Year : 2015

Reciprocal influences in individuals with traumatic brain injury (TBI) and their caregivers: neurocognitive status in TBI subjects, attachment style and burden in caregivers.

Brioschi Guevara Andrea

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Centre Leenaards de la Mémoire, Département des Neurosciences Cliniques, CHUV
National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NINDS/NIH)

Reciprocal influences in individuals with traumatic brain injury (TBI) and their caregivers: neurocognitive status in TBI subjects, attachment style and burden in caregivers.

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la
Faculté de Biologie et de Médecine
de l'Université de Lausanne

par

Andrea Brioschi Guevara
Psychologue diplômée de l'Université de Genève

Jury

Prof. Philippe Conus, Président
Prof. Jean-François Démonet, Directeur de thèse
Prof. Jordan Grafman, Co-directeur
Prof. Joseph Ghika, expert
Prof. Jean-Marie Annoni, expert
Prof. Armin von Gunten, expert

Lausanne, 2015

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Centre Leenaards de la Mémoire, Département des Neurosciences Cliniques, CHUV
National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NINDS/NIH)

Reciprocal influences in individuals with traumatic brain injury (TBI) and their caregivers: neurocognitive status in TBI subjects, attachment style and burden in caregivers.

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la
Faculté de Biologie et de Médecine
de l'Université de Lausanne

par

Andrea Brioschi Guevara
Psychologue diplômée de l'Université de Genève

Jury

Prof. Philippe Conus, Président
Prof. Jean-François Démonet, Directeur de thèse
Prof. Jordan Grafman, Co-directeur
Prof. Joseph Ghika, expert
Prof. Jean-Marie Annoni, expert
Prof. Armin von Gunten, expert

Lausanne, 2015

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président	Monsieur	Prof. Philippe **Conus**
Directeur de thèse	Monsieur	Prof. Jean-François **Demonet**
Co-directeur de thèse	Monsieur	Prof. Jordan **Grafman**
Experts	Monsieur	Prof. Joseph **Ghika**
	Monsieur	Prof. Jean-Marie **Annoni**
	Monsieur	Prof. Armin **von Gunten**

le Conseil de Faculté autorise l'impression de la thèse de

Madame Andrea Brioschi Guevara

DESS en psychologie clinique de l'Université de Genève

intitulée

Reciprocal influences in individuals with TBI and their caregivers: neurocognitive status in TBI subjects, attachment style and burden in caregivers

Lausanne, le 20 novembre 2015

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Philippe Conus

TABLE OF CONTENTS

Brioschi Guevara A, Démonet J-F, Polejaeva E, Knutson K, Wassermann E, Grafman J and Krueger F. Association between Traumatic Brain Injury-Related Brain Lesions and Long-term Caregiver Burden. J Head Trauma Rehabil. 2015 Jun 1.

Brioschi Guevara A, Démonet JF, Polejaeva E, Knutson KM, Wassermann EM, Krueger F, Grafman J. Association between Long-term Cognitive Decline in Vietnam Veterans With TBI and Caregiver Attachment Style. J Head Trauma Rehabil. 2015 Jan-Feb;30(1):E26-33.

Acknowledgements

There are so many people to thank for helping me during the last three and a half years; so many have contributed in one way or another to help in the completion of this work. First, I would like to thank all the veterans, TBI and non TBI, as well as their caregivers, who were extremely devoted, traveling from all over the United States of America to spend 5 full days at the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH/NINDS), Bethesda, MD.

I would like to express the deepest appreciation and gratitude to my director and co-director of thesis, Prof. Jean-François Démonet and Prof. Jordan Grafman. Prof. Démonet was the initiator of my PhD study and demonstrated trust in me first hand. He kept a spirit of adventure in regard to research (and clinical work) which I appreciated very much. Prof. Grafman gave me the opportunity to participate in this beautiful scientific project by analyzing some aspects of the VHIS cohort (Vietnam Head Injury Study). His amazing scientific accomplishments were a constant inspiration for this work.

I would like to thank Dr. Frank Krueger: without his guidance and steadfast help, this dissertation would not have been possible. His commitment was endless, from the data analyses to the writing process, with an amazing rigor that I still carry with me.

Many thanks also to Dr. Eric Wassermann, who accepted me to work in his lab and participated in all available teachings and journal clubs. He was very supportive and gave me significant valuable advice. I thank Ms. Lena Polejaeva, whose enthusiasm and efficiency were of great support at different stages of this work until the final editing of the papers. I would like to acknowledge Ms. Kris Knutson, who taught me neuroimaging analyses and tried very hard to introduce me to the arduous world of Linux and ABLe (among others). Thank you also to Dr. Daniel Damian whose comments and editing were very helpful at the end of the adventure.

I also thank my friends Leo, Aysha and Anne, who were so supportive and helpful in one way or another.

Finally, I am very grateful to all my family; my husband, Eric, and kids, Méline and Loïc, who were so patient and supportive and to all family members who did many hours of babysitting.

Summary

Traumatic Brain injury (TBI) in war veterans and civilians is a formidable health and socio-economic issue. Beyond the large number of deaths following a TBI, the survivors often live with physical, psychological, cognitive and social limitations related to the injury. The challenge faced by them is also shared by family members, friends, and even more specifically by the primary caregiver. In this context, it is necessary to include caregivers in the equation of the rehabilitation of TBI individuals. In a 40-year follow-up study of Vietnam War veterans, we were interested in the reciprocal relationship between these two partners: the TBI individual and his/her caregiver. The TBI patients we studied had suffered penetrating traumatic brain injuries (pTBI) and while they are rarer than blunt or blast head injuries, their lesions are much more focal and it is easier to interpret the effects of pTBI on particular functions.

In the first study, we investigated the effects of TBI-related brain lesions on long-term caregiver burden in relation to dysexecutive syndrome. Burden was greater overall in caregivers of TBI individuals compared to healthy controls veterans. Also, caregivers of individuals with brain lesions located in areas affecting cognitive and behavioral indicators of a dysexecutive syndrome (i.e., left dorsolateral prefrontal and dorsal anterior cingulate cortices) showed greater long-term burden than caregivers of participants with lesion(s) elsewhere in the brain.

In a second study, we investigated the role of the caregiver attachment style on the TBI individual's cognitive trajectory. After controlling for other factors, cognitive decline was more pronounced in TBI individuals with a highly fearful caregiver, compared to those with a caregiver who demonstrated low levels of fearfullness.

Consequently, there is a long-lasting reciprocal influence between these two partners. First, some TBI-related brain lesions have a lasting effect on long-term caregiver burden due

to cognitive and behavioral factors. Second, it seems that caregivers exercise a significant impact on TBI individuals' environments, sometimes negatively. These results, combined with compelling evidence in the literature about neural plasticity and cognitive reserve, lend support to the impact of the caregiver on the TBI individual; the caregiver can be a surrogate for the environment and provides key stimulation that can both modify and facilitate plasticity. Finally, we discuss potential intervention strategies based on these new findings.

Résumé

Le traumatisme crânio-cérébral (TCC) est un problème socio-économique et sanitaire important, voire dramatique, chez les militaires comme chez les civils. En plus de la haute prévalence de décès parmi les personnes présentant un TCC, les survivants sont souvent confrontés à des séquelles physiques, psychologiques et cognitives, associées à un possible isolement social. L'inévitable défi de vie imposé par ce TCC implique non seulement la personne elle-même, mais également l'entourage et, plus particulièrement, le proche-aidant. Dans ce contexte, il est nécessaire d'intégrer le proche-aidant dans l'équation de la prise en charge globale de la personne avec un TCC. Lors d'une étude de suivi prospectif sur 40 ans chez des vétérans de la guerre du Vietnam victimes d'un TCC, nous nous sommes intéressés à la relation réciproque entre les deux partenaires, à savoir la personne avec un TCC et son proche-aidant. Les TCC étudiés dans ce travail sont de type pénétrant. Alors qu'ils sont moins fréquents que les TCC fermés, les lésions sont plus focales, ce qui facilite l'interprétation de leur association avec des fonctions cognitives.

Dans notre première étude, nous avons investigué les effets des lésions cérébrales du sujet avec un TCC sur le fardeau de son proche-aidant, 40 ans après le TCC. Comme nous l'avions prédit, le fardeau des proche-aidants des sujets avec un TCC est plus sévère que celui des proche-aidants des sujets du groupe contrôle (vétérans de la guerre du Vietnam sans TCC). Par ailleurs, les proche-aidants des sujets avec un TCC qui présentent une lésion dans les aires cérébrales principalement impliquées dans les fonctions exécutives (à savoir les cortex préfrontal dorsolatéral et cingulaire antérieur gauches) ont une valeur de fardeau significativement supérieure à celle des proche-aidants dont les sujets n'ont pas de lésion dans les régions cérébrales précitées.

Dans notre seconde étude, nous avons exploré le rôle du style d'attachement du proche-aidant sur l'évolution cognitive du sujet avec un TCC. Après avoir contrôlé pour les

autres facteurs, nous avons mis en évidence un déclin cognitif significativement supérieur chez les sujets avec un TCC dont le proche-aidant présente un style d'attachement anxieux.

Par conséquent, il existe une influence réciproque entre ces deux partenaires avec, premièrement, un effet à long-terme de la localisation cérébrale des lésions du sujet avec un TCC sur le fardeau du proche-aidant, probablement dû à des facteurs cognitifs et comportementaux liés aux fonctions exécutives ; Deuxièmement, il semble que le proche-aidant exerce un effet important sur l'environnement du sujet avec un TCC, parfois négativement. Ces résultats sont interprétés à la lumière de la littérature existante sur la plasticité neuronale et la réserve cognitive et sont accompagnés d'une réflexion sur les interventions thérapeutiques potentielles.

General Introduction

Traumatic Brain Injury

Traumatic Brain Injury (TBI) results from an impact to the head, a penetrating head injury and/or a rapid acceleration-deceleration of the head, with consequent damage ranging from exclusive damage in white matter tracts in mild cases of TBI (also called concussion) to "diffuse enlargement of the ventricles, focal shearing and contusions, in more severe cases of TBI".[1,2] Leading causes of TBI in the USA are falls (40.5%), struck by/against (15.5%), motor vehicle accidents (14.3%), assaults (10.7%) and unknown/other (19%).[3] Some of those will result in penetrating TBI (pTBI), which are rarer than blunt or blast head injuries, but their lesions are much more focal and it is easier to interpret the effects of pTBI on particular functions. In this work, all participants sustained a pTBI.

TBI is a serious health and socio-economic issue in both civilian and military populations. It contributes each year to 30% of all injury-related deaths in the USA. Approximately ten million individuals worldwide sustain a TBI every year.[4,5] Fourteen percent of combat veterans sustained a brain injury during the Vietnam War,[6] and 294,172 active duty individuals sustained a TBI during the OEF (Operation Enduring Freedom)/OIF (Operation Iraqi Freedom)/OND (Operation New Dawn) conflicts (2000-2013).[7] Many individuals still demonstrate residual symptoms after a TBI. For example, in the USA, 3.2-5.3 million are currently living with a TBI-related disorder.[8,9] They are often faced with physical, cognitive, and social limitations that may persist for their lifetime. These limitations are challenging, not only for the individual who sustains the injury, but also for family members and friends,[10,11] and in particular for the primary informal caregiver. The unpaid contribution of care provided by a family caregiver corresponds to the estimated economic value of $470 billion in the U.S.A. in 2013.[12,13] This informal care reduces the need for professional care, but places a significant burden on the informal/primary caregiver, who takes on a toll financially, physically, and emotionally.[14-17] Eventually, when the caregiver is no longer able

to care for the patient, assisted living or nursing home options have to be sought, leading to an increased financial burden on public services.[12,13] In this context, taking care of patients is not enough; it is necessary to consider the caregivers' global health as well.

There has been growing interest in the relationship between TBI individuals and caregivers in the last 2 decades. Lately, research focused mainly on caregiver burden and its behavioral predictors in many diseases as well as post-TBI. In this work, we are interested in the reciprocal influence between individuals with a penetrating TBI and their caregiver.

More specifically, we investigated the impact of caregivers on the cognitive evolution of individuals with TBI as well as the relationship between brain lesion location of individuals with TBI and long-term caregiver burden.

Caregiver burden

The caregiver in our study provides informal care to TBI individuals. Informal care "has been defined as any person from the patients' environment voluntarily caring for or helping with activities of daily living".[18] This non-professional person will provide financial, physical and/or moral support to another individual with reduced autonomy in her/his daily life activities.

The burden of a caregiver refers to the physical, psychological, emotional, social, and financial challenges one faces when providing care to individuals with chronic illness.[18,19] It has been widely studied in many diseases such as stroke,[20] TBI,[21,22] diverse chronic illnesses,[23] cancer in particular,[24] and dementia.[19] Among dementias, caregivers of patients with a fronto-temporal dementia feel significantly more burden than in Alzheimer disease, probably due to high prevalence and severity of behavioral changes.[25,26] High levels of caregiver burden increase the risk of poor caregiver physical health, anxiety, depression, social isolation, decreased personal independence and reduced quality of life and

satisfaction.[18,27-33] Interestingly, it seems that male and female caregivers are not totally equal regarding some of these risks. For example, a study investigating blood pressure in caregivers compared with non-caregivers, found that female caregivers are at higher risk of developing high blood pressure.[34] Consequently, the authors argue that female - but not male - caregivers are more likely to have cerebral, cardiovascular or kidney disease than non caregiver individuals.[15,34]

The severity of caregiver burden over time is a question under debate. There is compelling evidence that the experience of care evolves over time; being a caregiver in an acute and post-acute disease is different than being a caregiver 6 months, 5 years or even longer after an injury/beginning of a chronic illness. Some studies showed that the severity of burden decreases over time, suggesting that once the environmental adjustment is made, new skills and coping strategies are developed and routines established, the distress reduces.[15,20,35] On the other hand, one can also argue that an extended time of tiredness, social isolation, absence of self-care, constant alertness, may increase - or at least maintain - the initial level of distress.[36,37]

The magnitude of burden is influenced by factors related to the patient, caregiver, and their support systems. Factors related to caregivers are time spent caring for the patient, coping strategies and perceived stigma associated with caregiving.[38,39] Furthermore, the caregiver's mental health is better when family needs are met via adequate health information and emotional and instrumental supports.[39] Factors related to the patient are related to cognitive, emotional and behavioral impairment.[18,19,40] For example, dysexecutive syndrome is characterized by a diverse pattern of behavioral and cognitive disorders related to impaired executive functions (EF).[41] Understanding the link between caregiver burden and EF, as well as its neural signature could be very useful for clinical practice and have a profound impact

on caregivers; those at risk of developing a significant burden would be identified early after the injury and should be carefully followed and wisely advised.

Executive function (EF)

Executive function (EF) is a complex cognitive domain that is constantly evolving and refers to a wide variety of "higher order" cognitive functions and related behaviors. The concept initially included "goal setting, initiation, inhibition, planning, shifting and verification".[42] Now, it is a broader domain that includes behavioral changes and additional cognitive aspects, such as social cognition, theory of mind, strategic processes of episodic memory, insight, and metacognition.[41] The main aims of EF are to facilitate adaptation to new situations and to maintain goal-directed behaviors.[15,16,43]

Dysexecutive syndrome (EF impairment), has been reported in several neurological and non-neurological disorders, such as Parkinson's disease, stroke, fronto-temporal dementia, attention-deficit/hyperactivity disorder, antisocial personality disorder, and schizophrenia.[44-49] Although it is extremely common and present in many diseases, with consequent related literature, the definition of EF remains inconsistent depending on the underlying model.[41] Therefore some authors emphasize the need for consensual criteria to define EF disorders.[41] These authors defined criteria for behavioral and cognitive aspects of the dysexecutive syndrome, some of these criteria being highly suggestive while others are supportive deficits (*Table 1*).

Table 1. ***Criteria for Behavioral and Cognitive Dysexecutive Syndrome***

Criteria for Behavioral and Cognitive Dysexecutive Syndrome[a]	
Behavioral Disorders	**Cognitive Disorders**
Highly suggestive	**Highly suggestive**
• Global hypoactivity with apathy and/or abulia	• Response inhibition
• Global hyperactivity with distractibility and/or psychomotor instability	• Rules deduction and generation
• Stereotyped and perseverative behavior	• Maintenance and shifting of sets
• Environmental dependency (imitation and utilization behavior)	• Information generation (fluency tasks)
Supportive deficits and developing areas	**Supportive deficits and developing areas**
• Disorders of emotional control (apathy, euphoria, moria, emotional lability)	• Planning
• Disorders of social behavior	• Response initiation and sustained alertness
• Disorders of sexual, eating and urinary behavior	• Coordination of dual tasks
• Spontaneous confabulation, reduplicative paramnesia	• Episodic memory strategic processes (retrieval and memory selection)
• Anosognosia, anosodiaphoria	• Theory of mind and metacognitive processes

"Higly suggestive = impairment demonstrated in at least 2 studies showing a significant relation between the impairment and the lesion of the frontal subcortical network (typically comparison between anterior and posterior lesions).
Supportive deficits and developing areas = impairment demonstrated in a group (or subgroup) of patients compared to healthy controls or controversial results across studies or limited number of studies.
[a]To be considered as dysexecutive, the disorder should not be more readily explained by perceptuo-motor, psychiatric (depression, manic state, or obsessive-compulsive disorder), or other cognitive (language, memory, visuo-spatial) disturbances." (Godefroy et al, 2010)[41]

The neural signature of EF has been widely studied in healthy individuals and participants with brain injuries.[44] Considering the diversity of functions hiding behind the executive construct, brain areas associated with executive tasks are numerous. Among the main areas involved in EF, we find the prefrontal cortex (PFC),[44,50-52] the anterior cingulate

cortex (ACC),[44,52,53] the inferior parietal lobes,[51,52,54] and the superior temporal lobes.[52,54-56] The PFC and ACC play key roles in higher-level processes of EF; the ACC is subdivided into two distinct anatomic parts: the rostro-ventral ACC, i.e. subgenual and perigenual parts of the ACC, associated with affective processes, and the dorsal ACC (dACC), posterior to the rostro-ventral AC, associated with cognitive processes (***Figure 1***).[57,58]

The PFC comprises all frontal areas anterior to the premotor cortex and is associated with cognition and behaviors related to EF. The dACC and PFC are highly interconnected and functionally complete one another.[59] More specifically, the PFC is implicated in executive control and decision making whereas the dACC is involved in monitoring performance and error detection.[59,60]

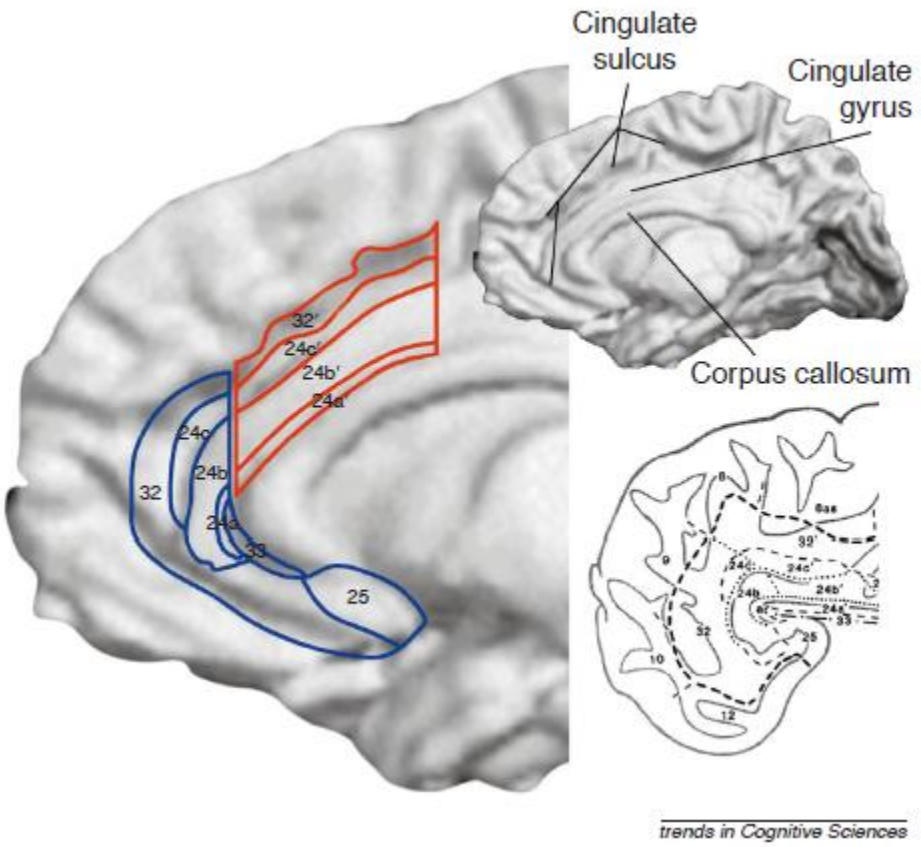


Figure 1. ***Anterior cingulate cortex (ACC) anatomy****. "The upper right part of the figure contains a reconstructed MRI of the medial surface of the right hemisphere of a single human brain (anterior towards the left, posterior towards the right). The cortical surface has been partially inflated to allow simultaneous viewing of gyri and sulci. In this example, a single cingulate gyrus lies between the cingulate sulcus and the corpus callosum. A schematic representation of cytoarchitectural areas (numbered) of ACC is shown on the enlarged section (left). Cognitive division areas are outlined in red and affective division are outlined in blue. These simplified localizations are only approximations for illustrative purposes. A schematized flat map of actual anterior cingulate cortical areas is shown in the bottom right panel. The borders of each sulcus appear as thin unbroken black lines, whereas a combination of broken and dotted lines outline cingulate areas." (Bush et al. 2000)*[57]

Although evidence exists that patients with dysexecutive syndrome increase caregiver burden, [15,18,61-64] limited data exists on neural correlates of caregiver burden. A study investigated caregiver burden in behavioral variant of fronto-temporal dementia (bv-FTD) and cortico-basal syndrome (CBS). Higher burden was associated with right orbitofrontal gyrus atrophy in bv-FTD, and with left inferior and middle temporal gyri in CBS.[65] Another

recent study examining the impact of social cognition impairment in bv-FTD patients on caregiver burden showed that caregiver burden increases with greater atrophy in left lateral premotor cortex. In animal models, this region is associated with the presence of mirror neurons which are possibly involved in empathy.[62]

Nevertheless, the effect of TBI-related brain lesions on long-term burden remains unexplored. Hence, we decided to address this particular question in **Study 1,** that we called "***The Invisible Side of War***" as burden in caregiver and family members was empathetically coined in a paper by Griffin et al.[66]

Reciprocal influence of TBI individual and his caregiver

Most of the studies investigating the relationship between TBI individuals and caregivers were interested in the impact of the TBI on the caregiver. However, evidence exists that the influence is bidirectional. Indeed, the caregiver has an important role in the TBI individual's rehabilitation process.[14] For example, a study by Taylor et al (2001) on TBI in children noted that the family's response to the new situation might affect the recovery of the child.[14] On the other end of the developmental spectrum, some research has examined individuals with dementia and their caregivers,[67-70] showing that a stimulating environment predicts a slower cognitive and functional decline in this population.[67] Individuals with dementia are able to delay nursing home placement when the caregiver is the spouse, is in good health, provides positive interactions, and spends less time providing care.[68,69] In other words, it is possible that the way a caregiver interacts with his disabled partner has an impact on certain outcomes. One available measure to assess an individual style of interacting is "Attachment style".

Attachment style (AS)

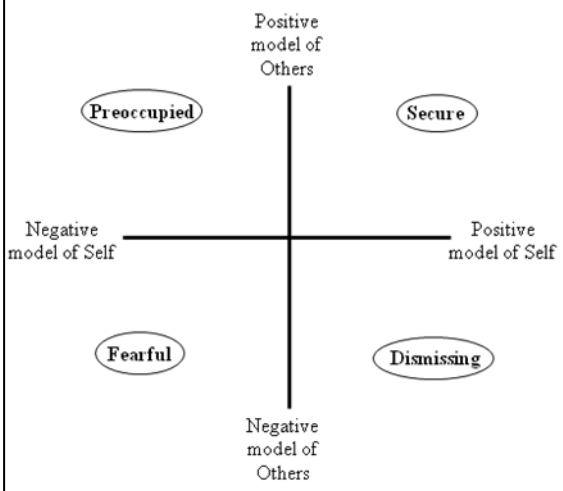
Attachment style (AS) affects the way individuals cope with emotional events and interact with others, including those to whom they are attracted.[71-73] The roots of AS lie in John Bowlby's work on what he called the "attachment behavioral system".[74] Bowlby believed that attachment behavior has a biological function such as protection and was innate in most mammals. Also, he highlighted that an AS was established during early childhood according to the primary attachment figure (mainly the mother) but then it remains mostly stable throughout life as confirmed by recent studies.[75-77] Individual differences in AS were predicted by Bowlby and then systematically studied in mother-infant relationships by Mary Ainsworth.[78]

Inspired by this developmental literature, it was shown that adults can be classified into 4 attachment categories.[79] The adult AS theory holds the view that an individual's AS is organized on two axis (model of Self and model of Others). The axis symbolizing the model of Self represents the individual view of himself, how worthy he is to be loved by others. In contrast, the model of Others represents the view an individual has of others, how positive this view is, and how much the individual will count on others. Preoccupied AS is defined by a negative self-esteem (negative on the model of Self) and positive sociability (positive on the model of Others), whereas dismissing AS individuals present a positive self-esteem but are socially avoidant. Secure AS consists of positive self-esteem and sociability, whereas fearful AS individuals have a low self-esteem and are socially anxious and avoidant (see ***Figure 2***). [80,81]

The association between caregiver AS and behavioral outcomes in individuals with TBI has not been explored yet. In ***Study 2 (The Remarkable Role of Caregiver)***, we argue that the caregiver has a strong influence on the TBI environment; we used her/his AS as an

environmental factor that might impact neural plasticity and cognitive reserve in TBI patients.

