Cognitive Impairment due to Traumatic Brain Injury: Investigation of the Cholinergic Hypothesis

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Introduction

Cognitive impairments are common consequences of traumatic brain injury (TBI). However, the neurobiological bases of impaired cognition due to TBI remain incompletely understood. In order to develop rational pharmacological, compensatory/ behavioral, technological, and environmental therapies for such impairments and the disability they produce, a better understanding of the neurobiology of cognitive impairment due to TBI is required. Toward that end, we suggest that impairment of the hippocampally-mediated, cholinergically-dependent, pre-attentive process of sensory gating may, at least in part, underlie attention and memory impairments following TBI **(1)**. Our cholinergic hypothesis of attention and memory impairment due to TBI states:

1) TBI results in dysfunction of hippocampal cholinergic systems
2) Hippocampal cholinergic dysfunction contributes to sensory gating impairments
3) Impaired sensory gating interferes with the development of normal selective attention
4) Impaired selective attention interferes with new learning (memory)

∴ 5) Impairments in attention and memory following TBI are, at least in part, a consequence of hippocampal cholinergic dysfunction.

The P50 evoked response to paired auditory stimuli (P50 ratio) reflects the function of a cholinergically-dependent inhibitory neuronal network in the hippocampus **(2)**. Therefore, abnormal P50 physiology following TBI might serve as a putative marker of hippocampal cholinergic dysfunction in cognitively impaired TBI survivors. Volumetric MRI can quantitate alterations in the structure of the brain and hippocampus; disproportionate hippocampal volume loss in persons with abnormal P50 physiology following TBI would provide convergent structural and functional evidence consistent with the above hypothesis. Additionally, well-tolerated pro-cholinergic medications are widely available and may be used as a probe of the cholinergic system among persons with persistent symptoms of impaired auditory gating, attention, memory, and P50 physiology following TBI.

Methods

Subjects:

For all studies presented here, participants were recruited from the Neuropsychiatry Clinic at University Hospital, via referral from physicians and neuropsychologists in the metropolitan Denver area, and through an advertisement placed in a Denver newspaper. Subjects reporting persistent problems with attention and memory for more than one year following a definable traumatic brain injury of at least mild severity (based on American Congress of Rehabilitation Medicine criteria, 1993) were sought. Telephone screening interviews were performed by the Neuropsychiatry Service Coordinator (JT) to establish eligibility for all of the studies described herein based on the following inclusion/exclusion criteria:

1) 18 - 60 years of age
2) History of clinically definite TBI
   a) non-penetrating (i.e., closed)
   b) not requiring neurosurgical intervention
   c) post-traumatic amnesia of at least 15 minutes
   d) loss of consciousness was not a required element of the injury
3) TBI at least one year prior to study
4) No diagnosable neurologic, psychiatric, or substance problems prior to injury
5) Absence of post-traumatic epilepsy
6) Immediate onset and persistence of symptoms of impaired auditory gating following TBI
7) No active mood, anxiety, or substance disorder at the time of study participation
8) Age and education adjusted Mini-Mental State Examination score (MMSE) ≥ 25th %-ile
9) Glasgow Outcome Score ≥ 4

Initial severity of TBI was based on duration of post-traumatic amnesia (PTA). PTA was selected for estimation of severity because this information could be derived from interview of patient/family, and other indices of severity such as the Glasgow Coma Scale score or the Galveston Orientation and Amnesia Test were not available for most subjects. Duration of PTA was based on patient/family interview and/or review of medical records. Initial severity was operationally defined as mild (15"-1 hr), moderate (1-24 hrs), severe (>24 hrs).

Experiment 1: P50 Recordings (3)

Hypothesis: Subjects with TBI and symptoms consistent with impaired auditory gating will be nonsuppressors of the P50 evoked waveform response to paired auditory stimuli.

Subjects: 20 persons with persistently impaired auditory gating, attention, and memory following TBI (mean age 42 ± 11 years) and 20 age, gender, and education matched non-injured comparison subjects (mean age 40 ± 11 years).

