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Identification des facteurs de risque de développer une démence de type Alzheimer à la suite d'un traumatisme craniocérébral et caractérisation des profils neuropsychologiques

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Cette thèse intitulée

Identification des facteurs de risque de développer une démence de type Alzheimer à la suite d'un traumatisme craniocérébral et caractérisation des profils neuropsychologiques

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Résumé

Il existe plusieurs causes de déclin cognitif pathologique chez la personne âgée. La plus répandue est la démence de type Alzheimer (DTA). Les traumatismes craniocérébraux (TCC), notamment ceux subis en âge avancé, seraient eux aussi une cause de déclin cognitif chez l'individu âgé. Malgré l'augmentation de la littérature portant sur le TCC au cours du vieillissement et la DTA, bien peu d'études s'entendent sur le risque de développer la DTA suite à un TCC, de même que sur les facteurs associés. Encore moins d'études se sont penchées sur l'identification des profils neuropsychologiques typiques de ces deux conditions neurologiques afin de mieux les départager et ainsi faciliter le diagnostic différentiel, notamment à la suite d'un TCC. Les cliniciens sont en effet de plus en plus amenés à se positionner sur le pronostic et le devenir des patients TCC sans nécessairement toujours avoir accès à leur historique médical ou à leurs vulnérabilités pré-accidentelles. De fait, bon nombre de personnes âgées en perte d'autonomie et qui subissent un TCC n'ont pas été préalablement dépistées pour un trouble neurodégénératif, et l'accident de même que l'hospitalisation sont ainsi les facteurs déclencheurs d'une investigation plus poussée. Afin de répondre, d'une part, à la question du risque de développer la DTA suite à un TCC en âge avancé et d'autre part, d'outiller les cliniciens à poser un diagnostic différentiel, notamment en identifiant la présence potentielle d'une DTA prémorbide à un TCC, la présente thèse vise à identifier les caractéristiques liées au TCC qui sont associées au risque de développer une démence de type Alzheimer, et à comparer les profils neuropsychologiques des patients TCC âgés des patients DTA et des individus sains.

La thèse est composée d'une revue systématique et d'un article empirique. Le premier article avait pour objectif d'identifier les caractéristiques liées au TCC qui sont associées au risque de développer une démence de type Alzheimer. Une revue systématique regroupant un total de dix-huit études a été effectuée afin d'identifier si la sévérité du TCC et la présence d'une perte de conscience et d'une amnésie post-traumatique (APT) étaient susceptibles de prédire le risque de développer la DTA. Aucune tendance significative n'est ressortie de cette analyse, ni la sévérité, ni la présence d'une perte de conscience, ni l'APT et ni le résultat à l'ÉCG ont été identifiés comme facteurs pronostics importants. La discussion de cette revue systématique soulève principalement les différences sur les plans de la méthodologie des études incluses dans la revue et des obstacles

liés à la comparaison de ces dernières et propose des recommandations pour les futures études sur le sujet.

Le deuxième article avait pour but de caractériser les profils neuropsychologiques des individus âgés souffrant d'un TCC léger (TCCL) (N= 24) des individus souffrant de la DTA en stade léger (N= 29) et des individus âgés sains (N= 24). Pour les deux groupes neurologiques, des variables influençant les performances neuropsychologiques ont également été explorées. La mémoire verbale, la mémoire visuelle, l'accès lexical, les fonctions exécutives, la mémoire de travail, la vitesse de traitement de l'information, les symptômes anxieux et les symptômes dépressifs ont été évalués. L'âge et le niveau de scolarisation, la sévérité du TCCL (c.-à.-d. mesurée en fonction du résultat sur l'Échelle de Coma de Glasgow (ÉCG)), le nombre de jours suivant le TCCL (mesure du temps de récupération) et le site de la lésion cérébrale traumatique ont aussi été explorés comme potentiels prédicteurs des performances neuropsychologiques chez les individus TCCL et les individus atteints de DTA (c.-à.-d. l'âge et le niveau de scolarisation ont été explorés pour ce groupe). Tel qu'attendu, les résultats démontrent des profils neuropsychologiques distincts entre les patients TCCL âgés, les patients DTA et ceux présentant un vieillissement normal. Les troubles mnésiques se sont avérés plus importants chez le groupe DTA que chez les deux autres groupes alors que les symptômes d'anxiété et de dépression se sont avérés plus élevés chez le groupe TCCL que chez les deux autres groupes. En outre, pour le groupe TCCL, seul le niveau d'éducation et le temps de récupération se sont révélés comme étant des facteurs contribuant de manière significative à certaines fonctions cognitives alors qu'aucune variable n'a été associée aux fonctions cognitives chez le groupe DTA.

En somme, ces résultats sont d'une grande importance sur le plan clinique considérant l'augmentation de la population âgée à prévoir lors des prochaines années qui amènera les cliniciens à devoir se positionner sur le devenir des patients présentant un déclin cognitif, de même que sur les plans d'intervention à privilégier chez ces clientèles neurologiques.

Mots-clés : traumatisme craniocérébral; Alzheimer; démence; personne âgée; gériatrie; profil neuropsychologique; fonctionnement cognitif; difficultés cognitives; facteur de risque.

Abstract

There are many causes of cognitive decline in older adults. The most prevalent is Alzheimer's disease (AD). Another common cause of cognitive decline in older adults is traumatic brain injury (TBI). Advanced age and cognitive decline in the elderly are also risk factors for falls. Thus, among some elderly individuals, AD and TBI may be comorbid conditions. It seems that TBI increases the risk of AD, but this link is still poorly understood in the literature. Despite the increase prevalence of TBI and AD in recent years, very few studies agree on the effect of TBI on the risk of developing AD and the associated risk factors. Also, few studies have looked at the neuropsychological profiles associated with those two neurological conditions in order to aid in differential diagnosis. This thesis aims to identify the characteristics linked to TBI which are associated with the risk of developing Alzheimer's type dementia, to characterize the neuropsychological profile of elderly TBI patients, AD patients and healthy individuals, as well as to identify the factors influencing the cognitive functions.

The thesis includes one systematic review and one empirical study. The first investigates if certain traumatic brain injury (TBI)-related variables can predict the risk of developing post-TBI Alzheimer's disease (AD) in adults. A total of 18 studies were included in the review. Specific TBI-related variables, such as TBI severity, loss of consciousness (LOC) and post-traumatic amnesia (PTA) were documented as possible predictors of AD. Failure to establish such a link may be related to methodological differences within and across studies.

The aim of the second article was to assess the differences in neuropsychological profiles of older adults with mild traumatic brain injuries (mTBI) and with Alzheimer's disease (AD). The sample included older adults with mTBI (n = 24), older adults with AD (n = 29), and healthy older adults (n = 24). A battery of cognitive tests and standardized questionnaires were administered to all participants in a standardized fashion during a neuropsychological evaluation. Demographic and injury factors were examined as potential predictors of cognitive outcomes. Results revealed group differences across all cognitive functions. Also, the number of years of education and the

number of days since the accident were associated with some cognitive functions for the TBI group. However, no variable was associated with cognitive functioning in the AD group.

Although this thesis does not clearly identify the factors related to TBI that would increase the risk of developing AD, it demonstrates that a TBI in old age can impair cognitive functioning. The neuropsychological profiles of elderly patients with mTBI differ significantly from that of AD patients and normal aging. This thesis also highlights that the recovery time as well as the level of education seem to be protective factors following mTBI for some cognitive functions. These results are of great importance considering that the population of seniors will increase considerably over the next decades and will lead clinicians to have to take a position on the diagnosis and the future of patients.

Key words: traumatic brain injury; Alzheimer's disease; dementia; cognitive decline; cognitive functioning; neuropsychology; outcome; older people; elderly.