(A)



(B)

		Model of Others	
		-	+
Model of Self	-	Fearful: "Avoid intimate contact with others because they fear being rejected" "less likely to seek social support"	Preoccupied: "their self-esteem is highly dependent on others' approval, and they are quick to become involved with others" "More likely to seek social support"
	+	Dismissing: "Avoid intimate contact with others, because they value independence and self reliance" "less likely to seek social support"	Secure: "They perceive themselves as worthy and competent, and are comfortable with intimate relationships" "More likely to seek social support"

*Figure 2. **Adult Attachment styles (AS).** Adapted from Griffin and Bartholomew, 1994, and from Ognibene and Collins 1998. (A) Representation of the 4 adult AS defined on two axis, the model of Self and the model of Others, each stretching along a continuum from the most negative to the most positive perception. (B) Short definition of each AS.*[71,82]

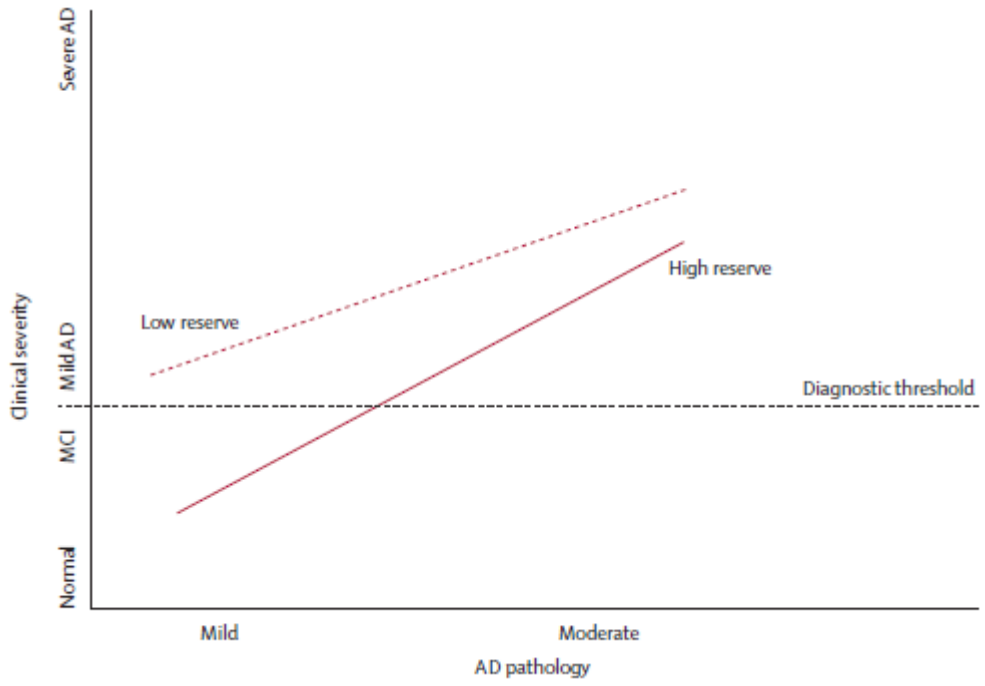
Reserve hypothesis

The reserve is the apparent result of lifetime intellectual activity; it influences the timing of cognitive decline in aging and delays clinical progression in neurodegenerative disorders.[1,83]

The remarkable contrast between brain pathology and clinical expression in Alzheimer's disease raised the hypothesis of reserve. Indeed, some individuals who exhibit excellent daily life functioning and an apparent healthy cognitive functioning were found to have advanced Alzheimer disease (AD) pathology based on autopsy diagnosis.[84] Also,

individuals with an equal amount of AD pathology had very different timing between onset of the disease and their death, that is: the more education the less time between diagnosis and death (***Graph 1***). [84,85]

Reserve hypothesis can be split into two main models: Brain reserve capacity (BRC) and Cognitive reserve (CR). These two models tend to overlap since cognitive reserve has a neuronal explanation too, although more at the level of synaptic organization and the use of specific brain areas (brain network), whereas BRC refer to the quantity of neural substrate.[86]



Graph 1. ***Clinical implications of cognitive reserve in patients with AD.*** *"Individuals with low cognitive reserve might seem to be clinically demented when AD pathology is mild, whereas those with higher cognitive reserve might remain clinically normal. At higher levels of pathology, both groups might appear to be clinically demented. Still, those with higher reserve will appear to be less clinically severe than those with lower reserve. AD=Alzheimer disease. MCI=Mild Cognitive Impairment."(Stern et al 2012)* [87]

The passive model of BRC holds the view that the bigger the brain, the more reserve, and is measured by brain volume, head circumference or neuronal count. In other words, it

implies that a certain amount of brain atrophy is needed to reach a threshold, at which one will express deficits.[86] The active CR model suggests that the brain compensates the damage by using pre-existing cognitive processes, [86,88] that is for the same amount of damage each individual will cope differently.

Measures used for CR are lifetime experience indicators, such as educational and occupational accomplishments, leisure or mentally stimulating activities, as well as pre-morbid IQ and socio-economic status, although these two last measures have shown inconsistent results.[84] Fratiglioni et al (2007), in a meta-analysis, demonstrated that social network was a consistent factor implicated in CR.[89] In particular, a longitudinal study evaluating 1203 elderly showed a clear association between the richness of this social network and the risk of dementia.[90] In this study, social network was characterized by frequency of contact and satisfaction of relationship with family and friends. The combination of frequency and satisfaction was significantly and negatively correlated with the risk of dementia; the absence of a close social tie represents a higher risk to develop a dementia.[90] This was confirmed by a cross-sectional study that reported also an association between the number of confidants and the odds ratio of dementia.[91] Further studies confirmed the presence of a "social factor" correlated with cognitive decline.[92,93] Beyond social network, the social factor is characterized by any activity that includes a social environment.[92,94]

Other leisure activities are not analyzed as variable of CR/BRC but have shown an effect on cognitive performance and brain structure;[95] One of them is bilingualism.[95-97] Interestingly, some authors argue that it is the social implication of being bilingual that has an impact on brain changes.[95] Indeed, bilinguals potentially have to adapt not only to language switching but also to cultural/community differences linked to language.

Regarding genetic factors (for example, the APOE), very few studies have investigated the interaction between genetics and leisure activities, and results are inconsistent. Some studies showed that leisure activities were protective against cognitive decline in carriers of APOE ε4, others argued for an association between leisure activities and cognitive decline in non-carriers of APOE ε4. Yet, another study did not find a correlation between APOE and leisure activities.[92,98-101]

Neural plasticity

Cognitive reserve and brain reserve are linked to the general concept of neural plasticity.[89] Neural plasticity is the "ability of the brain to change, either in response to experience or to injury".[102] Neural plasticity, whose function is for an animal to adapt his behavior to the environment,[103] occurs spontaneously, e.g. after a stroke, but also in the absence of a lesion and throughout the life span. Although we thought until recently that neural plasticity remained stable once the adult brain has fully developed,[104] there is now almost universal acceptance that some neurons are generated continually. It is true that the efficiency of neural plasticity declines with age, with a reduction of the proliferation of new cells, but the dendritic morphology of new and mature neurons is similar to those produced in the young brain.[105,106]

The efficiency of neural plasticity depends on genetic, biological and environmental factors,[106,107] the latter being the focus in this work.

Animal models have shown compelling evidence that enriched environments induce neurogenesis, synaptogenesis, and dendritic growth, which potentially propel recovery after a brain injury.[103,108-111] Living in an enriched environment enhances damage-induced neurogenesis after brain damage in adults; it improves memory and learning skills.[103,108,112,113] The description of an enriched environment differs slightly depending on the studies; it might

be characterized by (1) a large area with objects (toys, running wheels, tunnel), (2) the fact that the location of the objects is changed on a regular basis, and (3) the company of other animals, necessitating social interactions.[103] Most investigations regarding environment were applied on rodents, and one on adult non-human primates.[114] In this work, Kozorovitskiy et al. investigated the impact of enriched environments on dendritic spine density, dendritic length and dendritic complexity of neurons in the hippocampus and the prefrontal cortex, in a marmoset population. Marmosets were placed into three different cages: a new standard laboratory control cage, a complex single cage (larger than the standard ones, with vegetation, 15 objects and food placed in holes) or a complex double cage (compared with the single complex cage, the cage size, as well as the number and variety of objects were doubled). Also, objects were rotated regularly in both complex cages. After a month, marmosets received a lethal injection. Post-mortem results showed that living only one month in a complex environment has a significant impact on dendritic spines on cells in the hippocampus area (dentate gyrus, CA1) and the prefrontal cortex (PFC) (see ***Figure 3***).[114]

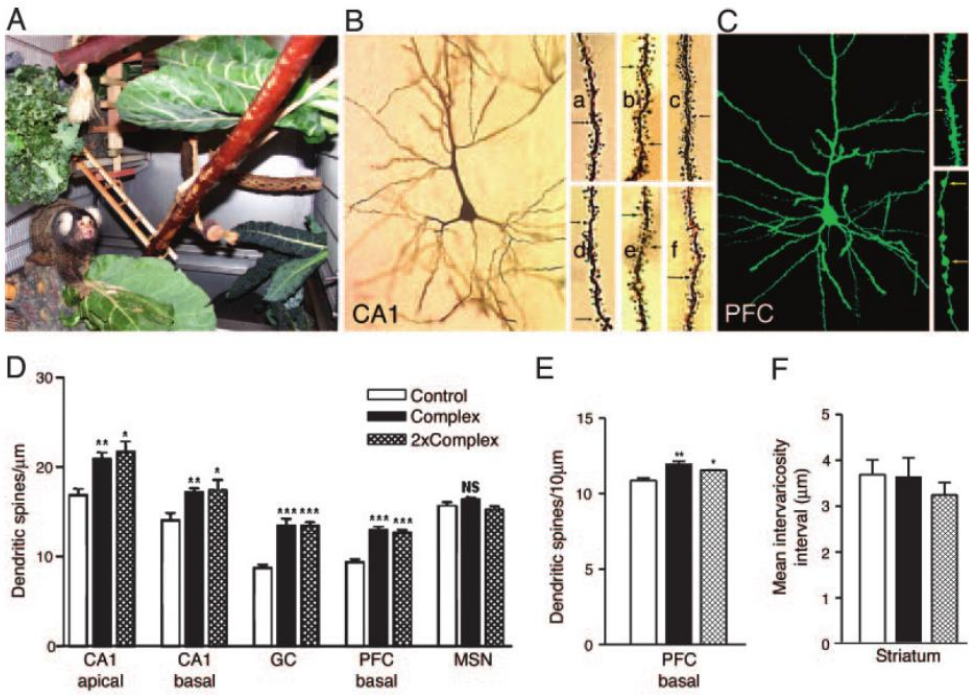


*Figure 3. "**Environmental complexity enhances dendritic spine density in the adult marmoset brain.** (A) Photograph of a marmoset in a complex environment representing ~40% of a complex single cage, with branches, vegetation, and objects typically included in the complex environment: a straw nest, a tree stump with holes, wooden swings, a wooden ladder, and blocks. (B) Photomicrograph of a Golgi impregnated CA1 pyramidal neuron, with close-up views of representative CA1 apical (a-c) and basal (d-f) dendrites, from animals in control (a and d), and complex single (b and e) and complex double cages (c and f). Arrows point the spines. (C) Photomicrograph of a Dil-labeled PFC pyramidal neuron (green color assigned for illustration purposes) with close-up views of a representative basal dendritic segment (upper right) and a cortico-striatal axonal segment (bottom right). Arrows point to spines and varicosities, respectively. (D) Marmosets living in complex environments for 4 weeks have greater dendritic spine density on several types of Golgi-impregnated neurons in the hippocampus and the PFC, compared with marmosets living in standard laboratory environments. Error bars represent SEM; asterisks reflect statistically significant differences from control group on Tukey post hoc comparison: *, P<0.05; **, P<0.01; *** P<0.001. (E) Marmosets living in complex environments have greater dendritic spine density on Dil-labeled neurons compared with animals living in standard laboratory conditions. (F) No differences in intervaricosity spacing on cortico-striatal axons were observed for marmosets living in standard and two types of complex housing." (Kozorovitskyi et al. 2005)[114]*

In contrast, an impoverished environment has a negative impact on neural plasticity. For instance, rats that live in a traditional laboratory cage develop hippocampal atrophy.[105] Interestingly, regions preferentially involved in anxiety, for example, the hippocampus, prefrontal cortex, and amygdala, are particularly plastic and capable of transformation as a result of activity and experience.[105,115,116]

Adaptive plasticity observed in the hippocampus and medial PFC (mPFC) is reversed or inhibited by chronic stress, which also causes dendritic atrophy in the mPFC and hippocampus, and hypertrophy in the amygdala.[116] The PFC and the amygdala are also some of the most common brain areas affected in TBI.[117]

The association between life experience and hippocampus plasticity has been shown in human studies, too. For example, a recent work investigating the correlation between cognitive leisure activities during early adulthood and the volume of different brain areas in individuals with MS found an association between cognitive leisure activities and hippocampus atrophy.[118]

Based on functional imaging studies, Stern and collaborators identify two types of neural processes underlying cognitive reserve: neural reserve and neural compensation.[87] Neural reserve implies that, in case of pathology, cognitive reserve is mediated by the same network than in the absence of pathology, whereas compensation reserve implies that, in addition to the usual network, another neural network is sought to compensate the initially involved and currently dysfunctional network.[87,119,120]

Cognitive decline after TBI

Recovery after TBI is variable and whether TBI is associated with dementia onset is a debated question. A meta-analysis of case-control studies demonstrated the existence of a correlation between TBI and Alzheimer's disease (AD): mild to severe TBI are predictive variables for the development of AD,[121] although the risk might increase with TBI severity.[1] The presence of amyloid-β plaques, which is also typical of AD, was found in 30% of TBI patients and the fact that APOE ε4 affects amyloid pathology and outcome after TBI were hypothesized to be responsible for that link.[1] In contrast, a more recent meta-analysis failed to show the association between TBI and AD.[122] A lack of association between TBI and AD does not mean that there is no difference between TBI and healthy controls in their cognitive trajectory. However, having a dementia or a mild cognitive impairment means that the patient crossed the threshold of pathological functioning (see Graph 1); before this threshold is reached, the analysis of a TBI individual's cognitive function can reveal an increased decline when compared with healthy controls.

Moretti et al, as well as others, argue that TBI is a risk factor for an exacerbated cognitive decline or even for precipitating dementia in some individuals. Indeed, there are structural and functional changes linked to normal ageing, as well as in individuals who sustained TBI, both with resultant neural losses. It is the interaction between these two phenomena that would differentiate TBI individuals from healthy controls (see ***Figure 4***).[1]

Cognitive decline is not always a fatality and can be modulated by the environment. The role of the environment on brain plasticity has been widely studied in animal models, as shown in a previous section ("Neural plasticity"), but less in humans. Based on these animal models and cognitive reserve hypothesis in humans, we argue that the caregiver can be a surrogate for the environment and provides key stimulation that can both modify and facilitate neural plasticity.

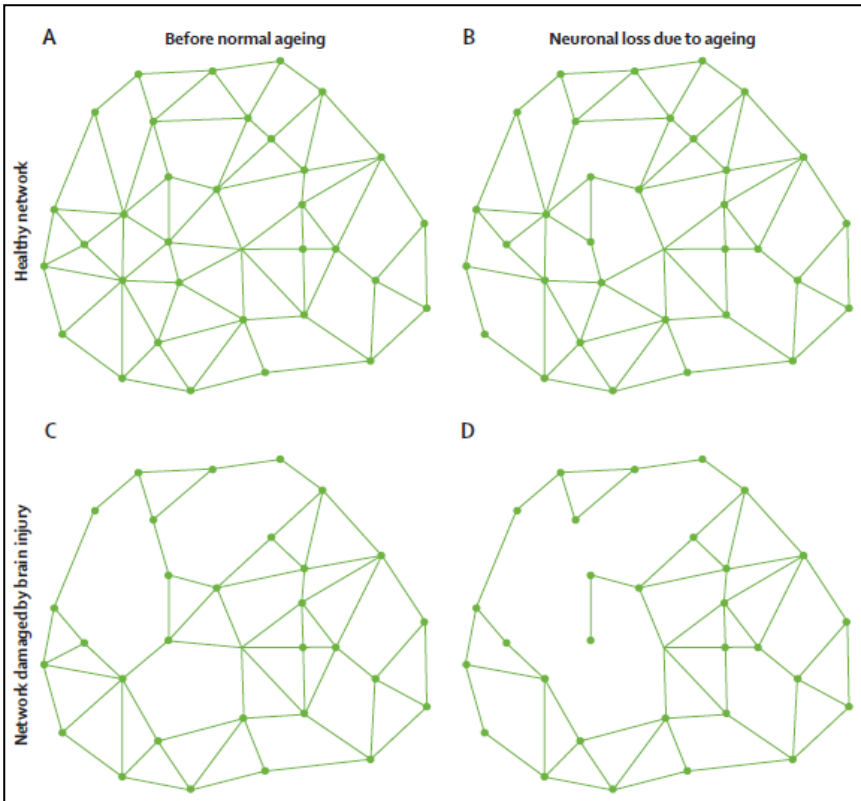


*Figure 4. "**Hypothetical changes in neural networks in normal ageing and after brain injury.** Initial brain damage resulting from traumatic brain injury combined with the expected pathological changes of normal ageing can result in an increased risk of exacerbated cognitive decline. (A) A healthy neural network. (B) Some connections in the healthy network are lost with normal ageing. (C) After traumatic brain injury, several nodes (small-scale neuronal networks within a brain region) are missing. (D) Whereas the healthy network is virtually unaffected by the loss of connections associated with normal ageing, the network damaged by traumatic brain injury can be severely impaired during normal ageing." (Moretti et al 2012)*[1]

Box 1. Summary of the Introduction

In summary :

- Individuals with Traumatic Brain Injury (TBI) face physical, cognitive and social limitations. These limitations are challenging for them and for their caregivers. It is necessary to take care of both the patients and their informal caregivers.
- Some caregivers of TBI individuals are at high risk to feel burden, with consequent physical and psychological health issues.
- The magnitude of burden is influenced by factors related to the caregiver, the patient or the support system. The patient's dysexecutive syndrome is one of them.
- Executive function is a broad and complex construct that is associated with a wide neural signature.
- Although studies showed the possible effect of executive impairment on caregiver burden, there is a lack of data regarding the direct link between TBI-related brain lesions and caregiver long-term burden (**Study 1: The Invisible Side of War**).

Reciprocally,

- It is possible that the way a caregiver interacts with her/his disabled partner has an impact on certain outcomes, triggering the concepts of reserve and neural plasticity.
- Attachment style (AS) is a measure to assess an individual style of interacting, with social implications.
- Cognitive reserve (CR) and brain reserve capacity (BRC), the result of lifetime intellectual activity, influence the timing of cognitive decline in aging and delay clinical progression in neurodegenerative disorders. Social factor is one indicator of CR and BRC.
- CR and BRC are linked to the general concept of neural plasticity.
- Neural plasticity is the "ability of the brain to change, either in response to experience or to injury"[102] and occurs throughout the life span; its efficiency depends on genetic, biological and environmental factors.

  The association between caregiver AS and behavioral outcomes in individuals with TBI has not been explored yet (**Study 2: The Remarkable Role of Caregivers**).

Aim of the Thesis

Our main goal was to investigate the reciprocal influence between individuals with TBI and their caregiver in terms of TBI's cognitive evolution, brain lesion location and long-term caregiver burden.

We questioned the possible relationship between TBI individuals' brain lesion location and long-term caregiver burden, as well as the association between caregiver attachment style and TBI individual's cognitive evolution.

Aims specific to each part of this project are described for each of the two studies.

Participants

PARTICIPANTS (Vietnam Head Injury Study)

Participants were drawn from the Vietnam Head Injury Study (VHIS), a prospective and wide-ranging study of male veterans with (mostly penetrating) TBI. The VHIS consisted of 4 phases that stretched over more than 40 years.[123] Recruitment period for the registry ran during Vietnam war, conducted by Dr William Caveness at the National Institutes of Health. Initially, military physicians based in Vietnam during the war filled out forms compiling information on demographic, injury and initial outcome data of any soldier who survived the first week after a severe head injury. Phase I occurred approximately 5 years post-injury, where available information was collected for the record (1221 men). Phase II (1981-1984) involved neuropsychological testing at the Walter Reed Army Medical Center; Phase III (2003-2006) involved neuropsychological testing, genetic testing, and computed tomography (CT) acquisition at the National Naval Medical Center in Bethesda, Maryland. Finally, in phase IV (2008-2012), i.e more than 40 years after sustaining the TBI, participants and their caregivers came to the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH/NINDS), Bethesda, MD, for a five-day study. During that stay, TBI participants underwent a complete neuropsychological and neurological examination; their caregivers filled several questionnaires and an interview. All participants gave written informed consent and the study was approved by the Institutional Review Board of the NINDS/NIH, Bethesda, MD.

Study 1

The Invisible Side of War…

Association between Traumatic Brain Injury-Related Brain Lesions and Long-term Caregiver Burden

Andrea Brioschi Guevara, Jean-François Démonet, Elena Polejaeva, Kristine Knutson, Eric Wassermann, Jordan Grafman and Frank Krueger.

See Appendix I for the full published article (Brioschi Guevara A, Démonet J-F, Polejaeva E, Knutson K, Wassermann E, Grafman J and Krueger F. Association between Traumatic Brain Injury-Related Brain Lesions and Long-term Caregiver Burden. J Head Trauma Rehabil. 2015 Jun 19)

Objective

Although the association between Traumatic Brain Injury (TBI) and caregiver burden has been widely studied, the implication of TBI-related brain lesions location remains unexplored. Thus, the goal of our study was 2-fold:

1. To investigate long-term caregiver burden in relation to dysexecutive syndrome in a group of participants with penetrating TBI,
2. To study the effect of TBI-related brain lesions on long-term caregiver burden.

Methods

Participants with penetrating TBI (TBI, N=105) were compared with healthy controls veterans (HCv, N=23) on perceived caregiver burden (Zarit Burden Interview [ZBI] at 40 years post-injury) and neuropsychological assessment measures. Data of computed tomographic scans and behavioral statistical analyses were combined to identify brain lesions associated with caregiver burden.

Results

1. Groups were matched on all demographics data, yet, perceived burden was significantly greater in caregivers of TBI group (ZBI total score: 15.51±12.57) than in caregivers of HCv group (ZBI total score: 8.17±5.18) (Z=-2.45; *P*=0.014).
2. Because of the lack of literature regarding the possible relationship between caregiver burden and TBI lesion location, we started with an overlay lesion map using the 24 participants with TBI whose caregivers had a relevant higher burden (ZBI≥24)(***Figure 5b***). For these, a maximum overlap of lesions was found in the left dACC (peak coordinate: *x*=-14; *y*=16; *z*=43, in Montreal Neurological Institute space). Based on this result, we built 2 groups of TBI: one comprising participants with a lesion involving dACC (TBI-T, ***Figure 5c***) and the other TBI group, including all other participants with a TBI (TBI-C)(***Figure 5d***) (for a flowchart detailing the criteria and triage of our groups, see ***Figure 6***).

Based on these neuroimaging data, we compared TBI-T, TBI-C and HCv on their caregiver burden, as well as on demographics, cognitive functions, mood, behavior, functional impairment. Descriptive and inferential statistics are presented in ***Table 2***. Non-parametric analyses (Kruskal-Wallis H test) demonstrated that groups differed significantly on EF measures (FAS, TMT, NBRS, FrSBe apathy, FrSBe disinhibtion, FrSBe EFs), memory (WMS), and post-injury IQ (AFQT total score). Follow-up planned non-parametric analyses (Mann-Whitney U tests, Bonferroni corrected) between lesion groups. As expected, the caregivers of the TBI-T group had a significantly higher burden than the caregivers of the TBI-C group (ZBI, Z=-2.08; *P*<0.037, *r*=0.20) and HCv (ZBI, Z=-3.25; *P*<0.001, *r*=0.541). Also, TBI-T performed significantly worse than TBI-C on verbal fluency (FAS: Z=-2.85, *P*<0.012), mental flexibility (TMT-S: Z=-2.72, *P*<0.021), caregiver assessment (FrSBe apathy: Z=-2.82; *P*=0.015, FrSBe disinhibition Z=-2.79; *P*=0.015, FrSBe EFs: Z=-2.67;

P=0.024), and examiner assessment (NBRS: Z=-3.00, *P*<0.009), but not on memory (WMS: Z=-1.72, *P*=0.258), a control task (TMT-C: Z=-1.65, *P*=0.100), or post-injury IQ (AFQT total score: Z=-1.98, *P*=0.141). Comparing the TBI-T group with the HCv group, non-parametric tests (Mann-Whitney U tests, Bonferroni corrected) demonstrated that the TBI-T group performed significantly worse on EF - verbal fluency (FAS: Z=-3.44, *P*<0.005), mental flexibility (TMT-S: Z=-3.83, *P*<0.001), caregiver assessments (FrSBe apathy: Z=-2.90; *P*=0.009, FrSBe disinhibition: Z=-2.34; *P*=0.048, FrSBe EF: Z=-2.34; *P*=0.048), and examiner assessment (NBRS: Z=-2.51, *P*<0.05) - but also on post-injury IQ (AFQT total score: Z=-3.20; *P*<0.001). TBI-T and HCv did not differ significantly on memory (WMS: Z=-1.87, *P*=0.195).

