

Traumatic Brain Injury as a Risk Factor for Alzheimer's Disease: A Review

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Accumulating epidemiological evidence implicates traumatic brain injury as a pathogenic agent in the development of Alzheimer's disease (AD). Considering the increase in the prevalence of both traumatic brain injury and AD in recent times, the possibility that brain trauma may provoke the early development of AD has important implications for health service planning, preventative efforts, and medico-legal compensation settlements. This paper evaluates the plausibility of the proposed link between traumatic brain injury and AD, largely by way of exploring a theoretical perspective advanced by Satz (1993) and considering recent contributions from the epidemiological, neuropathological, and biochemical literature that are pertinent to this issue. The literature reviewed provides sufficient support and empirical vindication to give credence to the proposed association between these two neuropsychological entities at the statistical, theoretical, and biological level.

KEY WORDS: Traumatic brain injury; Alzheimer's disease; brain reserve capacity; threshold.

Alzheimer's disease (AD) has gained recognition as a major cause of serious morbidity amongst the elderly population. It has been suggested that over the next 50 years, the gradual aging of the baby-boomer generation will provoke a concomitant increase in the number of AD cases by a factor of 4, with the majority of new cases occurring in individuals over 80 years of age (Mortimer, 1997). Although the factors involved in the pathogenesis of AD require further clarification, epidemiological studies have featured prominently in contemporary AD research, identifying a multitude of risk factors of possible etiological significance to AD. Accumulating evidence implicates traumatic brain injury (TBI) as a provocative event in the development of AD, although specification of whether and how TBI may trigger a long-term process of neurodegeneration remains controversial (Levin and Goldstein, 1995; Spear, 1995).

An insidious increase in TBI has been seen to parallel the technological advances of the twentieth century, with a large proportion of brain injuries arising from motor vehicle accidents (Badcock, 1987; Fearnside and Simpson,

1997). Advances in the management of the acute stages of neurotrauma have decreased the number of fatalities associated with TBI (Sosin *et al.*, 1995), yet the chronic sequelae of brain trauma in individuals surviving TBI remain a significant medical challenge.

TBI is typically characterized by pervasive disturbances in consciousness, behavior and cognition, along with specific deficits attributable to injury of particular brain regions (Schmidt and Grady, 1995). Research efforts, however, have been tarnished by the absence of a uniformly accepted diagnostic standard for TBI, and the resultant use of ambiguous and inconsistent definitions and inclusion criteria (Sorenson and Kraus, 1991). Whilst there is now more agreement regarding the definition of TBI (e.g., Teasdale, 1995), this definitional problem and the diverse terminologies used to denote sustained head trauma, to date, have made it difficult to set parameters and explicitly define TBI. In the course of this paper, TBI will be used as an encompassing term, including both transient and persistent disruptions of brain function induced by traumatic means.

In view of the increase in the prevalence of both TBI (Badcock, 1987) and AD (Jorm and Henderson, 1993) in recent times, the possibility that brain trauma may lead to earlier development of AD in later life has important social and medical implications for health service planning and

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preventative efforts. There are also medico-legal implications. If TBI is a risk factor for the earlier onset of AD, then this will need to be considered by the courts when determining compensation settlements. As cogently argued by Bell (1992), the full magnitude of the modern epidemic of high-momentum traffic accidents has yet to appear. Epidemiological studies addressing the risk factors for AD that were published in the 1970s and 1980s involved elderly individuals who had very limited exposure to TBI in their youth. It is the modern 18- to 25-year-olds who have the highest rates of TBI following motor vehicle accidents, and it will not be until some time into the new millennium that the long-term effects of the upsurge in road accidents will be fully known.

The major objective of this paper is to evaluate the plausibility of the proposed link between TBI and AD, both in light of available epidemiological evidence and in terms of a theoretical perspective advanced by Satz (1993). Although other theoretical perspectives revolving around similar issues have been advanced (e.g., Mortimer, 1988, 1994), Satz's model appears to be the most comprehensive and coherent and will therefore be the theoretical focus of this paper. Recent contributions from neuropathological and biochemical research will also be considered in an attempt to explore the biological feasibility of the putative relationship between TBI and AD.

Considering that there has been much research interest directed toward this controversial topic in recent times, practical considerations preclude an all-inclusive and exhaustive discussion of the available literature. Instead, the purpose of the current paper was to selectively review those papers that focus on investigating the link between TBI and AD, and which were considered most relevant in evaluating Satz's threshold theory for acquired brain injury. The literature reviewed was supplemented by entering key search terms (Alzheimer's disease and traumatic brain injury; brain reserve capacity) into internet literature search facilities (including Medline, Current Contents and UnCover), with the date of publication restricted to the time period from 1993 to mid-1998.

EPIDEMIOLOGICAL EVIDENCE

The epidemiological study of AD has spanned more than half a century, during which time over 20 putative risk factors have been identified (Mortimer, 1995). These studies have investigated a range of possible pathogenic agents in AD, with chronological age, Down's syndrome and family history of dementia being the most consistently reported across studies.

The role of TBI as a risk factor in the development of AD has been more controversial. Preliminary evidence for a contributory role of TBI in the development of AD

came from an early case report, which documented early-onset classic AD pathology in a 38-year-old man who had suffered a single episode of severe head trauma 16 years earlier (Rudelli *et al.*, 1982). Much epidemiological research investigating this potential association has ensued, with many of these studies employing either a case-control or cohort framework. The "odds ratio" has typically been used as a statistical tool to quantify an inferred association in terms of both strength and direction (Sandercock, 1989). In relatively rare diseases such as AD, this ratio is considered a good approximation of the relative risk—or the degree to which the disease is more likely to occur in exposed, as compared to unexposed, individuals (Jorm, 1990; Schlesselman, 1982). For instance, in a study by Heyman *et al.* (1984), which investigated risk factors for AD, an odds ratio of 5.31 was calculated as a measure of association between head injury and AD. This figure suggests that the odds of prior head injury were 5.31 times higher in AD cases than in controls.

Case-Control Studies

The odds ratios found in several case-control studies that have investigated head trauma as a risk factor for AD are summarized in Table I. This table shows the results of the early case-control studies predating and including the EURODEM meta-analysis (Mortimer *et al.*, 1991), as well as the findings of more recent case-control studies conducted since 1993. The EURODEM meta-analysis is a re-analysis, which incorporated the data from many of the individual studies listed in this table (i.e., Amaducci *et al.*, 1986; Broe *et al.*, 1990; Chandra *et al.*, 1987; Graves *et al.*, 1990; Mortimer *et al.*, 1985). The meta-analysis was an important undertaking that involved pooling the data from seven early case-control studies to allow for a more powerful statistical investigation of the association between TBI and AD.