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Liste des sigles

AD	Alzheimer's disease
ANOVA	Analysis of variance
ApoE4	Apolipoprotein
APT	Amnésie post-traumatique
ßA	Bêta-Amyloïdes
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BNT	Boston naming test
COWAT	Controlled oral word association test
CRM	Continuous recognition memory test
CT	Tomodensitométrie
CVLT	California verbal learning test
DSM-V	Diagnostic and statistical manual of mental disorders, 5th edition
DTA	Démence de type Alzheimer
DTI	Imagerie du tenseur de diffusion
ÉCG	Échelle de coma de Glasgow
ER	Emergency room
ESPT	État de stress post-traumatique
FRSQ	Fonds de recherche en santé du Québec
GAI	Geriatric anxiety inventory
GCS	Glasgow coma scale
GDS	Geriatric depression scale
ICD-10	International classification of diseases
INESSS	Institut national d'excellence en santé et en services sociaux
IRM	Imagerie par résonance magnétique
IRMf	Imagerie par résonance magnétique fonctionnelle
LCR	Liquide céphalorachidien
LOC	Loss of consciousness

M	Mean
MA	Maladie Alzheimer
MCST	Modified card sorting test
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
mTBI	Mild traumatic brain injury
ND	Participants without neurological disorder
NINCDS/ADRDA	National institute of neurological and communication disorders and stroke and Alzheimer's disease and related disorders association
PET	Hypométabolisme en tomographie par émission de positrons
PET-FDG	Hypométabolisme en tomographie par émission de positrons au flurodéoxyglucose
QI	Quotient intellectuel
RAMQ	Régie de l'assurance maladie du Québec
RAVLT	Rey auditory verbal learning test
RC	Hypothèse de la réserve cognitive
ROCF	Rey-Osterrieth complex figure test
SD	Standard deviation
SPECT	Hypoperfusion en tomographie d'émission monophotonique
TBI	Traumatic brain injury
TCC	Traumatisme craniocérébral
TCCL	Traumatisme craniocérébral léger
TEP	Tomographie par émission de positrons
TDM	Tomodensitométrie
TMT	Trail making Test
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test
WMS-IV	Weschsler memory scale 4th Edition

Listes des abréviations

c.-à.-d. C’est-à-dire

e.g. For example

i.e. That is

p. ex. Par exemple

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1.0 Contextualisation du problème

La population des aînés continuera à augmenter considérablement au cours des prochaines années, ce qui aura pour conséquence un accroissement de la prévalence du traumatisme craniocérébral (TCC) (Yokobori et al., 2016) et de la démence de type Alzheimer (DTA) chez les personnes âgées (Pouryamout, Dams, Wasem, Dodel, et Neumann, 2012). Les données montrent une augmentation importante des chutes chez des personnes âgées et par conséquent, une amplification de la prévalence du TCC chez cette population (Ho et al., 2014; Kumar et al., 2018). En outre, un nombre croissant d'auteurs ont suggéré un possible lien entre le TCC et l'apparition de la DTA post accident (Fleminger, Oliver, Lovestone, Rabe-Hesketh, et Giora, 2003; Guo et al., 2000; Lye et Shores, 2000; Mortimer et al., 1991; O'Meara et al., 1997; Plassman et al., 2000; Schofield et al., 1997), rendant essentiel de poursuivre la recherche afin notamment de mieux identifier les facteurs de risques de développer la DTA à la suite d'un TCC et de mieux comprendre les profils neuropsychologiques associés à ces deux conditions neurologiques. La recherche sur l'identification des facteurs de risques de développer la DTA à la suite d'un TCC et sur les profils neuropsychologiques associés à ces conditions demeure toutefois limitée, en dépit du fait que les cliniciens soient de plus en plus amenés à se positionner sur le pronostic et le devenir des patients TCC. Sur le terrain, les neuropsychologues cliniciens doivent répondre à deux principales questions qui leur sont fréquemment posées par les patients TCC en âge avancé et par leurs proches, de même que par l'équipe soignante et les gestionnaires, questions auxquelles peu de littérature ou de données probantes permettent actuellement de répondre. La première porte sur le risque de développer la DTA à la suite de cet événement qu'est le TCC ; la seconde, sur le pronostic et les services de réadaptation requis pour les patients. La réponse à cette dernière question réside en grande partie dans le diagnostic différentiel entre ce qui relève davantage d'une vulnérabilité prémorbide et ce qui appartient aux impacts secondaires typiques du TCC. De fait, de plus en plus de personnes âgées en perte d'autonomie et qui subissent un TCC n'ont pas été préalablement dépistées pour un trouble neurodégénératif. Ainsi, le neuropsychologue doit se positionner sur le profil cognitif observé à la suite du TCC subi et déterminer si le profil est davantage associé à un tableau neurodégénératif sous-jacent au TCC ou encore à un tableau typiquement traumatique. Cette distinction s'avère essentielle puisque les interventions requises diffèrent chez ces deux groupes. De même, l'évolution clinique de ces deux conditions neurologiques (TCC et DTA) est très différente.

En somme, la présente thèse a pour objectif d'étudier, dans un premier temps, les caractéristiques liées au TCC qui seraient des facteurs de risques de développer la DTA. À titre d'exemple, certaines caractéristiques liées au TCC et à l'individu, telles que la sévérité du TCC (McIntyre et al., 2011), l'âge auquel le patient a subi le TCC (Senathi-Raja, Ponsford et Schonberger, 2010 ; Spitz et al., 2012a) et le niveau d'éducation (Gardner, Dams-O'Connor, Morrissey, et Manley, 2018; Rabinowitz et Levin, 2014b), ont été suggérées comme influençant le risque de développer une DTA. Cette thèse tentera donc de mettre en évidence, s'il y a lieu, d'autres variables liées au TCC qui pourraient prédire le risque de développer la DTA, telles que la présence ou non d'une perte de conscience, le résultat à l'ÉCG ou la présence d'une APT. La présente thèse vise également à caractériser les profils neuropsychologiques des patients TCCL âgés, des patients atteints de la DTA au stade léger et de personnes âgées sans trouble cognitif, ainsi qu'à déterminer si l'âge et le niveau de scolarisation sont associés aux performances neuropsychologiques chez des patients atteints par l'une ou l'autre de ces deux conditions neurologiques. De surcroît, ce projet tentera d'explorer et d'identifier les variables reliées au TCC (c.-à.-d. la sévérité, le site des lésions et le nombre de jours depuis l'accident) associées aux performances neuropsychologiques pour le groupe TCC seulement. La caractérisation des profils neuropsychologiques typiques pourra donc aider les cliniciens à poser un diagnostic différentiel plus juste et à identifier, chez le patient TCC en âge avancé, la présence de caractéristiques typiques du tableau DTA ou relevant plutôt de celui du TCC.

2.0 Le traumatisme craniocérébral (TCC) chez la personne âgée

2.1 Définition

Le TCC est défini comme une perturbation du fonctionnement normal du cerveau causée par une force physique extérieure (Menon et al., 2010) telle qu'une secousse, un impact ou un choc à la tête (Faul, Xu, et Wald, 2010). Ce dommage au cerveau n'est pas lié à des troubles congénitaux, à une déficience développementale ou à des processus qui endommagent progressivement le cerveau (Teasell et al., 2018). Le TCC est catégorisé selon trois niveaux de sévérité : léger, modéré et grave. Généralement, la sévérité du TCC est déterminée en fonction du degré d'altération de l'état de conscience du patient à la suite de sa blessure. Les niveaux de l'état de conscience suivant un TCC peuvent aller de la désorientation transitoire au coma profond. Diverses mesures de l'état

de conscience sont utilisées dans la pratique clinique pour déterminer la gravité de la blessure : le résultat à l'ÉCG, la durée de l'APT et la durée de la perte ou de l'altération de l'état de conscience (Teasdale et Jennett, 1974; Teasell et al., 2018). De façon générale, les signes probants du TCCL sont : 1) un résultat entre 13-15 à l'ÉCG ; 2) une perte ou une altération de l'état de conscience entre 0 et 30 minutes et 3) une durée d'ATP de moins de 24 heures (Marshall, Bayley, McCullagh, Velikonja, et Berrigan, 2012; Ministère de la santé et des services sociaux, 2010; Teasell et al., 2018). Les TCC dont le niveau va de modéré à grave, quant à eux, se caractérisent par des lésions neurologiques, notamment visibles en imagerie, une altération ou une perte de conscience de plus de 30 minutes, un résultat à l'ÉCG de 9 à 12 et de 3 à 8 respectivement à l'ÉCG ainsi qu'une durée d'APT entre 1 et 7 jours pour le niveau modéré et de plus de 7 jours pour le TCC grave (Lezak, Howieson, Bigler, et Tranel, 2012; Teasell et al., 2018). En fonction de la sévérité du TCC, un large éventail de difficultés affectant le fonctionnement physique, neurocognitif et/ou psychologique peut être observé (Teasell et al., 2018).