P50 Recording Method

Auditory evoked potentials were assessed according to our previously described methods (Adler et al., 1993). Auditory stimuli were presented in pairs in a conditioning-testing design with a 0.5 second intrapair interval and a 10 second inter-stimulus interval. A pulse stimulus of approximately 1 msec duration, amplified with a bandwidth between 20 and 12,000 Hz, was delivered through headphones. The intensity at the subject's ear was set at 30 - 45 dB above hearing threshold. Three sets of average responses were constructed, each based on responses to 16 pairs of stimuli, and used to create an overall grand average of the conditioning and test P50 responses for each subject. The P50 wave was identified and measured in each set of averages using a previously described computer algorithm (Nagamoto et al., 1989). The algorithm identified the conditioning P50 wave as the most positive peak between 40 and 80 msec after the first stimulus. The test P50 wave was identified as the most positive peak with a latency from the test stimulus within 10 msec of the latency of the conditioning P50 response. The amplitude of the test P50 wave divided by the amplitude of the conditioning P50 wave, expressed as a percentage and referred to here as the P50 ratio, was used as a measure of auditory gating.

Results

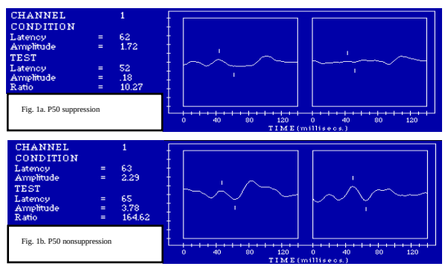

Figure 1. Examples of P50 evoked response to paired auditory stimuli. In each pair of tracings, the left window illustrates the average conditioning response and the right window illustrates the average test response as recorded at the vertex. The P50 evoked response is demarcated in each window by tick marks. Amplitude (vertical axis) is expressed in µVolts, latency (horizontal axis) is expressed in msecs. The P50 ratio is defined as test amplitude÷conditioning amplitude x 100..

Table 1. Descriptive statistics regarding post-traumatic amnesia, time elapsed since injury, Glasgow Outcome Scale, and Mini-Mental State Examination Score for the overall TBI and each TBI sub-group.

	Post-traumatic amnesia (hours)			Time elapsed since TBI (years)			Glasgow Outcome Scale Score			Mini-Mental State Exam Score		
	Mean	SD	Med.	Mean	SD	Med.	Mean	SD	Med.	Mean	SD	Med.
Overall TBI (n=20)	58.28	103.78	10.00	7.81	7.91	5.00	4.95	0.22	5.00	29.1	1.02	29.0
Mild TBI (n=5)	0.33	0.18	0.25	5.60	3.13	5.00	5.00	0.00	5.00	29.8	0.45	30.0
Moderate TBI (n=6)	5.00	4.10	3.00	6.83	4.22	5.50	5.00	0.00	5.00	28.67	1.03	29.0
Severe TBI (n=9)	126.00	127.21	72.00	9.69	11.17	6.00	4.89	0.33	5.00	29.0	1.12	29.0

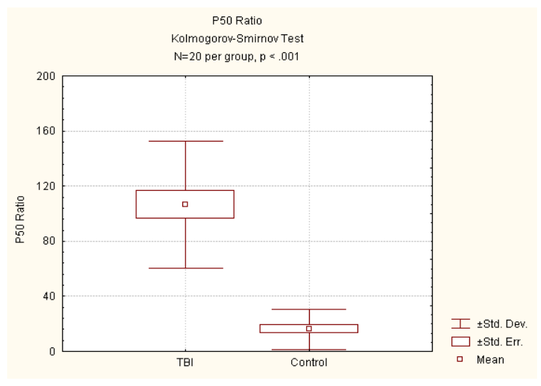

Figure 2. Box-whisker plot of P50 ratio differences between the TBI and control groups using the nonparametric Kolmogorov-Smirnov test. TBI group in this plot includes subjects with mild, moderate, and severe TBI, and demonstrates a significant difference (p<.001) in P50 ratio between the groups.