As a consequence of the conflicting results of these case-control studies, the question of whether prior brain trauma is a predisposing factor in the pathogenesis of AD has become a contentious issue. However, the lack of consistency in the results arising from case-control investigations may be at least partially attributable to several difficulties underlying these studies.

Firstly, since AD diagnosis cannot be definitively established until postmortem investigation, misdiagnosis of "cases" based on probable AD criteria presents as a major problem in epidemiological studies of AD. Salib and Hillier (1997) pointed out that a number of AD cases are likely to be misclassified (false positives) based on the commonly used NINCDS-ADRDA criteria, which have an estimated specificity of 0.65—whereby specificity represents the true negative rate, or the proportion of subjects

Table I. Odds Ratios Calculated in Case-Control Studies that Have Investigated the Association Between Traumatic Brain Injury and the Development of Alzheimer's Disease

Study	Number of cases	Number of controls	Odds ratio ^a
Heyman <i>et al.</i> (1984)	40	80	5.31*
Mortimer <i>et al.</i> (1985)	78	48 ^b	2.80
	78	76 ^c	4.50*
French <i>et al.</i> (1985)	78	76	4.50*
Amaducci <i>et al.</i> (1986)	116	97 ^b	2.00
	116	116 ^c	3.50
Chandra <i>et al.</i> (1987)	64	64	6.00
Sullivan <i>et al.</i> (1987)	17	17	2.00*
Chandra <i>et al.</i> (1989)	274	274	1.25
Broe <i>et al.</i> (1990)	170	170	1.33
Graves <i>et al.</i> (1990)	130	130	3.50*
Mortimer <i>et al.</i> (1991) ^d	—	—	1.82* ^e
Mayeux <i>et al.</i> (1993)	138	193	3.70*
Canadian study of health and aging (1994)	184	453	1.66 ^f
Kondo <i>et al.</i> (1994)	60	120	5.50*
Mayeux <i>et al.</i> (1995)	113	123	1.00
	113	123	10.2* ^g
Rasmusson <i>et al.</i> (1995)	68	34	13.75*
Salib and Hillier (1997)	198	136	2.10* ^h

^aOdds ratio: estimate of relative risk. Asterisks (*) indicate that the association between traumatic brain injury and Alzheimer's disease was found to be significant.

^bPopulation controls.

^cHospital controls.

^dCollaborative re-analysis of seven earlier case-control studies.

^eRelative risk statistic.

^fBorderline significance.

^gOdds ratio for Alzheimer's disease associated with *both* a history of traumatic brain injury and the presence of at least one $\epsilon 4$ allele of the apolipoprotein E gene.

^hSignificant only in male patients.

without the disorder who are correctly identified by a negative test result (Elwood, 1993). Clearly, without a definitive diagnosis of Alzheimer's cases, a reliable association between TBI and AD is difficult to establish and replicate. Furthermore, this difficulty is compounded by the lack of a uniformly accepted diagnostic standard for TBI (Sorenson and Kraus, 1991). To illustrate, Chandra *et al.* (1989) failed to find a statistically significant association between TBI and AD, defining brain injury as head trauma with loss of consciousness followed by complete recovery, whereas Graves *et al.* (1990) found statistical support for such an association defining TBI as head trauma not necessarily causing unconsciousness, but requiring medical care.

Secondly, limitations intrinsically related to the case-control design may underlie some of the observed discrepancies. For instance, the necessary reliance on retrospective surrogate-informant interviews to document subjects' exposure history leaves such studies open to the possibility of recall bias. That is, informants for the AD patients may

be more motivated than control informants to recall previous incidents of TBI if they feel that the head injury may have created a predisposition towards dementia (Chandra *et al.*, 1989).

Although these two considerations undoubtedly complicate the interpretation of the findings of many of these studies, there is also a third difficulty plaguing many of the early case-control studies, namely that of statistical power. Due to the low base rate of TBI in the population, the majority of early case-control studies lacked sufficient statistical power to identify such an infrequently reported risk factor (Mendez *et al.*, 1992; Mortimer *et al.*, 1991). In recognition of this fact, Mortimer *et al.* (1991) undertook a re-analysis of the data from seven case-control studies, using a powerful meta-analytic technique highly appropriate for examining infrequently reported risk factors. By pooling data across studies, Mortimer and colleagues achieved a high level of statistical power (.92), in contrast to the low mean statistical power of the individual studies (.22), and demonstrated a highly significant association between TBI and AD, which remained essentially unchanged after controlling for several other putative risk factors (Mortimer, 1995).

The findings of the EURODEM re-analysis (Mortimer *et al.*, 1991) appear to highlight the importance of designing a study with adequate statistical power, and suggest that many of the early negative findings stem from an underlying methodological flaw in the form of insufficient statistical power to address the hypothesis. Moreover, adequate statistical power is particularly crucial when the risk factor under investigation occurs only infrequently in the general population, as is the case with TBI. The incidence rate in USA has been estimated to be 200 per 10⁵ of the population (Fearnside and Simpson, 1997).

As can be seen in Table I, the more recent case-control studies have largely divulged significant associations between AD and TBI (Kondo *et al.*, 1994; Mayeux *et al.*, 1993; Rasmusson *et al.*, 1995; Salib and Hillier, 1997). It is noteworthy that many of these studies explicitly acknowledge the inadequacies of early studies, and have attempted to refine their design to avoid these methodological flaws (e.g., Rasmusson *et al.*, 1995).

For instance, in the study yielding the largest odds ratio, Rasmusson *et al.* (1995) pointed out that the inconsistent findings of the early case-control studies may, in part, stem from the reliance on surrogate informants of varying relation (siblings, children, friends, and spouses) to the subjects. Considering that spouses are the preferred informant source for elderly study subjects due to increased response accuracy, Rasmusson and colleagues required that all informants be spouses for both the case and control subjects. This was thought to have substantially

improved the reliability and validity of the informant responses on the head injury questions. It is interesting to note that a significant association between TBI and AD was found in the only other study that limited selection of AD cases to those individuals with a spouse informant (Graves *et al.*, 1990). An additional strength of the Rasmusson *et al.* (1995) study is that it examined the association between AD and head injury of any severity (i.e., not only TBI with loss of consciousness, or requiring medical care), thereby suggesting "that head injury of even mild severity may serve as a predisposing factor for some cases of AD" (p. 217).