2.2 Prévalence du TCC

Statistique Canada (2010) prévoit que près de 25% de la population sera âgée de plus de 65 ans en 2036. Aux États-Unis, 155 000 cas de TCC sont diagnostiqués par année chez la population âgée, et 12 000 d'entre eux en décèdent (Richmond et al., 2011). L'augmentation estimée d'hospitalisation de la population TCC âgée représentera donc un problème de santé publique majeur ainsi qu'un important fardeau économique lors des prochaines années (Thompson, Weir, et al., 2012). En outre, la prévalence la plus élevée de visites à l'urgence, d'hospitalisations et de décès liés aux TCC se retrouve chez les personnes âgées (Faul, Xu, Wald, Coronado, et Dellinger, 2010; Ramanathan, McWilliams, Schatz, et Hillary, 2012; Taylor, Bell, Breiding, et Xu, 2017). Les personnes âgées constituent la tranche d'âge la plus affectée par le TCC et les conséquences délétères qui en découlent ont un impact majeur sur leur autonomie et leur qualité de vie (Sasse et al., 2013; Stalnacke, Elgh, et Sojka, 2007). En 2013, chez les 65-74 ans, plus d'une personne sur 200 ayant subi un TCC a fréquenté l'urgence, a été hospitalisée ou est décédée à la suite d'un TCC. Cette proportion augmente à 1/50 chez les 75 ans et plus (Taylor et al., 2017). Toujours en 2013, aux États-Unis, 31.4% des hospitalisations et 26.5% des décès des suites d'un TCC ont eu lieu chez les personnes de plus de 75 ans. Entre 2006 et 2008 aux États-Unis, 800 000 adultes de plus de 65 ans ont été évalués suite à un TCC (Pearson, Sugerman, McGuire, et Coronado, 2012). De plus,

entre 2007 et 2013, la proportion de personnes de plus de 75 ans ayant été hospitalisées à la suite d'un TCC a augmenté de 25% (Taylor et al., 2017). Cette augmentation d'hospitalisations et de décès à la suite des séquelles d'un TCC dans la population vieillissante a été confirmée par de multiples études épidémiologiques effectuées dans différents états américains ainsi que dans l'ensemble du pays (Fletcher, Khalid, et Mallonee, 2007; Haring et al., 2015; Nwaiwu, Phillips, et Ohsfeldt, 2016; Ramanathan et al., 2012). Cette même tendance a pu être observée dans plusieurs pays occidentaux à hauts revenus, comme l'Espagne (Perez et al., 2012), l'Angleterre (Hawley, Sakr, Scapinello, Salvo, et Wrenn, 2017), l'Écosse (Hamill, Barry, McConnachie, McMillan, et Teasdale, 2015), les Pays-Bas (Scholten, Haagsma, Panneman, van Beeck, et Polinder, 2014), l'Autriche (Brazinova, Mauritz, Majdan, Rehorcikova, et Leitgeb, 2015), la Finlande (Korhonen, Niemi, Parkkari, Sievanen, et Kannus, 2013), le Canada (de Guise et al., 2014; Fu, Jing, McFaull, et Cusimano, 2015) et l'Australie (Harvey et Close, 2012). Par conséquent, l'ensemble des données épidémiologiques met en évidence que l'âge avancé augmente significativement le risque de subir un TCC (Seidler et al., 2010b). Néanmoins, il semblerait que les personnes âgées soient les moins portées à aller chercher de l'aide médicale suite à un TCC (Setnik et Bazarian, 2007). De plus, lorsqu'évalué, le diagnostic médical serait également moins précis chez les personnes âgées. Ces résultats suggèrent donc que la prévalence des TCC dans la population vieillissante serait sous-estimée dans la littérature (Albrecht et al., 2016).

2.3 Le TCC chez la personne âgée

Les mécanismes de blessure, les caractéristiques des patients et les séquelles biologiques du TCC dit « gériatrique » diffèrent de ceux des personnes plus jeunes et nécessitent donc une approche unique dans la gestion clinique et dans la recherche (Kinsella, 2011 ; Stocchetti, Paterno, Citerio, Beretta, et Colombo, 2012; Thompson, Dikmen, et Temkin, 2012). Sur le plan épidémiologique, le mécanisme de blessure le plus répandu chez les personnes âgées est la chute (de Guise et al., 2015; Harvey et Close, 2012; Kannus, Niemi, Parkkari, Palvanen, et Sievanen, 2007; Taylor et al., 2017; Watson et Mitchell, 2011). Une combinaison de plusieurs facteurs permet d'expliquer les raisons pour lesquelles les gens âgés sont particulièrement vulnérables à la survenue d'un TCC. Au même titre que les autres organes, le cerveau subit une série de changements structuraux et fonctionnels au cours du processus de vieillissement (Liu et al., 2017). Par exemple, des études longitudinales et transversales d'imagerie cérébrale ont rapporté des volumes cérébraux

globaux plus faibles (Driscoll et al., 2009; Seidler et al., 2010a), une épaisseur corticale réduite (Salat et al., 2004) et une expansion du système ventriculaire (Scahill et al., 2003) dans le cerveau des personnes âgées. Les pathologies cérébrales telles que les lésions de matière blanche (e.g. hyperintensités de la matière blanche), les infarctus et les microhémorragies cérébrales sont également plus fréquents chez les cerveaux âgés (Salat et al., 2004). De plus, parallèlement à ces changements structuraux, les taux cérébraux de neurotransmetteurs tels que la dopamine (Wenk, Pierce, Struble, Price, et Cork, 1989), l'acétylcholine (Gottfries, 1990), la sérotonine (Gottfries, 1990), la norépinéphrine (Mei et al., 2015), et les neurotropes (Terry, Kutiyanawalla, et Pillai, 2011) sont considérablement réduits dans les cerveaux vieillissants.

En ce sens, si la structure anatomique du cerveau reflète le fonctionnement physiologique, il n'est pas surprenant que de nombreuses fonctions cérébrales soient également affectées par le vieillissement. Par exemple, le déclin des capacités motrices (Seidler et al., 2010), des fonctions sensorielles (Brodoehl et al., 2013) et des habiletés cognitives a été observé avec le vieillissement naturel (Edwards et al., 2002; Fried, Bandeen-Roche, Chaves, et Johnson, 2000; Salthouse, 2012). En effet, les personnes âgées sont susceptibles de vivre une diminution du contrôle de la motricité fine, des problèmes d'équilibre et de marche ainsi qu'un déclin cognitif. Ces altérations peuvent ainsi nuire à la qualité de vie, aux habilités à réaliser les activités de la vie quotidienne et au maintien de l'indépendance, mais sont surtout liées au risque de subir une chute et d'être hospitalisé (Fried et al., 2000; Seidler et al., 2010a; Stenhagen, Ekstrom, Nordell, et Elmstahl, 2013). Plus spécifiquement, le déclin général associé au vieillissement augmenterait le risque de chutes et par le fait même, l'incidence de TCC (Kannus et al., 2007; Watson et Mitchell, 2011). Ainsi, cette fragilité dans diverses sphères (anatomique, structurale, cognitive et physique) augmenterait dramatiquement le risque de subir un TCC (Seidler et al., 2010a) et rendrait la personne aînée plus vulnérable aux conséquences d'un TCC (Ferrell et Tanev, 2002).

3.0 Conséquences du TCC

Les conséquences post-TCC peuvent être physiques, cognitives et psychologiques (Gardner et al., 2018). Une étude réalisée par notre équipe de recherche a montré que deux semaines suivant l'accident, la majorité des patients TCCL présentait des symptômes post-TCC dans l'ensemble des domaines nommés précédemment, même si ces derniers étaient peu spécifiques (Annexe A)

(Julien, Tinawi, et al., 2017). Le tableau semble toutefois quelque peu différent chez les personnes en âge avancé. En ce sens, la personne âgée atteinte d'un TCC est reconnue comme ayant un plus grand risque de morbidité et de mortalité (Dams-O'Connor, Gibbons, et al., 2013; McIntyre, Mehta, Aubut, Dijkers, et Teasell, 2013; Ramanathan et al., 2012). Il est assez fréquent que les personnes âgées expérimentent des conséquences fonctionnelles, cognitives et psychologiques qui peuvent durer plusieurs mois voire plusieurs années aux suites d'un TCC (Cuthbert et al., 2015; Stocchetti, Paterno, Citerio, Beretta, et Colombo, 2012; Thompson, Dikmen, et Temkin, 2012). Or, malheureusement, ces conséquences affectent directement la qualité de vie des victimes d'un TCC (Sasse et al., 2013; Stalnacke et al., 2007; Thompson, McCormick, et Kagan, 2006) et leur autonomie (Thompson et al., 2006), tout en venant limiter leurs activités (activité de la vie quotidienne, travail, etc.) (Rabinowitz et Levin, 2014b).

