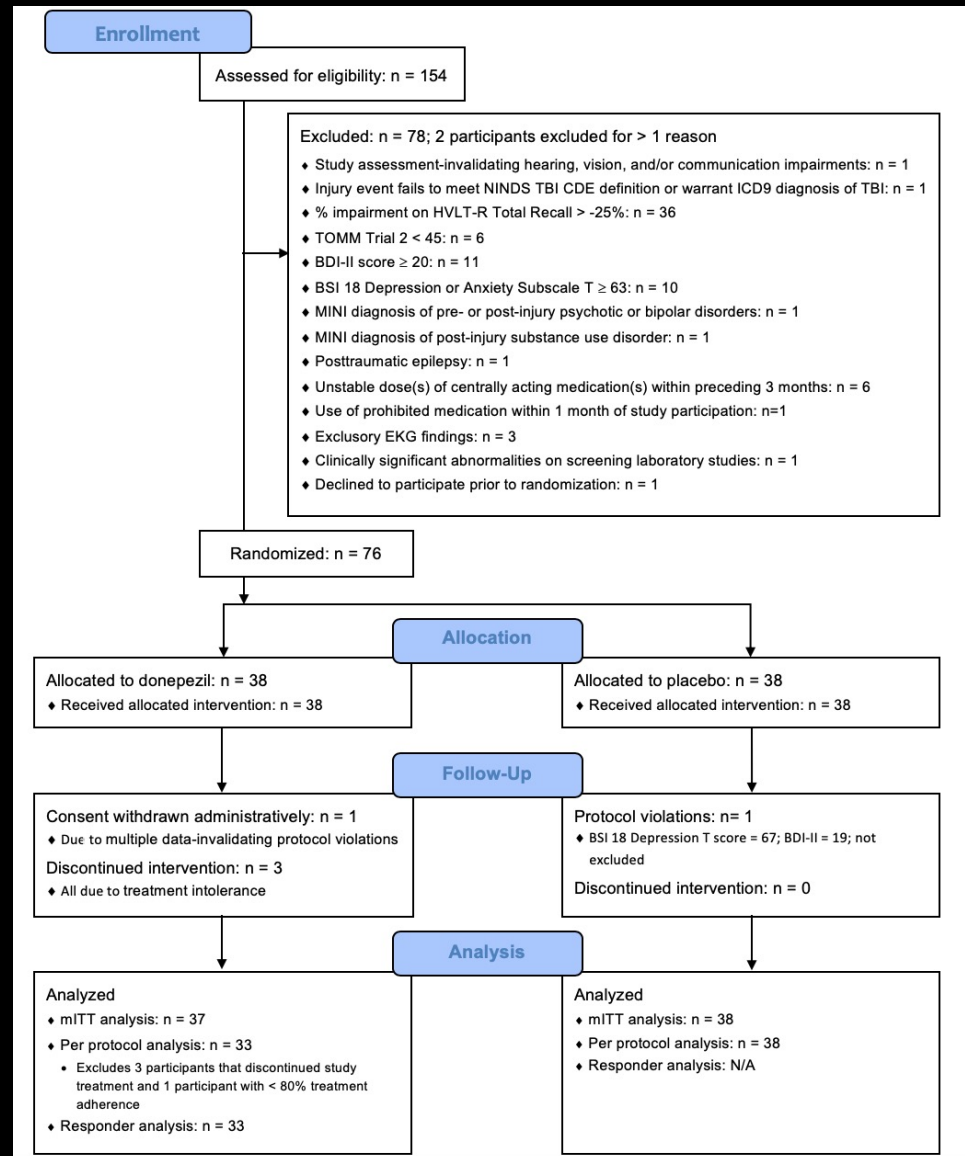
# MEMRI-TBI-D Study

## Inclusion Criteria

- Man or woman of any race, color, ethnicity, or national origin
- 18-60 years old
- Primary language English
- Clinical diagnosis of traumatic brain injury
  - anchored to the National Institute of Neurological Disorders and Stroke TBI Common Data Elements definition of TBI and meriting assignment of ICD-9-CM codes 850.0-850.9, 851.0, 851.2, 852.0, 852.2, 852.4, 853.0, or 854.0
- Non-penetrating TBI
- Complicated mild, moderate, or severe TBI
- TBI occurred at least 6 months prior to study participation
- Persistent posttraumatic memory impairment, as defined by HVLT-R Total Trials 1-3 (Form 3 T-score  $\geq 25\%$  below performance expectations based on WTAR T-score)
- Memory impairments are functionally significant, as defined by participant and/or caregiver endorsement of at least 3 memory problems, occurring at least weekly, on the EMQ
- Stable doses of allowed centrally-acting medications (i.e., medications acting on the central nervous system) for at least 3 months prior to study participation
- Availability and willingness of a knowledgeable informant (caregiver) to attend study visits or to provide required information by telephone interview on the day of study visits
- Participant and caregiver commitment not to alter doses of allowed medications during the study

## Exclusion Criteria

- Hearing, vision, and/or communication impairments that invalidate neuropsychological or other study assessments
- Pre-injury neurological and/or neurocognitive disorder
- Penetrating brain injury or cerebral lobectomy
- Primary diagnosis of hypoxic-ischemic brain injury or clinically definite post-TBI hypoxic-ischemic event (i.e., respiratory arrest and/or cardiac arrest) or non-TBI-related stroke
- Posttraumatic epilepsy (i.e., recurrent unprovoked seizures)