Definitive support for a statistical association, however, has not been observed in every instance. For example, the Canadian Study of Health and Aging (CSHA, 1994) employed a population-based case-control design to investigate a large number of risk factors for AD hypothesized in the literature. The study was conducted in 18 CSHA study centers in 10 Canadian provinces, and involved 184 cases and 453 controls aged 65 years or older who were recruited from both the community and institutions. The odds ratio for a history of head injury was found to be elevated, and reached borderline significance. The authors concluded that the study confirmed a number of putative risk factors for AD, including "head injury, even though it was not quite significant" (p. 2078).

The study by Mayeux *et al.* (1995) specifically attempted to determine the risks of AD associated with TBI and possession of the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene. APOE, which exists in three major isoforms encoded by three alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$), is a constituent of several plasma lipoproteins and has a crucial role in the regulation of lipid metabolism (Yasuda *et al.*, 1998). Extensive research has led to universal consensus that APOE $\epsilon 4$ is a powerful risk factor for AD (Growdon, 1998; Jonker *et al.*, 1998; Nicoll *et al.*, 1995, 1996; Poirier, 1996; Poirier *et al.*, 1993; Slioter *et al.*, 1998; Yasuda *et al.*, 1998). In fact, Mayeux *et al.* found that the presence of at least one APOE $\epsilon 4$ allele conferred a twofold increase in the risk of AD in their sample of 236 community-dwelling elderly individuals. When the joint effect of APOE $\epsilon 4$ and a history of head injury was considered, the risk of AD was elevated 10-fold, suggesting a synergistic relationship. However, head injury in the absence of APOE $\epsilon 4$ was not found to confer an increased risk, a finding interpreted as suggestive that TBI may only serve as a provocative agent in the development of AD in individuals who are either homozygous or heterozygous for APOE $\epsilon 4$.

This finding is difficult to reconcile with those of other case-control studies, as the overwhelming majority have not dichotomized subjects on the basis of APOE

status. Nevertheless, the findings of Mayeux *et al.* (1995) certainly do not argue against the hypothesized link between TBI and AD, but rather indicate that a history of TBI may contribute to the development of AD by exacerbating the effect of a predisposition conferred by APOE status.

Thus, when taken together, the case-control data generally provide statistical support for the proposed relationship between TBI and the subsequent development of AD.

Cohort Studies

Perhaps the major advantage of prospective cohort studies is that they decrease the chance that subjective biases (such as recall bias) will taint the data collected because information is obtained before an outcome is known (Lilienfeld and Lilienfeld, 1980). In one such prospective cohort study, Katzman *et al.* (1989) followed 434 elderly volunteers aged between 75 and 85 years over a 5-year period. Although 56 subjects became demented during the course of their follow-up investigations (with 32 meeting diagnostic criteria for AD), these authors concluded that head injury was not a significant risk factor. Similarly, Williams *et al.* (1991) failed to find support for the hypothesis that TBI is a risk factor for AD in a cohort study of 821 head trauma victims.

In a more recent incidence study, Schofield *et al.* (1997b) found that length of loss of consciousness was an important variable when investigating the association between previous TBI and AD. They found a significantly increased risk for AD in subjects who had sustained a head injury associated with a loss of consciousness for 5 min or more (relative risk = 11.2), but no evidence of a significantly elevated risk in individuals sustaining a head injury with loss of consciousness of less than 5 min. Schofield *et al.* interpreted their findings as supportive of the proposed association between TBI and AD. In addition, these investigators highlighted that in an earlier cohort study by Williams *et al.* (1991), dementia was diagnosed by the subjects' own physician, cases of very early onset dementia (40 years of age) were not excluded, and standardization of estimates of dementia onset may have been difficult. The fact that the research conducted by Schofield *et al.* was devoid of these problems might at least partially explain the divergent results from these two cohort studies.

However, the results emerging from a recent population-based study (Nemetz *et al.*, 1999) may be the most pertinent available to date in terms of providing a possible explanation for the ongoing contention surrounding the proposed relationship between TBI and AD. Using the resources of the Rochester Epidemiology Project, these researchers considered all documented episodes of TBI

occurring from 1935 to 1984 among residents of Olmsted County, Minnesota. Community-based medical records were used to follow those TBI cases aged 40 years or older at last medical contact (prior to June 1, 1988) for evidence of AD until last contact, death, or June 1, 1988. Nemetz *et al.* found that the number of cases of AD among individuals with a history of TBI was not significantly greater than would be expected based on incidence rates of AD among residents of Rochester Minnesota with no previous head trauma. However, the study yielded compelling evidence that the risk of early-onset AD was more than twice that expected. Moreover, in the TBI cases who subsequently developed AD, the observed time from injury to AD onset was shorter than expected.

The important implication of these findings is that TBI may interact with other risk factors “to hasten the onset of Alzheimer’s disease in persons susceptible to the disease” (Nemetz *et al.*, 1999, p. 38). It follows that a history of TBI might not increase the risk of developing AD per se, but may instead serve to alter the temporal onset of the disease process in individuals who, for some as yet unspecified reason, are predisposed to develop AD. In this case, the inconsistency and contradiction apparent in the available literature may stem from a failure in the majority of studies to consider vulnerability factors and the timing of AD onset. Factors that have been proposed to confer increased susceptibility to AD and the role of TBI in the temporal onset of AD will be further explored in subsequent sections.

Summary of Epidemiological Evidence

The epidemiological research reviewed underscores the increasing trend in the literature to support the proposition that TBI is a significant risk factor for AD. The case-control evidence generally lends statistical support for the hypothesized relationship between TBI and AD. The significant findings of the powerful EURODEM re-analysis (Mortimer *et al.*, 1991) and the methodological criticisms discussed have cast doubt on the validity of many of the early negative case-control findings. A large majority of more recent case-control investigations have implicated TBI as an environmental risk factor for AD, although one study found that a history of TBI may play a contributory role in pathogenesis of AD by exacerbating a pre-existing genetic susceptibility in individuals with at least one APOE $\epsilon 4$ allele (Mayeux *et al.*, 1995).

Cohort studies have effectively highlighted the importance of considering factors such as duration of loss of consciousness associated with TBI, and the temporal onset of AD symptoms. The study by Schofield *et al.* (1997b) revealed that head trauma associated with a loss of

consciousness for 5 min or more significantly elevated the risk of developing AD, whereas the findings of Nemetz *et al.* (1999) indicated that TBI more than doubles the risk of early-onset AD in persons susceptible to the disease.

In light of the available epidemiological evidence, it appears most appropriate to conclude that TBI should be considered as a probable risk factor for AD. However, using refined methodologies, further research in the area is warranted before more definitive conclusions can be reached. Epidemiological case-control and cohort studies per se are incapable of establishing causality; they can merely demonstrate a statistical association between AD occurrence and antecedent TBI (Jorm, 1990; McConway, 1994). To more thoroughly investigate the proposition that TBI can trigger the early onset of AD and to explore the possibility of a causal relationship, it is necessary to consider whether an association between TBI and AD is both theoretically and biologically plausible.