De fait, il existe de nombreuses différences entre les cerveaux plus jeunes et ceux plus âgés qui peuvent entraîner des dissemblances dans la cascade de changements neurochimiques, physiologiques et structuraux après un choc au cerveau (Vollmer et al., 1991). En outre, le processus de vieillissement normal du cerveau, caractérisé par une perte d'intégrité de la substance blanche cérébrale (Madden, Bennett et Song, 2009) et la réduction de la matière grise (Raz et Rodrigue, 2006), est susceptible d'altérer la plasticité et la capacité de réparation après une blessure en augmentant la susceptibilité aux complications à la suite du TCC (Kinsella, 2011 ; Stocchetti et al., 2012). Ainsi, l'impact du TCC interagit avec le processus de vieillissement, pouvant donner lieu à des conséquences physiques, psychologiques et fonctionnelles, de même que des difficultés cognitives (Gardner, Dams-O'Connor, Morrissey et Manley, 2018).

3.1 Fonctionnement cognitif à la suite d'un TCC

Malgré l'augmentation de la prévalence du TCC et les taux plus élevés de morbidité et de mortalité post-TCC chez cette tranche de la population, relativement peu de recherches a été menée sur les conséquences cognitives post-TCC chez les personnes âgées par rapport au nombre d'études portant sur les autres groupes d'âge. On constate la nécessité d'examiner les profils cognitifs spécifiques aux personnes TCC âgées séparément des adultes d'âge jeune à moyen, car les résultats de la littérature à ce sujet, qui comprend principalement des échantillons adultes, ne peuvent être simplement transposés à une population plus âgée (Senathi-Raja, Ponsford et Schönberger, 2010).

Bien que le profil d'impact du TCC soit très hétérogène, il existe tout de même un profil lésionnel prédominant qui détermine les déficits cognitifs de l'individu, qu'il soit jeune ou plus âgé. Les régions frontales et temporales ainsi que les circuits cérébraux qui leur sont reliés sont les plus susceptibles d'être endommagés lors d'un TCC (Lezak et al., 2012; Rabinowitz et Levin, 2014b; Smith, Meaney, et Shull, 2003). La force mécanique produite par le coup ou la secousse à la tête peut engendrer une série de réactions physiques et mécaniques complexes induisant des contraintes/tensions et des dommages affectant plusieurs structures (c.-à.-d. la matière blanche et grise du cerveau, les vaisseaux sanguins, etc.) et dont résultent souvent des difficultés cognitives (Lezak et al., 2012). Les recherches portant sur les difficultés cognitives chez la personne âgée à la suite d'un TCC divergent les unes des autres sur le plan méthodologique, rendant ainsi difficile l'identification des fonctions cognitives atteintes. Par exemple, la sévérité du TCC, le délai depuis l'accident, l'âge des patients et les tests utilisés pour évaluer les fonctions varient énormément d'une étude à l'autre. À ce jour, une méta-analyse exécutée par An et Monette (2018), qui recense les différentes études portant sur le sujet, suggère que les personnes âgées ayant eu un TCC toutes sévérités confondues performent significativement moins bien que les personnes âgées sans historique de TCC dans les différents domaines cognitifs tels que la mémoire, le langage, la vitesse de traitement de l'information, l'attention, la mémoire de travail et les fonctions exécutives.

4.0 Pronostic à la suite d'un TCC

Tel que précédemment mentionné, la population âgée est considérablement plus à risque de mortalité et de morbidité suite à un TCC, contrairement aux jeunes adultes (Dams-O'Connor, Gibbons, et al., 2013; Gaetani et al., 2012; LeBlanc, de Guise, Gosselin, et Feyz, 2006; McIntyre, Mehta, Aubut, et al., 2013; McIntyre, Mehta, Janzen, Aubut, et Teasell, 2013; Ramanathan et al., 2012). L'incidence des patients TCC transférés en maison de retraite au cours des dernières années ne cesse d'augmenter (de Guise et al., 2015; Karon, Lazarus, et Holman, 2007). Dans le même sens, une étude réalisée par notre groupe de recherche a mis en évidence que les patients TCC âgés seraient plus susceptibles d'être transférés en établissement de réadaptation ou dans des établissements de soins de longue durée, ou encore de décéder des suites du traumatisme, que les patients jeunes et d'âge moyen (LeBlanc et al., 2006). Il a aussi été démontré que les patients TCC âgés sont plus susceptibles de requérir une implication accrue de la famille et d'utiliser des services de soutien communautaire (Rothweiler, Temkin, et Dikmen, 1998; Wilson, Pentland, Currie, et

Miller, 1987) ou encore d'avoir besoin de soins à domicile ou un changement de domicile (Wilson et al., 1987). Testa, Malec, Moessner, et Brown (2005) ont effectivement constaté que les personnes âgées risquent d'être moins autonomes et plus dépendantes d'autrui à la suite du TCC. Bref, on considère que les patients âgés souffrant d'un TCC ont un pronostic moins favorable que les patients plus jeunes. Plus précisément, certains auteurs (Marquez de la Plata et al., 2008) ont observé un plus grand déclin fonctionnel chez la personne âgée dans les cinq ans suivant son TCC par rapport aux jeunes adultes, alors que d'autres ont mis en évidence les conséquences négatives post-TCC à long terme plus nombreuses que chez l'adulte d'âge moyen (Luukinen, Viramo, Koski, Laippala, et Kivela, 1999; Susman et al., 2002). D'autres études mentionnent même que, contrairement aux jeunes adultes, la personne âgée serait davantage susceptible de ne pas récupérer complètement sur le plan du fonctionnement psychosocial (Aharon-Peretz et al., 1997; Luukinen et al., 1999; Rapoport et Feinstein, 2001) et, à long terme, de vivre un déclin neurologique suite à un TCC (Luukinen et al., 2005). Toutefois, une étude réalisée en 2012 a souligné qu'avec des ressources adéquates et suffisantes, une intervention appropriée, des soins neuro-intensifs et une réadaptation agressive, les résultats fonctionnels et cognitifs des patients TCC âgés pouvaient être comparables à ceux de leurs homologues plus jeunes (Mak et al., 2012). Le pronostic à la suite d'un TCC en âge avancé semble donc dépendre de plusieurs variables liées au TCC en question mais également aux caractéristiques personnelles du patient. Ces variables seront décrites dans la section suivante.

4.1 Influence des caractéristiques liées au TCC sur le pronostic

4.1.1 Sévérité du TCC. Certains auteurs avancent que le pronostic post-TCC des patients vieillissants est influencé par la sévérité du TCC (mesurable notamment à l'aide de l'ÉCG, la durée de l'APT et l'altération ou la perte de conscience). À cet égard, il semble que les TCC modéré et grave soient associés à des conséquences et des déficits cognitifs plus sévères et persistants comparativement aux conséquences du TCCL et ce, particulièrement chez la personne âgée (Rabinowitz et Levin, 2014b). Par exemple, Ritchie, Cameron, Ugoni, et Kaye (2011) ont pu montrer que les gens âgés de 65 ans et plus ayant obtenu un résultat à l'ÉCG de 11 et moins subissaient à la sortie de l'hôpital de nombreuses conséquences négatives à la suite de leur TCC, contrairement aux personnes âgées qui avaient obtenu un résultat à l'ÉCG plus élevé. De surcroît, une étude réalisée par notre équipe de recherche a montré le lien entre la sévérité du TCC et le

devenir fonctionnel des patients TCC en âge avancé (Julien, Alsideiri, et al., 2017). Cette étude, qui figure en annexe B à cette thèse, a même permis de déterminer que la sévérité du TCC, exprimée par le résultat à l'ÉCG, était un meilleur facteur de prédiction du devenir fonctionnel que la présence d'une médication anticoagulante. Il est enfin intéressant d'observer que certains auteurs (Lilley et al., 2016) constatent qu'une personne âgée atteinte d'un TCC, y compris d'un TCC sévère, pourrait bien se rétablir.

4.1.2 Lésions cérébrales suivant le TCC. Des études ont montré qu'en plus de la sévérité du TCC, le type de lésions cérébrales traumatiques aurait également une prévalence et un impact différents sur les personnes plus jeunes que sur les plus âgées. En outre, le type de lésions cérébrales suivant un TCC observé sur l'imagerie radiologique (c.-à.-d. *head CT scan)* différerait selon l'âge du patient. À titre d'exemple, la prévalence d'hématomes extraduraux diminuerait avec l'âge tandis que la prévalence d'hématomes sous-duraux avec déviation de la ligne médiane augmenterait en fonction de l'âge, ce type de blessure étant associé à un pronostic moins favorable (Stocchetti et al., 2012). En effet, environ 45% des personnes âgées de plus de 65 ans admises à l'hôpital pour un TCC, toutes sévérités confondues, présentaient un hématome sous-dural apparent à la tomodensitométrie (TDM) (Hawley et al., 2017). Il semblerait toutefois que les caractéristiques du TCC, telles que la sévérité et la présence de lésions cérébrales, ne pourraient à elles seules expliquer totalement l'évolution de la condition des patients âgés (Gardner et al., 2018; Leary et al., 2018).