Finally, since TBI-T and TBI-C groups differed significantly on percentage of brain volume loss, a Spearman's coefficient correlation was applied between percentage of brain volume loss and ZBI total score; no significant correlation was found (r_s=0.45; *P*=0.121).

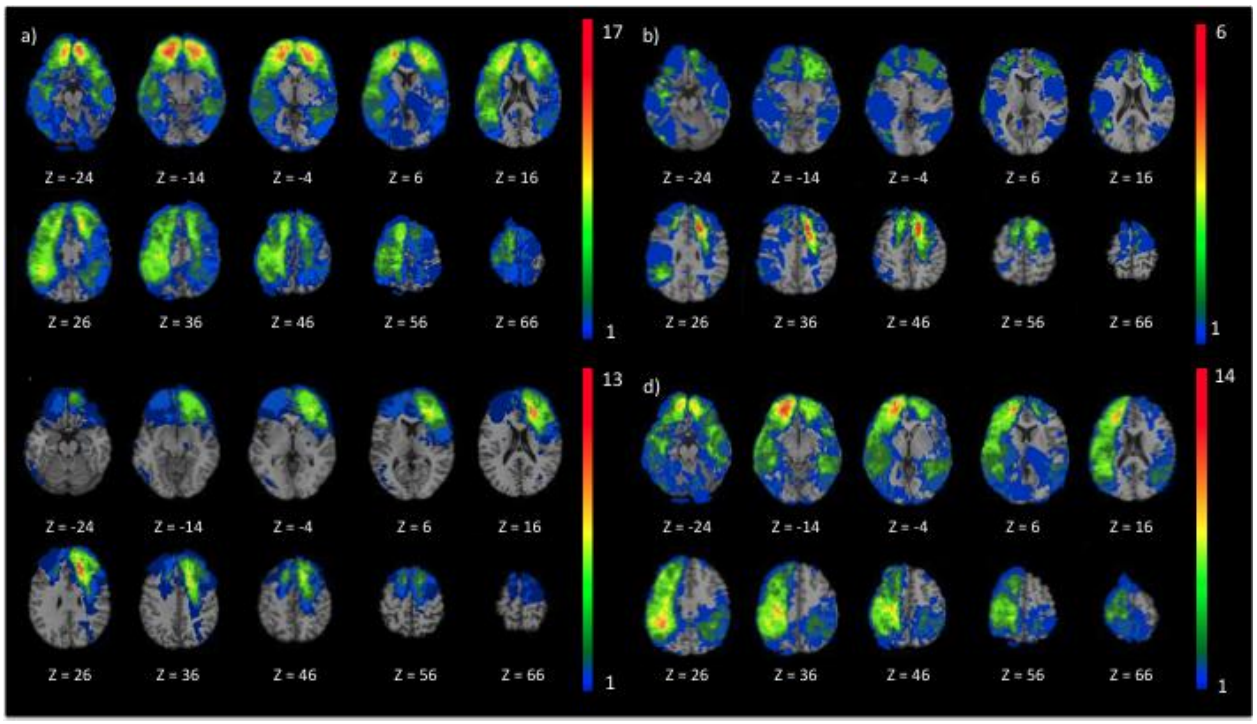


Figure 5. *Lesion overlay map. Z: superior-inferior coordinate in the Talairach space. (**a**) Entire TBI sample (n=105), (**b**) participants with TBI (n=24) whose caregiver had significant perceived burden (ZBI total score ≥ 24), (**c**) TBI-T, participants whose lesion comprised left dACC and dlPFC (n=13), and (**d**) TBI-C, participants whose lesion does not comprise left dACC and dlPFC (n=92). The color bar represents the number of overlapping lesions at each voxel. Red indicates a greater number of participants with TBI who have a lesion on a particular voxel. In each image, the right hemisphere is on the reader's left.*

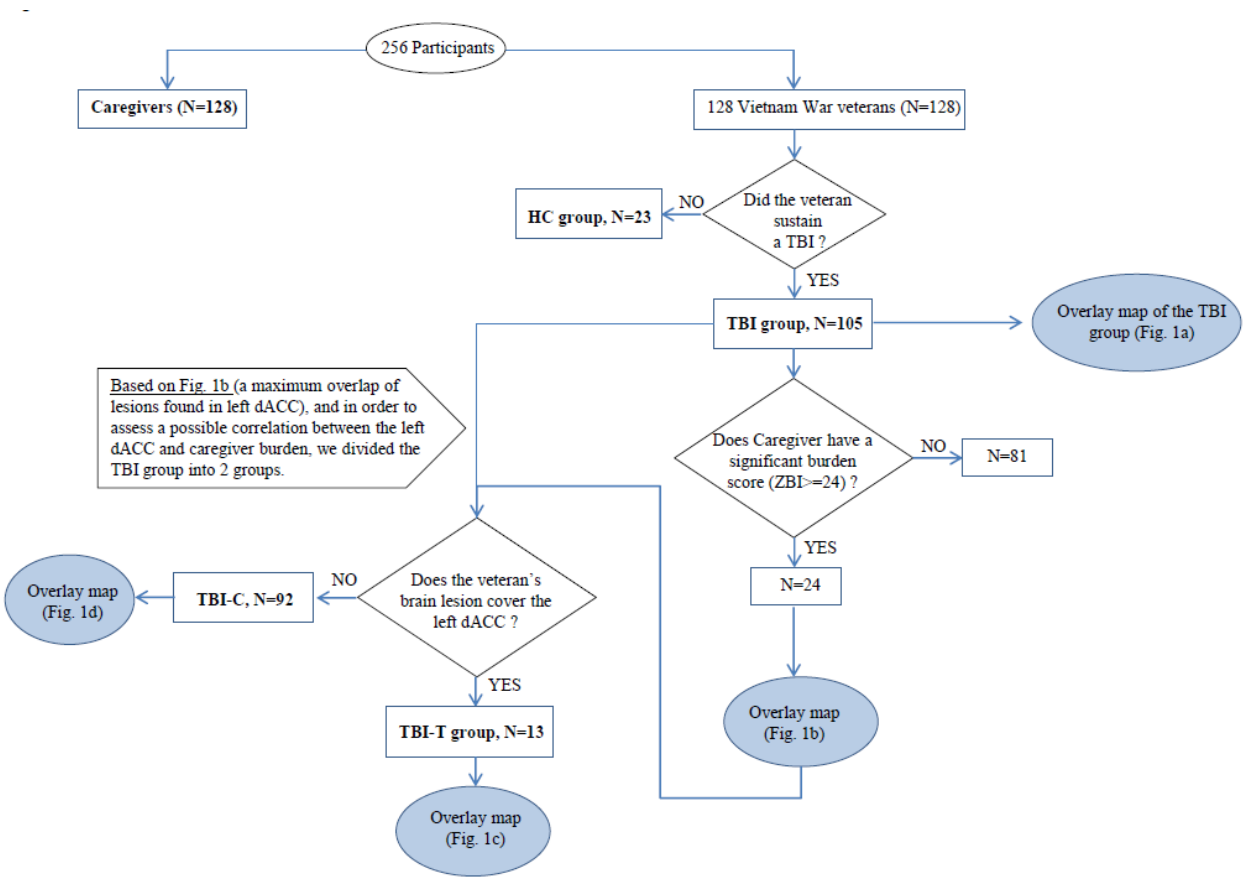


Figure 6. *Flow chart for the criteria and triage of our groups' constitution, as well as the number of participants. HCv, Healthy Control veterans; TBI, Traumatic Brain Injury.*

Table 2. ***Descriptive and inferential statistics for demographics and clinical data for TBI-T (n=13), TBI-C (n=92), and HCv (n=23) groups.***

	TBI-T Mean (s.d.) [Min;Max]	TBI-C Mean (s.d.) [Min;Max]	HCv Mean (s.d.) [Min;Max]	Statistics
DEMOGRAPHICS				
Age (years)	62.15 (1.35)	63.59 (3.12)	62.70 (1.74)	H(2)=3.68; *P*=.159
Education (years)	14.31 (2.02)	14.77 (2.19)	15.13 (1.94)	H(2)=1.35; *P*=.508
Handedness (R:A:L)	10:00:03	77:02:13	17:01:05	X^2 (4)=2.00; *P*=.735
Pre-injury IQ (percentile)	62.92 (27.52)	64.01 (23.23)	73.00 (18.39)	H(2)=2.58; *P*=.275
FSQ (total scaled score)	89.77 (17.30)	96.51 (18.41)	97.35 (20.65)	H(2)=2.22; *P*=.329
Brain volume loss (percentage)	6.00 (3.64)	2.29 (3.05)	-	**Z=-4.10; *P*<.001**
PERCEIVED CAREGIVER BURDEN				
ZBI (total score)	22.38 (10.83) [2;39]	14.54 (12.55) [0;49]	8.17 (5.18) [0;18]	**H(2)=12.89; *P*=.002**
EXECUTIVE FUNCTIONING MEASURES				
FAS (total scaled score)	5.54 (2.60)	9.10 (3.65)	11.09 (3.73)	**H(2)=18.73; *P*<.001**
TMT control (scaled score)	8.38 (3.73)	9.60 (3.61)	11.83 (1.50)	**H(2)=12.49; *P*=.002**
TMT switching (scaled score)	6.92 (3.43)	9.42 (4.03)	11.13 (2.67)	**H(2)=13.13; *P*=.001**
NBRS (total pathology score)	47.23 (22.65)	35.99 (11.24)	35.17 (9.35)	**H(2)=9.13; *P*=.009**
FrSBe Apathy (Total score)	77.31 (20.28)	60.98 (17.58)	57.74 (18.30)	**H(2)=9.84; *P*=.007**
FrSBe Disinhibition (Total score)	71.46 (17.20)	56.98 (15.77)	56.09 (15.63)	**H(2)=7.97; *P*=0.019**
FrSBe EF (Total score)	76.08 (18.73)	60.99 (16.87)	60.17 (19.79)	**H(2)=7.55; *P*=.023**
CONTROL MEASURES				
Post-injury IQ (percentile)	44.23 (27.08)	55.87 (25.42)	72.65 (18.14)	**H(2)=12.29; *P*=.002**
BDI-II (total raw score)	12.69 (11.76)	6.83 (6.95)	9.48 (7.91)	H(2)=4.31; *P*=.116
M-PTSD (total score)	87.00 (21.04)	77.23 (22.34)	80.57 (22.62)	H(2)=3.57; *P*=.168
BNT (total score)	49.15 (13.74)	53.58 (6.30)	55.91 (3.87)	H(2)=3.65; *P*=.161
WMS (delay Memory scaled score)	93.23 (21.32)	101.28 (16.25)	106.87 (17.04)	H(2)=5.12; *P*=.077
VOSP (average percentage)	81.89 (10.11)	84.83 (10.01)	89.26 (4.19)	H(2)=5.37; *P*=.068

Bold statistics are significant. *TBI-T, TBI target; TBI-C, TBI control; HCv, Healthy Control veterans; IQ, Intelligence quotient; FSQ, Functional Status Questionnaire; ZBI, Zarit Burden Inventory; FAS, Verbal Fluency (letter F, A, S); TMT, Trail making test; NBRS, Neurobehavioral Rating Scale; FrSBe, Frontal System Behavioral Scale; EF, Executive function; BDI-II, Beck Depression Inventory; M-PTSD, Mississippi – Post-traumatic stress disorder scale; BNT, Boston Naming test; WMS, Wechsler Memory scale abbreviated; VOSP, Visual Object and Space Perception battery.*

Box 2. Summary of the results and conclusion of Study 1.

Main results:

- Burden was greater in caregivers of veterans with TBI than in caregivers of HCv.
- Caregivers of participants with lesions affecting cognitive and behavioral indicators of dysexecutive syndrome (ie, left dorsolateral prefrontal cortex and dorsal anterior cingulate cortex) showed greater long-term burden than caregivers of participants with lesions elsewhere in the brain.

Conclusion:

- The TBI-related brain lesions have a lasting effect on long-term caregiver burden due to cognitive and behavioral factors associated with dysexecutive syndrome.

Study 2

The Remarkable Role of Caregivers…

Association between Long-Term Cognitive Decline in Vietnam Veterans With TBI and Caregiver Attachment Style

Andrea Brioschi Guevara, Jean-François Démonet, Elena Polejaeva, Kristine Knutson, Eric Wassermann, Frank Krueger and Jordan Grafman

See Appendix II for the full published article (Brioschi Guevara A, Démonet JF, Polejaeva E, Knutson KM, Wassermann EM, Krueger F, Grafman J. Association between Long-term Cognitive Decline in Vietnam Veterans With TBI and Caregiver Attachment Style. J Head Trauma Rehabil. 2015 Jan-Feb;30(1):E26-33)

Objective

The association between caregiver AS and behavioral outcomes in individuals with TBI has not been explored yet. In this study, we hypothesized that the caregiver plays a key role in determining the richness of the individual's environment, thereby affecting the trajectory of long-term cognitive change after TBI. More specifically, we sought to examine whether a caregiver's attachment style is associated with patient cognitive trajectory after TBI, in a 40-year follow-up study.

Methods

On the basis of caregivers' AS (secure, fearful, preoccupied, dismissing), participants with TBI (TBI, N=40) were grouped into a high or low group. To examine the association between cognitive trajectory of participants with TBI and caregivers' AS, we ran four 2 × 2 analysis of covariance on cognitive performances. Those were measured by the Armed Forces

Qualification Test (AFQT, the standardized cognitive evaluation used by the US Army) percentile score, completed at 2 time points: pre-injury and 40 years post-injury.

Results

Fearful AS

On the basis of a median split on caregivers' fearful AS z-scores, 20 patient-caregiver pairs were assigned to the low fearful (LF) and 20 pairs to the high fearful (HF) group. There were no significant differences between the groups on demographic, clinical, or total percent volume loss (see ***Table 3a***, ***Table 3b***).

The ANCOVA evaluating the association between cognitive trajectory for participants with TBI and caregivers' fearful AS showed a significant interaction effect for Trajectory × AS ($F_{1,34}$ =9.328; P = .004) (effect size : η^2=0.215) but no main effect for Trajectory ($F_{1,34}$ =2.155; P = .151) or for AS ($F_{1,34}$ =0.508; P = .481). The covariates, dismissing AS ($F_{1,34}$ =0.597; P = .445), secure AS ($F_{1,34}$ =1.962; P = .170), and NEO conscientiousness ($F_{1,34}$ =1.237; P = .274), were not significantly related to trajectory. Post hoc analysis showed that participants with TBI with HF caregivers performed significantly worse 40 years post-injury than at pre-injury (t_{19} = 4.360; P< .001), whereas participants with TBI with LF caregivers were stable (t_{19} = 0.545; P = .592) (see ***Figures 7 and 8***).

Secure, preoccupied, and dismissing ASs

Using secure caregiver AS as a between-subjects factor, we found a main effect for trajectory ($F_{1,34}$ =8.554; P = .006; η^2=0.201) but no main effect for AS ($F_{1,34}$ =0.037; P = .849), nor a significant interaction effect for trajectory × AS ($F_{1,34}$ =3.455; P = .072).

Using dismissing caregiver AS as a between-subjects factor, we found no main effects for trajectory ($F_{1,34}$ =5.555; P = .024) or AS ($F_{1,34}$ =0.056; P = .815), nor a significant interaction effect for trajectory × AS ($F_{1,34}$ =0.355; P = .555).

Finally, using preoccupied caregiver AS as a between-subjects factor, we found a main effect for Trajectory ($F_{1,34}$ =4.591; P = .039; η^2=0.119), but no main effect for AS ($F_{1,34}$ =0.025; P = .243), nor a significant interaction effect for trajectory × AS ($F_{1,34}$ =0.000; P = .983).

Table 3a. Participants with TBI of the LF and HF groups: Descriptive and inferential statistics (mean and standard deviation) of demographic, neuropsychological, and psychiatric data.

	LF n=20 mean (s.d.)	**HF** n=20 mean (s.d.)	**Statistics** P-value
Participants with TBI			
Age (years)	63.85 (4.38)	62.70 (1.98)	0.291
Education (years)	14.15 (2.11)	13.80 (1.74)	0.57
Handedness (R:L)	16:04	17:03	0.667
Secure AS (z score)	0.099 (0.974)	-1.134 (0.727)	0.398
Fearful AS (z score)	-0.243 (0.580)	0.215 (0.903)	0.065
Preoccupied AS (z score)	-0.243 (0.750)	0.155 (0.811)	0.116
Dismissing AS (z score)	-0.003 (0.894)	0.068 (0.989)	0.813
NEO Neurotic	44.300 (9.370)	49.25 (15.172)	0.222
NEO Extrovert	50.60 (9.779)	45.40 (12.592)	0.153
NEO Openness	44.60 (9.422)	45.15 (8.425)	0.847
NEO Agreeable	50.40 (10.065)	49.60 (12.424)	0.824
NEO Conscientiousness	54.95 (10.650)	46.65 (13.747)	**0.039***
Functional Status Questionnaire	96.50 (18.763)	92.30 (20.846)	0.507
Mississippi PTSD (total raw)	73.35 (21.3555)	84.30 (26.821)	0.161
Beck depression	5.35 (7.527)	10.65 (10.358)	0.073
Wechsler Memory scale (total Memory scaled score)	95.10 (19.523)	95.84 (15.446)	0.993
Boston naming test (total raw)	53.00 (6.936)	53.47 (5.531)	0.816
Token test (total correct)	97.05 (5.424)	97.37 (2.543)	0.817
Verbal fluency (letter, raw)	28.05 (12.931)	28.25 (9.358)	0.931
Sorting test (combined description composite scaled score)	10.20 (3.04)	9.68 (2.89)	0.590
Trail making test (number letter set loss error)	0.40 (0.821)	0.21 (0.419)	0.374
Visual Object and Space Perception Battery	19.20 (1.056)	19.74 (0.562)	0.057
Total percent volume loss (cm^3)	3.9 (4.69)	2.51 (2.30)	0.243

Table 3b. ***<u>Caregivers</u> of the LF and HF groups: Descriptive and inferential statistics (mean and standard deviation) of demographic, neuropsychological, and psychiatric data.***

	LF n=20 mean (s.d.)	**HF** n=20 mean (s.d.)	**Statistics** P-value
Caregivers			
Age (years)	62.15 (4.660)	60.9 (3.076)	0.323
Education (years)	13.65 (1.872)	13.85 (2.300)	0.765
Gender (M:F)	02:18	01:19	0.545
Relation to participant with TBI (spouse:sibling:friend)	17:02:01	19:01:00	0.486
Center for Epidemiologic Studies Depression scale	7.20 (8.40)	13.10 (7.45)	**0.024***
Zarit Burden Inventory	15.45 (13.617)	21.35 (13.743)	0.181
Secure AS (z score)	0.411 (0.855)	-0.372 (0.818)	**0.005***
Fearful AS (z score)	-0.725 (0.327)	0.646 (0.786)	**<0.001***
Preoccupied AS (z score)	-0.083 (0.941)	0.014 (0.810)	0.731
Dismissing AS (z score)	-0.452 (0.740)	0.408 (0.901)	**0.002***

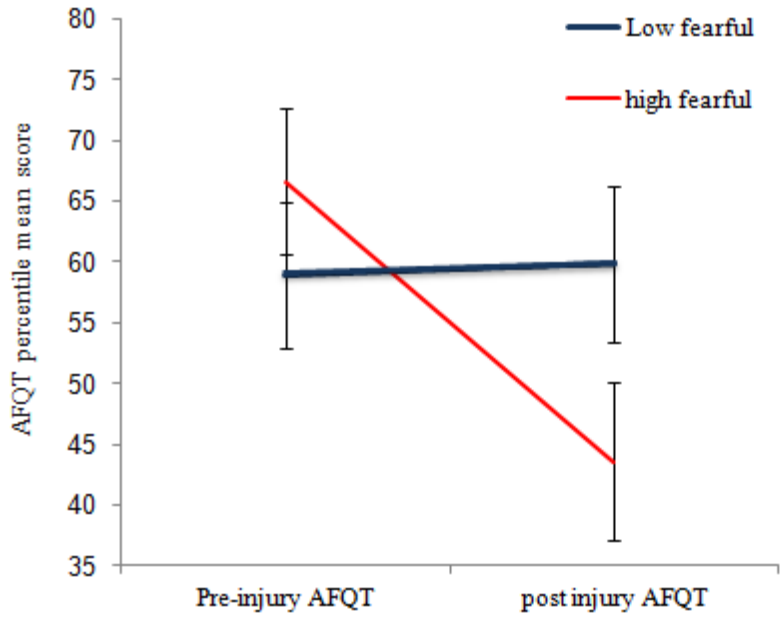


Figure 7. *Cognitive persormances measured with AFQT over time. Mean values and standard error of the mean for the AFQT percentile scores are shown for the paticipants with TBI of the low and high fearful caregiver groups at preinjury. AFQT indicates Armed Forces Qualification Test; TBI, traumatic brain injury.*

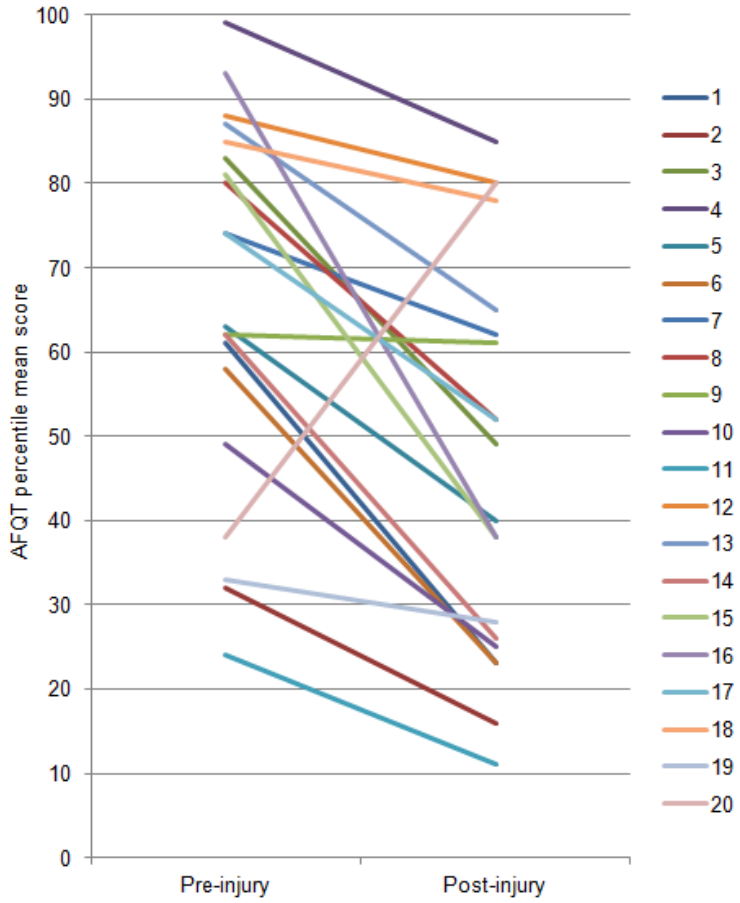


Figure 8. *Individual cognitive decline slopes of the 20 participants with TBI of the high fearful group. AFQT indicates Armed Forces Qualification Test; TBI, traumatic brain injury. Participant with TBI 20 is an outlier but it is not unheard of for someone to show improvement over a lifetime of experience. In his case, he completed his GED after leaving the military (which means after his pre-injury AFQT). He also reported experiencing some difficulties with English and reading while in school. In the port-injury AFQT, his vocabulary subscore is about the same than his arithmetic one. Although we don't have the detail of his pre-injury AFQT, we can speculate that he might have improved greatly his semantic knowledge in the meanwhile.*

Box 3. ***Summary of the results and conclusion of Study 2***

Main results:

- After controlling for other factors, cognitive decline was more pronounced in participants with TBI with a high fearful caregiver than among those with a low fearful caregiver.
- Other attachment styles were not associated with decline.

Conclusion:

- Caregiver fearful attachment style is associated with a significant decline in cognitive status after TBI, probably due to the social consequence of this style.

Discussion

DISCUSSION

We drew our TBI and caregiver participants from the VHIS study, a 40-year follow-up study of a homogeneous population of participants with TBI individuals: US males of similar age and education, who sustained their TBI during combat in Vietnam. Beyond matching the TBI groups for all demographics variables, our controls were also all combat veterans from Vietnam War.

We investigated the reciprocal influence of these two partners, TBI individuals and their caregivers. On one hand, we showed an association between TBI lesion location and caregiver burden; on the other hand, we found an association between caregiver attachment style and TBI cognitive trajectory.