THEORETICAL CONSIDERATIONS

Brain Reserve Capacity and Threshold Concepts

It has long since been suggested that a substantial safety factor, or an inbuilt reserve, may be inherent in the neuronal circuitry of the human brain (Teuber, 1974), but may be considerably reduced by cerebral maturation and the degenerative changes of aging (Glassman and Smith, 1988). This argument seems plausible considering that without some degree of reserve capacity, every neuron would be a critical participant in the neuronal circuitry of the brain, and consequently single neuron failure would jeopardize overall system functioning (Glassman, 1987). Thus, the evolutionary significance of neuronal redundancy may not be to solely protect the brain against insult, but also to maintain normal functioning.

This concept of a cerebral reserve implicitly raises the notion of a “threshold effect,” whereby an individual may remain functionally intact and neurologically asymptomatic until a critical threshold of neuronal loss is surpassed. A threshold theory of causation pertaining to the onset of Parkinson’s disease is quite well established and has gained empirical support (Roth, 1986). The possibility that threshold and reserve concepts could similarly underlie the onset of AD has been raised by a series of observations. Most notably, it has been shown that when degenerative neuropathology surpasses a quantitative threshold, a clinical dementia typically emerges (Tomlinson *et al.*, 1970). Additionally, Alzheimer’s-type neuropathology has been found to be present in the brains of cognitively intact persons of advanced age, but is thought to stay clinically silent due to the intensity and distribution of

these pathologic lesions remaining at subthreshold levels (Blessed *et al.*, 1968; Gedye *et al.*, 1989).

Satz's Threshold Theory

Much of the early literature that suggested that a threshold effect may dictate dementia onset assumed that threshold effects involve an absolute quantity of cell loss before clinical symptoms emerge. This assumption has recently been challenged by Satz (1993). He theorizes that available brain reserve capacity (BRC) probably varies between individuals, creating different threshold levels and accounting for individual protection from, and susceptibility to, clinical symptoms after brain injury. That is, reserve capacity may be normally distributed across individuals so that those endowed with excessive neuronal redundancy may be able to tolerate more cell loss than those with less reserve before clinical symptoms manifest.

Using BRC as his central theoretical construct, Satz's threshold theory of acquired brain injury addresses how individual differences in BRC could underlie individual differences in risk morbidity, via a threshold effect (Satz, 1993). In this way, Satz's theoretical framework potentially provides a means of explaining how a brain reserve artificially lowered by TBI may predispose an individual to a neurodegenerative disorder such as AD.

The Model

The essence of Satz's threshold theory is most clearly illustrated by examination of the model in Fig. 1, which is based on that provided by Satz (1993). The central postulates of the model (A and B₁) depict two hypothetical cases endowed with differing degrees of BRC. Satz explains the necessity of considering these cases from a longitudinal and cross-sectional perspective in order to address the neuropsychological impact of both lesions with a progressive course and those chronic-static in nature.

According to the model, clinical symptoms emerge when brain lesions or neuronal loss deplete available BRC beyond the functional impairment cutoff, which is analogous to a neuropathological threshold. The model shows how individual differences in reserve capacity may be reflected in distinct threshold levels, resulting in variation in the amount of cell loss that can be accommodated by different individuals before clinical symptoms emerge.

Postulate A describes how a high degree of BRC can act as a protective factor, making individuals with greater reserve less susceptible to functional impairment. In this case, a brain lesion may remain subthreshold and clinically silent due to neuronal redundancy preventing cell loss from reaching the functional impairment cutoff

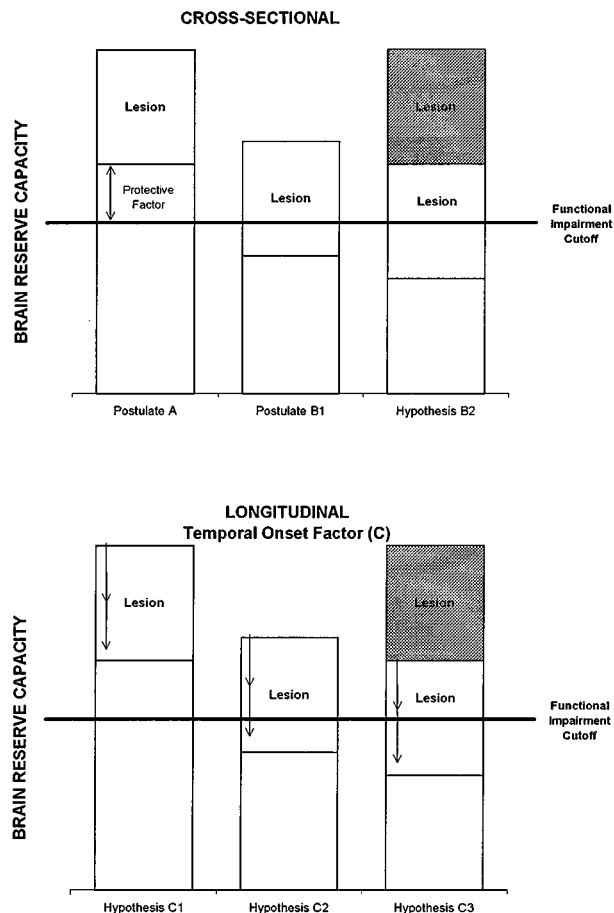


Fig. 1. Brain reserve capacity and threshold concepts as proposed by Satz (1993).

(threshold). Alternatively, Postulate B₁ illustrates how a similar brain lesion may reveal itself as neuropsychological impairment in a "vulnerable" individual with comparatively lower BRC and a lower threshold level.

Satz's theoretical subpostulates stem from these primary postulates. Hypothesis B₂, like Postulate B₁, involves the operation of a vulnerability factor that in this case stems not from low BRC, but from the impact of aggregate lesions. The central claim of this hypothesis is that brains that have been damaged on more than one occasion are likely to succumb more rapidly to subsequent neuropathological trauma.

Hypothesis C addresses primarily progressive brain diseases and considers the temporal onset of symptoms under three different conditions: addressing the protection and vulnerability postulates and the aggregate lesion hypothesis from a longitudinal perspective. Hypothesis C is probably the most pertinent when considering how TBI could predispose an individual to the later development of

AD in that it states that a progressive brain disease may remain subthreshold or clinically silent until a variety of factors that alter symptom threshold (such as age-related neuronal attrition or head trauma) summate to accelerate symptom onset. Hypothesis C₁ suggests that in individuals with a progressive brain lesion and a high degree of neuronal redundancy, onset of symptoms will be delayed due to the protective effects of high BRC. Conversely, Hypothesis C₂ maintains that given a comparable lesion and progression rate, individuals with low reserve are vulnerable to early symptom onset. Hypothesis C₃ predicts that the aggregation of a chronic–static lesion and a subsequent subthreshold progressive lesion may reverse the protective effect associated with greater BRC, resulting in an early emergence of clinical symptoms.