4.2 Influence des caractéristiques personnelles sur le pronostic

4.2.1 L'âge. Parmi les facteurs qui influencent le pronostic post-TCC, l'âge au moment de la blessure serait déterminant. Non seulement l'âge avancé serait lié à une augmentation du risque de TCC, mais avoir un TCC en âge avancé aurait un impact significatif sur ses conséquences (de Guise et al., 2015; Seidler et al., 2010a). Parmi les études consacrées à l'examen de cette variable, celle de Mushkudiani et al. (2007) a montré une association linéaire entre l'âge et les difficultés fonctionnelles six mois suivant l'accident chez des individus ayant subi un TCC modéré à sévère. Les études rapportent majoritairement qu'à intensité égale, les personnes âgées tendent à avoir des conséquences plus graves que les jeunes (Susman et al., 2002; Testa et al., 2005). Par ailleurs, les patients TCC plus âgés sont particulièrement susceptibles de vivre des changements d'humeur et un déclin des fonctions psychosociales et cognitives plus importants que les jeunes adultes

(Aharon-Peretz et al., 1997; Cifu et al., 1996; Cuthbert et al., 2015; Luukinen et al., 1999; Rapoport et al., 2006; Rothweiler et al., 1998; Thompson, Dikmen, et al., 2012; Wilson, Barnes, et Bennett, 2003).

4.2.2 La réserve cognitive. L'hypothèse de la réserve cognitive (RC) comme facteur explicatif potentiel de la variabilité de la symptomatologie clinique post-TCC a été suggérée, tous âges confondus. Cette hypothèse a été proposée par Stern (2009) pour expliquer la dissociation entre le niveau de dommage cérébral et sa présentation clinique attendue. D'une part, le modèle « passif » propose que la réserve cérébrale puisse rendre compte des variabilités anatomiques et structurales individuelles du cerveau (c.-à.-d. taille et composition du cerveau), dans la mesure où un cerveau plus volumineux pourrait davantage compenser pour les dommages avant que des déficits cognitifs deviennent observables. D'autre part, le modèle dit « actif » réfère quant à lui à l'utilisation des ressources cognitives disponibles ou résiduelles dans le cas d'un dommage cérébral (Stern, 2002, 2012, 2013). Par ailleurs, le concept de réserve cognitive évoque implicitement la notion de « seuil critique » : les symptômes cognitifs deviennent cliniquement évidents seulement au moment où la perte neuronale est suffisamment importante et dépasse le seuil critique (Lye et Shores, 2000). Selon ce principe, tous les individus n'auraient pas le même seuil (Lye et Shores, 2000).

Suite à un TCC, le cerveau tenterait ultimement de fonctionner de manière efficace malgré les séquelles de la blessure cérébrale en utilisant des processus cognitifs préexistants (capacités innées et expositions environnementales vécues) ou compensatoires (stratégies alternatives ou utilisation de réseaux neuronaux additionnels de compensation) (Stern, 2002). En ce sens, l'éducation aurait un impact sur les conséquences post-accident et le pronostic des patients (Dik, Deeg, Visser, et Jonker, 2003; Manly, Schupf, Tang, et Stern, 2005; Mortimer, Snowdon, et Markesbery, 2003; Wilson et al., 2003). Le niveau de scolarité complété par les patients TCC serait un facteur prédictif particulièrement fiable pour mesurer les conséquences post-accident. Ce fait pourrait s'expliquer en posant l'hypothèse qu'un individu ayant un niveau d'éducation faible compenserait plus difficilement les dommages cérébraux causés par le TCC (Kesler, Adams, Blasey, et Bigler, 2003; Ponsford, Draper, et Schonberger, 2008) qu'un individu resté aux études plus longtemps. De fait, la personne âgée ayant reçu un niveau d'éducation supérieur bénéficierait d'une plus grande protection face au TCC.

4.2.3 Les comorbidités. La relation entre la pathologie cérébrale (TCC) et son expression clinique est en partie médiée par les facteurs prémorbides et les caractéristiques du patient (Stern, 2002). Les comorbidités, telles que la démence, sont souvent identifiées comme facteurs de mauvais pronostics associés à un TCC. Par ailleurs, ces conditions préexistantes viennent augmenter le risque de chute et, par conséquent, le risque de subir un TCC en âge avancé (Dams-O'Connor, Gibbons, Landau, Larson, et Crane, 2016). La fréquence de chutes chez la personne atteinte de la DTA serait en effet trois fois plus élevée que chez l'individu sans trouble neurodégénératif (Sheridan et Hausdorff, 2007). Ainsi, il n'est pas rare qu'un individu atteint de DTA subisse un TCC, ces deux conditions étant souvent associées (Ho et al., 2014; Kumar et al., 2018).

5.0 La démence de type Alzheimer

5.1 Définition de la DTA

La DTA est une maladie neurodégénérative, soit une atteinte cérébrale d'aggravation progressive et d'installation insidieuse conduisant à la mort neuronale et au déclin cognitif et fonctionnel. Cette maladie est l'une des causes les plus fréquentes du trouble neurocognitif majeur (Barker et al., 2002; Wilson et al., 2012). Le trouble neurocognitif majeur est défini selon le DSM-V comme une réduction importante de deux ou plusieurs domaines cognitifs (attention complexe, fonctions exécutives, apprentissage et mémorisation, langage, activités perceptivomotrices ou cognition sociale), menant à un déficit fonctionnel dans diverses sphères de la vie de la personne (professionnelle, interpersonnelle, activités de la vie quotidienne) (American Psychiatric Association, 2015). Plus spécifiquement, un trouble neurocognitif majeur de type Alzheimer probable est diagnostiqué si l'un des éléments suivants est présent : une mutation génétique responsable de la MA ou la présence évidente d'un déclin se manifestant dans la mémoire et dans l'apprentissage, et dans au moins un autre domaine cognitif. Le déclin des fonctions cognitives doit être constant, progressif et graduel, sans plateaux prolongés, et ne peut être expliqué par une autre condition (American Psychiatric Association, 2015). Enfin, la sévérité de la maladie peut être légère, modérée ou sévère en fonction de l'évaluation du déclin cognitif de l'individu (Lezak et al., 2012).

5.2 Prévalence de la DTA

On estime à 35,6 millions le nombre de personnes souffrant de la DTA à l'échelle mondiale. On s'attend à une augmentation significative du fardeau de la DTA avec le vieillissement de la population (Pouryamout et al., 2012). De fait, on prévoit que sa prévalence va quasiment quadrupler au cours des 40 prochaines années. Par ailleurs, un Américain sur 45 et une personne sur 85 dans le monde seront touchés par cette maladie (Brookmeyer, Johnson, Ziegler-Graham, et Arrighi, 2007). Néanmoins, certains chercheurs ont souligné que les chiffres rapportés dans les études ne représentent pas réellement l'envergure du problème puisque la DTA est trop souvent sous-diagnostiquée par le système de santé dû à l'absence de plaintes des patients ou encore par manque de ressources ou de temps. Ainsi, il est fort possible que le nombre de cas soit beaucoup plus élevé (Alzheimer's association report, 2019).

5.3 Mécanisme de la DTA

Les causes précises de la maladie ne sont pas encore clairement identifiées, mais les travaux de recherche en cours sur le sujet permettent de mieux connaître les mécanismes biologiques sous-jacents à cette pathologie. Les plaques bêta-amyloïdes (ßA), entre autres, sont reconnues comme étant une signature neuropathologique de la DTA (Alzheimer's Association, 2015; Johnson, Stewart, et Smith, 2010; Mufson et al., 2016; Roberts et al., 1994; Victor et Ropper, 2001). La DTA se distingue par une augmentation graduelle des lacunes au niveau du transfert d'informations aux synapses qui mène progressivement à son échec complet, le nombre de synapses diminuant et les neurones finissant par mourir. On pense que l'accumulation de bêta-amyloïde interfère avec la communication neuronale au niveau des synapses et contribue ainsi à la mort cellulaire. En effet, il y a une accumulation des protéines ßA à l'extérieur des synapses chez les patients atteints de la DTA (Alzheimer's Association, 2015; Cummings, Vinters, Cole, et Khachaturian, 1998; Mufson et al., 2016). Par ailleurs, l'accumulation de protéines Tau anormalement phosphorylées bloque le transport des nutriments vers d'autres molécules essentielles à l'intérieur des neurones et ces protéines sont également soupçonnées de contribuer à la mort cellulaire (Alzheimer's Association, 2015). Les études ont mis en évidence que le cerveau des individus atteints de la DTA en phase avancée montrait un grand nombre de débris cellulaires (c.-à.-d. neurones morts et mourants) et un rétrécissement spectaculaire du volume neuronal (c.-à.-d. la perte de cellules) (Alzheimer's Association, 2015).