- Beck Depression Inventory-II (BDI-II) score  $\geq 20$  (i.e., moderate or severe depression) or BDI-II item 9 ("Suicidal Thoughts or Wishes")  $> 0$
- Brief Symptom Inventory 18 (BSI 18) Depression Subscale or Anxiety Subscale T score  $\geq 63$
- Pre- or post-injury psychotic and/or bipolar disorders
- Post-injury substance use disorder (i.e., alcohol abuse or dependence diagnoses as well as other substance abuse or dependence diagnoses)
- Test of Memory Malingering (TOMM) Trial 2 score  $< 45$  (i.e., suboptimal effort on testing)
- Active, severe, or unstable pulmonary condition, including severe asthma
- Signs or symptoms of gastrointestinal bleeding or active peptic ulcer disease within three months prior to study participation
- Use of a prohibited medication in the month prior to study participation
- Known allergy to donepezil, or documented intolerance to donepezil
- Symptomatic bradycardia, cardiac conduction abnormality (i.e., first- or second-degree atrioventricular blockade Mobitz type I), atrial fibrillation, or unstable cardiovascular disease, including myocardial infarction within three months prior to study participation
- Clinically significant abnormalities on screening laboratory studies
- For female participants, serum human chorionic gonadotropin (HCG)-confirmed pregnancy or unable/unwillingness to use barrier contraception during study participation, intrauterine device, or other implantable contraceptive method, or unable/unwilling to forego breastfeeding infants or children during study participation.



# MEMRI-TBI-D Study

	mITT Sample					
	Donepezil (n=37)			Placebo (n=38)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	35.57	12.40	(18, 59)	39.11	11.56	(21, 58)
Education (years)	14.11	2.31	(10, 19)	14.03	2.39	(9, 19)
	Median	IQR	Range	Median	IQR	Range
Time Since Injury (months)	45.00	(23, 90)	(6, 206)	41.50	(14, 116)	(7, 349)