In our first study, we showed that caregiver of participants with TBI still perceive burden more than 40 years after the injury. Burden was less severe than shown in previous studies on severe TBI,[18,124] probably due to time since injury in our investigation: about 40 years against 6 months to 5 years, more rarely 10 years, in previous works. A decrease in the intensity of burden over time concurs with the hypothesis that caregivers develop new skills and coping strategies, on top of an adjusted environment, leading to distress reduction.[15,20,35] Moreover, TBI participants mean age is over 60 years old, and their caregivers are mostly their spouse. This generation is less likely to have additional care recipients; children in particular are usually adults at this point.

This study demonstrated also an association between left dACC/dlPFC lesions and caregiver burden, which might be mediated by cognitive and behavioral factors such as executive function. PFC and ACC are among the brain areas involved in EF, along with inferior parietal lobes and superior temporal lobes;[44,51-56] more specifically they are highly interconnected and complete each other in the role they play in higher-level processes of EF.[57,58]

Although the behavioral and cognitive factors have been widely studied in caregiver burden, lesion location has been less frequently addressed;[65] our study aimed to bridge the gap through the design we described above. While previous studies have shown an association between the behavioral expression of an injured brain and caregiver burden, we demonstrated that there is a direct link between brain injury location and caregiver burden.

We argue that the brain location association is clinically relevant. Indeed, clinicians must be aware that a caregiver whose spouse/offspring/parent suffered a lesion including the dACC/dlPFC is at higher risk of feeling burdened and developing mental health issues. This special risk doesn't involve only caregivers of TBI patients, but possibly caregivers of any other diseases with a dysfunctional dACC/dlPFC, such as some forms of multiple sclerosis, stroke, frontotemporal or vascular dementias. This additional attention to these caregivers is important not only for the individuals but also for society; it is a well-established fact that at least at the chronic stage in these patients, a great proportion of care costs is covered via the informal care provided by close relatives.[12]

On top of a possible psychological therapy to work for example on caregiver's coping strategies, one may recommend to intervene on some factors that are now well-known to reduce the caregiver burden, such as instrumental (helping the caregiver to take care of the house, so that he/she has enough rest) and social supports. It might also be helpful to provide caregivers with information on TBI (including the progression expectations) hence making sure that the whole familial system is prepared to face the behavioral and cognitive consequences of TBI.[124,125]

While raising here a red flag about a specific risk of caregivers of patients with damaged dlPFC and dACC, we should acknowledge that patients' outcomes are sometimes dissociated from imaging results. For example, in individuals with neurodegenerative

diseases, it is not rare to notice a double dissociation between brain atrophy and cognitive or behavioral disorders, and even more specifically, with autonomy in daily life activities.[84,85]

In our second study, we showed an association between the caregivers' Attachment Style (AS) and participants with TBIs' cognitive trajectory. The two partners, the participant with TBI and his caregiver, knew each other for 42 years on average. We found that participants with TBI whose caregiver scored high on fearful AS had a significantly larger cognitive decline from pre-injury to the present. Animal literature on neural plasticity supports the fact that a stimulating environment enhances neurogenesis, synaptogenesis and dendrite growth. Reciprocally, a deprived environment has negative effects on neural plasticity. Moreover, studies involving human participants regarding cognitive reserve and/or brain reserve capacity confirm the influence of lifetime experience indicators on cognitive performances. Among these indicators, social activities and social networks were consistently found to be essential for maintaining and improving cognitive reserve, as it has been shown through influencing longitudinal and cross-sectional studies, then confirmed by meta-analyses.[89-94] A social indicator is characterized by any activity that includes a social environment, from attending social events to taking care of any dependant individual.

The current study confirmed that caregivers exercise important effects on the individuals with TBIs' environment beyond providing physical, social, and emotional support. Referring to the initial definition, an individual with a fearful AS, will avoid intimate contact with others because they fear being rejected and they are less likely to seek social support. Therefore, we hypothesized that a caregiver with a fearful AS might be more socially isolated and might be a factor of the TBI individual's cognitive decline by depriving him of the protective effect of more positive styles. In addition, by being more anxious, it is likely that these caregivers increased stress in the environment of the individual with TBI and

reduced richness of their social activities. In contrast, LF caregivers may allow participants with TBI to be challenged more and increase the variety and interaction potential of their environments. Along those lines, a study showed that a caregiver who spent less time taking care of her/his partner postponed the time of admission to nursing home. Interestingly, the large effect size found for the association between caregivers' AS and cognitive decline of individuals with TBI is equal to or even greater than the medium to large effect size reported in cognitive reserve studies.[126,127]

Future research should take into account the possible effects of the caregiver behavior on recovery and maintenance of functional abilities. Also, one may recommend to evaluate caregivers' AS when establishing long-term rehabilitation strategies in individuals with TBI in order to design cost-effective caregiver interventions targeting AS, thereby preventing long-term cognitive decline in the patient. Very few studies have investigated the impact of a therapy on AS; this limitation is probably due to the concept itself of AS, being considered a trait. One recent study demonstrated an increase in secure attachment along with a decrease in fearful attachment after 6 weeks of intensive psychotherapy.[128] Another strategy would be to explore therapies that prove to have an effect on symptoms associated with fearful AS. For example, cognitive-behavioral therapy has short-term and long-term efficacy for anxiety.[129] Since fearful AS is associated with anxiety disorder,[130] it might be valuable to treat anxiety in caregivers in order to benefit the caregiver as well as in hope of protecting or enhancing cognition in participants.

Limitations

Our studies have some limitations. Some strong advantages of the VHIS population, such as the homogeneity of our all male TBI sample, the uniqueness of the kind of injury and the time frame from injury, can also become a disadvantage as it may limit the potential of generalization of the results to other populations that may differ in terms of sex, age, ethnicity and socioeconomic status. Additionally, our study design did not allow one to explore causal links between our variables. Instead of causal relationships, we could argue for association between brain lesion location and caregiver burden in Study 1, and cognitive decline and AS in Study 2.

In Study 1, we had relatively few participants with a lesion to the left dACC/dlPFC, therefore path analysis was not a suitable option. Computed tomographic scans were used as an imaging technique in this study rather than magnetic resonance imaging (MRI) or even diffusion tensor imaging (DTI); those would have been optimal techniques to observe more accurately brain regions of atrophy. Unfortunately, penetrating injuries often resulted in the participant retaining metallic fragments or shrapnel at the site of injury, MRI scans were not feasible.

In Study 2, the variable we used to assess the cognitive evolution of the TBI participants - the AFQT - did not allow us to determine associations between TBI's specific cognitive impairments and AS.

Future directions

An interesting direction for Study 1 would be to select a larger number of patients with lesions in the left dACC/dlPFC and run path analyses to replicate our work and better determine the links between dACC/dlPFC, EFs and caregiver burden, including a longitudinal perspective from the acute to chronic and long lasting stages.

In Study 2, an interesting research exploration would be to analyze caregiver's behavioral data, measuring, for example, how much the caregiver controls the environment of participants with TBI or how much the caregiver protects the participants with TBI.

Conclusion

In conclusion, taking care of the caregiver of a brain damaged patient should be a priority; supporting the caregiver might facilitate her/his caring activity towards the patient. These studies are clinically relevant. First, they give additional cues to clinicians on who among the caregivers are at risk to be more burdened. Also, we provided evidence that perceived burden persist for a very long time post-injury, particularly when the injury involves brain areas linked to executive function. Inversely, the caregiver exercises a significant impact on a TBI individual's environment; this impact can be deleterious although without ill-intention. We believe that a cost-effective caregiver intervention which targets AS could be beneficial to potentially reducing long-term cognitive decline in the patient. Indeed, as shown in animal and human models, a deprived environment has negative effects on neurogenesis, synaptogenesis and dendrite growth. Hence, enriching TBI individual's environment through the improvement of caregiver's behavior, could have an impact on TBI neural plasticity.

References

REFERENCES

1. Moretti L, Cristofori I, Weaver SM, Chau A, Portelli JN, Grafman J. Cognitive decline in older adults with a history of traumatic brain injury. *Lancet neurology.* 2012;11(12):1103-1112.
2. Armstrong RC, Mierzwa AJ, Sullivan GM, Sanchez MA. Myelin and oligodendrocyte lineage cells in white matter pathology and plasticity after traumatic brain injury. *Neuropharmacology.* 2015.
3. CDC. Center for Disease Control and Prevention. 2015; http://www.cdc.gov/traumaticbraininjury/severe.html.
4. Ozen LJ, Fernandes MA, Clark AJ, Roy EA. Evidence of cognitive decline in older adults after remote traumatic brain injury: an exploratory study. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition.* 2015;22(5):517-533.
5. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation.* 2007;22(5):341-353.
6. Raymont V, Greathouse A, Reding K, Lipsky R, Salazar A, Grafman J. Demographic, structural and genetic predictors of late cognitive decline after penetrating head injury. *Brain : a journal of neurology.* 2008;131(Pt 2):543-558.
7. Department of Defense. DoD Worldwide total Numbers for TBI, 2000-2012. http://www.dvbic.org/dod-worldwide-numbers-tbi
8. Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. *The Journal of head trauma rehabilitation.* 2008;23(6):394-400.
9. Silver J.M. MTW, Yudofsky S.C. *Textbook of Traumatic Brain Injury* Washington DC: American Psychiatric Pub.; 2011.
10. Schmidt AT, Orsten KD, Hanten GR, Li X, Levin HS. Family environment influences emotion recognition following paediatric traumatic brain injury. *Brain injury : [BI].* 2010;24(13-14):1550-1560.
11. Yeates KO, Swift E, Taylor HG, et al. Short- and long-term social outcomes following pediatric traumatic brain injury. *Journal of the International Neuropsychological Society : JINS.* 2004;10(3):412-426.
12. Feinberg L, Reinhard SC, Houser A, Choula R. *Valuing the Invaluable: 2011 Update. The growing contributions and costs of family caregiving.* Washington DC: AARP Public Policy Institute;2011.
13. Reinhard SC, Feinberg L.F., Choula R., and Houser A. Valuing the Invaluable: 2015 Update: Undeniable Progress, but Big Gaps Remain. *Washington DC: AARP Public Policy Institute.* July 2015.
14. Taylor HG, Yeates KO, Wade SL, Drotar D, Stancin T, Burant C. Bidirectional child-family influences on outcomes of traumatic brain injury in children. *Journal of the International Neuropsychological Society : JINS.* 2001;7(6):755-767.
15. Marsh NV, Kersel DA, Havill JH, Sleigh JW. Caregiver burden during the year following severe traumatic brain injury. *Journal of clinical and experimental neuropsychology.* 2002;24(4):434-447.
16. Draper K, Ponsford J. Long-term outcome following traumatic brain injury: A comparison of subjective reports by those injured and their relatives. *Neuropsychol Rehabil.* 2009;19(5):645-661.

17. Draper K, Ponsford J, Schonberger M. Psychosocial and emotional outcomes 10 years following traumatic brain injury. *The Journal of head trauma rehabilitation.* 2007;22(5):278-287.
18. Bayen E, Pradat-Diehl P, Jourdan C, et al. Predictors of Informal Care Burden 1 Year After a Severe Traumatic Brain Injury: Results From the PariS-TBI study. *The Journal of head trauma rehabilitation.* 2012.
19. Leggett AN, Zarit S, Taylor A, Galvin JE. Stress and Burden Among Caregivers of Patients with Lewy Body Dementia. *Gerontologist.* 2011;51(1):76-85.
20. Jaracz K, Grabowska-Fudala B, Gorna K, Jaracz J, Moczko J, Kozubski W. Burden in caregivers of long-term stroke survivors: Prevalence and determinants at 6 months and 5 years after stroke. *Patient education and counseling.* 2015;98(8):1011-1016.
21. Anderson MI, Parmenter TR, Mok M. The relationship between neurobehavioural problems of severe traumatic brain injury (TBI), family functioning and the psychological well-being of the spouse/caregiver: path model analysis. *Brain injury : [BI].* 2002;16(9):743-757.
22. Anderson MI, Simpson GK, Morey PJ, Mok MMC, Gosling TJ, Gillett LE. Differential pathways of psychological distress in spouses vs. parents of people with severe traumatic brain injury (TBI): Multi-group analysis. *Brain Injury.* 2009;23(12):931-943.
23. Savundranayagam MY, Montgomery RJ, Kosloski K. A dimensional analysis of caregiver burden among spouses and adult children. *Gerontologist.* 2011;51(3):321-331.
24. Son KY, Lee CH, Park SM, et al. The factors associated with the quality of life of the spouse caregivers of patients with cancer: a cross-sectional study. *Journal of palliative medicine.* 2012;15(2):216-224.
25. Riedijk S, Duivenvoorden H, Rosso S, Van Swieten J, Niermeijer M, Tibben A. Frontotemporal dementia: change of familial caregiver burden and partner relation in a Dutch cohort of 63 patients. *Dement Geriatr Cogn Disord.* 2008;26(5):398-406.
26. Riedijk SR, De Vugt ME, Duivenvoorden HJ, et al. Caregiver burden, health-related quality of life and coping in dementia caregivers: a comparison of frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2006;22(5-6):405-412.
27. Moules S, Chandler BJ. A study of the health and social needs of carers of traumatically brain injured individuals served by one community rehabilitation team. *Brain injury : [BI].* 1999;13(12):983-993.
28. Kolakowsky-Hayner SA, Miner KD, Kreutzer JS. Long-term life quality and family needs after traumatic brain injury. *The Journal of head trauma rehabilitation.* 2001;16(4):374-385.
29. Kreutzer JS, Livingston LA, Everley RS, et al. Caregivers' concerns about judgment and safety of patients with brain injury: a preliminary investigation. *PM & R : the journal of injury, function, and rehabilitation.* 2009;1(8):723-728.
30. Livingston LA, Kennedy RE, Marwitz JH, et al. Predictors of family caregivers' life satisfaction after traumatic brain injury at one and two years post-injury: A longitudinal multi-center investigation. *NeuroRehabilitation.* 2010;27(1):73-81.
31. Ponsford J, Schonberger M. Family functioning and emotional state two and five years after traumatic brain injury. *J Int Neuropsych Soc.* 2010;16(2):306-317.

32. Schonberger M, Ponsford J, Olver J, Ponsford M. A longitudinal study of family functioning after TBI and relatives' emotional status. *Neuropsychol Rehabil.* 2010;20(6):813-829.
33. Marsh NV, Kersel DA, Havill JH, Sleigh JW. Caregiver burden at 1 year following severe traumatic brain injury. *Brain Injury.* 1998;12(12):1045-1059.
34. Torimoto-Sasai Y, Igarashi A, Wada T, Ogata Y, Yamamoto-Mitani N. Female family caregivers face a higher risk of hypertension and lowered estimated glomerular filtration rates: a cross-sectional, comparative study. *BMC public health.* 2015;15:1519-1519.
35. Quinn K, Murray C, Malone C. Spousal experiences of coping with and adapting to caregiving for a partner who has a stroke: a meta-synthesis of qualitative research. *Disability and rehabilitation.* 2014;36(3):185-198.
36. Greenwood N, Mackenzie A, Wilson N, Cloud G. Managing uncertainty in life after stroke: a qualitative study of the experiences of established and new informal carers in the first 3 months after discharge. *Int J Nurs Stud.* 2009;46(8):1122-1133.
37. Visser-Meily A, Post M, van de Port I, Maas C, Forstberg-Warleby G, Lindeman E. Psychosocial functioning of spouses of patients with stroke from initial inpatient rehabilitation to 3 years poststroke: course and relations with coping strategies. *Stroke; a journal of cerebral circulation.* 2009;40(4):1399-1404.
38. Papastavrou E, Tsangari H, Karayiannis G, Papacostas S, Efstathiou G, Sourtzi P. Caring and coping: the dementia caregivers. *Aging & mental health.* 2011;15(6):702-711.
39. Phelan SM, Griffin JM, Hellerstedt WL, et al. Perceived stigma, strain, and mental health among caregivers of veterans with traumatic brain injury. *Disabil Health J.* 2011;4(3):177-184.
40. Cosseddu M, Alberici A, Pelizzola S, Padovani A, Borroni B. The other face of the coin: the caregiver burden in frontotemporal lobar degeneration. *International Journal of Geriatric Psychiatry.* 2013;28(6):655-657.
41. Godefroy O, Azouvi P, Robert P, Roussel M, LeGall D, Meulemans T. Dysexecutive syndrome: diagnostic criteria and validation study. *Annals of neurology.* 2010;68(6):855-864.
42. Lezak MD. The problem of assessing executive functions. Int J Psychol 1982;17:281–297. *Int J Psychol.* 1982;17:281-297.
43. Seron X, Van der Linden M. *Traité de neuropsychologie clinique de l'adulte.* Neuropsychologie ed: De Boeck; 2015.
44. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology review.* 2006;16(1):17-42.
45. Soeroes P, Harnadek M, Blake T, Hachinski V, Chan R. Executive dysfunction in patients with transient ischemic attack and minor stroke. *Journal of the Neurological Sciences.* 2015;354(1-2):17-20.
46. Takacs A, Kobor A, Tarnok Z, Csepe V. Verbal fluency in children with ADHD: Strategy using and temporal properties. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence.* 2013.
47. Skorvanek M, Rosenberger J, Gdovinova Z, et al. Apathy in elderly nondemented patients with Parkinson's disease: clinical determinants and relationship to quality of life. *Journal of geriatric psychiatry and neurology.* 2013;26(4):237-243.

48. Hsieh S, Irish M, Daveson N, Hodges JR, Piguet O. When one loses empathy: its effect on carers of patients with dementia. *Journal of geriatric psychiatry and neurology.* 2013;26(3):174-184.
49. Martin AK, Mowry B, Reutens D, Robinson GA. Executive functioning in schizophrenia: Unique and shared variance with measures of fluid intelligence. *Brain and cognition.* 2015;99:57-67.
50. Hagen K, Ehlis AC, Haeussinger FB, et al. Activation during the Trail Making Test measured with functional near-infrared spectroscopy in healthy elderly subjects. *NeuroImage.* 2014;85 Pt 1:583-591.
51. Yuan P, Raz N. Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. *Neuroscience and biobehavioral reviews.* 2014;42C:180-192.
52. Buchsbaum BR, Greer S, Chang WL, Berman KF. Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Human brain mapping.* 2005;25(1):35-45.
53. Laird AR, McMillan KM, Lancaster JL, et al. A comparison of label-based review and ALE meta-analysis in the Stroop task. *Human brain mapping.* 2005;25(1):6-21.
54. Jacobson SC, Blanchard M, Connolly CC, Cannon M, Garavan H. An fMRI investigation of a novel analogue to the Trail-Making Test. *Brain and cognition.* 2011;77(1):60-70.
55. Merkley TL, Larson MJ, Bigler ED, Good DA, Perlstein WM. Structural and functional changes of the cingulate gyrus following traumatic brain injury: relation to attention and executive skills. *Journal of the International Neuropsychological Society : JINS.* 2013;19(8):899-910.
56. Spitz G, Bigler ED, Abildskov T, Maller JJ, O'Sullivan R, Ponsford JL. Regional cortical volume and cognitive functioning following traumatic brain injury. *Brain and cognition.* 2013;83(1):34-44.
57. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends in cognitive sciences.* 2000;4(6):215-222.
58. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain : a journal of neurology.* 1995;118 (Pt 1):279-306.
59. Beckmann M, Johansen-Berg H, Rushworth MF. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2009;29(4):1175-1190.
60. Mars RB, Sallet J, Rushworth MF, Yeung N. *Neural Basis of Motivational and Cognitive Control.* Boston, MA: Massachusetts Institute of Technology; 2011.
61. Rivera P, Elliott TR, Berry JW, Grant JS, Oswald K. Predictors of caregiver depression among community-residing families living with traumatic brain injury. *NeuroRehabilitation.* 2007;22(1):3-8.
62. Brioschi Guevara A, Knutson KM, Wassermann EM, Pulaski S, Grafman J, Krueger F. Theory of mind impairment in patients with behavioural variant fronto-temporal dementia (bv-FTD) increases caregiver burden. *Age and ageing.* 2015.
63. Nonterah CW, Jensen BJ, Perrin PB, et al. The influence of TBI impairments on family caregiver mental health in Mexico. *Brain injury : [BI].* 2013;27(11):1287-1293.
64. de Vugt ME, Riedijk SR, Aalten P, Tibben A, van Swieten JC, Verhey FR. Impact of behavioural problems on spousal caregivers: a comparison between Alzheimer's

disease and frontotemporal dementia. *Dement Geriatr Cogn Disord.* 2006;22(1):35-41.
65. Knutson KM, Zamboni G, Tierney MC, Grafman J. Neural correlates of caregiver burden in cortical basal syndrome and frontotemporal dementia. *Dement Geriatr Cogn Disord.* 2008;26(5):467-474.
66. Griffin JM, Friedemann-Sanchez G, Jensen AC, et al. The invisible side of war: families caring for US service members with traumatic brain injuries and polytrauma. *The Journal of head trauma rehabilitation.* 2012;27(1):3-13.
67. Tschanz JT, Piercy K, Corcoran CD, et al. Caregiver coping strategies predict cognitive and functional decline in dementia: the cache county dementia progression study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2013;21(1):57-66.
68. Wright LK. AD spousal caregivers. Longitudinal changes in health, depression, and coping. *J Gerontol Nurs.* 1994;20(10):33-48.
69. Wright LK. Alzheimer's disease afflicted spouses who remain at home: can human dialectics explain the findings? *Soc Sci Med.* 1994;38(8):1037-1046.
70. Perren S, Schmid R, Herrmann S, Wettstein A. The impact of attachment on dementia-related problem behavior and spousal caregivers' well-being. *Attachment & human development.* 2007;9(2):163-178.
71. Ognibene TC, Collins NL. Adult attachment styles, perceived social support and coping strategies. *Journal of Social and Personal Relationships.* 1998;15(3):323-345.
72. Vrticka P, Vuilleumier P. Neuroscience of human social interactions and adult attachment style. *Frontiers in human neuroscience.* 2012;6:212.
73. Mikulincer M, Shaver P. *Attachment in adulthood. Structure, Dynamics, and change.* New York: The Guilford press; 2007.
74. Bowlby J. The making and breaking of affectional bonds. I. Aetiology and psychopathology in the light of attachment theory. An expanded version of the Fiftieth Maudsley Lecture, delivered before the Royal College of Psychiatrists, 19 November 1976. *The British journal of psychiatry : the journal of mental science.* 1977;130:201-210.
75. Kirkpatrick LA, Davis KE. Attachment style, gender, and relationship stability: a longitudinal analysis. *Journal of personality and social psychology.* 1994;66(3):502-512.
76. Klohnen EC, Bera S. Behavioral and experiential patterns of avoidantly and securely attached women across adulthood: a 31-year longitudinal perspective. *Journal of personality and social psychology.* 1998;74(1):211-223.
77. Main M, Kaplan, N., & Cassidy, J. Security in infancy, childhood, and adulthood: A move to the level of representation. *Monographs of the Society for Reasearch in Child Development.* 1985;50(1):66-104.
78. Ainsworth MD. Infant--mother attachment. *The American psychologist.* 1979;34(10):932-937.
79. Bartholomew K, Horowitz LM. Attachment styles among young adults: a test of a four-category model. *Journal of personality and social psychology.* 1991;61(2):226-244.
80. Lopez FG, Gormley B. Stability and change in adult attachment style over the first-year college transition: Relations to self-confidence, coping, and distress patterns. *Journal of Counseling Psychology.* 2002;49(3):355-364.

81. Hamam-Raz YS, Z. Psychological Adjustment of Melanoma Survivors. *Journal of Individual Differences.* 2006;27(3):172-182.
82. Griffin DWB, K. The metaphysics of measurement: The case of adult attachment. *Advances in Personal Relationships.* 1994;5:17-52.
83. Nithianantharajah J, Hannan AJ. The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Progress in neurobiology.* 2009;89(4):369-382.
84. Harrison SL, Sajjad A, Bramer WM, Ikram MA, Tiemeier H, Stephan BC. Exploring strategies to operationalize cognitive reserve: A systematic review of reviews. *Journal of clinical and experimental neuropsychology.* 2015:1-12.
85. Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology.* 2007;68(3):223-228.
86. Bigler ED, Stern Y. Traumatic brain injury and reserve. *Handbook of clinical neurology / edited by P.J. Vinken and G.W. Bruyn.* 2015;128:691-710.
87. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet neurology.* 2012;11(11):1006-1012.
88. Stern Y. Cognitive reserve. *Neuropsychologia.* 2009;47(10):2015-2028.
89. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. *Journal of Alzheimer's disease : JAD.* 2007;12(1):11-22.
90. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet.* 2000;355(9212):1315-1319.
91. Seidler A, Bernhardt T, Nienhaus A, Frolich L. Association between the psychosocial network and dementia--a case-control study. *Journal of psychiatric research.* 2003;37(2):89-98.
92. Paillard-Borg S, Fratiglioni L, Winblad B, Wang HX. Leisure activities in late life in relation to dementia risk: principal component analysis. *Dement Geriatr Cogn Disord.* 2009;28(2):136-144.
93. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. *American journal of epidemiology.* 2002;155(12):1081-1087.
94. Hindle JV, Hurt CS, Burn DJ, et al. The effects of cognitive reserve and lifestyle on cognition and dementia in Parkinson's disease-a longitudinal cohort study. *Int J Geriatr Psychiatry.* 2015.
95. Olsen RK, Pangelinan MM, Bogulski C, et al. The effect of lifelong bilingualism on regional grey and white matter volume. *Brain research.* 2015.
96. Stein M, Federspiel A, Koenig T, et al. Structural plasticity in the language system related to increased second language proficiency. *Cortex; a journal devoted to the study of the nervous system and behavior.* 2012;48(4):458-465.
97. Martensson J, Eriksson J, Bodammer NC, et al. Growth of language-related brain areas after foreign language learning. *NeuroImage.* 2012;63(1):240-244.
98. Rovio S, Kareholt I, Viitanen M, et al. Work-related physical activity and the risk of dementia and Alzheimer's disease. *Int J Geriatr Psychiatry.* 2007;22(9):874-882.
99. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *American journal of epidemiology.* 2005;161(7):639-651.