Les changements cérébraux associés à la DTA peuvent s'échelonner sur une période allant jusqu'à 20 ans ou plus (Jack et al., 2009; Reiman et al., 2012; Villemagne et al., 2013) et ce, avant que les premiers symptômes n'apparaissent. Au début du continuum, les individus peuvent fonctionner normalement malgré l'accumulation des biomarqueurs dans le cerveau. À mesure que la maladie progresse néanmoins, les dommages neuronaux évoluent au point où les individus présentent un déclin cognitif évident, caractérisé par des symptômes comme la perte de mémoire ou la désorientation spatio-temporelle. À l'autre extrêmité du spectre, les fonctions corporelles de base, telle la déglutition, sont altérées (Alzheimer's Association, 2015). La grande majorité des individus atteints de la DTA contracte la maladie à un âge tardif, généralement après 65 ans (Alzheimer's Association, 2015).

Le cerveau subit aussi une série de transformations structurales macroscopiques au cours de l'évolution de la DTA. Les études rapportent une atrophie importante de l'hippocampe (Chapleau, Aldebert, Montembeault, et Brambati, 2016; Schuff et al., 2009), du cortex temporo-pariétal, du cortex entorhinal, du gyrus cingulaire postérieur et les precunéus adjacents, ainsi qu'une atrophie du lobe temporal médial (DeCarli, 2000; Janke et al., 2001; Thompson et al., 2001). On constate aussi une augmentation du volume des ventricules (Silbert et al., 2003). Il est pertinent de souligner que, chez les patients en début de maladie, l'atrophie au niveau des régions frontales, visuelles primaires et sensorimotrices est peu observée (Thompson et al., 2003). L'hippocampe est, quant à lui, considérablement endommagé dès l'apparition des premiers symptômes (Schuff et al., 2009).

6.0 Conséquences de la DTA sur l'individu

Comme la mort neuronale survient dans de nombreuses régions du cerveau, il n'est pas surprenant que les personnes atteintes de DTA éprouvent de nombreuses difficultés cognitives et fonctionnelles. Des pertes de mémoire, des difficultés à planifier ou à résoudre des problèmes, des difficultés à compléter des tâches familières à la maison ou au travail, une confusion avec le temps et l'espace, des difficultés à comprendre les images et les relations visuo-spatiales, des difficultés à nommer des mots ou à les écrire, la tendance à égarer des choses et des difficultés à les retrouver, une diminution des capacités de jugement, une tendance à s'isoler des activités sociales ainsi que

des changements d'humeur et de personnalité (c.-à.-d. apathie et dépression) sont des exemples de symptômes souvent rapportés par les proches ou par l'individu lui-même. Au stade avancé de la maladie, une aide devient nécessaire au patient pour assurer la réalisation d'activités quotidiennes (Alzheimer's Association, 2015). Par ailleurs, les premiers symptômes rapportés par les patients relèvent de difficultés cognitives, particulièrement de troubles associés à la mémoire (c.-à.-d. enregistrer des nouvelles informations) (Weintraub, Wicklund, et Salmon, 2012).

6.1 Déclin cognitif dans la DTA

Les difficultés cognitives dans la DTA s'installent de façon insidieuse et s'aggravent lentement, quoique progressivement. Le déclin dans les différentes fonctions cognitives suit une évolution particulière dans la maladie (Joubert, Joncas, Barbeau, Joanette, et Ska, 2007). De plus, ce déclin peut être différent d'un individu à l'autre. Néanmoins, de manière générale, la mémoire à long terme, verbale et visuelle, est touchée sévèrement dans la maladie. La plupart des fonctions mnésiques (c.-à.-d. à l'exception de la mémoire procédurale qui est préservée jusqu'au dernier stade de la maladie) sont touchées, incluant la mémoire immédiate, la mémoire de travail, ainsi que la mémoire rétrograde des évènements récents et anciens. Les difficultés langagières constituent un élément important dans le diagnostic de la DTA. En ce sens, le manque du mot est une difficulté qui apparaît très tôt dans la maladie ; l'individu éprouve des problèmes à trouver le bon mot. Des mots-valises étant souvent utilisés, la discussion peut donc être difficile à suivre. Les difficultés en mémoire sémantique sont probablement la cause première de ces déficits langagiers (Joubert et al., 2007). Des atteintes au plan de l'attention et des fonctions exécutives composent également le profil neuropsychologique retrouvé dans la DTA (c.-à.-d. attention sélective et divisée ainsi que l'inhibition, la flexibilité mentale, la planification, la conscience de ces difficultés). Enfin, une réduction de la vitesse de traitement de l'information et des difficultés praxiques sont aussi retrouvées (Joubert et al., 2007). Bien que les problèmes de mémoire soient souvent les premières plaintes des patients, on retrouve aussi parmi les premiers symptômes l'émoussement affectif, la distraction, le retrait social et l'agitation, qui sont souvent confondus avec les symptômes de la dépression (Lezak et al., 2012).

7.0 Facteurs pronostiques de la DTA

De façon analogue au TCC, les études sur la DTA constatent une grande variabilité du niveau de l'altération cérébrale et de la présentation clinique (Stern, 2009, 2012). Le rythme du déclin cognitif varie en effet considérablement d'un individu à l'autre. Certains patients présentent des symptômes cognitifs qui évoluent plus rapidement, tandis que d'autres demeurent stables pendant plusieurs années (Capitani, Cazzaniga, Francescani, et Spinnler, 2004; Lye et Shores, 2000). Ainsi, la relation entre la pathologie cérébrale et son expression clinique semble en partie médiée par des facteurs prémorbides, c'est-à-dire les caractéristiques du patient (Sona, Ellis, et Ames, 2013; Stern, 2002, 2012). En ce sens, plusieurs auteurs s'entendent pour dire que de nombreux facteurs propres à l'individu peuvent augmenter le risque ou modifier l'évolution de la maladie (Sona et al., 2013; Stern, 2002, 2012). Bien que certains facteurs de risque tels que l'âge, l'historique familial, les maladies préexistantes et la génétique ne puissent pas être modifiés, plusieurs facteurs (ex. l'éducation, l'exercice physique, l'engagement social et professionnel, la correction du déclin sensoriel) permettent quant à eux de modifier la trajectoire du déclin cognitif (Sona et al., 2013; Stern, 2002, 2012). Malheureusement, un patient souffrant de DTA avec un déclin cognitif rapide a un pronostic beaucoup plus sombre en ce qui a trait à son autonomie fonctionnelle et à sa mortalité (Holtzer et al., 2003). Ainsi, l'identification des différents facteurs de protection et de risque est nécessaire afin d'identifier les patients à risque d'un moins bon pronostic et ainsi offrir une prise en charge précoce et adaptée. Dans le cadre de cette thèse, l'âge et le niveau d'éducation des patients seront considérés.

7.1 Influence des caractéristiques personnelles sur la prévalence

7.1.1 Âge. Au même titre que l'individu atteint d'un TCC, l'âge avancé serait un facteur qui augmenterait significativement le risque de développer une démence de type Alzheimer. En fait, l'âge est le principal facteur de risque de la DTA. La plupart des personnes atteintes de la DTA sont diagnostiquées après l'âge de 65 ans mais le fait d'avoir une DTA à début précoce (<65 ans) est associe à une évolution plus rapide et une espérance de vie réduite (Braak et Braak, 1997; Guerreiro et Bras, 2015; Riedel, Thompson, et Brinton, 2016).