	mITT Sample			
	Donepezil (n=37)		Placebo (n=38)	
	Count (n)	%	Count (n)	%
<b>Sex</b>				
Male	25	67.6%	31	81.6%
Female	12	32.4%	7	18.4%
<b>Severity</b>				
Complicated Mild	0	0.0%	1	2.6%
Moderate	2	5.4%	4	10.5%
Severe	35	94.6%	33	86.8%
<b>Marital Status</b>				
Never Married	21	56.8%	24	63.2%
Married/Partnered	12	32.4%	12	31.6%
Divorced	4	10.8%	2	5.3%
<b>Employment Status</b>				
Employed	12	32.4%	9	23.7%
Not Employed	25	67.6%	29	76.3%
<b>Race / Ethnicity</b>				
Hispanic or Latino	8	21.6%	3	7.9%
American Indian	1	2.7%	0	0.0%
Asian	0	0.0%	0	0.0%
African American	3	8.1%	5	13.2%
Native Hawaiian or other Pacific Islander	0	0.0%	0	0.0%
White	34	91.9%	32	84.2%
<b>Site of Residence</b>				
Private residence	35	94.6%	37	97.4%
Assisted Living	0	0.0%	1	2.6%
College Dormitory	2	5.4%	0	0.0%

# MEMRI-TBI-D Study

- mITT analysis ( $n = 75$ ) of donepezil efficacy on HVLT-R Total Trials 1-3 (primary outcome, LOCF), adjusted for baseline performance, age, education, and time since injury:
  - $t = 1.85, p < 0.04$ , effect size  $d = 0.46$
- Per Protocol analysis (completers,  $\geq 80\%$  adherence,  $n = 71$ ) of donepezil efficacy on HVLT-R Total Trials 1-3, adjusted for baseline performance, age, education, and time since injury:
  - $t = 1.88, p < 0.04$ , effect size  $d = 0.46$
- Responder analysis, with MCID set at  $\geq 0.5$  SD improvement over baseline performance:
  - 42% donepezil responders vs. 18% placebo responders (Chi-square = 4.9,  $p < 0.03$ ),  $NNT = 3.5$

# MEMRI-TBI-D Study

	Responder Analysis Sample					
	Responders (n=14) vs. Nonresponders (n=19)					
	Baseline Adjusted			Fully Adjusted		
	ES	t (* $\chi^2$ )	p	ES	t (* $\chi^2$ )	p
<b>Cognitive Outcomes</b>						
HVLT-R Total Trials 1-3 (Total Recall) (raw)	<b>2.6</b>	<b>7.45</b>	<b>0.001</b>	<b>2.52</b>	<b>6.95</b>	<b>0.001</b>
HVLT-R Delayed Recall (raw)	<b>1.64</b>	<b>4.61</b>	<b>0.001</b>	<b>1.59</b>	<b>4.41</b>	<b>0.001</b>
HVLT-R Recognition Discrimination Index	0.52	1.48	0.074	0.47	1.32	0.098
HVLT-R Retention (raw)	0.58	1.61	0.058	0.50	1.37	0.090
Trail Making Test Part A – T score	0.50	1.25	0.110	0.33	0.91	0.186
Trail Making Test Part B – T score	0.52	1.46	0.077	0.52	1.42	0.083
Trail Making Test Part A – Time* (sec)	0.92	2.03	0.077	0.97	0.22	0.318
Trail Making Test Part B – Time* (sec)	<b>0.75</b>	<b>46.03</b>	<b>0.001</b>	<b>0.80</b>	<b>27.44</b>	<b>0.001</b>
WAIS-IV DS Total	0.41	-1.14	0.869	0.50	-1.37	0.914
WAIS-IV DS Forward – Longest Span (raw)	0.07	0.19	0.426	0.09	-0.28	0.600
WAIS-IV DS Forward Total (raw)	0.29	-0.81	0.788	0.37	-1.02	0.843
WAIS-IV DS Backward – Longest Span (raw)	0.41	-1.13	0.816	0.54	-1.43	0.919
WAIS-IV DS Backward Total (raw)	0.49	-1.37	0.909	0.57	-1.58	0.937
WAIS-IV Symbol Search (raw)	0.03	0.07	0.471	0.04	-0.12	0.548
WAIS-IV Coding (raw)	0.35	1.00	0.162	0.29	0.81	0.213
WAIS-IV Processing Speed Index	0.23	0.64	0.263	0.15	0.40	0.345
WAIS-IV LNS (raw)	0.25	0.68	0.250	0.15	0.41	0.342
COWAT (raw score) <sup>△</sup>	0.45	1.27	0.107	0.54	1.45	0.08