100. Weaver SM, Portelli JN, Chau A, Cristofori I, Moretti L, Grafman J. Genetic polymorphisms and traumatic brain injury: the contribution of individual differences to recovery. *Brain imaging and behavior.* 2012.
101. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. *Neurobiology of aging.* 2011;32(1):63-74.
102. Raymont V, Grafman J. Cognitive neural plasticity during learning and recovery from brain damage. *Progress in brain research.* 2006;157:199-206.
103. Hirase H, Shinohara Y. Transformation of cortical and hippocampal neural circuit by environmental enrichment. *Neuroscience.* 2014;280:282-298.
104. Deppermann S, Storchak H, Fallgatter AJ, Ehlis AC. Stress-induced neuroplasticity: (mal)adaptation to adverse life events in patients with PTSD--a critical overview. *Neuroscience.* 2014;283:166-177.
105. Leuner B, Gould E. Structural plasticity and hippocampal function. *Annual review of psychology.* 2010;61:111-140, C111-113.
106. Pascual-Leone A, Freitas C, Oberman L, et al. Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. *Brain topography.* 2011;24(3-4):302-315.
107. Mainardi M, Fusco S, Grassi C. Modulation of hippocampal neural plasticity by glucose-related signaling. *Neural plasticity.* 2015;2015:657928.
108. Saucier DM, Yager JY, Armstrong EA. Housing environment and sex affect behavioral recovery from ischemic brain damage. *Behavioural brain research.* 2010;214(1):48-54.
109. Briones TL, Rogozinska M, Woods J. Environmental experience modulates ischemia-induced amyloidogenesis and enhances functional recovery. *Journal of neurotrauma.* 2009;26(4):613-625.
110. Rosenzweig MR. Effects of differential experience on the brain and behavior. *Developmental neuropsychology.* 2003;24(2-3):523-540.
111. Markham JA, Greenough WT. Experience-driven brain plasticity: beyond the synapse. *Neuron glia biology.* 2004;1(4):351-363.
112. Briones TL, Rogozinska M, Woods J. Modulation of ischemia-induced NMDAR1 activation by environmental enrichment decreases oxidative damage. *Journal of neurotrauma.* 2011;28(12):2485-2492.
113. Nithianantharajah J, Hannan AJ. Dysregulation of synaptic proteins, dendritic spine abnormalities and pathological plasticity of synapses as experience-dependent mediators of cognitive and psychiatric symptoms in Huntington's disease. *Neuroscience.* 2012.
114. Kozorovitskiy Y, Gross CG, Kopil C, et al. Experience induces structural and biochemical changes in the adult primate brain. *Proceedings of the National Academy of Sciences of the United States of America.* 2005;102(48):17478-17482.
115. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature reviews. Neuroscience.* 2009;10(9):647-658.
116. Leuner B, Shors TJ. Stress, anxiety, and dendritic spines: What are the connections? *Neuroscience.* 2012.
117. Arciniegas DB, Zasler ND, Vanderploeg RD, Jaffee MS. Management of adults with traumatic brain injury. 2013:10-11.
118. Sumowski JF, Rocca MA, Leavitt VM, et al. Searching for the neural basis of reserve against memory decline: intellectual enrichment linked to larger

hippocampal volume in multiple sclerosis. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* 2015.
119. Steffener J, Stern Y. Exploring the neural basis of cognitive reserve in aging. *Biochimica et biophysica acta.* 2012;1822(3):467-473.
120. Stern Y. Cognitive reserve: implications for assessment and intervention. *Folia phoniatrica et logopaedica : official organ of the International Association of Logopedics and Phoniatrics (IALP).* 2013;65(2):49-54.
121. Mortimer JA, van Duijn CM, Chandra V, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *International journal of epidemiology.* 1991;20 Suppl 2:S28-35.
122. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *Journal of neurology, neurosurgery, and psychiatry.* 2003;74(7):857-862.
123. Raymont V, Salazar AM, Krueger F, Grafman J. "Studying injured minds" - the Vietnam head injury study and 40 years of brain injury research. *Frontiers in neurology.* 2011;2:15.
124. Doyle ST, Perrin PB, Diaz Sosa DM, Espinosa Jove IG, Lee GK, Arango-Lasprilla JC. Connecting family needs and TBI caregiver mental health in Mexico City, Mexico. *Brain injury : [BI].* 2013.
125. Jackson D, Turner-Stokes L, Murray J, Leese M, McPherson KM. Acquired brain injury and dementia: a comparison of carer experiences. *Brain injury : [BI].* 2009;23(5):433-444.
126. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2009;17(3):179-187.
127. Honer WG, Barr AM, Sawada K, et al. Cognitive reserve, presynaptic proteins and dementia in the elderly. *Translational psychiatry.* 2012;2:e114.
128. Kinley JL, Reyno SM. Attachment Style Changes Following Intensive Short-term Group Psychotherapy. *International journal of group psychotherapy.* 2013;63(1):53-75.
129. DiMauro J, Domingues J, Fernandez G, Tolin DF. Long-term effectiveness of CBT for anxiety disorders in an adult outpatient clinic sample: a follow-up study. *Behaviour research and therapy.* 2013;51(2):82-86.
130. Marganska A, Gallagher M, Miranda R. Adult attachment, emotion dysregulation, and symptoms of depression and generalized anxiety disorder. *The American journal of orthopsychiatry.* 2013;83(1):131-141.

Appendix 1

J Head Trauma Rehabil

Association Between Traumatic Brain Injury-Related Brain Lesions and Long-term Caregiver Burden

Andrea Brioschi Guevara, MA; Jean-Francois Demonet, MD, PhD; Elena Polejaeva, BSc; Kristine M. Knutson, MA; Eric M. Wassermann, MD; Jordan Grafman, PhD; Frank Krueger, PhD

Objective: To investigate the association between traumatic brain injury (TBI)–related brain lesions and long-term caregiver burden in relation to dysexecutive syndrome. **Setting:** National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland. **Participants:** A total of 256 participants: 105 combat veterans with TBI, 23 healthy control combat veterans (HCv), and 128 caregivers. **Outcome Measure:** Caregiver burden assessed by the Zarit Burden Interview at 40 years postinjury. **Design:** Participants with penetrating TBI were compared with HCv on perceived caregiver burden and neuropsychological assessment measures. Data of computed tomographic scans (overlay lesion maps of participants with a penetrating TBI whose caregivers have a significantly high burden) and behavioral statistical analyses were combined to identify brain lesions associated with caregiver burden. **Results:** Burden was greater in caregivers of veterans with TBI than in caregivers of HCv. Caregivers of participants with lesions affecting cognitive and behavioral indicators of dysexecutive syndrome (ie, left dorsolateral prefrontal cortex and dorsal anterior cingulate cortex) showed greater long-term burden than caregivers of participants with lesions elsewhere in the brain. **Conclusion and Implication:** The TBI-related brain lesions have a lasting effect on long-term caregiver burden due to cognitive and behavioral factors associated with dysexecutive syndrome. **Key words:** *caregiver burden*, *dorsal anterior cingulate cortex (dACC)*, *dorsolateral prefrontal cortex (dlPFC)*, *dysexecutive syndrome*, *executive functions (EFs)*, *traumatic brain injury (TBI)*

TRAUMATIC BRAIN INJURY (TBI) is a serious health and socioeconomic issue that leads to physical, cognitive, and/or social limitations that may persist throughout life. These limitations also affect the family unit, particularly the primary caregiver for whom these limitations take a financial, health, and emotional toll.[1–4] The estimated economic value of the care provided by family caregivers was $450 billion in the United States in 2009.[5] Notably, the caregiver plays a crucial role in the rehabilitation process of an individual with TBI.[1,6]

Caregiver burden refers to the physical, psychological, emotional, social, and financial challenges one faces when providing care for patients with chronic illness.[7,8] High levels of caregiver burden increase the risk of poor caregiver physical health, anxiety, depression, social isolation, decreased personal independence, and reduced quality of life and satisfaction.[7,9–14] Eventually, when the caregiver is no longer able to care for the patient, assisted living or nursing home options have to be sought, leading to an increased financial burden on public services.[5]

Short-term caregiver burden has been prominently studied in individuals with frontotemporal dementia,[15] Alzheimer disease,[16] and more recently in TBI.[3,7,17] These investigations demonstrated that the magnitude of burden is influenced by factors related to the patient, caregiver, and their support systems. Factors related to caregivers are time spent caring for the patient, positive coping strategies, and perceived stigma associated with caregiving.[18,19] Furthermore, the caregiver's mental health benefits from positive environmental factors, such as family needs being met via adequate health information as well as emotional and instrumental support.[19]

Author Affiliations: *Behavioral Neurology Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (Mss Guevara, Polejaeva, and Knutson, and Dr Wassermann); Faculty of Biology and Medicine, University of Lausanne (Ms Guevara), and Leenaards Memory Center at CHUV, Lausanne University (Ms Guevara and Dr Demonet), Lausanne, VD, Switzerland; Brain Injury Research, Cognitive Neuroscience Laboratory, Rehabilitation Institute of Chicago, Department of Physical Medicine and Rehabilitation, Psychiatry and Behavioral Sciences & Cognitive Neurology (Alzheimer Disease Center), Northwestern University Medical School, Department of Psychology, Northwestern University, Chicago, Illinois (Dr Grafman); and Molecular Neuroscience Department and Department of Psychology, George Mason University, Fairfax, Virginia (Dr Krueger).**Conflicts of interest and source of funding: none declared.*

The authors declare no conflicts of interest.

Corresponding Author: *Frank Krueger, PhD, Molecular Neuroscience Department, George Mason University, 4400 University Drive, Mail Stop 2A1, Fairfax, VA 22030 (FKrueger@gmu.edu)*

DOI: 10.1097/HTR.0000000000000151

Factors related to the patient consist of motor disability as well as cognitive and behavioral impairment.[7,19] Although many variables affect caregiver burden, in the current study we focused on the impact of dysexecutive syndrome, a cognitive and behavioral factor, since it is a major predictor of caregiver burden.[7,20,21] Dysexecutive syndrome is characterized by a diverse pattern of behavioral and cognitive disorders related to impaired executive functions (EFs).[22] Dysexecutive syndrome is observed in several medical conditions, including TBI, stroke, and Alzheimer disease.[22] Executive functions encompass higher-order processes such as planning, problem-solving, and abstract thinking to amend goal-directed behavior.[2,3] Evidence exists that patients' planning and abstract thinking deficits, disinhibition, depression, apathy, social isolation, and impairment increase caregiver burden.[2,7,14,17,23] Dysexecutive syndrome can be assessed by cognitive testing of the patient, through behavioral assessment by a clinician during an interview, and via observation by a caregiver in daily life.

The neural signatures of EFs have been widely studied in healthy individuals and participants with damage to brain areas,[24,25] including prefrontal cortex (PFC),[25–28] anterior cingulate cortex (ACC),[25,28,29] inferior parietal lobes,[27,28,30] and superior temporal lobes.[28,30-32] The PFC and ACC play key roles in higher-level processes of EF; The ACC is subdivided in 2 distinct anatomic parts, the rostroventral ACC, that is, subgenual and perigenual parts of the ACC, associated with affective processes, and the dorsal ACC (dACC), posterior to the caudal-dorsal ACC, associated with cognitive processes.[33,34] The PFC comprises all frontal areas anterior to the premotor cortex and is associated with cognition and behaviors related to EFs. The dACC and PFC are highly interconnected and functionally complete each other.[35] More specifically, the PFC is implicated in executive control and decision making, whereas the dACC is involved in monitoring performance and error detection.[35,36]

Although the effect of TBI on caregiver burden has been widely studied in the past 2 decades, the effect of penetrating TBI-related brain lesions on long-term burden remains unexplored. The goal of our study was 2-fold. First, we investigated long-term caregiver burden in relation to dysexecutive syndrome in a group of participants with penetrating TBI and a healthy control group of Vietnam veterans 40 years after injury. We predicted that long-term burden is greater for caregivers of the TBI group than for caregivers of the control group because of participants' dysexecutive syndrome. Second, we studied the effect of TBI-related brain lesions on long-term caregiver burden and predicted that long-term burden associated with dysexecutive syndrome is greater in caregivers of participants with lesions in key areas involved in EFs than in caregivers of participants with TBI lesions not typically associated with EFs.

METHODS

Participants

Participants were drawn from Phase IV (2008–2012) of the W.F. Caveness Vietnam Head Injury Study (VHIS) registry, a longitudinal study of male veterans with mostly focal penetrating TBI. The VHIS consisted of 4 phases described in detail elsewhere.[37] Phase I was a recruitment period for the registry; phase II (1981–1984) involved neuropsychological testing at the Walter Reed Army Medical Center; phase III (2003–2006) involved neuropsychological testing, genetic testing, and computed tomography (CT) acquisition at the National Naval Medical Center in Bethesda, Maryland; and phase IV (2008–2012) included neuropsychological testing at the National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, Maryland.

A total of 134 male veterans with brain injury and 35 male veterans without brain injury participated in phase IV. To ensure study eligibility, a phone interview was conducted before enrollment, and a screening neurological history and examination were performed at the test site. For this study, we enrolled 128 veterans who were accompanied by their primary caregiver (or family member for the healthy control veteran [HCv] group) and whose caregiver completed the burden scale described later. The total number of participants can be divided into 2 groups: a group with brain injury (TBI, n = 105) and a control group of veterans who had served in combat during the Vietnam era (HCv, n = 23) (note that we will also use the term "caregiver" for the HCv group instead of "family member"). Caregivers of the TBI and HCv groups were not significantly different with respect to age (TBI: mean = 58.31, SD = 8.80; HCv: mean = 56.65, SD = 9.24; $t_{126} = 0.81$, $P = .418$), years of education (TBI: mean = 14.31, SD = 2.35; vHC: mean = 14.30, SD = 2.12; $t_{126} = 0.02$, $P = .985$), gender (TBI: 96 females, 9 males ; HCv: 21 females, 2 males; $\chi^2 = 0.00$, $P = .985$) and type of relationship (TBI: 83 spouses, 6 children, 4 siblings and 12 others; HCv: 17 spouses, 3 children, 2 siblings, 1 other; $\chi^2 = 5.14$, $P = .526$).

All participants gave written informed consent, and the study was approved by the institutional review board of the NINDS/NIH.

Computed Tomography Acquisition

Computed tomographic scans were acquired on a GE Medical Systems Light Speed Plus CT scanner in helical mode. Images were reconstructed with 1-mm overlapping slice thickness and a 1-mm interval. Location and volume of lesion were determined from CT images by

manual tracing using Analysis of Brain Lesion (ABLe) software[38,39] implemented in MEDx (Medical Numerics Inc, Sterling, Virginia) with enhancements to support the Automated Anatomical Labeling atlas.[40] The tracing was performed by a trained neuropsychiatrist and then reviewed by J.G., an experienced observer, who was blind to the results of the clinical evaluations. A consensus judgment determined the final lesion outline. On the basis of the lesion volume, we determined the percentage of volume loss (lesion volume in cc) × 100/total brain volume in cc).

Clinical assessment–Caregiver burden

We assessed perceived caregiver burden with the 22-item version of the *Zarit Burden Interview* (ZBI).[41] Caregivers rated statements expressing specific feelings that arose when taking care of someone else (5-point Likert scale: 0 = never, 4 = nearly always). Caregivers were verbally instructed to respond to this questionnaire as it pertains to the participant they were accompanying for this study. The last item measured overall burden felt from caring for someone else using the same 5-point Likert scale. A total score was obtained by summing the first 21 items; higher scores indicated greater burden. A cutoff score of 24 was determined to be clinically relevant, since it identifies caregivers who are more likely to develop depression and are thus in need of further assessment and potential interventions.[42]

Clinical assessment--Executive functions

We assessed participants' EFs with 2 cognitive tasks: the phonologic verbal fluency task and the trail making test from the Delis-Kaplan EF system (D-KEFS) battery.[43] The *verbal fluency task* assesses one's capacity to produce as many words as possible that start with a given letter (F, A, and S) within 60 seconds per letter (*FAS*). The scaled score of the total number of new words listed (repetitions not counted) (FAS-T) was used. The *trail making test* switching condition (*TMT-Switching*, TMT-S) assesses mental flexibility to connect in alternation letters and numbers, respecting alphabetic and numeric order. A second *TMT* condition was used to control for alphabetic order. Participants had to link letters in alphabetic order without alternating with numbers (*TMT-control*, TMT-C). The scaled score of the sum of sequences produced was used for each condition (TMT-S, TMT-C).

In addition, the *Frontal System Behavioral (FrSBe)* scale[44] and the *Neurobehavioral Rating Scale (NBRS)*,[45] clinically relevant measures related to participants' EFs, were collected from the caregivers and the test examiner, respectively. The *FrSBe* consists of 46 statements assessing apathy, disinhibition, and EFs. The caregivers rated the responses (5-point Likert scale: 1 = almost never, 5 = almost always) to reflect the care recipient's observed behavior. Note that although each statement was rated twice during phase IV–once assessing dysexecutive syndrome before the injury and once assessing it at present (with higher scores indicating greater "frontal syndrome" behavior)–only the present scores were used for this study (FrSBe apathy, FrSBe disinhibition, FrSBe EF). The *NBRS* is based on the examiner's observation of the care recipient's behavior, including affect (eg, emotional withdrawal, decreased initiative/motivation, lability of mood) and cognitive aspects (eg, disinhibition, conceptual disorganization, poor planning) of EFs. The total pathology score on the 27 items (7-point Likert scale: 1 = the symptom is not present, 7 = the symptom is extremely severe) was used. The test examiner typically spent a total of 30 hours observing the participant before completing the NBRS.

Clinical assessment--Instrumental functions, PTSD, and mood

We included additional neuropsychological tests as instrumental measures. We administered the *Armed Forces Qualification Test (AFQT-7A)*, a global intelligence test of word knowledge, arithmetic word problems, object function matching, and mental imagery. Scores on this test correlate highly with performance on the Wechsler Adult Intelligence Scale.[46,47] Participants completed the AFQT prior to military entry (preinjury IQ) and during their visit for phase IV (postinjury IQ). The total AFQT score was converted to a percentage score of correct answers. We assessed language abilities with the *Boston Naming Test* (2nd edition),[48] on which participants viewed black and white drawings of common objects and were asked to name each object. We used the total score–the number of correct answers.

We evaluated visual and auditory declarative memory with the *Wechsler Memory Scale abbreviated (WMS-III a)*,[49] using the delayed memory scaled score. We assessed aspects of visual perception with the *Visual Object and Space Perception battery*,[50] which consists of 8 subtests: incomplete letters, silhouettes, object decision, progressive silhouettes, dot counting, position discrimination, number location, and cube analysis. For our purpose, we selected 2 of 4 tasks assessing object perception (ie, silhouette and object decision) and 2 of 4 tasks assessing space perception (ie, position discrimination and cube analysis), avoiding the use of letter or number as stimuli to minimize the involvement of cognitive factors related to letter and number knowledge (for the description of the tasks, see Schintu et al[51]). We converted the total score of each subtest into a percentage and used the average of these 4 percentages for further statistical analyses. Finally, we used the *Beck Depression Inventory*[52] to assess severity of depression and the Mississippi

Scale (*M-PTSD*) to evaluate posttraumatic stress disorder.[53] The total raw scores of these self-report measures were used for our analyses. Finally, we assessed global disability, using the total scaled score of the *Functional Scale Questionnaire*.[54]

Statistical Analysis

We used IBM SPSS (version 16 for Mac, www.spss.com) and applied a threshold of $P < .05$ (2-tailed). To investigate long-term caregiver burden, we first compared TBI and HCv groups on demographics and clinical assessments, using Mann-Whitney *U* tests. Then partial correlations were computed between caregiver burden (ZBI total score) and EF measures (FAS, TMT-C, TMT-S, FrSBe, and NBRS), while controlling for language (Boston Naming Test) since our targeted brain region is located in the left hemisphere. Second, to investigate the effect of brain lesion location on long-term caregiver burden, lesion maps for the entire TBI population were overlaid to ensure coverage of regions previously identified in dysexecutive syndrome. Next, lesion maps for those participants with TBI whose caregivers had a clinically relevant high burden score (ZBI $\geq$ 24) were overlaid to identify a consistent lesion pattern associated with caregiver burden. Participants whose injury was included in the identified lesion pattern were separated into a target group (TBI-T) and the remaining participants into a control group (TBI-C). In addition, 3 overlap maps were created, including 2 subtraction maps (1 displaying only lesions of the TBI-T group and another only lesions of the TBI-C group) and a conjunction map (showing the overlap in both groups) (see Figure 1).

Finally, to investigate the effect of lesion location on deficits in dysexecutive syndrome that may mediate long-term caregiver burden, demographics and clinical assessment measures were compared using Kruskal-Wallis *H* tests among groups (TBI-T, TBI-C, and HCv) and planned follow-up Mann-Whitney *U* tests between groups (TBI-T vs TBI-C, TBI-T vs HCv).

RESULTS

The groups (TBI, HCv) were matched on age, years of education, handedness, and preinjury IQ (see Table 1). The caregivers of those in the TBI group showed a significantly higher burden than the caregivers of the HCv group ($Z = -2.45$; $P < .05$). Participants with TBI performed significantly worse than HCv on EF tasks (FAS,

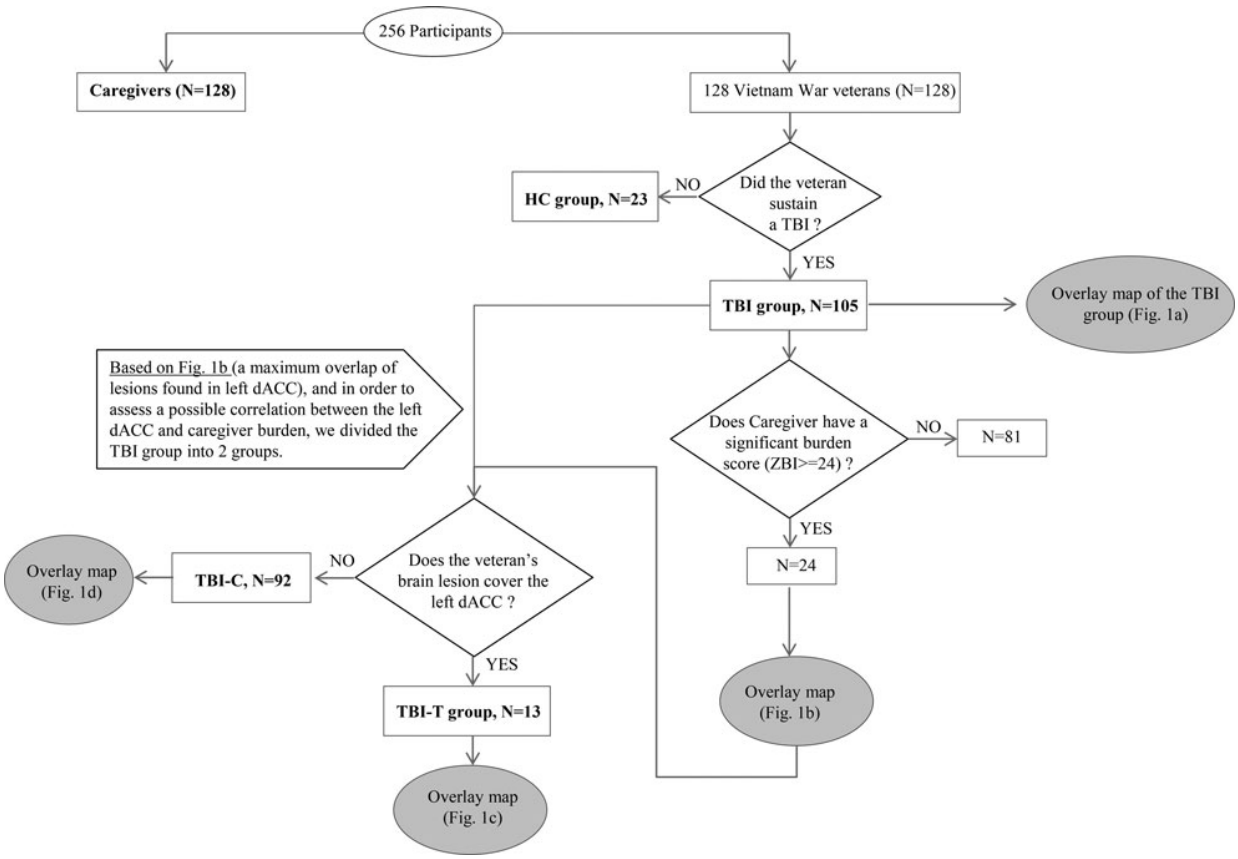


Figure 1. Flow chart for the criteria and triage of our groups' constitution, as well as the number of participants.