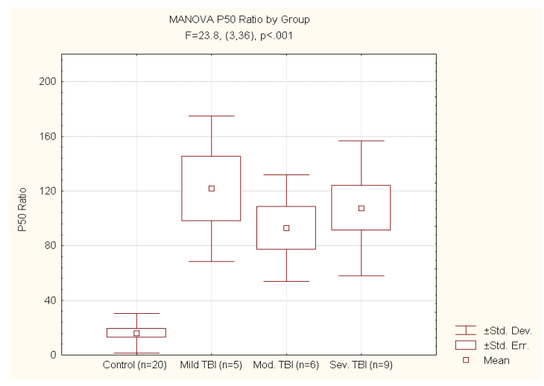

Figure 3. Box-whisker plot of the effect of group on P50 ratio using MANOVA (p<.001). Planned post-hoc comparisons using Tukey's HSD test for unequal sample sizes demonstrates significant differences between each TBI sub-group and the control group (p<.001 for each comparison) and no statistically significant differences between the TBI sub-groups.

Experiment 2: Volumetric MRI Analyses of the Hippocampus (4)

Hypothesis: Subjects with TBI and P50 nonsuppression will demonstrate reduced hippocampal volume on MRI of the brain.

Subjects: 10 persons with persistently impaired auditory gating, attention, and memory and abnormal P50 physiology following TBI and 10 age, gender, and education matched non-injured comparison subjects.

Volumetric MRI Method

MRI of the brain was performed on a Phillips Gyroscan 1.5 T system. A standard head coil using a 3-D spoiled gradient echo acquisition was used to obtain a series of 124, 1.7 mm thick, T1-weighted coronal images of the head, with a TR/TE of 40/5 ms and a 40 degree flip-angle. A 256 x 256 matrix acquisition produced 0.94 x 0.94 x 1.7 mm voxel dimensions. Total brain volume and left and right hippocampal volumes were determined using a manual segmentation routine written in Interactive Data Language 3.0 (Research Systems, Boulder, CO). Intrarater reliabilities on total brain volume and hippocampal volume were 0.94 and 0.99, respectively (Pearson product-moment correlation, p < .05).

Results

	TBI (All) Group (N=10)		TBI Mild/Moderate (N=4)		TBI Severe (N=6)		Comparison Group (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	37.50	9.08	33.75	7.23	38.67	10.63	37.80	9.44
Education	15.90	2.56	15.75	2.87	16.00	2.61	15.90	1.10
MMSE	29.00	1.56	29.25	.96	28.80	1.94		
Glasgow Outcome Score	5.00		5.00		5.00			
Time since injury (yrs)	6.68	3.99	6.00	2.45	7.13	4.94		
Length of PTA (hours)	184.48	352.79	.69	.88	307.00	423.08		
P50 Ratio	93.38	25.38	89.53	31.96	95.95	22.95		
Hippocampal Volume (ml)								
Left	2.65	.42	2.27	.34	2.71	.51	3.61	.41
Right	2.92	.62	2.70	.46	3.00	.73	3.93	.47
Total Brain Volume (ml)	1247.96	100.41	1178.84	49.96	1294.04	101.38	1346.22	92.31

Table 1. Demographic and descriptive data for traumatic brain injury (TBI) and normal comparison groups.

Figure 1. Preliminary analysis of the effect of group (based on severity of injury) on hippocampal volume using a two-way ANCOVA, with total brain volume as the covariate. Mean (right, left), standard error (box), and standard deviation (whiskers) are shown. There is a significant effect of group on hippocampal volume (F=5.8, df(2,16), p<.015). Post-hoc comparisons using the Tukey HSD for unequal sample sizes demonstrated significant differences in hippocampal volumes between the mild/moderate TBI and comparison group (right: p<.02, left: p<.003) and the severe TBI and comparison group (right: p<.02, left: p<.002), but not between the mild/moderate and severe TBI groups (right: p=.86, left: p=.86). There is a significant effect of hemisphere on hippocampal volume in all groups (F=23.94, df(1,17), p<.001) left hippocampus being smaller than the right, but there was no interaction between group and hemisphere.