**Efficacy of donepezil on cognitive outcomes at week 10 among persons with persistent verbal memory impairments after TBI in the Responder Analysis Sample.** For the ANCOVA in the Responder Analysis Sample, two models are presented: Baseline Adjusted, in which baseline performance on the measure of interest is entered as a covariate; and Fully Adjusted, in which baseline performance on the measure of interest, age (years), and education (years) are entered as covariates. Bolded items indicate results significant at  $p < 0.05$ , and red indicates effect sizes ( $d$ -family) of 0.2 (or greater) favoring donepezil. Abbreviations: HVLT-R = Hopkins Verbal Learning Test-Revised (raw scores); WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition; DS = Digit Span; LNS = Letter-Number Sequence; COWAT = Controlled Oral Word Association Test (aka FAS Test). \* indicates that the ANCOVA model assumed a Poisson distribution for the outcome and a log link function. <sup>△</sup> indicates that TMT-A Time (as a measure of processing speed) was used as an additional covariate to improve the estimate of effect on executive function rather than the combination of executive function and processing speed otherwise represented by Controlled Oral Word Association Test performance.  $p$  values here are  $p = x$ ; ES is absolute value;  $t$  values and ES are rounded to two decimal places in the Per Protocol Sample and to three decimal places in the Responder Analysis Sample; ES in red indicates Cohen's  $d \geq 0.2$  in favor of donepezil. (Manuscript in preparation).

# MEMRI-TBI-D Aim 3 (Non-Cognitive Neuropsychiatric) Results

	Per Protocol Sample Donepezil (n=33) vs. Placebo (n=38)					
	Model 1			Model 2		
	ES	$\chi^2$	<i>p</i>	ES	$\chi^2$	<i>p</i>
<i>Neuropsychiatric Inventory Domain</i>						
Aberrant Motor Disturbances	0.125	1.05	0.847	0.028	2.06	0.924
Agitation	0.524	0.75	0.806	0.885	0.06	0.600
Aggression	0.352	5.92	0.993	0.418	4.12	0.979
Anxiety	1.042	0.01	0.472	<b>3.846</b>	<b>2.86</b>	<b>0.045</b>
Apathy	0.272	3.26	0.965	0.353	1.69	0.903
Appetite and Eating Disorders	1.053	0.04	0.418	1.176	0.28	0.298
Disinhibition	<b>7.937</b>	<b>5.53</b>	<b>0.009</b>	<b>3.745</b>	<b>10.26</b>	<b>0.001</b>
Dysphoria	0.459	2.04	0.924	0.493	1.59	0.896
Irritability/Lability	1.370	0.77	0.160	1.390	0.78	0.188
Sleep Disorders	0.602	3.26	0.965	0.556	2.87	0.955
Total Score	0.629	2.81	0.953	0.645	2.51	0.946

**Efficacy of donepezil on Neuropsychiatric Inventory scores at week 10 among persons with persistent verbal memory impairments after TBI.** Two models of ANCOVA results for Per Protocol Sample (donepezil n = 33, placebo n = 38). Model 1 is an ANCOVA that assumes equal slopes and compares between-group scores on each Neuropsychiatric Inventory domain score at week 10, adjusted for baseline scores on that NPI domain. This model assumed a Negative Binomial distribution for the outcome and a zero-inflated model to accommodate for excessive number of outcomes zeros. Model 2 extends this comparison to include adjustment for time since injury (in months). Effect sizes are expressed 1 over as the baseline-adjusted ratio of week 10 scores in the donepezil group versus the placebo group, and one-sided *p* values are expressed in relation to the hypothesis that donepezil efficacy on neuropsychiatric symptoms is greater than that of placebo. Bolded items indicate results significant at  $p < 0.05$ , and red indicates effect sizes (*d*-family) of 0.2 (or greater) favoring donepezil Note: There were insufficient numbers of participants with scores  $> 0$  in the Aberrant Vocalizations, Euphoria, Delusions, and Hallucinations domains to permit valid preliminary analysis of donepezil efficacy on symptoms in these neuropsychiatric domains. Given the exploratory nature of this analysis, the finding of donepezil efficacy on disinhibition and anxiety in Model 2 must be regarded as preliminary, at best.