7.1.2 Éducation. Bien que l'âge soit le facteur de risque principal, la DTA n'est pas un élément normal du vieillissement et l'âge seul ne suffit pas à provoquer la maladie. Un faible niveau d'éducation est aussi considéré comme un facteur de risque (Evans et al., 2003; Fitzpatrick et al.,

2004; Kukull et al., 2002; Sando et al., 2008; Stern, 2012; Valenzuela et Sachdev, 2006). Certains chercheurs rapportent qu'un nombre plus élevé d'années de scolarité constitue une « réserve cognitive ». Tel que présenté antérieurement, selon l'hypothèse de la RC, le niveau d'éducation serait corrélé à une augmentation des connexions entre les neurones dans le cerveau et lui permettrait de compenser les premiers changements cérébraux responsables de la DTA en utilisant d'autres voies neuronales pour réaliser des opérations cognitives (Stern, 2002). Par ailleurs, le niveau éducation, au même titre que l'âge, jouerait un rôle dans la vitesse de progression de la maladie. Bref, il semble que l'éducation retarde l'apparition des premiers symptômes, mais d'autres facteurs viendraient possiblement moduler le développement de la maladie, le TCC étant l'un de ces derniers.

8.0 Relations entre le TCC et la DTA

Depuis les dernières décennies, on trouve un nombre croissant de publications portant sur la relation entre un antécédent de TCC et la DTA dans la littérature scientifique. Le TCC a été évoqué comme étant un autre facteur de risque possible de développer une DTA. Certains évoquent le fait que le TCC pourrait être un facteur précipitant (Plassman et al., 2000; Shively, Scher, Perl, et Diaz-Arrastia, 2012; Sivanandam et Thakur, 2012). Les évidences épidémiologiques montrent qu'un TCC unique serait associé à une augmentation du risque de développement de troubles cognitifs menant à la DTA (Fleminger et al., 2003; Guo et al., 2000; Lye et Shores, 2000; Mortimer et al., 1991; O'Meara et al., 1997; Plassman et al., 2000; Schofield et al., 1997). Néanmoins, ce n'est pas toutes les études qui confirment ce possible lien entre le TCC et le risque de développer la DTA (Helmes, Ostbye, et Steenhuis, 2011; Mehta et al., 1999).

Bien que plusieurs études antérieures soutiennent une telle association (Barnes et al., 2018; Guo et al., 2000; Lye et Shores, 2000; Plassman et al., 2000; Wang et al., 2012), des désaccords subsistent encore au sein de la communauté scientifique (Helmes et al., 2011; Julien, Joubert, et al., 2017). Certains chercheurs avancent qu'un historique de TCC augmenterait le risque de développer une DTA, chez une population de non-athlètes. Par exemple, Wang et al. (2012) mettent en évidence le fait que les patients TCC sont 1,68 fois plus à risque de développer une démence que les individus sans historique de TCC. Plassman et al. (2000) rapportent eux aussi une augmentation du risque de souffrir d'une démence à la suite du TCC modéré ou grave. Ces résultats

sont corroborés également par l'étude *Mirage* de Guo et al. (2000), par celle d'O'Meara et al. (1997) ainsi que par l'étude de Lye et Shores (2000). Trois méta-analyses (Bazarian, Cernak, Noble-Haeusslein, Potolicchio, et Temkin, 2009; Fleminger et al., 2003; Mortimer et al., 1991) vont également dans ce même sens. Celles-ci proposent même que les antécédents de TCC, même léger, seraient associés au développement de maladies neurologiques telle que la DTA (Perry et al., 2016). De plus, les études menées par Fleminger et al. (2003); Nemetz et al. (1999); Schofield et al. (1997) indiquent quant à elles qu'un historique de TCC pourrait précipiter l'apparition de la DTA.

À l'inverse, d'autres études ne retrouvent aucun lien entre un historique de TCC et le développement de la DTA. Mehta et al. (1999) et Helmes et al. (2011), par exemple, ne confirment pas l'hypothèse selon laquelle le TCC augmenterait les risques de développer une DTA. La divergence qui subsiste entre les différents groupes pourrait en partie être expliquée par les limites et différences méthodologiques des études. En effet, l'âge moyen de l'échantillon, le moment du suivi post-TCC ou encore l'hétérogénéité de la définition du TCC et des critères diagnostiques de la DTA sont des exemples de limites rencontrées dans les études citées précédemment (Julien, Joubert, et al., 2017). À titre d'exemple, les auteurs qui n'avaient pas observé de liens entre le TCC et la DTA avaient étudié un groupe de patients jeunes (c.-à.-d. 55 ans) et le délai de suivi post TCC était court (Mehta et al., 1999; Nemetz et al., 1999; Rapoport et al., 2006).

Certains mécanismes permettant d'expliquer une relation entre TCC et DTA ont été proposés par les partisans de la théorie de l'augmentation du risque de développer la DTA à la suite d'un TCC. Certains auteurs proposent entre autres que la combinaison des changements cérébraux associés au vieillissement et la survenue d'un TCC pourrait contribuer à l'exacerbation du déclin cognitif (Lye et Shores, 2000). Plus spécifiquement, cette association serait expliquée par une perte progressive des cellules cérébrales conséquemment au TCC modéré ou grave, qui causerait une vulnérabilité neurocognitive et une vulnérabilité aux maladies dégénératives (Lye et Shores, 2000). D'autres études rapportent même que le TCC pourrait augmenter le risque de développer la DTA par une voie neuropathologique commune. Plus précisément, ce modèle suggère que le TCC entraînerait un dépôt cérébral de bêta-amyloïde, ce qui augmenterait la probabilité de modifications neurodégénératives plus tard dans la vie (Bondi et al., 1999). Des études suggèrent aussi que la

présence de l'allèle apoE4 chez l'individu pourrait avoir un impact négatif sur le rétablissement neurologique après un TCC. De fait, la survenue d'un TCC combiné à la présence de l'allèle apoE4 pourraient augmenter la probabilité de développer un déclin cognitif tel que la DTA. (Friedman et al., 1999 ; Horsburgh et al., 2000 ; Mayeux et al., 1993 ; Samatovicz, 2000). Cette hétérogénéité des résultats montre que les mécanismes associés au lien entre la DTA et le TCC sont encore mal compris par la communauté scientifique (Coronado, Thomas, Sattin, et Johnson, 2005; Gardner et al., 2018; Thompson et al., 2006).

Cette comorbidité rend ainsi le diagnostic différentiel plus complexe. En neuropsychologie clinique, l'identification des profils cognitifs des clientèles neurologiques est très utile pour poser un diagnostic différentiel. En outre, pour déterminer le tableau neurocognitif prédominant à la suite d'un TCC (TCC prédominant *vs* DTA prédominante) et ainsi orienter la personne vers les services de réadaptation adéquats, prenant en compte ses besoins spécifiques, une comparaison des profils neuropsychologiques des patients TCC et des patients DTA prend toute son importance. En pratique et dans les milieux cliniques, lorsque les deux conditions sont présentes, un patient TCC qui présente un tableau DTA prédominant ne se verra pas proposer les mêmes services ou traitements que le patient ayant une DTA déjà présente mais non diagnostiquée et qui présente un tableau TCC dominant (centre de jour ou soins de longue durée plutôt qu'une réadaptation intensive). Lorsque le patient TCC est hospitalisé tôt à la suite de son accident et que ses antécédents de DTA sont déjà clairement diagnostiqués, cela pose peu de problèmes pour l'établissement d'un diagnostic différentiel puisque les deux conditions médicales sont bien connues. Toutefois, lorsque les antécédents du patient admis à la suite d'un TCC ne sont pas connus, si le patient n'a jamais été traité dans le passé pour des troubles neurocognitifs ou si l'équipe traitante soupçonne une vulnérabilité cognitive pré-accidentelle, une bonne connaissance du profil typique de la DTA par rapport à celui du TCC sera essentiel pour poser le diagnostic différentiel du patient en question.