Experiment 3: Pharmacology Probe Study

Hypothesis: Subjects with TBI and P50 nonsuppression will demonstrate relative normalization of P50 physiology during treatment with donepezil HCl (a cholinesterase inhibitor).

Subjects: 10 persons with persistently impaired auditory gating, attention, and memory and abnormal P50 physiology following TBI. For this study, all subjects had a GOS score of 5.

Study Design

Randomized, double-blind, placebo-controlled, crossover design. Group 1 received donepezil HCl 5 mg daily for six weeks, then donepezil 10 mg daily for six weeks, then crossed-over to placebo; two placebo phases of six weeks each followed thereafter. Group 2 received placebo for 12 weeks, followed by donepezil 5 mg daily for six weeks, and then donepezil 10 mg daily for six weeks. Placebo and donepezil were administered in identical fashion. P50 recordings were performed at baseline and at the end of each treatment phase.

Results

	Mean	SD	Median	Range
Age (years)	45	9	49	25-53
Education (years)	17	3	16.5	13-22
Time since injury (years)	9.4	11.8	5	3-14
Duration of PTA (hours)	72	139	3.5	.25-336
MMSE	29	1	29	28-30

Table 1. Demographic data for pharmacologic probe study.

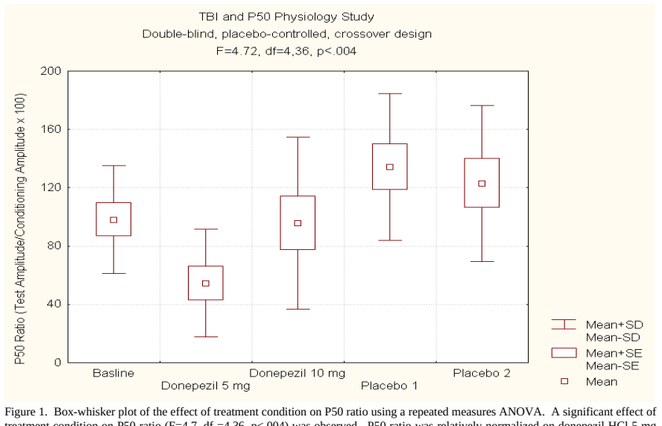

Figure 1. Box-whisker plot of the effect of treatment condition on P50 ratio using a repeated measures ANOVA. A significant effect of treatment condition on P50 ratio (F=4.7, df =4,36, p<.004) was observed. P50 ratio was relatively normalized on donepezil HCl 5 mg daily when compared to baseline and all other conditions (all p<.04). However, P50 ratios on donepezil HCl 10 mg daily and both placebo conditions did not differ significantly from baseline, suggesting the possibility that there may be a "therapeutic window" for the effect of donepezil on P50 phsyiology in this population.

Conclusions

These findings suggest that symptoms of impaired auditory gating following TBI are associated with abnormal P50 physiology and disproportionate hippocampal volume loss. Since it is known that P50 physiology reflects hippocampal cholinergic function, abnormal P50 physiology among individuals with the relevant symptom profile may serve as a useful clinical marker of hippocampal cholinergic dysfunction following TBI. Understanding the clinical symptoms associated with this physiologic disturbance may permit identification of individuals whose post-concussive symptoms may respond to treatment with pro-cholinergic medications, including the cholinesterase inhibitor donepezil HCl. Additional research is needed to determine if the P50 metric can facilitate identification of TBI survivors that may benefit from compensatory strategies, assistive technologies, and/or environmental interventions designed to improve multimodal sensory filtering and thereby enhance attention and memory.

References

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