# MEMRI-TBI-D Study: Treatment-Emergent AEs: >5%

	Treatment-Emergent Adverse Events (X%)		Persistent Treatment-Emergent Adverse Events (% of X%)		Severity of Treatment-Emergent Adverse Events (Mild / Moderate / Severe)	
	Donepezil	Placebo	Donepezil	Placebo	Donepezil	Placebo
Agitation	10.8	2.6	75	100	2 / 2 / 0	1 / 0 / 0
Diarrhea*	13.5	0	20	-	1 / 4 / 0	-
Insomnia	10.8	2.6	50	100	1 / 3 / 0	0 / 1 / 0
Irritability	8.1	0	100	-	1 / 1 / 1	-
Nausea*	16.2	0	50	-	2 / 4 / 0	-
Sleepiness	8.1	0	33	-	0 / 1 / 2	-
Vivid Dreams	10.8	0	50	-	2 / 2 / 0	-
Vomiting	8.1	0	33	-	1 / 1 / 1	-

Note: Donepezil n = 37, placebo n = 38. \* Significant between-group difference in the frequency of treatment-emergent adverse events (donepezil > placebo).

**Fisher Exact Tests:** agitation:  $p = 0.20$ ; insomnia:  $p = 0.20$ ; irritability:  $p = 0.12$ ; sleepiness:  $p = 0.12$ ; vomiting:  $p = 0.12$ ; vivid dreams:  $p = 0.05$ ; diarrhea:  $p = 0.03$ ; nausea:  $p = 0.01$ .

# MEMRI-TBI-D Study: Study Discontinuations due to Treatment-Emergent Adverse Events

- Three participants discontinued treatment due to treatment-emergent AEs
- All of these participants:
  - were receiving donepezil, with one discontinuing treatment while receiving donepezil 5 mg daily and the others discontinuing treatment while receiving donepezil 10 mg daily;
  - were treated at a single study site; and
  - reported intolerance of gastrointestinal side effects (nausea, vomiting, and/or diarrhea) as their principal reason for discontinuing study treatment
- This yields an 8.1% rate of donepezil discontinuation due to treatment intolerance



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## Rivastigmine Transdermal Patch Treatment for Moderate to Severe Cognitive Impairment in Veterans with Traumatic Brain Injury (RiVET Study): A Randomized Clinical Trial

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### Abstract

Cognitive impairment is common in veterans with TBI. Cholinergic deficits have been hypothesized as contributors to this impairment. We report the effects of cholinesterase inhibitor rivastigmine transdermal patch treatment in veterans with TBI and post-traumatic memory impairment. Our objective was to evaluate the efficacy and safety of 9.5 mg/24 hours (10cm<sup>2</sup>) rivastigmine patch in veterans of military conflicts with persistent moderate to severe memory impairment at least 12 weeks following TBI. This randomized, outpatient, double-blind, placebo-controlled 12-week trial with exploratory double-blind phase of additional 14 weeks was conducted at 5 VA Medical Centers, among veterans with closed, non-penetrating TBI who met or exceeded modified ACRM criteria for mild TBI with verbal memory deficits, as assessed by the Hopkins Verbal Learning Test, Revised (HVLT-R). Patients were randomized 1:1 to rivastigmine or matching placebo patches following 1-week single-blind, placebo run-in phase. At randomization, patients received 4.6 mg/24hr rivastigmine patches or matching placebo increased to 9.5 mg/24 hours patch after 4 weeks. The primary efficacy outcome measure was the proportion of participants who had at least 5-word improvement on HVLT-R Total Recall Index (Trials 1-3). A total 3671 participants were pre-screened, of whom 257 (7.0%) were screened; 96 (37%) randomized and 94 included in study analyses. The responder rates were 40.8% (20/49) and 51.1% (23/45) in rivastigmine and placebo groups respectively (p=0.41). A mixed-effect model including treatment, time, and treatment by time interaction indicated no significant difference in treatment effect over time between the groups (p=0.24). Overall, there were no significant differences in changes for all secondary outcomes between the rivastigmine and placebo groups. The most commonly observed AEs were application site reactions. This trial provides the largest sample to date of veterans with TBI and posttraumatic memory deficits enrolled in a pharmacological trial.