By developing his model as a threshold theory of acquired brain injury, Satz (1993) alludes to the usefulness of his model in clarifying how TBI could alter an individual's threshold for neurological symptoms. Hence, Satz's theoretical model provides a means to explain why brain injury has repeatedly been implicated as a risk factor for AD in epidemiological studies. Trauma-induced neuronal damage may reduce threshold and brain reserve yet remain clinically silent until, after substantial age-related neuronal loss, a clinical dementia emerges. Yet, in order to ascertain whether Satz's model represents an adequate theoretical basis to explain why TBI may increase individual susceptibility to AD, it is necessary to consider his theoretical stance in the context of empirical evidence that is pertinent to this issue.

Evaluation of Satz's Threshold Theory

Although BRC has been widely referred to within the literature, quantification of this reserve capacity has proven difficult. Mortimer (1997) proposed that the concept of brain reserve has at least three different meanings: (1) the collection of cognitive strategies available for problem solving ("cognitive brain reserve"); (2) the number of neurons or the density of their interconnections (or both) in youth; and (3) the amount of functional brain tissue remaining at any age.

As an underlying assumption of his threshold theory, Satz (1993) suggests that education level and psychometric intelligence serve as indirect psychosocial measures of the BRC construct. Similarly, other investigators have argued that "cognitive brain reserve" may be dependent on education or premorbid IQ (Cummings *et al.*, 1998; Mortimer, 1997). Sufficient evidence from both case-control studies and population-based prevalence and incidence studies has come to light to justify theorizing that individual susceptibility to dementia may vary inversely

as a function of education (Bonaiuto *et al.*, 1990; Jorm *et al.*, 1994; Stern *et al.*, 1994). The literature suggests that high education may afford a higher baseline of functioning tissue, protecting against AD onset (Mortimer and Graves, 1993; Reyes-Ortiz, 1997; Stern *et al.*, 1995), whereas limited educational experience may be associated with low BRC, inducing a predisposition towards the development of AD (Hill *et al.*, 1993; Mortimer *et al.*, 1991; Ott *et al.*, 1995).

Shuttleworth-Jordan (1997) proposed that lower education may even be conceptualized as a form of cerebral "insult," which decreases BRC and cumulatively enhances the probability of neuropsychological dysfunction amongst "already cerebrally compromised individuals" (p. 208). Unverzagt *et al.* (1998) demonstrated that at the same level of clinical dementia severity, individuals with more education showed greater decline from estimated premorbid levels than those with less education. That is, at a given level of dementia severity, those with higher educational status (greater reserve) were found to have a greater disease burden than those with less education. These researchers concluded that their findings support the notion that education, through its association with BRC, can influence the clinical expression of brain disease.

It has been argued that the impact of education on disease expression may have a physiological basis, and that there may be a biological mechanism underlying the concept of "brain reserve." Katzman (1993) asserted that physiologic data provide indirect affirmation of the reserve hypothesis, and postulated that higher education affords greater brain reserve due to stimulation increasing synaptic density in neocortical association cortex. Along similar lines, it has been suggested that neuronal activation leads to the maintenance and survival of neurons by stimulating the action of protective mechanisms, including increased dendritic branching, protein synthesis, DNA repair and functioning of the cholinergic system (Reyes-Ortiz, 1997; Swaab, 1991).

Numerous studies have documented the usefulness of premorbid IQ in predicting long-term outcome after TBI, suggesting that psychometric intelligence may also, in some way, index the amount of reserve available to afford functional compensation after brain damage. An example from the literature illustrates this point and shows how the theory by Satz (1993) has a practical application for clinicians. In a study of pediatric brain damage, Chadwick *et al.* (1981) observed a marked cognitive recovery phase in a group of children sustaining severe TBI, but no such progressive improvement in a group with mild TBI. This finding at first seems counterintuitive because mild TBI might logically be expected to afford greater opportunity for cognitive recovery, but this finding was

attributed to the substantially poorer premorbid intellectual performance of the mild TBI group.

The brain reserve theory predicts that the emergence of dementia should be more strongly related to intelligence than education because educational attainment is determined by other factors in addition to the capacities of the individual (Schmand *et al.*, 1997). This theorizing was the impetus for a recent study, which investigated whether intelligence is a more valid indirect measure of BRC than education. Using the Dutch version of the National Adult Reading Test as a measure of premorbid IQ, Schmand and colleagues concluded that premorbid intelligence is a more powerful determinant of incident dementia than is education. In addition to providing support for the brain reserve theory, this finding can be viewed as consistent with results from the Nun Study (Snowdon *et al.*, 1996). The Nun Study is a longitudinal study of aging and Alzheimer's disease in a group of aged American Catholic Nuns. Using autobiographies written at an average age of 22 years to characterize linguistic ability in early life, Snowdon *et al.* found that low linguistic ability in early life was a strong predictor of poor cognitive function and Alzheimer's disease as assessed (at an average of) 58 years later. Early intellectual functioning, as gauged by linguistic ability, was a more robust indicator of later cognitive performance and risk for Alzheimer's disease than was educational attainment.

In addition to the aforementioned indirect evidence, direct postmortem (e.g., Katzman *et al.*, 1988) and neuroimaging (e.g., Andreason *et al.*, 1993; Willerman *et al.*, 1991) evidence has emerged, which supports Satz's theorizing that individual differences in BRC may confer different degrees of susceptibility to clinical symptoms when the brain is damaged. For instance, Katzman *et al.* (1988) revealed that a subset of functionally and cognitively intact elderly individuals who had definite histological markers of AD at autopsy exhibited higher brain weights and more large neurons than did the age-matched controls. The investigators surmised that these individuals had incipient dementia that had failed to clinically manifest itself as a consequence of their larger brains and greater endowment of neurons conferring protection through providing greater reserve.

More recent investigations have suggested that premorbid brain size, as indexed by both average intracranial area of two adjacent computerized tomographic (CT) scan sections satisfying angulation criteria (Schofield *et al.*, 1995), and head circumference measured above the eyebrows and over the occipital protuberance (Schofield *et al.*, 1997a), may be an important variable in the development of AD. As a corollary to his suggestion that neuronal numbers and the density of their interconnections during youth are determinants of brain reserve, Mortimer (1997) pre-

dicted that indices of brain volume (such as head circumference and intracranial area) should be associated with the risk and severity of dementia in later life.