TABLE 1 *Descriptive (Mean [SD]) and Inferential Statistics of Demographics and Clinical Data for TBI (n = 105) and HCv (n = 23) Groups*[a]

	TBI	HCv	Statistics
Demographics			
Age, y	63.41 (2.99)	62.70 (1.74)	$Z = -0.76$; $P = .448$
Education, y	14.71 (2.17)	15.13 (1.94)	$Z = -0.78$; $P = .437$
Handedness (R:A:L)	87:2:16	17:1:5	χ^2 (2) = 1.15 $P = .562$
FSQ (total score)	95.68 (18.33)	97.35 (20.65)	$Z = -0.39$ $P = .700$
Preinjury IQ (percentile)	63.87 (23.66)	73.00 (18.39)	$Z = -1.57$; $P = .116$
Perceived caregiver burden			
ZBI (total score)	15.51 (12.57)	8.17 (5.18)	$\mathbf{Z = -2.45}$; $P = .014$
Executive functioning measures			
FAS (total scaled score)	8.66 (3.72)	11.09 (3.73)	$\mathbf{Z = -2.98}$; $P = .003$
TMT control (scaled score)	9.44 (3.63)	11.83 (1.50)	$\mathbf{Z = -3.10}$; $P = .002$
TMT switching (scaled score)	9.10 (4.03)	11.13 (2.67)	$\mathbf{Z = -2.31}$; $P = .021$
NBRS (total pathology score)	37.38 (13.55)	35.17 (9.35)	$Z = -0.77$; $P = .440$
FrSBe Apathy (total score)	63.02 (18.64)	57.74 (18.30)	$Z = -1.44$; $P = .151$
FrSBe Disinhibition (total score)	58.79 (16.58)	56.09 (15.63)	$Z = -0.53$; $P = .594$
FrSBe EF (total score)	62.88 (17.74)	59.57 (17.42)	$Z = -0.777$; $P = .437$
Control measures			
Postinjury IQ (percentile)	54.38 (25.79)	72.65 (18.14)	$\mathbf{Z = -3.16}$; $P = .002$
BDI-II (total raw score)	7.55 (7.87)	9.48 (7.91)	$Z = -1.14$; $P = .256$
M-PTSD (total score)	78.44 (22.32)	80.57 (22.62)	$Z = -0.48$; $P = .630$
BNT (total score)	53.02 (7.69)	55.91 (3.87)	$Z = -1.87$; $P = .062$
WMS (delay memory scaled score)	100.25 (17.07)	106.87 (17.04)	$Z = -1.99$; $P = .077$
VOSP (average percentage)	84.45 (10.02)	89.26 (4.19)	$\mathbf{Z = -2.00}$; $P = .045$

Abbreviations: BDI-II, Beck Depression Inventory; BNT, Boston Naming Test; EFs, executive functions; FAS, verbal fluency (letter F, A, S); FrSBe, Frontal System Behavioral Scale; FSQ, Functional Status Questionnaire; HCv, healthy control veterans; IQ, intelligence quotient; M-PTSD, Mississippi–Posttraumatic Stress Disorder Scale; NBRS, Neurobehavioral Rating Scale; TBI-T, TBI target; TBI-C, TBI control; TMT, trail making test; VOSP, Visual Object and Space Perception battery; WMS, Wechsler Memory scale abbreviated; ZBI, Zarit Burden Interview.

[a]Bold statistics are significant.

TMT), postinjury IQ, and visual perception. However, these groups did not differ significantly on caregiver and test examiner EFs' assessments (respectively FrSBe and NBRS) or the remaining measures (global disability, depression, posttraumatic stress disorder, memory, language) (see Table 1). For the TBI group, significant correlations between ZBI and all EF measures were found after controlling for language (FAS: $r = -0.19$, $P < 0.05$; TMT-S: $r = -0.25$, $P = 0.005$; FrSBe EF: $r = 0.65$, $P < .001$; FrSBe apathy: $r = 0.59$, $P < .001$; FrSBe disinhibition: $r = 0.60$, $P < 0.001$; and NBRS: $r = 0.38$; $P < .001$).

To investigate the effect of lesion location on long-term caregiver burden, an overlay lesion map for the entire TBI sample was examined and showed coverage of brain regions previously identified in dysexecutive syndrome (see Figure 2a). Another overlay lesion map was created using the 24 participants with TBI whose caregivers had a clinically relevant higher burden (ZBI total score ≥ 24) (see Figure 2b). For these, a maximum overlap of lesions (6 participants) was found in the left dACC (peak coordinate: $x = -14$; $y = 16$; $z = 43$, in Montreal Neurological Institute space). Participants with injury to the left dACC were placed into a TBI-T subgroup (n = 13) (see Figure 2c) and the remaining participants into a TBI-C subgroup (n = 92) (see Figure 2d). Subtraction maps between groups showed that the TBI-T group had lesions covering predominantly the left dACC and dorsolateral PFC (dlPFC) (left frontal superior and middle gyri), but also the left frontal inferior gyrus, left precentral gyrus, left supplementary motor area, left insula and, to a lesser extent, the right inferior gyrus, right supplementary motor area, right ACC and right olfactory bulb (see Figure 3a). The TBI-C group had lesions that cover most of the right frontal lobe (except for the middle and superior orbital gyri), a limited portion of the left frontal lobe (precentral gyrus), most of the left and right parietal, temporal, and occipital lobes (see Figure 3b). The conjunction map showed that the groups had common lesions in the left and right anterior parts of the frontal superior, middle, and inferior gyri and, to a lesser extent, the left and right rostroventral ACC (see Figure 3c).

To investigate the effect of brain lesion location on deficits in EF affecting long-term caregiver burden, we compared groups (TBI-T, TBI-C, and HCv) on age, years of education, handedness, global disability, TBI severity,

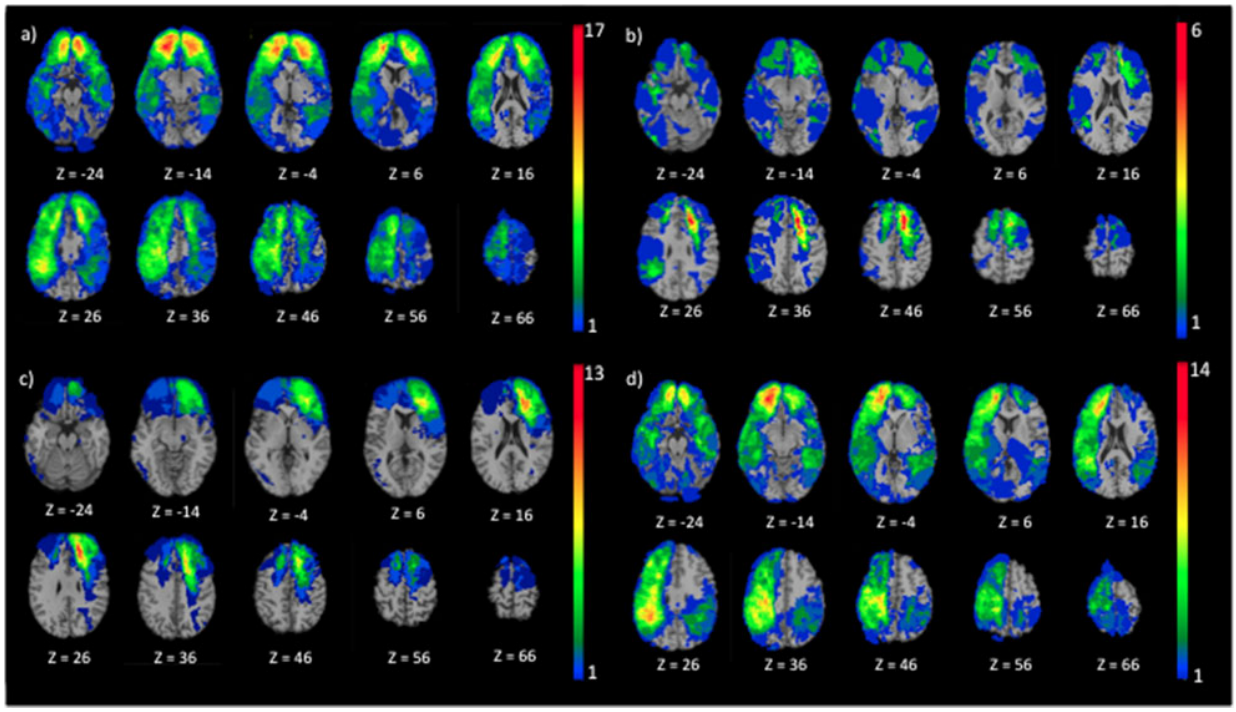


Figure 2. Lesion overlay map. *Z*: superior-inferior coordinate in the Talairach space. (a) Entire TBI sample (n = 105), (b) participants with TBI (n = 24) whose caregiver had significant caregiver burden (ZBI total score ≥ 24), (c) TBI-T, participants whose lesion comprised left dACC and dlPFC (n = 13), and (d) TBI-C, participants whose lesion does not comprise left dACC and dlPFC (n = 92). The color bar represents the number of overlapping lesions at each voxel. Red indicates a greater number of participants with TBI who have a lesion on a particular voxel. In each image, the right hemisphere is on the reader's left.

and preinjury IQ, and found no significant differences, but the TBI-T group had a significantly larger percentage of volume loss than the TBI-C group (see Table 2). As expected, the caregivers of those in the TBI-T group had a significantly higher burden than the caregivers of participants in the TBI-C group ($Z = -2.08$; $P < .037$, $r = 0.20$) and HCv (ZBI, $Z = -3.25$; $P < .001$, $r = 0.541$). Since TBI-T and TBI-C groups differed significantly on percentage of brain volume loss, a Spearman coefficient correlation was applied between percentage of brain volume loss and ZBI total score, but the correlation was not significant ($r_s = 0.45$; $P = .121$).

Nonparametric analyses (Kruskal-Wallis *H* test) demonstrated that groups differed significantly on EF measures (FAS, TMT, NBRS, FrSBe apathy, FrSBe disinhibition, FrSBe EFs), memory (WMS), and postinjury IQ (AFQT total score) (see Table 2). Follow-up planned nonparametric analyses (Mann-Whitney *U* tests, Bonferroni corrected) between lesion groups revealed that the TBI-T participants performed significantly worse than those in the TBI-C group on verbal fluency (FAS: $Z = -2.85$, $P < .012$), mental flexibility (TMT-S: $Z = -2.72$, $P < .021$), caregiver assessment (FrSBe apathy: $Z = -2.82$, $P = .015$; FrSBe disinhibition: $Z = -2.79$, $P = .015$; FrSBe EFs: $Z = -2.67$, $P = .024$), and examiner assessment (NBRS: $Z = -3.00$, $P < .009$), but not on memory (WMS: $Z = -1.72$, $P = .258$), a control task (TMT-C: $Z = -1.65$, $P = .100$), or postinjury IQ (AFQT total score: $Z = -1.98$, $P = .141$). Comparing the TBI-T group with the HCv group, nonparametric tests (Mann-Whitney *U* tests, Bonferroni corrected) demonstrated that the TBI-T group performed significantly worse on EF–verbal fluency (FAS: $Z = -3.44$, $P < .005$), mental flexibility (TMT-S: $Z = -3.83$, $P < .001$), caregiver assessments (FrSBe apathy: $Z = -2.90$, $P = .009$; FrSBe disinhibition: $Z = -2.34$, $P = .048$; FrSBe EF: $Z = -2.34$, $P = .048$), and examiner assessment (NBRS: $Z = -2.51$, $P < .05$)–but also on postinjury IQ (AFQT total score: $Z = -3.20$, $P < .001$). TBI-T and HCv did not differ significantly on memory (WMS: $Z = -1.87$, $P = .195$).

DISCUSSION

Our study investigated the association between brain lesion location in penetrating TBI and long-term perceived burden in caregivers as it related to dysexecutive syndrome in participants with TBI. Our first goal was to assess caregiver burden in a cohort of participants with TBI who sustained their injury 40 years earlier. As predicted, we found that burden was significantly higher in caregivers of participants with TBI than in

TABLE 2 *Descriptive and Inferential Statistics for Demographics and Clinical Data for TBI-T (n = 13), TBI-C (n = 92), and HCv (n = 23) Groups*[a]

	TBI-T, Mean (SD) [Min; Max]	TBI-C, Mean (SD) [Min; Max]	HCv, Mean (SD) [Min; Max]	Statistics
Demographics				
Age, y	62.15 (1.35)	63.59 (3.12)	62.70 (1.74)	H(2) = 3.68; *P* = .159
Education, y	14.31 (2.02)	14.77 (2.19)	15.13 (1.94)	H(2) = 1.35; *P* = .508
Handedness (R:A:L)	10:0:3	77:2:13	17:1:5	χ^2 (4) = 2.00 *P* = .735
Preinjury IQ (percentile)	62.92 (27.52)	64.01 (23.23)	73.00 (18.39)	H(2) = 2.58; *P* = .275
TBI severity				
Mild	N = 6	N = 52		χ^2 (2) = 3.50 *P* = .174
Moderate	N = 0	N = 3		
Severe	N = 7	N = 22		
FSQ (total scaled score)	89.77 (17.30)	96.51 (18.41)	97.35 (20.65)	H = 2.22; *P* = .329
Brain volume loss (percentage)	6.00 (3.64)	2.29 (3.05)	. . .	**Z = −4.10**; *P* < .001
Perceived caregiver burden				
ZBI (total score)	22.38 (10.83) [2; 39]	14.54 (12.55) [0; 49]	8.17 (5.18) [0; 18]	**H(2) = 12.89**; *P* = .002
Executive functioning measures				
FAS (total scaled score)	5.54 (2.60)	9.10 (3.65)	11.09 (3.73)	**H(2) = 18.73**; *P* < .001
TMT control (scaled score)	8.38 (3.73)	9.60 (3.61)	11.83 (1.50)	**H(2) = 12.49**; *P* = .002
TMT switching (scaled score)	6.92 (3.43)	9.42 (4.03)	11.13 (2.67)	**H(2) = 13.13**; *P* = .001
NBRS (total pathology score)	47.23 (22.65)	35.99 (11.24)	35.17 (9.35)	**H(2) = 9.13**; *P* = .009
FrSBe Apathy (Total score)	77.31 (20.28)	60.98 (17.58)	57.74 (18.30)	**H(2) = 9.84**; *P* = .007
FrSBe Disinhibition (Total score)	71.46 (17.20)	56.98 (15.77)	56.09 (15.63)	**H(2) = 7.97**; *P* = 0.019
FrSBe EF (Total score)	76.08 (18.73)	60.99 (16.87)	60.17 (19.79)	**H(2) = 7.55**; *P* = .023
Control measures				
Postinjury IQ (percentile)	44.23 (27.08)	55.87 (25.42)	72.65 (18.14)	**H(2) = 12.29**; *P* = .002
BDI-II (total raw score)	12.69 (11.76)	6.83 (6.95)	9.48 (7.91)	H(2) = 4.31; *P* = .116
M-PTSD (total score)	87.00 (21.04)	77.23 (22.34)	80.57 (22.62)	H(2) = 3.57; *P* = .168
BNT (total score)	49.15 (13.74)	53.58 (6.30)	55.91 (3.87)	H(2) = 3.65; *P* = .161
WMS (delay memory scaled score)	93.23 (21.32)	101.28 (16.25)	106.87 (17.04)	H(2) = 5.12; *P* = .077
VOSP (average percentage)	81.89 (10.11)	84.83 (10.01)	89.26 (4.19)	H(2) = 5.37; *P* = .068

Abbreviations: BDI-II, Beck Depression Inventory; BNT, Boston Naming test; EF, Executive function; FAS, Verbal Fluency (letter F, A, S); FrSBe, Frontal System Behavioral Scale; FSQ, Functional Status Questionnaire; HCv, Healthy Control veterans; IQ, Intelligence quotient; M-PTSD, Mississippi–Post-Traumatic Stress Disorder Scale; NBRS, Neurobehavioral Rating Scale; TBI-C, TBI control; TBI-T, TBI target; TMT, Trail making test; VOSP, Visual Object and Space Perception battery; WMS, Wechsler Memory scale abbreviated; ZBI, Zarit Burden Interview.

[a]Bold statistics are significant.

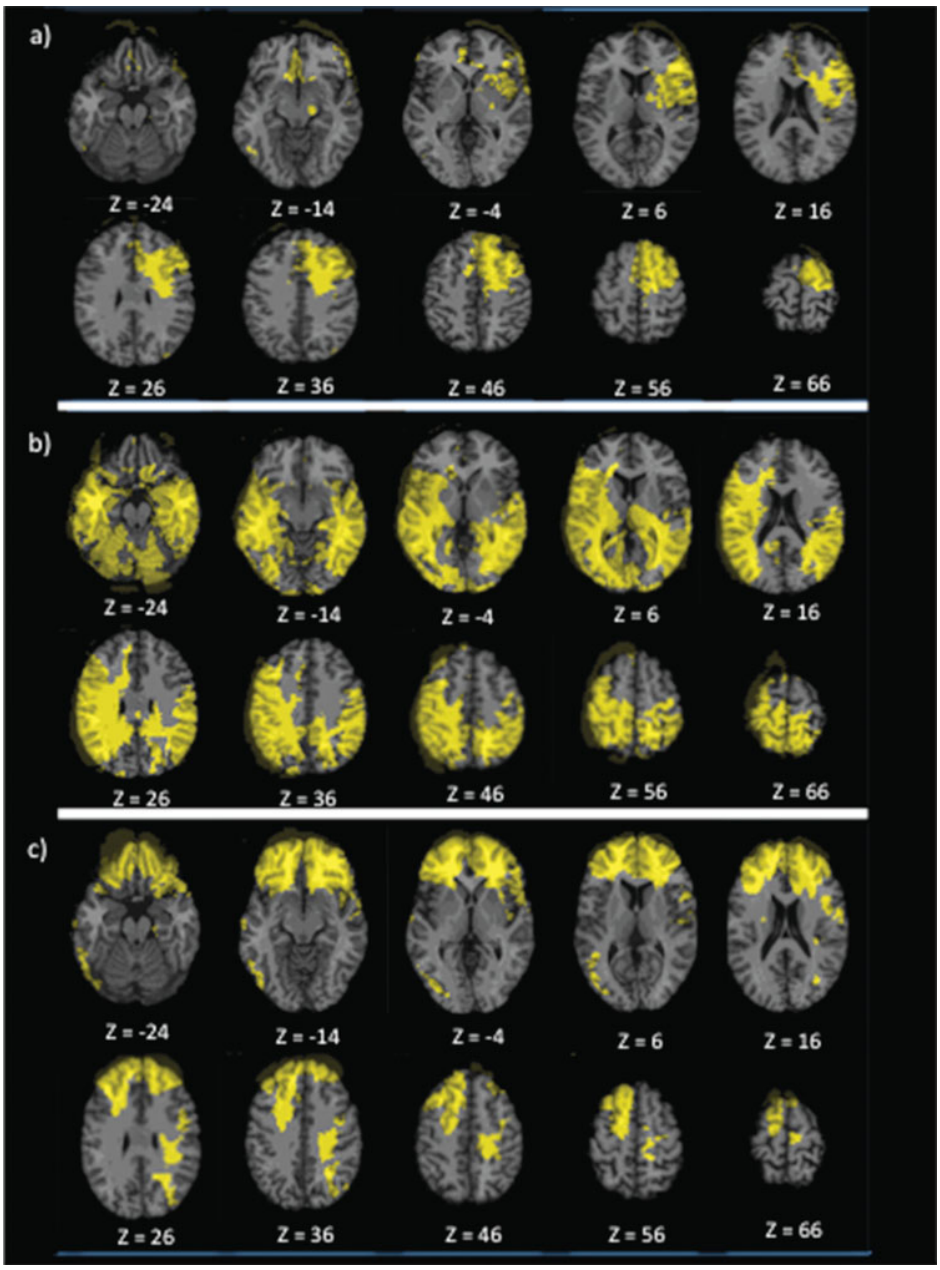


Figure 3. Subtraction and conjunction maps: (a) Subtraction overlay map showing lesions present only in the TBI-T group, (b) subtraction overlay map showing lesions present only in the TBI-C group, and (c) conjunction overlay map showing lesions present in both TBI groups. In each slice, the right hemisphere is on the reader's left and the lesions are represented in yellow.

caregivers of matched healthy controls. Our reported measure of burden was lower than previously reported in studies with severe TBI,[7,55] probably because of the time since injury in our investigation. Previous studies focused on a time frame ranging from 6 months to 5 years postinjury and demonstrated that caregiver burden is already substantially decreased from 6 months to 1 year postinjury.[2,12] While our study involved a cross-sectional sample approximately 40 years after injury, those in the TBI group still exhibited cognitive deficits, and their caregivers demonstrated greater burden than the control group.

Our second goal was to identify any relation between TBI-related brain lesions and long-term caregiver burden. As hypothesized, we found that long-term caregiver burden was associated with impaired EF from lesions to the left dACC and dlPFC, 2 highly interconnected key regions involved in executive control and decision making, particularly in novel situations, as well as monitoring of performance and error detection,

respectively.[26,56-59] Participants with lesions in these areas demonstrated deficits in cognitive and behavioral indicators associated with dysexecutive syndrome but not in other control measures (ie, language abilities, space and object perception, memory, depression, posttraumatic stress). These participants were impaired on EF laboratory tasks such as verbal fluency and mental flexibility. Given that verbal fluency requires inhibition of inappropriate responses, error detection, and monitoring of conflicting responses,[56,60] previous imaging studies demonstrated consistent activation in the left dACC and dlPFC for this task in healthy controls.[56,60-62] Furthermore, although bilateral PFC has been implicated in mental flexibility, some evidence points to a more dominant role of the left PFC (ie, dlPFC)[58,63] and functionally connected regions such as ACC in mental flexibility.[64]

Moreover, these participants also showed deficits in behaviors associated with dysexecutive syndrome reported by the caregiver (evaluation of apathy, disinhibition, and EFs in daily life) and the examiner (evaluation of cognitive and affective aspects of EFs).

We found that participants with a TBI in the left dlPFC and dACC have greater brain volume loss than in those with TBI without a lesion in these areas. This can be explained by the location of the ACC deep in the brain; since they were all penetrating brain injuries, to reach a midline structure like the ACC, the lesion needed to penetrate deeply, hence affecting on average more cortical tissue than a lesion restricted to the lateral surface of the cortex. However, further correlation analysis between brain volume loss and caregiver burden did not show an association.

We argue that the lesion localization we identified has clinical significance. Indeed, clinicians should be aware that a caregiver whose spouse/offspring/parent has a left dACC/dlPFC lesion is at higher risk of feeling burdened and developing mental health issues. This specific risk may relate not only to caregivers of TBI patients, but possibly also to caregivers of patients affected by any disease involving dysfunctional left dACC/dlPFC, such as some forms of multiple sclerosis, stroke, and frontotemporal or vascular dementias. Paying special attention to caregivers of these patients is important not only at the individual level but also at the societal level, since the health care system does not offer comprehensive services and private caregivers often serve a complementary role in providing such care. Social and instrumental support reduces caregiver burden. Psychological therapy that teaches coping strategies would be beneficial for reducing caregiver burden. Providing caregivers with information on TBI (including expectations for progression) is also recommended so that they can develop an appropriate care plan.[16,55]

It is important to take care of caregivers of individuals suffering from TBI in the left dACC/dlPFC brain, probably associated with dysexecutive syndrome. Nevertheless, one has to be aware that patients' outcomes are sometimes dissociated from imaging results. For example, in individuals with dementia, it is not rare to notice a double dissociation between brain atrophy and cognitive outcomes, and even more specifically, autonomy in daily life.[65,66]

Our study had some limitations. Given the homogeneity of our all male TBI sample (uniqueness of the injury, time frame since the injury) and the relatively few subjects with a left dACC/dlPFC lesion, path analysis was not a suitable option. An interesting study direction would be to select a larger group of participants with left dACC/dlPFC lesions and run path analyses to replicate our work and better determine the links among brain lesion, EFs and caregiver burden. Computed tomographic scans were used as an imaging technique in this study rather than more optimal techniques such as magnetic resonance imaging (MRI) and diffusion tensor imaging. Since penetrating injuries often resulted in the participant retaining metallic fragments or shrapnel at the site of injury, MRI scans were not feasible. The use of CT scans may have limited our ability to see more detailed structures within the brain, particularly fiber tracks and brain connectivity that can be demonstrated with diffusion tensor imaging techniques. Note that there was approximately a 6-year gap between the acquisition of CT scans and of the administration of the cognitive measures used in this study. However, clinical evaluation of the phase IV CT scans done currently with the cognitive measures did not reveal any additional pathology besides the pTBI. Nonetheless, we cannot exclude additional incidental, nontraumatic and ischemic lesions in the white matter due to aging that may have been detected had the participants received MRI scans more recently.

In conclusion, we showed that some caregivers of participants with TBI still perceived burden 40 years after injury. We also showed an association between brain lesion location and long-term caregiver burden likely due to the cognitive and behavioral factors associated with dysexecutive syndrome.

REFERENCES

1. Taylor HG, Yeates KO, Wade SL, Drotar D, Stancin T, Burant C. Bidirectional child-family influences on outcomes of traumatic brain injury in children. *J Int Neuropsychol Soc.* 2001;7(6):755–767.