Cognitive impairment is common in veterans with histories of traumatic brain injury (TBI). Cholinergic deficits have been hypothesized as contributors to this impairment. We report the effects of cholinesterase inhibitor rivastigmine transdermal patch treatment in veterans with TBI and post-traumatic memory impairment. Our objective was to evaluate the efficacy and safety of 9.5 mg/24 hours (10cm<sup>2</sup>) rivastigmine patch in veterans of military conflicts with persistent moderate to severe memory impairment at least 12 weeks following TBI. This randomized, outpatient, double-blind, placebo-controlled 12-week trial with exploratory double-blind phase of additional 14 weeks was conducted at 5 VA Medical Centers, among veterans with closed, non-penetrating TBI who met or exceeded modified ACRM criteria for mild TBI with verbal memory deficits, as assessed by the Hopkins Verbal Learning Test, Revised (HVLT-R). Patients were randomized 1:1 to rivastigmine or matching placebo patches following 1-week single-blind, placebo run-in phase. At randomization, patients received 4.6 mg/24hr rivastigmine patches or matching placebo increased to 9.5 mg/24 hours patch after 4 weeks. The primary efficacy outcome measure was the proportion of participants who had at least 5-word improvement on HVLT-R Total Recall Index (Trials 1-3). A total 3671 participants were pre-screened, of whom 257 (7.0%) were screened; 96 (37%) randomized and 94 included in study analyses. The responder rates were 40.8% (20/49) and 51.1% (23/45) in rivastigmine and placebo groups respectively (p=0.41). A mixed-effect model including treatment, time, and treatment by time interaction indicated no significant difference in treatment effect over time between the groups (p=0.24). Overall, there were no significant differences in changes for all secondary outcomes between the rivastigmine and placebo groups. The most commonly observed AEs were application site reactions. This trial provides the largest sample to date of veterans with TBI and posttraumatic memory deficits enrolled in a pharmacological trial.





	Rivastigmine (n=49)	Placebo (n=45)	p-value
Age, mean (SD)	41.3 (10.7)	40.2 (11.4)	0.63
Male, no. (%)	47 (95.9)	43 (95.6)	0.99
Race, no. (%)			
White	30 (61.2)	34 (75.6)	0.12
African American	11 (22.4)	4 (8.9)	
Other	8 (16.3)	7 (15.6)	
Ethnicity (Non-Hispanic), no. (%)	37 (75.5)	33 (73.3)	0.82
Education, no. (%)			
High school diploma or below	7 (14.2)	6 (13.3)	0.48
College credit but no degree	26 (53.1)	19 (42.2)	
Associate degree	7 (14.3)	10 (22.2)	
Bachelor's degree or above	9 (18.4)	10 (22.2)	
Living Situation, no. (%)			
Alone	5 (10.2)	10 (22.2)	0.38
With family	40 (81.6)	31(68.9)	
With non-family	3 (6.1)	2 (4.4)	
Nursing home/Assisted living	1 (2.0)	2 (14.4)	
Body Mass Index (BMI), mean (SD)	32.5 (9.4)	31.5 (8.5)	0.59
Combat zone service, no. (%), yes	40 (81.6)	31 (68.9)	0.23
Blast Injury, no. (%), yes	25 (52.1)	19 (45.2)	0.53
TBI severity, no. (%)			
Mild and complicated mild	33 (68.8)	26 (61.9)	0.35
Moderate	8 (16.7)	6 (14.3)	
Severe	7 (14.6)	10 (23.8)	
Total number of TBIs, mean (SD)	3.4 (7.2)	2.3 (3.0)	0.34