Premorbid brain size has been found to be inversely associated with the age-specific risk for AD (Schofield *et al.*, 1997a) and positively correlated with the age of onset of AD symptoms (Schofield *et al.*, 1995). In fact, Schofield *et al.* (1995) found that AD onset was delayed by a third of a year for each 1 cm² increase in brain size in a sample of 28 female patients with a diagnosis of probable AD. These findings, along with those from a magnetic resonance imaging (MRI) study conducted by Mori *et al.* (1997), lend support to the proposition that premorbid brain size is a determinant of cognitive reserve in patients with Alzheimer's disease. It has been argued that a larger brain might afford a higher degree of reserve capacity by providing extra neurons and more extensive synaptic connectivity, thereby allowing for greater functional compensation as some neurons are lost during the early stages of the disease process (Cummings *et al.*, 1998; Mori *et al.*, 1997; Schofield *et al.*, 1997a).

The literature also supports the claim made by Satz (1993) that the temporal onset of dementia is dependent upon an individual's unique level of reserve. Several studies attest to the delayed clinical presentation of AD in individuals believed to have high BRC, as indexed by education level and direct measures of brain anatomy and physiology (Katzman *et al.*, 1988; Stern *et al.*, 1992). The study of individuals with Down's syndrome has provided corroboratory evidence for Satz's prediction of early symptom onset in individuals with reduced reserve and threshold levels. The early onset of AD in cases of Down's syndrome appears to be potentiated by a low BRC which results from a developmental arrest at birth and causes subsequent deceleration in brain growth (Lott, 1992; Satz, 1993). Similarly, low BRC has been advanced as a possible explanation for the finding that dementia is markedly more prevalent amongst elderly individuals with learning disabilities than those without them (Cooper, 1997).

However, it is Satz's Hypothesis C₃ that provides the best theoretical framework to explain how TBI could trigger the later development of AD. This hypothesis states that the aggregation of a chronic-static brain lesion (e.g., TBI) and a subsequent subthreshold progressive lesion (e.g., age-related neuronal attrition) accelerates the presentation of neuropsychological symptoms, even in those with initially high BRC. Subthreshold neuronal damage resulting from head trauma diminishes neuronal reserves (Calne *et al.*, 1986; Gedye *et al.*, 1989), thereby serving to hasten the crossing of the threshold for dementia as neurons are further compromised in the course of normal aging.

Empirical evidence supporting this proposed course of events comes from both experimental animal research (Kanayama *et al.*, 1996) and documentation of the insidious development of the dementia pugilistica (or punch-drunk) syndrome in former boxers (Corsellis *et al.*, 1973). Instances of ex-boxers exhibiting anomalous motor signs and marked neuropsychological impairments have been widely cited. In accordance with Satz's theory, the dementia pugilistica syndrome can be attributed to the damage inflicted by repeated blows to the head, aggregating with age-related depletion of cerebral reserves (Roth, 1986).

Additional support for Satz's theoretical hypotheses comes from documentation that antecedent TBI is more pervasive amongst early-onset Alzheimer's cases (Naugle, 1987), a finding clearly consistent with expectation if TBI serves as a predisposing factor to the premature development of dementia. Similarly, a history of TBI has been found to elevate the risk for early-onset AD (Nemetz *et al.*, 1999; Sullivan *et al.*, 1987). Furthermore, Gedye *et al.* (1989) demonstrated that clinical symptoms appeared an average of 6.8 years earlier in AD patients with a history of TBI, and that age of onset decreased as a function of TBI severity.

As previously alluded to, Nemetz *et al.* (1999) employed the population-based resources of the Rochester Epidemiology Project to investigate the time to disease onset in TBI survivors who subsequently developed AD. These authors used data from a previously identified cohort (consisting of all Alzheimer's disease incidence cases in Rochester during the period 1965–1984) to construct a life table which afforded the calculation of the expected length of survival free of AD for each age group. Using this approach, these researchers were able to compare the observed time to AD onset in the TBI cases (calculated as the date of AD onset minus the date of first documented TBI) with the expected length of survival without AD for their age. In this way, Nemetz *et al.* demonstrated that AD cases with a history of TBI exhibited a reduced time to disease onset, with TBI found to exert the greatest impact on time of onset in those individuals sustaining a TBI prior to age 65. The authors interpreted this finding as suggestive that the effect of TBI on the timing of AD onset may be “diluted by the exponential increase in the risk of Alzheimer's disease that occurs with advancing age” (p. 38). In any case, consistent with the predictions of Satz's model, the findings of Nemetz *et al.* provide compelling support for the role of TBI in accelerating the temporal onset of AD.

In a study specifically addressing long-term deterioration after head injury, Lewin *et al.* (1979) reported evidence of a slowly progressive dementia in 11% of their head-injured subjects at follow-up 10 years after injury. On the basis of these findings, Roberts (1979) concluded that “a slowly progressing dementia following severe head

injury, either from the time of injury or after a delay of a few years, far from being a rarity, is a relatively common occurrence” (p. 139). In an attempt to address the question of how long after TBI progressive deterioration should be expected to manifest, Bell (1992) pointed out that the factor that determines the onset of the progressive deterioration would seem to be the magnitude of the surviving population of brain cells. More specifically, Bell speculates that “a conservative estimate for the young adult affected by very severe head injury, in whom atrophy is demonstrated or reasonably suspected, would be that the process of senile dementia will appear 20 years earlier than would otherwise have been the case” (p. 278). This conjecture is concordant with the notion that premature dementia may result from the combined effect of cell loss brought about by prior TBI merging with age-related neuronal attrition. However, empirical studies are required to evaluate the accuracy of this estimate.

NEUROPATHOLOGICAL AND BIOCHEMICAL ISSUES

If TBI is to be viewed as a genuine risk factor for AD, it is necessary to explain how a history of head trauma can increase susceptibility to the disease process. Several studies conducted in the 1980s generated speculation that possible mechanisms underpinning the putative association between TBI and AD may include (1) damage to the blood brain barrier causing leakage of plasma proteins into the brain and increasing permeability to toxins and viruses (Henderson, 1988; Mortimer *et al.*, 1985; Mortimer and Pirozzolo, 1985); (2) liberation of free oxygen radicals (Henderson, 1988); and (3) injury-related neuronal loss lowering the threshold for dementia onset (Henderson, 1988; Mortimer *et al.*, 1985). The latter mechanism alludes to the operation of a threshold effect and can be seen as consistent with Satz's theoretical framework. However, little research effort has been devoted to coherently integrating theoretical concepts and biological findings that pertain to the relationship between TBI and AD.