2. Marsh NV, Kersel DA, Havill JA, Sleigh JW. Caregiver burden during the year following severe traumatic brain injury. *J Clin Exp Neuropsychol.* 2002;24(4):434–447.

3. Draper K, Ponsford J. Long-term outcome following traumatic brain injury: a comparison of subjective reports by those injured and their relatives. *Neuropsychol Rehabil.* 2009;19(5):645–661.
4. Draper K, Ponsford J, Schonberger M. Psychosocial and emotional outcomes 10 years following traumatic brain injury. *J Head Trauma Rehabil.* 2007;22(5):278–287.
5. Feinberg L, et al. *Valuing the Invaluable: 2011 Update. The Growing Contributions and Costs of Family Caregiving, in Insight on the Issues 512011*, Washington DC: AARP Public Policy Institute.
6. Guevara AB, Démonet JF, Polejaeva E, et al. Association between long-term cognitive decline in Vietnam Veterans with TBI and caregiver attachment style. *J Head Trauma Rehabil.* 2015;30:E26-E33.
7. Bayen E, Pradat-Diehl P, Jourdan C, et al. Predictors of informal care burden 1 year after a severe traumatic brain injury: results from the Paris-TBI study. *J Head Trauma Rehabil.* 2013;28:408–418.
8. Leggett AN, Zarit S, Taylor A, Galvin JE. Stress and burden among caregivers of patients with Lewy body dementia. *Gerontologist.* 2011;51(1):76–85.
9. Moules S, Chandler BJ. A study of the health and social needs of carers of traumatically brain injured individuals served by one community rehabilitation team. *Brain Inj.* 1999;13(12):983–993.
10. Kolakowsky-Hayner SA, Miner KD, Kreutzer JS. Long-term life quality and family needs after traumatic brain injury. *J Head Trauma Rehabil.* 2001;16(4):374–385.
11. Livingston LA, Kennedy RE, Marwitz JH, et al. Predictors of family caregivers' life satisfaction after traumatic brain injury at one and two years postinjury: a longitudinal multi-center investigation. *NeuroRehabilitation.* 2010;27(1):73–81.
12. Ponsford J, Schonberger M. Family functioning and emotional state two and five years after traumatic brain injury. *J Int Neuropsychol Soc.* 2010;16(2):306–317.
13. Marsh NV, Kersel DA, Havill JH, Sleigh JW. Caregiver burden at 1 year following severe traumatic brain injury. *Brain Injury.* 1998;12(12):1045–1059.
14. Rivera P, Elliott TR, Berry JW, Grant JS, Oswald K. Predictors of caregiver depression among community-residing families living with traumatic brain injury. *NeuroRehabilitation.* 2007;22(1):3–8.
15. Knutson KM, Zamboni G, Tierney MC, Grafman J. Neural correlates of caregiver burden in cortical basal syndrome and frontotemporal dementia. *Dement Geriatr Cogn Disord.* 2008;26(5):467–474.
16. Jackson D, Turner-Stokes L, Murray J, Leese M, McPherson KM. Acquired brain injury and dementia: a comparison of carer experiences. *Brain Inj.* 2009;23(5):433–444.
17. Nonterah CW, Jensen BJ, Perrin PB, et al. The influence of TBI impairments on family caregiver mental health in Mexico. *Brain Inj.* 2013;27(11):1287–1293.
18. Papastavrou E, Tsangari H, Karayiannis G, Papacostas S, Efstathiou G, Sourtzi P. Caring and coping: the dementia caregivers. *Aging Ment Health.* 2011;15(6):702–711.
19. Phelan SM, Griffin JM, Hellerstedt WL, et al. Perceived stigma, strain, and mental health among caregivers of veterans with traumatic brain injury. *Disabil Health J.* 2011;4(3):177–184.
20. Anderson MI, Parmenter TR, Mok M. The relationship between neurobehavioural problems of severe traumatic brain injury (TBI), family functioning and the psychological well-being of the spouse/caregiver: path model analysis. *Brain Inj.* 2002;16(9):743–757.
21. Cosseddu M, Alberici A, Pelizzola S, Padovani A, Borroni B. The other face of the coin: the caregiver burden in frontotemporal lobar degeneration. *Int J Geriatr Psychiatry.* 2013;28(6):655–657.
22. Godefroy O, Azouvi P, Robert P, et al. Dysexecutive syndrome: diagnostic criteria and validation study. *Ann Neurol.* 2010;68(6):855–864.
23. de Vugt ME, Riedijk SR, Aalten P, et al. Impact of behavioural problems on spousal caregivers: a comparison between Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord.* 2006;22(1):35–41.
24. Su YL, Huang J, Wang N, Wang JY, Luo F. The effects of morphine on basal neuronal activities in the lateral and medial pain pathways. *Neurosci Lett.* 2012;525(2):173–178.
25. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev.* 2006;16(1):17–42.
26. Hagen K, Ehlis AC, Haeussinger FB, et al. Activation during the Trail Making Test measured with functional near-infrared spectroscopy in healthy elderly subjects. *Neuroimage.* 2014;85(Pt 1):583–591.
27. Yuan P, Raz N. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. *Neurosci Biobehav Rev.* 2014;42C:180–192.
28. Buchsbaum BR, Greer S, Chang WL, Berman KF. Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Hum Brain Mapp.* 2005;25(1):35–45.
29. Laird AR, McMillan KM, Lancaster JL, et al. A comparison of label-based review and ALE meta-analysis in the Stroop task. *Hum Brain Mapp.* 2005;25(1):6–21.
30. Jacobson SC, Blanchard M, Connolly CC, Cannon M, Garavan H. An fMRI investigation of a novel analogue to the Trail-Making Test. *Brain Cogn.* 2011;77(1):60–70.
31. Merkley TL, Larson MJ, Bigler ED, Good DA, Perlstein WM. Structural and functional changes of the cingulate gyrus following traumatic brain injury: relation to attention and executive skills. *J Int Neuropsychol Soc.* 2013;19(8):899–910.
32. Spitz G, Bigler ED, Abildskov T, Maller JJ, O'Sullivan R, Ponsford JL. Regional cortical volume and cognitive functioning following traumatic brain injury. *Brain Cogn.* 2013;83(1):34–44.
33. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci.* 2000;4(6):215–222.
34. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain.* 1995;118(Pt 1):279–306.
35. Beckmann M, Johansen-Berg H, Rushworth MF. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J Neurosci.* 2009;29(4):1175–1190.
36. Mars RB, et al. *Neural Basis of Motivational and Cognitive Control.* Boston, MA: Massachusetts Institute of Technology; 2011.
37. Raymont V, Salazar AM, Krueger F, Grafman J. "Studying injured minds"–the Vietnam head injury study and 40 years of brain injury research. *Front Neurol.* 2011;2:1–15.
38. Makale M, Solomon J, Patronas NJ, Danek A, Butman JA, Grafman J. Quantification of brain lesions using interactive automated software. *Behav Res Methods Instrum Comput.* 2002;34(1):6–18.
39. Solomon J, Raymont V, Braun A, Butman JA, Grafman J. User-friendly software for the analysis of brain lesions (ABLe). *Comput Methods Programs Biomed.* 2007;86(3):245–254.
40. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* 2002;15(1):273–289.
41. Zarit SH, Todd PA, Zarit JM. Subjective burden of husbands and wives as caregivers: a longitudinal study. *Gerontologist.* 1986;26(3):260–266.
42. Schreiner AS, Morimoto T, Arai Y, Zarit S. Assessing family caregiver's mental health using a statistically derived cut-off score for the Zarit Burden Interview. *Aging Ment Health.* 2006;10(2):107–111.
43. Delis DC, Kaplan AS, Kramer A. *Delis-Kaplan Executive Function System.* San Antonio, TX: The Psychological corporation; 2001.
44. Grace J, Malloy P. *Frontal Systems Behavior Scale: Professional Manual.* Lutz, FL: Psychological Assessment Resources, Inc; 2001.

45. Levin HS, High WM, Goethe KE, et al. The neurobehavioural rating scale: assessment of the behavioural sequelae of head injury by the clinician. *J Neurol Neurosurg Psychiatry*. 1987;50(2):183–193.
46. Grafman J, Jonas BS, Martin A, et al. Intellectual function following penetrating head injury in Vietnam Veterans. *Brain*. 1988;111(Pt 1):169–184.
47. U.S. Department of Defense. *A Test Manual for the Armed Services Vocational Aptitude Battery*. Chicago, IL: US Military Entrance Processing Command; 1984.
48. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
49. Wechsler D, *Wechsler Memory Scale*. San Antonio, TX: Psychological Corporation; 1997.
50. Warrington EK, James M. *Visual Object and Space Perception Battery (VOSP)*. Suffolk, England: Thames Valley Test Company; 1991.
51. Schintu S, Hadj-Bouziane F, Dal Monte O, et al. Object and space perception–Is it a matter of hemisphere. *Cortex*. 2014;57:244–253.
52. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories–IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67(3):588–597.
53. Keane TM, Caddell JM, Taylor KL. Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. *J Consult Clin Psychol*. 1988;56(1):85–90.
54. Jette AM, Davies AR, Cleary PD, et al. The Functional Status Questionnaire: reliability and validity when used in primary care. *J Gen Intern Med*. 1986;1(3):143–149.
55. Doyle ST, Perrin PB, Díaz Sosa DM, et al. Connecting family needs and TBI caregiver mental health in Mexico City, Mexico. *Brain Inj*. 2013;27(12):1441–1449.
56. Senhorini MC, Cerqueira CT, Schaufelberger MS, et al. Brain activity patterns during phonological verbal fluency performance with varying levels of difficulty: a functional magnetic resonance imaging study in Portuguese-speaking healthy individuals. *J Clin Exp Neuropsychol*. 2011;33(8):864–873.
57. Badre D. Opening the gate to working memory. *Proc Natl Acad Sci U S A*. 2012;109(49):19878–19879.
58. Zakzanis KK, Mraz R, Graham SJ. An fMRI study of the Trail Making Test. *Neuropsychologia*. 2005;43(13):1878–1886.
59. Pa J, Possin KL, Wilson SM, et al. Gray matter correlates of set-shifting among neurodegenerative disease, mild cognitive impairment, and healthy older adults. *J Int Neuropsychol Soc*. 2010;16(4):640–650.
60. Audenaert K, Brans B, Van Laere K, et al. Verbal fluency as a prefrontal activation probe: a validation study using 99mTc-ECD brain SPET. *Eur J Nucl Med*. 2000;27(12):1800–1808.
61. Barch DM, Braver TS, Sabb FW, Noll DC. Anterior cingulate and the monitoring of response conflict: evidence from an fMRI study of overt verb generation. *J Cogn Neurosci*. 2000;12(2):298–309.
62. Gauthier CT, Duyme M, Zanca M, Capron C. Sex and performance level effects on brain activation during a verbal fluency task: a functional magnetic resonance imaging study. *Cortex*. 2009;45(2):164–176.
63. Kramer JH, Quitania L, Dean D, et al. Magnetic resonance imaging correlates of set shifting. *J Int Neuropsychol Soc*. 2007;13(3):386–392.
64. Shafritz KM, Kartheiser P, Belger A. Dissociation of neural systems mediating shifts in behavioral response and cognitive set. *Neuroimage*. 2005;25(2):600–606.
65. Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep*. 2004;4(5):374–380.
66. Stern Y. Cognitive reserve: implications for assessment and intervention. *Folia Phoniatr Logop*. 2013;65(2):49–54.

Appendix 2

Association Between Long-Term Cognitive Decline in Vietnam Veterans With TBI and Caregiver Attachment Style

Andrea Brioschi Guevara, MA; Jean-François Démonet, PhD; Elena Polejaeva, BSc; Kristine M. Knutson, MA; Eric M. Wassermann, MD; Frank Krueger, PhD; Jordan Grafman, PhD

Objective: To examine whether a caregiver's attachment style is associated with patient cognitive trajectory after traumatic brain injury (TBI). **Setting:** National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland. **Participants:** Forty Vietnam War veterans with TBI and their caregivers. **Main Outcome Measure:** Cognitive performance, measured by the Armed Forces Qualification Test percentile score, completed at 2 time points: preinjury and 40 years postinjury. **Design:** On the basis of caregivers' attachment style (secure, fearful, preoccupied, dismissing), participants with TBI were grouped into a high or low group. To examine the association between cognitive trajectory of participants with TBI and caregivers' attachment style, we ran four 2 × 2 analysis of covariance on cognitive performances. **Results:** After controlling for other factors, cognitive decline was more pronounced in participants with TBI with a high fearful caregiver than among those with a low fearful caregiver. Other attachment styles were not associated with decline. **Conclusion and Implication:** Caregiver fearful attachment style is associated with a significant decline in cognitive status after TBI. We interpret this result in the context of the neural plasticity and cognitive reserve literatures. Finally, we discuss its impact on patient demand for healthcare services and potential interventions. **Key words:** *attachment style (AS)*, *caregiver*, *cognitive reserve*, *fearful*, *neural plasticity*, *traumatic brain injury (TBI)*

TRAUMATIC BRAIN INJURY (TBI) is a worldwide health and socioeconomic concern. Approximately 3.2 to 5.3 million Americans are currently living with a TBI-related disorder. Fourteen percent of combat veterans sustained a brain injury during the Vietnam War,[1] and 294,172 active-duty individuals sustained a TBI during OEF (Operation Enduring Freedom)/OIF (Operation Iraqi Freedom)/OND (Operation New Dawn) conflicts (2000-2013).[2] In the Vietnam War, there were more gunshot and fragment wounds (35% of the injuries vs 19% in OEF/OIF), whereas blast-related injuries were more prevalent during OIF/OEF combat (81% vs 65% during the Vietnam War).[3] As a consequence, there were more penetrating TBIs during the Vietnam War, whereas OIF/OEF injuries were mainly mild or moderate closed-head injuries with only 1.4% being penetrating TBIs.[4,5] Individuals with a TBI are often faced with physical, cognitive, and social limitations that may persist for their lifetime. These limitations are challenging not only for the individual but also for family members and friends.[6,7] However, there are limited data concerning the impact of caregivers on cognitive evolution of individuals with TBI.

A study by Taylor et al,[8] on TBI in children noted that the family's response to the new situation may affect the recovery of the child. On the other end of the developmental spectrum, some research has examined individuals with dementia and their caregivers,[9–12] showing that

Author Affiliations: *Behavioral Neurology Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland (Mss Brioschi Guevara, Polejaeva, and Knutson and Dr Wassermann); Faculty of Biology and Medicine, University of Lausanne, Lausanne, VD, Switzerland (Ms Brioschi Guevara and Prof. Démonet); Department of Clinical Neuroscience, Memory Center, CHUV, University Hospital Lausanne, Lausanne, Switzerland (Prof. Démonet); Molecular Neuroscience Department and Department of Psychology, George Mason University, Fairfax, Virginia (Dr Krueger); and Brain Injury Research, Rehabilitation Institute of Chicago, Chicago, Illinois (Prof. Grafman).*

Drs Krueger and Grafman have joint senior authorship.

The authors declare no conflicts of interest.

Corresponding Author: *Jordan Grafman, PhD, Brain Injury Research, Rehabilitation Institute of Chicago, 345 E Superior St, Ste 1796, Chicago, IL 60611 (jgrafman@ric.org).*

DOI: 10.1097/HTR.0000000000000046

a stimulating environment predicts a slower cognitive and functional decline in this population.[9] Individuals with dementia are able to delay nursing home placement when the caregiver is the spouse, is in good health, provides positive interactions, and spends *less* time providing care.[10,11] Also, the caregiver's attachment style (AS) plays a role in the behavior of the individual with dementia: the more avoidant the caregiver's AS, the more aggression and agitation are exhibited by the patient.[12]

Attachment style affects the way individuals cope with emotional events and interact with others, including those to whom they are attracted.[13–15] The roots of AS lie in John Bowlby's[16] work on what he called the attachment behavioral system. Bowlby[16] believed that attachment behavior has a biological function such as protection and was innate in most mammals. Also, he highlighted that an AS was established during early childhood according to the primary attachment figure (mostly the mother) but then it remains mainly stable throughout life, as confirmed by recent studies.[17–19] Individual differences in AS were predicted by Bowlby and then systematically studied in mother-infant relationships by Mary Ainsworth.[20] Inspired by this developmental literature, it was shown that adults can be classified into 4 attachment categories (secure, preoccupied, fearful, and dismissing).[21] Preoccupied AS is defined by a negative self-esteem and positive sociability, whereas dismissing AS individuals present a positive self-esteem but are socially avoidant. Secure AS consists of positive self-esteem and sociability, whereas fearful AS individuals have a low self-esteem and are socially anxious and avoidant.[22,23] The association between caregiver AS and behavioral outcomes in individuals with TBI has not been explored yet.

Animal models show compelling evidence that enriched environments induce neurogenesis, synaptogenesis, and dendritic growth, which potentially propel recovery after a brain injury.[24,25] Living in an enriched environment enhances damage-induced neurogenesis in the adult brain[26] and has been shown to slow functional deterioration in neurodegenerative disorders, such as in a rat model of Huntington disease.[27] Interestingly, a recent study of adult rats showed that an enriched environment has a protective effect on glutamate excitotoxicity, reducing oxidative damage.[28] In contrast, an impoverished environment has a negative impact on neural plasticity. For instance, rats that live in a traditional laboratory cage develop hippocampal atrophy.[29] There are few such studies on nonhuman primates, but in adult marmosets, exposure to a complex environment for 1 month enhanced the length and complexity of dendrites and increased dendritic spines and synaptophysin in the hippocampus and frontal cortex.[30]

Regions preferentially involved in anxiety, for example, the hippocampus, prefrontal cortex (PFC), and amygdala, are particularly plastic and capable of transformation as a result of activity and experience.[29,31,32] Adaptive plasticity observed in the hippocampus and medial PFC (mPFC) is reversed or inhibited by chronic stress, which also causes dendritic atrophy in the mPFC and hippocampus, and hypertrophy in the amygdala.[32] The PFC and the amygdala are also some of the most common brain areas affected in TBI.[33]

In humans, cognitive reserve, the apparent result of lifetime intellectual activity, influences the timing of cognitive decline in aging and delays clinical progression in neurodenerative disorders.[34,35] Intelligence, education, and occupation are associated with increased synaptic density, neurogenesis, and synaptic plasticity.[34,35]

We hypothesize that the caregiver plays a key role in determining the richness of the individual's environment, thereby affecting the trajectory of long-term cognitive change after TBI. Anxious individuals experience increased distress, as has been shown among melanoma survivors.[23] This suggests that a caregiver with a fearful AS might not only limit social interactions of individuals with TBI but also increase stress in the environment with a resultant negative effect on plastic or protective processes or capacities important for recovery or preservation of cognitive capacities in individual with TBI across the life span. We hypothesize that cognitive decline in an individual with TBI, which is greater than in controls,[1] could be exacerbated if his or her caregiver has a high fearful AS than if his or her caregiver has a low fearful AS. While the current observational study could not be used to determine a causal relationship between AS and cognitive decline, we sought to establish whether an association could be detected.

METHODS

Participants

A subgroup of male participants was selected from the Vietnam Head Injury Study (VHIS), a prospective and wide-ranging study of veterans who sustained brain damage from penetrating head injuries (TBI) during the Vietnam War. The VHIS consists of 4 phases that stretched over more than 40 years. Phase 1 occurred during the Vietnam War (1967-1970) and included medical records of 1221 veterans who survived the first week post-TBI. Phase 2 occurred between 1981 and 1984 at the Walter Reed Army Medical Center and was a follow-up of 520 individuals with TBI among the initial 1221 participants collected in phase 1. Phase 3 occurred from 2003 to 2006 at the National Naval Medical Center (Bethesda, Maryland), with an extensive neuropsychological follow-up of 199 individuals with TBI. In phase 4 (2008-2012), participants and their caregivers came to the National Institute of Neurological Disorders and Stroke of the

National Institutes of Health (NINDS/NIH), Bethesda, Maryland, for a 5-day study. The caregivers completed a series of questionnaires and an interview.

From the 134 phase 4 participants with penetrating injuries, we selected individuals if (*a*) they had a documented induction Armed Forces Qualification Test (AFQT) score (preinjury), (*b*) they were accompanied by a caregiver during their phase 4 evaluation, (*c*) the caregiver had known the individual since preinjury or within 5 years postinjury (mean years since caregiver and participant with TBI knew each other: 42.10 ± 6.57 years). The final sample consisted of 40 couples (see Table 1). All veterans had completed the AFQT-7A upon military induction and during VHIS phase 4.

All participants gave written informed consent, and the study was approved by the institutional review board of the NINDS/NIH, Bethesda, Maryland.

Clinical assessment

Participants underwent assessments of their global functioning (Functional Status Questionnaire[36]), personality (NEO-Five Factor Inventory[37]), posttraumatic stress disorder (Mississippi PTSD [posttraumatic stress disorder][38]), depression (Beck Depression Inventory[39]), memory (Wechsler Memory Scale[40]), language (Boston Naming Test[41] and Token Test[42]), executive functions (from the Delis-Kaplan Executive Function System[43]: Verbal Fluency, Sorting Test, Trail Making Test), and visual perception (Visual Object and Space Perception Battery[44]). Also, caregivers' depression (Center for Epidemiological Studies Depression Scale)[45] and burden (Zarit Burden Inventory)[46] were evaluated.

TABLE 1 *Demographic characteristics of the entire sample (40 participants with TBI and 40 caregivers)*

	Mean (SD)
Participants with TBI	
Age, y	63.28 (3.404)
Education, y	13.97 (1.915)
Handedness (right:left)	37:3
Gender (male:female)	40:0
Loss of consciousness	
None	$n = 13$
Momentary	$n = 5$
1-15 min	$n = 8$
15 min to 1 d	$n = 5$
>1 d	$n = 6$
Unknown	$n = 3$
Posttraumatic amnesia	
None	$n = 20$
<1 h	$n = 2$
1 h to <1 d	$n = 0$
1 d to <1 wk	$n = 7$
1 wk to <1 mo	$n = 5$
≥1 mo	$n = 4$
Unknown	$n = 2$
Caregivers	
Age, y	61.52 (3.948)
Education, y	13.75 (2.072)
Gender (male:female)	3:37
Relation to participant with TBI (spouse:sibling:friend)	36:3:1

Abbreviations: SD, standard deviation; TBI, traumatic brain injury.

Measures

Armed Forces Qualification Test

The AFQT-7A contains 100 multiple-choice questions on word knowledge, arithmetic word problems, object function matching, as well as mental imagery. Fifty minutes is allowed for completion. The difference in the AFQT percentile score from preinjury to phase 4 was used as the measure of cognitive trajectory. AFQT correlates strongly with the Wechsler Adult Intelligence Test[47] and has a good validity and reliability (0.7 and 0.73, respectively).[48]

Relationship Questionnaire and Relationship Scale Questionnaire

The Relationship Questionnaire (RQ) is a measure of adult attachment based on a 4-category model: secure, preoccupied, dismissing, and fearful.[21] In this model, secure attachment consists of a positive view of self and others, preoccupied attachment is a negative view of self but a positive view of others, dismissing attachment is a positive view of self and negative view of others, and fearful attachment is a negative view of self and other.[49,50] The RQ consists of 4 paragraphs; participants rate how much each of the 4 paragraphs represent them on a 7-point Likert scale. The Relationship Scale Questionnaire (RSQ) is a similar measure that contains 30 statements in which participants respond on a 5-point Likert scale to the extent that each statement is consistent with their feelings about close relationships.[13] The participants with TBI and their caregiver completed both questionnaires. A recent study confirmed good test-retest short-time reliability and internal consistency, as well as a solid factor analysis.[51]

A combination of the RQ and RSQ scores for each person, on each of the 4 ASs, was used to establish a continuous rating.[13] Continuous indexes were obtained by first converting the raw scores for each AS on the RQ and the RSQ to standardized *z*-scores.

Computed tomographic acquisition and analysis

Computed tomographic (CT) scans were acquired on a GE Medical Systems Light Speed Plus CT scanner in helical mode. Images were reconstructed with 1-mm

overlapping slice thickness and a 1-mm interval. Lesion volume was determined from CT scans by manual tracing using the Analysis of Brain Lesion (ABLe) software[52,53] implemented in MEDx (Medical Numerics Inc, Sterling, Virginia) with enhancements to support the Automated Anatomical Labeling atlas. The tracing was performed by a trained neuropsychiatrist and then reviewed by J.G., an experienced observer, who was blind to the results of the clinical evaluations. A consensus judgment determined the final outline of the lesion. On the basis of the lesion volume, we determined the percentage of volume loss [lesion volume (cm^3) × 100/total brain volume (cm^3)].

Statistical analysis

We used IBM SPSS (version 16 for Mac, www.spss.com) and applied a level of significance of $P < .05$ (2-tailed) to all analyses and a Bonferroni correction to analyses of covariance (ANCOVAs) (a level of significance for $P < .013$). We report the effect size when the analyses reached the level of significance.

On the basis of our hypothesis, we split the patient-caregiver pairs by the median score of the caregiver fearful AS and placed them into a "high fearful" (HF) or "low fearful" (LF) group. To compare the LF and HF groups on demographic, clinical variables, percentage of brain volume loss, and AS (i.e., secure, fearful, dismissing and preoccupied) of the caregiver and the participants with TBI, we used independent-samples *t* tests.