	Rivastigmine (n=49)	Placebo (n=45)	p-value
<b>Blast Injury, n (%)</b>	<b>25 (52.1)</b>	<b>19 (45.2)</b>	0.53
TBI severity, no. (%)			
<b>Mild and complicated mild</b>	<b>33 (68.8)</b>	<b>26 (61.9)</b>	0.35
Moderate	8 (16.7)	6 (14.3)	
Severe	7 (14.6)	10 (23.8)	
Sleep disorder, no. (%)			
No	30 (61.2)	31 (68.9)	0.68
<b>Current, onset pre-TBI</b>	<b>2 (4.1)</b>	<b>1 (2.2)</b>	
<b>Current, post-TBI</b>	<b>17 (34.7)</b>	<b>13 (28.9)</b>	
Posttraumatic stress disorder, no. (%)			
No	14 (28.6)	21 (46.7)	0.23
<b>Current, onset pre-TBI</b>	<b>5 (10.2)</b>	<b>4 (8.9)</b>	
<b>Current, post-TBI</b>	<b>28 (57.1)</b>	<b>17 (37.8)</b>	
Lifetime	2 (4.1)	3 (6.7)	
Major depressive episode, no. (%)			
No	18 (36.7)	25 (55.6)	0.06
<b>Current, onset pre-TBI</b>	<b>3 (6.1)</b>	-	
<b>Current, onset post-TBI</b>	<b>11 (22.4)</b>	<b>12 (26.7)</b>	
Lifetime	17 (34.7)	8 (17.8)	
Alcohol dependence, no. (%)			
No	41 (83.7)	44 (97.8)	0.07
<b>Current, onset pre-TBI</b>	-	<b>1 (2.2)</b>	
Current, onset post-TBI	-	-	
Lifetime (not in the last 5years)	8 (16.3)	-	
Drug dependence, no. (%)			
No	47 (95.9)	44 (97.8)	1.00
Current, onset pre-TBI	-	-	
<b>Current, onset post-TBI</b>	<b>1 (2.0)</b>	-	
Lifetime (not in the last 5years)	1 (2.0)	1 (2.0)	
<b>BDI-II, mean (SD)</b>	<b>19.0 (11.4)</b>	<b>20.6 (14.8)</b>	0.88
<b>PCL-M, mean (SD)</b>	<b>48.7 (11.7)</b>	<b>46.9 (19.0)</b>	0.24

# Summary

- Considered the relationship between cognitive impairment and cholinergic dysfunction after TBI over the translational neuroscience course that these investigations followed:
  - observations made “at the bedside” generated questions about cognition and cholinergic function after TBI
  - those questions were taken back to the lab and placed in context with the extant basic and clinical neuroscience literature on cerebral cholinergic function and TBI
  - that integration led to the hypothesis that potentially remediable posttraumatic cerebral cholinergic deficits contribute to cognitive, and particularly memory, impairments after TBI
  - that hypothesis was tested in human subjects with TBI, first in the lab and then in multicenter RCTs

# Summary

- Based on the findings from these experiments and a raft of contemporaneously performed studies elsewhere, there is evidence supporting both the cholinergic hypothesis of posttraumatic cognitive impairments and the potential benefits of AChEI treatments in this population
- Persistent posttraumatic verbal memory impairments after moderate or severe TBI appear to be the cognitive target most responsive to cholinergic augmentation – however, treatment response may be greater in those with relatively more severe TBI and in whom other conditions (especially PTSD and depression) are adequately managed or not present
- Continued translation back to the “bedside” will benefit from effectiveness studies with longer observation periods, identification of biomarkers that predict response to AChEIs, and studies of AChEI-augmented cognitive rehabilitation



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