Despite this obvious shortcoming in the literature, for an association between TBI and AD to be regarded as credible, in addition to having a plausible theoretical basis, it should make biological sense. Therefore, it is necessary to consider whether TBI may initiate the same molecular pathology as demonstrated in the early stages of AD, namely providing unifying pathogenic mechanisms.

Common Pathogenic Mechanisms: A Potential Link Between TBI and AD

Recently, empirical attention has focused on determining whether concrete pathological links may underlie

the proposed association between TBI and AD. It has been extensively documented that the classic neuropathological hallmarks of AD are senile plaques and neurofibrillary tangles, and it is these parameters that quantitatively distinguish a normal elderly person's (aged) brain from that with AD (Esiri, 1994; Perry and Perry, 1988).

Compelling support for the etiological role of TBI in the development of AD has emerged from studies which reveal similarities in the symptomatology and neuropathology of AD and the dementia pugilistica syndrome (Rasmusson *et al.*, 1995). Firstly, the characteristic tangles of dementia pugilistica have been found to be morphologically indistinguishable from the neurofibrillary tangles central to the disease process in AD (Allsop *et al.*, 1990; Roberts, 1988). Secondly, modern immunocytochemical methods using antibodies raised to the β -amyloid protein (β AP) present in AD plaques have revealed extensive deposition of diffuse β AP plaques in Dementia Pugilistica cases with substantial tangle formation (Roberts *et al.*, 1990). Despite being morphologically distinct from "classical" AD plaques, these diffuse plaques have been found to be the most preponderant plaque type in AD (Clinton *et al.*, 1991).

Thus, β AP deposition appears to be a crucial initiating event in the pathogenesis of AD (Klunk, 1998; Morris *et al.*, 1996; Nicoll *et al.*, 1996). In fact, all mutations known to cause AD increase the production of β AP (Cummings *et al.*, 1998). In view of this fact, there has been much speculation in the literature that β AP deposition may be the common underlying pathogenic process linking brain injury and AD. TBI may trigger increased cerebral β AP deposition, thereby inducing the development of the full spectrum of AD in later life (Nicoll *et al.*, 1995). Along similar lines, it has also been theorized that the overexpression of β -amyloid precursor protein (APP) observed in the human brain after trauma may augment the deposition of its derivative β AP, triggering the pathological cascade of neurodegeneration characteristic of AD (Roberts *et al.*, 1994; Storey and Masters, 1995). In support of the argument that increased APP levels after TBI may potentiate AD pathology, Murakami *et al.* (1998) demonstrated that experimental TBI in rats induced overexpression and accumulation of APP in the cerebral cortex and hippocampus, and subsequently lead to neuronal degeneration in the CA3 subsector of the hippocampal region.

Evidence corroborating the role of β AP in the acute phase response to brain trauma comes from documentation that approximately one-third of individuals dying after severe brain injury (age: 8 weeks–81 years) have been found to have cortical β AP deposits at postmortem, whereas neurologically normal controls under 60 years

were devoid of such deposits (Roberts *et al.*, 1994). Although β AP deposits were found in patients as young as 10 years, increasing age was associated with enhanced β AP deposition, indicating that the phenomenon is pathological in nature and not merely an artifact of aging. Similarly, Raby *et al.* (1998) observed elevated levels of the $A\beta_{1-42}$ form of β AP in the cerebrospinal fluid (CSF) of six patients (age: 19–51 years) following severe TBI. $A\beta_{1-42}$, a β -amyloid peptide 42 amino acids in length, is the major component of amyloid depositions (Neve and Robakis, 1998) and has been referred to as "long $A\beta$ " in the literature to differentiate this form from the more predominant species of β -amyloid peptide ($A\beta_{1-40}$), which features just 40 residues (Hardy, 1997). Raby *et al.* (1998) indicated that the increased deposition of $A\beta_{1-42}$ in the traumatized brain might account for the epidemiologically observed increased risk of AD after TBI. These authors also highlighted that the need for future studies to consider whether or not monitoring CSF concentrations of $A\beta_{1-42}$ may be an effective means of both assessing the degree of neuronal damage after TBI and identifying those TBI survivors who may be most vulnerable to the development of AD.

There is some evidence, however, that TBI may trigger β AP deposition predominantly in individuals with the APOE $\epsilon 4$ allele. As previously discussed, the literature indicates that prior TBI and possession of APOE $\epsilon 4$ act synergistically as risk factors for AD (Jordan *et al.*, 1997; Mayeux *et al.*, 1995; Nicoll *et al.*, 1995; Tang *et al.*, 1996; Teasdale *et al.*, 1997). However, the mechanisms by which the APOE $\epsilon 4$ allele may augment the risk for dementia remain to be clearly defined. There has been conjecture in the literature that the APOE molecule may have a direct neurotoxic role (Neve and Robakis, 1998), whereas others have speculated that APOE $\epsilon 4$ may interact with amyloid and impact on the metabolism of β AP (Growdon, 1998). Along similar lines, it has been argued that the association between AD and APOE status results from APOE playing a direct role in β AP deposition in vivo, such that the APOE $\epsilon 4$ allele binds closely to the β -amyloid 4 peptide and consequently transports β AP into brain cells (Nemetz *et al.*, 1999; Nicoll *et al.*, 1995; Poirer *et al.*, 1993; Wisniewski and Frangione, 1992).

The possession of an APOE $\epsilon 4$ allele has also recently been linked with more severe chronic neurological deficits in high-exposure boxers (Jordan *et al.*, 1997). Jordan *et al.* interpreted their findings as giving credence to the hypothesis that AD arises from the interaction of inherited susceptibilities and environmental exposures, including APOE genotype and head trauma. A gene dose effect has been documented, which suggests that the proportion of head-injured individuals with β AP deposition

increases in line with the number of APOE ϵ 4 alleles they possess (Nicoll *et al.*, 1995, 1996).

Thus, available evidence indicates that β AP deposition may constitute a well-defined biological mechanism through which TBI may play a role in the pathogenesis of AD.

A Biochemical Link: The Cholinergic System

Studies exploring the biochemistry of dementia have unveiled a multitude of neurotransmitter and neuropeptide deficits in AD (Decker and McGaugh, 1991; Francis *et al.*, 1985; Whitehouse *et al.*, 1993), yet none have been regarded as prominent in the pathogenesis of this disease as cholinergic system dysfunction (Coyle *et al.*, 1983; Palmer and Gershon, 1990; Whitehouse *et al.*, 1985).