To examine the association between cognitive trajectory of participants with TBI and caregivers' fearful AS, we ran a 2 × 2 ANCOVA on cognitive performances (mean AFQT percentile scores) with trajectory (preinjury, postinjury) as a within-subjects factor and AS (LF, HF) as a between-subjects factor. Caregiver secure and dismissing ASs, as well as caregiver depression and NEO Conscientiousness variable of participants with TBI were integrated as covariates in the model (the only measures, with caregiver fearful AS, that were significantly different between LF and HF).

Also, we controlled for the other AS by repeating the aforementioned analysis 3 more times, each time using a different AS as the between-subjects factor and the remaining behavioral variables that differed significantly between LF and HF as covariates.

RESULTS

Fearful AS

On the basis of a median split on caregivers' fearful AS *z*-scores, 20 patient-caregiver pairs were assigned to the LF and 20 pairs to the HF group. There were no significant differences between the groups on demographic, clinical, or total percent volume loss (see Table 2).

The ANCOVA evaluating the association between cognitive trajectory of participants with TBI and caregivers' fearful AS showed a significant interaction effect for trajectory × AS ($F_{1,34} = 9.328$; $P = .004$) (effect size: $\eta^2 = 0.215$) but no main effect for trajectory ($F_{1,34} = 4.252$; $P = .047$) or for AS ($F_{1,34} = 0.508$; $P = .481$). The covariates, dismissing AS ($F_{1,34} = 0.597$; $P = .445$), secure AS ($F_{1,34} = 1.962$; $P = .170$), caregiver depression ($F_{1,34} = 1.167$; $P = .288$), and NEO Conscientiousness ($F_{1,34} = 1.237$; $P = .274$), were not significantly related to trajectory. Post hoc analysis showed that participants with TBI with HF caregivers performed significantly worse 40 years postinjury than at preinjury ($t_{19} = 4.360$; $P < .001$), whereas participants with TBI with LF caregivers were stable ($t_{19} = 0.545$; $P = .592$) (see Figures 1 and 2).

Secure, preoccupied, and dismissing ASs

Using secure caregiver AS as a between-subjects factor, we found a main effect for trajectory ($F_{1,34} = 8.554$; $P = .006$; $\eta^2 = 0.201$) but no main effect for AS ($F_{1,34} = 0.037$; $P = .849$), nor a significant interaction effect for trajectory × AS ($F_{1,34} = 3.455$; $P = .072$).

Using dismissing caregiver AS as a between-subjects factor, we found no main effects for trajectory ($F_{1,34} = 5.555$; $P = .024$) or AS ($F_{1,34} = 0.056$; $P = .815$), nor a significant interaction effect for trajectory × AS ($F_{1,34} = 0.355$; $P = .555$).

Finally, using preoccupied caregiver AS as a between-subjects factor, we found a main effect for trajectory ($F_{1,34} = 8.554$; $P = .006$; $\eta^2 = 0.201$) but no main effect for AS ($F_{1,34} = 0.037$; $P = .849$), nor a significant interaction effect for trajectory × AS ($F_{1,34} = 3.455$; $P = .072$).

DISCUSSION

In a 40-year follow-up study, we investigated the association between caregiver AS and the cognitive decline of a homogeneous population of participants with TBI: US males of similar age and education, who sustained their TBI during combat in Vietnam and who knew their caregivers for 42 years on average. Our results indicate that participants with TBI whose caregiver scored high on fearful AS (as measured at follow-up) had a significantly larger cognitive decline from preinjury to the present. Since we used an observational study design and the AS and the final cognitive outcome were measured concurrently, it is not possible to draw firm conclusions regarding causal relationships. The relationship observed could be due to a third unmeasured variable, and it is also conceivable that cognitive decline led to a more fearful AS. However, we can consider several alternative hypotheses.

On the basis of animal and human research on neural plasticity and cognitive reserve, we predicted

TABLE 2 *Descriptive and inferential statistics (mean and standard deviation) of demographic, neuropsychological, and psychiatric data of the LF and HF groups*

	LF ($n = 20$), mean (SD)	HF ($n = 20$), mean (SD)	Statistics, *P*
Participants with TBI			
Age, y	63.85 (4.38)	62.70 (1.98)	.291
Education, y	14.15 (2.11)	13.80 (1.74)	.570
Handedness (right:left)	16:4	17:3	.667
Secure AS (*z* score)	0.099 (0.974)	− 1.134 (0.727)	.398
Fearful AS (*z* score)	− 0.243 (0.580)	0.215 (0.903)	.065
Preoccupied AS (*z* score)	− 0.243 (0.750)	0.155 (0.811)	.116
Dismissing AS (*z* score)	− 0.003 (0.894)	0.068 (0.989)	.813
NEO Neurotic	44.300 (9.370)	49.25 (15.172)	.222
NEO Extrovert	50.60 (9.779)	45.40 (12.592)	.153
NEO Openness	44.60 (9.422)	45.15 (8.425)	.847
NEO Agreeable	50.40 (10.065)	49.60 (12.424)	.824
NEO Conscientiousness	54.95 (10.650)	46.65 (13.747)	.039[a]
Functional Status Questionnaire	96.50 (18.763)	92.30 (20.846)	.507
Mississippi PTSD (total raw)	73.35 (21.3555)	84.30 (26.821)	.161
Beck Depression Inventory	5.35 (7.527)	10.65 (10.358)	.073
Wechsler Memory Scale (total Memory scaled score)	95.10 (19.523)	95.84 (15.446)	.993
Boston Naming Test (total raw)	53.00 (6.936)	53.47 (5.531)	.816
Token Test (total correct)	97.05 (5.424)	97.37 (2.543)	.817
Verbal Fluency (letter, raw)	28.05 (12.931)	28.25 (9.358)	.931
Sorting Test (combined description composite scaled score)	10.20 (3.04)	9.68 (2.89)	.590
Trail Making Test (number letter set loss error)	0.40 (0.821)	0.21 (0.419)	.374
Visual Object and Space Perception Battery	19.20 (1.056)	19.74 (0.562)	.057
Total percent volume loss, cm^3	3.9 (4.69)	2.51 (2.30)	.243
Caregivers			
Age, y	62.15 (4.660)	60.9 (3.076)	.323
Education, y	13.65 (1.872)	13.85 (2.300)	.765
Gender (male:female)	2:18	1:19	.545
Relation to participant with TBI (spouse:sibling:friend)	17:2:1	19:1:0	.486
Center for Epidemiological Studies Depression Scale	7.20 (8.40)	13.10 (7.45)	.024[a]
Zarit Burden Inventory	15.45 (13.617)	21.35 (13.743)	.181
Secure AS (*z* score)	0.411 (0.855)	− 0.372 (0.818)	.005[a]
Fearful AS (*z* score)	− 0.725 (0.327)	0.646 (0.786)	<.001[a]
Preoccupied AS (*z* score)	− 0.083 (0.941)	0.014 (0.810)	.731
Dismissing AS (*z* score)	− 0.452 (0.740)	0.408 (0.901)	.002[a]

Abbreviations: AS, attachment style; HF, high fearful; LF, low fearful; PTSD, posttraumatic stress disorder; SD, standard deviation.
[a]Measures that survived statistical significance.

that a fearful AS would be associated with cognitive decline in individuals with TBI, possibly by depriving persons with TBI of the protective effect of more positive styles. In line with our prediction, participants with TBI whose caregiver scored high on fearful AS showed a significantly greater degree of cognitive decline than those whose caregiver scored low on fearful AS.

By being generally more anxious and avoiding social situations, it is likely that HF caregivers' increased stress in the environment of participants with TBI and reduced the richness of social activities of participants with TBI. In contrast, LF caregivers may allow participants with TBI to be challenged more and increase the richness of their environments.

The consequences of environmental complexity on brain recovery and cognitive decline have been thoroughly studied in animals[24,25,28,30,54,55] and show the protective effect of complex housing by modulating the damage-induced neurogenesis and dendritic

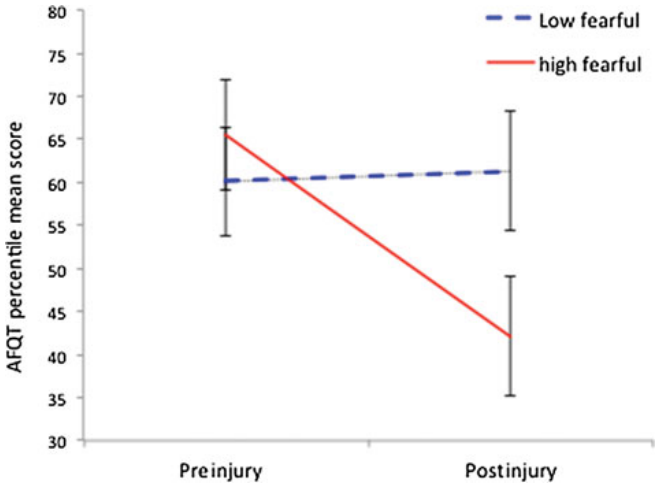


Figure 1. Cognitive performances measured with AFQT over time. Mean values and standard error of the mean for the AFQT percentile scores are shown for the participants with TBI of the low and high fearful caregiver groups at preinjury and 40 years postinjury. AFQT indicates Armed Forces Qualification Test; TBI, traumatic brain injury.

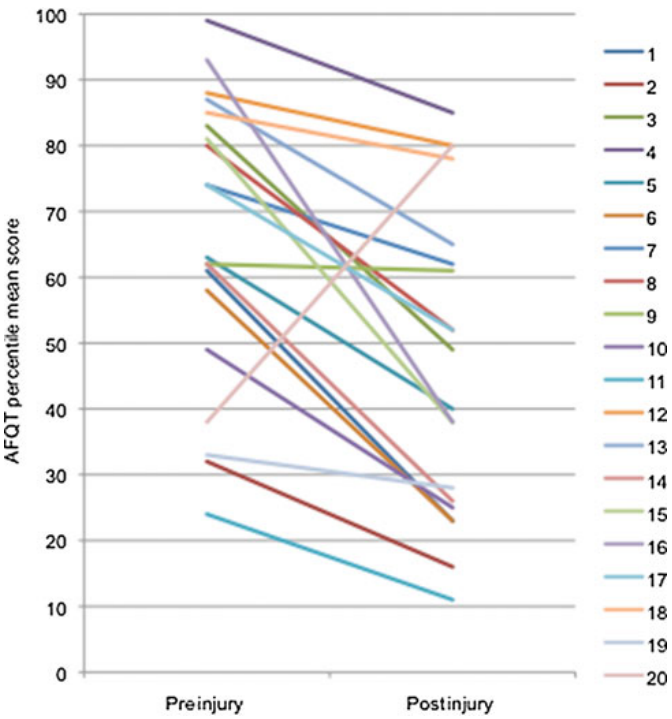


Figure 2. Individual cognitive decline slopes of the 20 participants with TBI of the high fearful group. AFQT indicates Armed Forces Qualification Test; TBI, traumatic brain injury. Participant with TBI 20 is an outlier but it is not unheard of for someone to show improvement over a lifetime of experience. In his case, he completed his GED after leaving the military (which means after his pre-injury AFQT). He also reported experiencing some difficulties with english and reading while in school. In the post-injury AFQT, his vocabulary subscore is about the same than his arithmetic one. Although we don't have the detail of his pre-injury AFQT, we can speculate that he might have improved greatly his semantic knowledge in the meanwhile.

growth.[24–26,30,54] These findings in rodents are supported by research on nonhuman primates.[30] Cognitive enrichment not only is a protective factor for cognitive decline but also potentially improves cognition in aging populations via cognitive stimulation.[56] In addition, some authors argued that if participants engaged in cognitively stimulating activities such as completing puzzles, reading, or learning new games or activities as they are aging or postinjury, this would increase their cognitive reserve.[57,58] Interestingly, the large effect size found for the association between caregivers' AS and cognitive decline of individuals with TBI is equal to or even greater than the medium to large effect size found in cognitive reserve studies.[59,60]

Factors other than the caregiver certainly influence cognitive decline and might have confounded the group differences we report. However, we found no significant between-group differences for AS participants on language (naming, comprehension), executive functions (mental flexibility, verbal fluency, abstract reasoning), memory or visual perception, posttraumatic stress disorder, functional status, or brain volume loss at their phase 4 evaluation.

It is also possible that participants predisposed to particular cognitive trajectories might have become paired with caregivers with particular ASs. Although individuals, regardless of their own AS, are overall more attracted by secure individuals, some studies found other patterns of attraction.[15,61] Those with an insecure AS are more likely to be attracted by insecure partners than secure individuals. In the current study, we didn't find any significant difference between LF and HF participants' AS and personality traits.

There have been very few studies that have examined interventions to modify AS; this limitation may be due to AS being considered a trait. A recent study by Kinley and Reyno[62] found increased secure attachment and decreased fearful attachment after 6 weeks of intensive group psychotherapy. Another intervention that could be explored is cognitive-behavioral therapy, as it has shown short-term and long-term efficacy for anxiety.[63] Since fearful AS is associated with anxiety disorder,[64] it might be valuable to treat anxiety in caregivers in the hope of protecting or enhancing cognition in participants.

The study has some limitations. While the VHIS sample has many advantages, such as homogeneity and baseline data, it may limit the generalizability of the results to populations more diverse in terms of sex, age, race, and socioeconomic status. Moreover, the study design did not allow for conclusions regarding the direction of the association between cognitive decline and AS, nor does it allow inference of causal relationship. Although

we showed a large effect size of the association between caregivers' AS and cognitive trajectory of participants with TBI, we are unsure of the mediator factor(s) of this association. An interesting research direction would be to analyze caregiver's behavioral data, measuring, for example, how much the caregiver controls the environment of participants with TBI or how much the caregiver protects the participant with TBI. Finally, the association between caregivers' AS and specific cognitive functions could not be determined because of the limitations of the AFQT; we were not able to address this issue. Our participants with TBI were older than 60 years at the time of this evaluation. On the basis of our extensive 1-week inpatient evaluation, we did not detect symptoms of dementia in this cohort but we were able to document exacerbated cognitive decline that was dependent on a number of factors such as lesion characteristics, preinjury cognitive status, presence or absence of epilepsy, and so on.

CONCLUSION

Animal and human literature on neural plasticity supports the fact that a stimulating environment enhances neurogenesis, synaptogenesis, and dendrite growth. Similarly, a deprived environment has negative effects on neural plasticity and can reduce cognitive reserve. Caregivers exercise important effects on the environment of individuals with TBI beyond providing physical, social, and emotional support. In the current study, we found an association between caregivers' AS and cognitive trajectory of individuals with TBI. While caregiver burden and coping have been studied extensively, we urge future research to also take into account the possible effects of the caregiver on recovery and maintenance of functional abilities. Also, it might be prudent to evaluate caregivers along with individuals with TBI after the injury in order to develop cost-effective caregiver interventions targeting AS, thereby potentially reducing long-term cognitive decline in the patient.

REFERENCES

1. Raymont V, Greathouse A, Reding K, Lipsky R, Salazar A, Grafman J. Demographic, structural and genetic predictors of late cognitive decline after penetrating head injury. *Brain.* 2008;131(pt 2):543–558.
2. Department of Defense. DoD worldwide total numbers for TBI, 2000-2013. http://www.dvbic.org/dod-worldwide-numbers-tbi. Accessed March 5, 2014.
3. Owens BD, Kragh JF Jr, Wenke JC, Macaitis J, Wade CE, Holcomb JB. Combat wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *J Trauma.* 2008;64(2):295–299.
4. Terrio H, Brenner LA, Ivins BJ, et al. Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. *J Head Trauma Rehabil.* 2009;24(1):14–23.
5. French LM. Military traumatic brain injury: an examination of important differences. *Ann N Y Acad Sci.* 2010;1208:38–45.
6. Schmidt AT, Orsten KD, Hanten GR, Li X, Levin HS. Family environment influences emotion recognition following paediatric traumatic brain injury. *Brain Inj.* 2010;24(13/14):1550–1560.
7. Yeates KO, Swift E, Taylor HG, et al. Short- and long-term social outcomes following pediatric traumatic brain injury. *J Int Neuropsychol Soc.* 2004;10(3):412–426.
8. Taylor HG, Yeates KO, Wade SL, Drotar D, Stancin T, Burant C. Bidirectional child-family influences on outcomes of traumatic brain injury in children. *J Int Neuropsychol Soc.* 2001;7(6):755–767.
9. Tschanz JT, Piercy K, Corcoran CD, et al. Caregiver coping strategies predict cognitive and functional decline in dementia: the cache county dementia progression study. *Am J Geriatr Psychiatry.* 2013;21(1):57–66.
10. Wright LK. AD spousal caregivers. Longitudinal changes in health, depression, and coping. *J Gerontol Nurs.* 1994;20(10):33–48.
11. Wright LK. Alzheimer's disease afflicted spouses who remain at home: can human dialectics explain the findings? *Soc Sci Med.* 1994;38(8):1037–1046.
12. Perren S, Schmid R, Herrmann S, Wettstein A. The impact of attachment on dementia-related problem behavior and spousal caregivers' well-being. *Attach Hum Dev.* 2007;9(2):163–178.
13. Ognibene TC, Collins NL. Adult attachment styles, perceived social support and coping strategies. *J Soc Pers Relat.* 1998;15(3):323–345.
14. Vrticka P, Vuilleumier P. Neuroscience of human social interactions and adult attachment style. *Front Hum Neurosci.* 2012;6:212.
15. Mikulincer M, Shaver P. *Attachment in Adulthood. Structure, Dynamics, and Change*. New York, NY: Guilford Press; 2007.
16. Bowlby J. The making and breaking of affectional bonds, part I: aetiology and psychopathology in the light of attachment theory. An expanded version of the Fiftieth Maudsley Lecture, delivered before the Royal College of Psychiatrists, 19 November 1976. *Br J Psychiatry.* 1977;130:201–210.
17. Kirkpatrick LA, Davis KE. Attachment style, gender, and relationship stability: a longitudinal analysis. *J Pers Soc Psychol.* 1994;66(3):502–512.
18. Klohnen EC, Bera S. Behavioral and experiential patterns of avoidantly and securely attached women across adulthood: a 31-year longitudinal perspective. *J Pers Soc Psychol.* 1998;74(1):211–223.
19. Main M, Kaplan N, Cassidy J. Security in infancy, childhood, and adulthood: a move to the level of representation. *Monogr Soc Res Child.* 1985;50(1):66–104.
20. Ainsworth MD. Infant-mother attachment. *Am Psychol.* 1979;34(10):932–937.
21. Bartholomew K, Horowitz LM. Attachment styles among young adults: a test of a four-category model. *J Pers Soc Psychol.* 1991;61(2):226–244.
22. Lopez FG, Gormley B. Stability and change in adult attachment style over the first-year college transition: relations to self-confidence, coping, and distress patterns. *J Couns Psychol.* 2002;49(3):355–364.
23. Hamam-Raz Y, Solomon Z. Psychological adjustment of melanoma survivors. *J Individ Diff.* 2006;27(3):172–182.
24. Saucier DM, Yager JY, Armstrong EA. Housing environment and sex affect behavioral recovery from ischemic brain damage. *Behav Brain Res.* 2010;214(1):48–54.

25. Briones TL, Rogozinska M, Woods J. Environmental experience modulates ischemia-induced amyloidogenesis and enhances functional recovery. *J Neurotrauma.* 2009;26(4):613–625.
26. Kozorovitskiy Y, Gould E. Adult neurogenesis: a mechanism for brain repair? *J Clin Exp Neuropsychol.* 2003;25(5):721–732.
27. Hockly E, Cordery PM, Woodman B, et al. Environmental enrichment slows disease progression in R6/2 Huntington's disease mice. *Ann Neurol.* 2002;51(2):235–242.
28. Briones TL, Rogozinska M, Woods J. Modulation of ischemia-induced NMDAR1 activation by environmental enrichment decreases oxidative damage. *J Neurotrauma.* 2011;28(12):2485–2492.
29. Leuner B, Gould E. Structural plasticity and hippocampal function. *Annu Rev Psychol.* 2010;61:111–140, C111–C113.
30. Kozorovitskiy Y, Gross CG, Kopil C, et al. Experience induces structural and biochemical changes in the adult primate brain. *Proc Natl Acad Sci U S A.* 2005;102(48):17478–17482.
31. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat Rev Neurosci.* 2009;10(9):647–658.
32. Leuner B, Shors TJ. Stress, anxiety, and dendritic spines: what are the connections? *Neuroscience.* 2013;251:108–119.
33. Arciniegas DB, Zasler ND, Vanderploeg RD, Jaffee MS. *Management of Adults With Traumatic Brain Injury*. Arlington, VA: American Psychiatric Association; 2013:10–11.
34. Moretti L, Cristofori I, Weaver SM, Chau A, Portelli JN, Grafman J. Cognitive decline in older adults with a history of traumatic brain injury. *Lancet Neurol.* 2012;11(12):1103–1112.
35. Nithianantharajah J, Hannan AJ. The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Prog Neurobiol.* 2009;89(4):369–382.
36. Jette AM, Davies AR, Cleary PD, et al. The Functional Status Questionnaire: reliability and validity when used in primary care. *J Gen Intern Med.* 1986;1(3):143–149.
37. Costa PT, McCrae RR. *The NEO Personality Inventory Manual.* Odessa, FL: Psychological Assessment Resources; 1985.
38. Keane TM, Caddell JM, Taylor KL. Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. *J Consult Clin Pyschol.* 1988;56(1):85–90.
39. Beck AT, Rush AJ, Shaw BF, Emery D. *Cognitive Therapy of Depression*. New York, NY: Guilford Press; 1979.
40. Wechsler D. *Wechsler Adult Intelligence Scale*. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997.
41. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
42. Boller F, Vignolo LA. Latent sensory aphasia in hemisphere-damaged patients: an experimental study with the Token Test. *Brain.* 1966;89(4):815–830.
43. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation; 2001.
44. Warrington EK, James M. *Visual Object and Space Perception Battery (VOSP).* Suffolk, English: Thames Valley test Company; 1991.
45. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977;1:385–401.
46. Zarit SH, Todd PA, Zarit JM. Subjective burden of husbands and wives as caregivers: a longitudinal study. *Gerontologist.* 1986;26(3):260–266.
47. Grafman J, Jonas BS, Martin A, et al. Intellectual function following penetrating head injury in Vietnam veterans. *Brain.* 1988;111(pt 1):169–184.
48. US Department of Defense. *A Test Manual for the Armed Services Vocational Aptitude Battery*. Chicago, IL: US Military Entrance Processing Command; 1984.
49. Griffin DW, Bartholomew K. The metaphysics of measurement: the case of adult attachment. *Adv Pers Relationships.* 1994;5:17–52.
50. Bartholomew K, Shaver PR. Methods of assessing adult attachment: do they converge? In: Simpson JA, Rholes WS, eds. *Attachment Theory and Close Relationships*. New York, NY: Guilford Press; 1998:25–45.
51. Guedeney N, Fermanian J, Bifulco A. [Construct validation study of the Relationship Scales Questionnaire (RSQ) on an adult sample]. *Encephale.* 2010;36(1):69–76.
52. Makale M, Solomon J, Patronas NJ, Danek A, Butman JA, Grafman J. Quantification of brain lesions using interactive automated software. *Behav Res Methods Instrum Comput.* 2002;34(1):6–18.
53. Solomon J, Raymont V, Braun A, Butman JA, Grafman J. User-friendly software for the analysis of brain lesions (ABLe). *Comput Methods Programs Biomed.* 2007;86(3):245–254.
54. Briones TL, Klintsova AY, Greenough WT. Stability of synaptic plasticity in the adult rat visual cortex induced by complex environment exposure. *Brain Res.* 2004;1018(1):130–135.
55. Leuner B, Kozorovitskiy Y, Gross CG, Gould E. Diminished adult neurogenesis in the marmoset brain precedes old age. *Proc Natl Acad Sci U S A.* 2007;104(43):17169–17173.
56. Milgram NW, Siwak-Tapp CT, Araujo J, Head E. Neuroprotective effects of cognitive enrichment. *Ageing Res Rev.* 2006;5(3):354–369.
57. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA.* 2002;287(6):742–748.
58. Baldivia B, Andrade MA, Amodeo Bueno OF. Contribution of education, occupation and cognitively stimulating activities to the formation of cognitive reserve. *Dement Neuropsychol.* 2008;2(3):173–182.
59. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *Am J Geriatr Psychiatry.* 2009;17(3):179–187.
60. Honer WG, Barr AM, Sawada K, et al. Cognitive reserve, presynaptic proteins and dementia in the elderly. *Transl Psychiatry.* 2012;2:e114.
61. Carnelley KB, Pietromonaco PR, Jaffe K. Depression, working models of others, and relationship functioning. *J Pers Soc Psychol.* 1994;66(1):127–140.
62. Kinley JL, Reyno SM. Attachment style changes following intensive short-term group psychotherapy. *Int J Group Psychother.* 2013;63(1):53–75.
63. DiMauro J, Domingues J, Fernandez G, Tolin DF. Long-term effectiveness of CBT for anxiety disorders in an adult outpatient clinic sample: a follow-up study. *Behav Res Ther.* 2013;51(2):82–86.
64. Marganska A, Gallagher M, Miranda R. Adult attachment, emotion dysregulation, and symptoms of depression and generalized anxiety disorder. *Am J Orthopsychiatry.* 2013;83(1):131–141.