In view of evidence suggesting cholinergic neurotransmission is central to memory processing (Coyle *et al.*, 1983; Perry *et al.*, 1978), several researchers have set out to ascertain whether the memory deficits which characterize TBI survivors may similarly stem from cholinergic system disruption. These studies have demonstrated that TBI in experimental animals induces enduring neurotransmitter deficits and substantial morphological change within the cholinergic system, prompting speculation that this system may have a heightened vulnerability to disruption after trauma (Dixon *et al.*, 1993, 1997; Hayes *et al.*, 1992; Schmidt and Grady, 1995). Cortical cholinergic deficits have also been documented in Dementia Pugilistica patients known to have extensive previous exposure to TBI (Uhl *et al.*, 1982). In addition, a deficit of cholinergic presynaptic terminals in postmortem human brains following head injury has been reported (Murdoch *et al.*, 1998).

Accumulating evidence suggesting a significant presynaptic cholinergic deficit in AD, together with documentation of the role of acetylcholine in memory processing, led to the formulation of the "cholinergic hypothesis of AD." This hypothesis maintained that the characteristic cognitive deterioration of AD was largely attributable to degeneration of cholinergic neurons in the basal forebrain and the associated loss of cortical cholinergic neurotransmission (Francis *et al.*, 1999). It should be noted, however, that Francis and colleagues (1999) have recently proposed a refined version of the cholinergic hypothesis, whereby a glutamatergic hypothesis has been advanced as an auxiliary hypothesis. This revised hypothesis upholds that a major target of cholinomimetic action is excitatory amino acid (EAA) pyramidal neurons, and that cholinergic hypofunction compounds the loss of EAA function. That is, Francis *et al.* have asserted that cholinergic dysfunction may not exert a direct impact on cognitive function in

AD, but rather may act indirectly by interfering with attentional processes and modulating EAA neurotransmission. Whether or not this refined hypothesis may expound the observed association between TBI and AD remains to be addressed in future research. Nevertheless, cholinergic dysfunction presents as a feasible neurochemical link between TBI and AD, and in this way can be seen as a unifying mechanism to explicate how the biochemical characteristics of AD could be induced by TBI.

In view of these findings and those suggesting that β AP deposition consequent to TBI may initiate the development of AD, there appears to be a sizeable body of neuropathological and biochemical evidence that suggests that the association between TBI and AD is biologically plausible.

SUMMARY AND CONCLUSIONS

Accumulating epidemiological evidence implicates TBI as a probable risk factor for AD. The theoretical basis for this phenomenon has been explored within the context of Satz's threshold theory of acquired brain injury (Satz, 1993). Satz's brain reserve and threshold concepts appear to have made a valuable contribution toward establishing a plausible theoretical foundation to explain the association between these two neuropsychological conditions. That is, trauma-induced neuronal damage may interact with age-related neuronal attrition to exhaust BRC, thereby lowering the neuropathological threshold for dementia onset. Additionally, neuropathological and biochemical findings provide powerful evidence that brain trauma could trigger the central neurodegenerative processes of AD. Thus, the identification of several unifying physiological mechanisms that underlie both TBI and AD, such as β AP deposition and cholinergic system dysfunction, can be seen to provide attestation that the proposed association between TBI and AD is biologically credible. When taken together, the literature reviewed gives credence to the proposition that neurotrauma is a provocative agent in the development of AD, and serves support to the association between TBI and AD at the statistical, theoretical, and biological level.

Nevertheless, it must be acknowledged that TBI is neither a necessary nor sufficient event for the development of AD. AD cases do not always have a history of TBI, and TBI victims do not invariably acquire AD. Instead, TBI more than likely constitutes only one of many risk factors that combine in predisposed individuals to induce the complex cascade of events that lead to the development of AD. There is inherent difficulty involved with the process of identifying any one risk factor in what appears to be a multifactorial disease process, as only a fraction of those affected individuals under study will be

demented due to that particular etiology. However, it is not argued here that TBI is the only, or even the strongest, risk factor for the later development of AD, but rather that the current body of evidence suggestive of a link between TBI and AD is sufficiently compelling to warrant further study.

Although the literature upholds the validity of the theoretical postulates by Satz (1993) in a number of different experimental and disease settings, several issues demand clarification and resolution, and are therefore worthy of vigorous pursuit in future research.

In order to eliminate the definitional problem marring epidemiological investigations into TBI, it is imperative that future research be directed toward establishing uniform standards for identifying, diagnosing, and classifying TBI along the lines of those recommended by Teasdale (1995). Furthermore, epidemiological efforts have failed to ascertain whether focal or diffuse TBI arising from various means, such as a fall, repeated minor trauma, or a high-speed road accident, may confer different degrees of risk for the later development of AD. In addition, further epidemiological research should attempt to clearly discern whether TBI inducing amnesia, but not loss of consciousness, imparts a predisposition toward AD onset. Documentation that the degree of risk for AD is progressively linked with the extent of TBI would also provide compelling evidence suggestive of a causal link between TBI and AD.

Although the literature generally provides empirical vindication for the brain reserve and threshold concepts that form the crux of the theory by Satz (1993), Satz himself acknowledges that these constructs remain to be formally integrated into theory. Thus, future research should be directed toward achieving this end, as well as establishing a more definitive measure, and explicit definition, of the BRC construct. It would prove beneficial if subsequent research attempted to elucidate the environmental and genetic variables, which presumably contribute to unique neuropathological thresholds for dementia onset, as this may have important implications for the prevention of AD.

In terms of defining concrete, empirically verified biological links between TBI and AD, further research should focus on discerning whether BRC and threshold concepts underlie the observed neuropathological and biochemical findings pertinent to TBI and AD. Current investigators have not attempted to bring physiological phenomena into an unequivocal relationship with these theoretical constructs. Future efforts to do so will undoubtedly facilitate efforts to integrate the various fields of research contributing to current understanding of the association between TBI and AD.

From the medico-legal point of view, it is recommended that TBI patients undergo comprehensive neuropsychological testing soon after recovery of continuous memory functioning, so as to document the degree of cognitive loss. This may require repeating at yearly intervals until a plateau of recovery is reached. However, follow-up testing until old age should be considered for those individuals known to have the APOE $\epsilon 4$ genotype, as they are at greatest risk of developing early AD. There are at least two estimates in the literature that address how much earlier AD symptoms may manifest as a consequence of sustained head trauma; these estimates, however, vary from an average of 6.8 years (Gedye *et al.*, 1989) to 20 years (Bell, 1992). Longitudinal neuropsychological studies are recommended to ascertain more precisely how much sooner progressive deterioration may be expected to become clinically evident in an individual with a history of TBI. Such studies would assist in developing algorithms for estimating the probabilities of the likelihood and period before early AD may develop in individual cases of TBI.

Readers interested in an update and commentaries on the literature since 1998 are referred to the web site at <http://www.psy.mq.edu.au/psy/publications/tbiad/>.

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