8.1 Comparaison des profils neuropsychologiques des populations TCC et DTA

Étonnamment, très peu d'études se sont intéressées à la comparaison du profil neuropsychologique de ces deux populations cliniques, malgré l'importance et la nécessité clinique du diagnostic différentiel entre ces deux conditions neurologiques fréquentes. De fait, la nécessité

d'une meilleure caractérisation clinique de ces conditions deviendra de plus en plus importante dans les années à venir, compte tenu du nombre croissant de personnes touchées. Certains auteurs suggèrent que l'occurrence d'un TCC chez la personne âgée pourrait imiter des symptômes démentiels de type DTA. Par ailleurs, les changements cognitifs suivant un TCCL mal ou non diagnostiqué chez la personne âgée peuvent être graduels et survenir des semaines, voire des mois suivant l'accident, et ainsi être diagnostiqués à tort comme symptomatiques d'une démence (Flanagan, Hibbard, et Gordon, 2005). Cette difficulté à différencier les profils neuropsychologiques associés au TCC et à la DTA est due aux similitudes que présentent ces deux conditions en ce qui a trait aux types de difficultés cognitives et psychologiques éprouvées par les patients, rendant ainsi complexe l'établissement d'un diagnostic différentiel. Par exemple, des difficultés mnésiques, langagières, exécutives, attentionnelles, psychologiques, de mémoire de travail et de vitesse de traitement sont présentes et chez les patients souffrant d'un TCC (Ashman et al., 2008; Gardner et al., 2018; Rapoport et al., 2006), et chez ceux souffrant de DTA (Baudic et al., 2006; Flanagan, Copland, Chenery, Byrne, et Angwin, 2013; Hinkebein, Martin, Callahan, et Johnstone, 2003; Weintraub et al., 2012). En ce sens, les personnes d'âge avancé atteintes de difficultés cognitives liées au TCC en fin de vie pourraient être mal diagnostiquées en raison de la proximité des symptômes cognitifs du TCC et de la DTA, et des nombreuses comorbidités souvent présentes. Néanmoins, on ne sait pas encore à ce jour si les difficultés cognitives des patients atteints de TCC ressemblent à celles des personnes atteintes de la DTA ou si elles présentent un profil unique lié à la blessure. Très peu de littérature existe sur le sujet et celle-ci est encore hétérogène quant à la distinction neuropsychologique précise. En effet, certains auteurs suggèrent un profil neuropsychologique similaire (Hinkebein et al., 2003) entre les deux conditions neurologiques tandis que d'autres proposent un profil neuropsychologique distinct (Breed et al. (2008).

8.1.1 Profils neuropsychologiques similaires. En appui à cette hypothèse, les profils neuropsychologiques des personnes atteintes de TCC et des personnes atteintes de DTA seraient très similaires et partageraient des caractéristiques communes (Hinkebein et al., 2003). En ce sens, la revue de littérature de Hinkebein et al. (2003) présente un nouveau modèle conceptuel dérivé du profil de déficits cognitifs propre à chacune des pathologies. À la suite d'une comparaison entre deux études, l'une sur le profil cognitif TCC et l'autre sur la DTA, les auteurs proposent que le

TCC engendrerait un profil de déficits neuropsychologiques similaire à celui observé dans la DTA. Autrement dit, l'occurrence d'un TCC chez la personne âgée pourrait imiter certains symptômes démentiels de type Alzheimer. De fait, selon eux, l'effet du vieillissement normal sur le cerveau combiné à l'effet du TCC viendraient amplifier le profil de déclin cognitif et ainsi créer un profil de déclin cognitif similaire à celui de la DTA, sans que le patient en soit nécessairement atteint. De manière plus spécifique, la première étude citée rapporte que des individus ayant subi un TCC (sévérité inconnue) et âgés en moyenne de 33 ans présentaient des difficultés au niveau de la vitesse de traitement de l'information (c.-à.-d. TMT *A*) et de la flexibilité mentale (c.-à.-d. TMT *B*), avec des performances se situant à -1.90 et -2.65 écarts-types de la norme, respectivement. Les tâches d'attention et de mémoire, notamment en rappel différé, étaient toutefois réussies dans la moyenne, soit avec des performances se situant entre -0.31 et -0.57 écart-type (Johnstone, Hexum, et Ashkanazi, 1995). La seconde étude, utilisée comme comparatif à la précédente, a rapporté que des individus âgés en moyenne de 72 ans et ayant un diagnostic de DTA avaient des difficultés dans l'ensemble des tâches cognitives, et plus particulièrement sur le plan de la vitesse de traitement de l'information (c.-à.-d. TMT *A*), en flexibilité mentale (c.-à.-d. TMT *B*), en attention (c.-à.-d. *attention index*) et en rappel différé. De façon similaire au profil TCC, la vitesse de traitement de l'information et les fonctions exécutives étaient les plus atteintes, respectivement, suivies par des difficultés mnésiques en rappel différé et de l'attention (Johnstone, Hogg, Schopp, Kapila, et Edwards, 2002). Bref, en comparant et en analysant les profils neuropsychologiques de ces deux études, les auteurs de cette revue de littérature ont tout de même proposé que le TCC imiterait les symptômes de la DTA en produisant un profil de déficits neuropsychologiques similaire à celui observé dans la DTA (Hinkebein et al., 2003). Bien que les fonctions cognitives touchées soient les mêmes dans les deux cas, notamment la vitesse de traitement et la flexibilité mentale, les auteurs rapportent néanmoins que les déficits étaient beaucoup plus sévères chez les individus souffrant de DTA pour l'ensemble des fonctions cognitives. Force est de constater que cette revue de la littérature présente des lacunes, notamment en termes de comparaisons des groupes dont l'âge différait de manière importante. Par conséquent, elle ne semble pas non plus considérer les effets du vieillissement cognitif normal. Cependant, à notre connaissance, cette étude est la seule à appuyer le modèle des profils neuropsychologiques similaires entre les patients TCC et DTA. Il paraît donc important de présenter un autre modèle, celui-là appuyant davantage l'hypothèse des profils neuropsychologiques distincts.

8.1.2 Profils neuropsychologiques distincts. À l'inverse, certains auteurs mettent en évidence des profils neuropsychologiques différents dans les deux conditions neurologiques (TCC et DTA). Par exemple, Breed et al. (2008) ont comparé le profil neurocognitif de patients (âgés en moyenne de 65 ans) ayant un TCC auto-rapporté (toutes sévérités confondues) avec celui d'individus atteints de DTA (âgés en moyenne de 78 ans) et d'individus sans histoire de troubles neurologiques (âgés en moyenne de 66 ans). Le profil cognitif DTA était significativement plus faible que le profil cognitif TCC pour les rappels immédiat et différé en mémoire épisodique verbale et visuelle, de même que pour la vitesse de traitement de l'information et la fluence verbale. Contrairement au groupe DTA, le groupe TCC présentait de bonnes performances aux rappels immédiats en mémoires verbale et visuelle, ainsi qu'un bon rappel différé en mémoire visuelle. Notons toutefois que les deux groupes avaient des performances inférieures au groupe contrôle dans des tâches de vitesse de traitement et de langage. Par ailleurs, aucun de ces deux groupes ne montrait des difficultés en mémoire de travail comparativement au groupe contrôle. En somme, les profils des déficits cognitifs seraient différents entre les groupes de patients TCC et DTA, surtout sur les plans de la mémoire, de la vitesse de traitement de l'information et du langage. Ainsi, il semble que les performances en mémoire épisodique soient au centre des différences entre les deux groupes. Cette étude comparative, quoique très pertinente, présente une lacune méthodologique assez importante. En effet, les patients du groupe TCC n'ont pas été diagnostiqués et évalués de manière prospective et leur diagnostic était auto-rapporté, ce qui demeure un biais notable. En outre, les caractéristiques propres au TCC, telle que la sévérité, sont inconnues. Aucune autre étude à notre connaissance n'a appuyé cette hypothèse de profils neuropsychologiques distincts. En ce sens, les objectifs de cette thèse sont donc novateurs et permettront d'éclairer cette controverse.

9.0 Objectifs et hypothèses

En raison du vieillissement de la population, ainsi que du nombre croissant de personnes qui seront victimes d'un TCC ou qui développeront la DTA au cours des prochaines années et décennies, et sur la base de nouvelles données qui suggèrent de possibles liens entre ces deux conditions, il s'avère essentiel de poursuivre la recherche afin de mieux identifier les facteurs de risque liés au développement d'une DTA suite à un TCC et de mieux comprendre les profils neuropsychologiques associés à ces deux conditions neurologiques. En effet, les cliniciens seront de plus en plus confrontés à la nécessité de se positionner sur le pronostic et le devenir des patients

TCC ainsi que sur les risques de ces derniers de développer la DTA, puis d'en informer les patients, familles ou proches. Ils devront également bien identifier les profils neuropsychologiques spécifiques à ces clientèles afin d'émettre un diagnostic différentiel juste. À la suite d'un TCC, l'historique médical souvent absent ou inconnu du personnel médical, combiné à la forte prévalence à la comorbidité chez la personne âgée, complexifie le diagnostic différentiel. La précision de ce dernier se révèle particulièrement importante car l'évolution clinique de ces deux conditions neurologiques (TCC et DTA) est très différente. De fait, la trajectoire de soins et les traitements requis doivent correspondre à la bonne pathologie, chacune ayant ses caractéristiques propres. À ce jour, et compte tenu du peu de données probantes disponibles sur les profils neuropsychologiques associés à un TCC ou à la DTA dans la littérature, il demeure difficile de bien dissocier ces conditions. La situation clinique la plus souvent rencontrée pour le clinicien consiste à déterminer si une DTA non diagnostiquée n'est pas en lien avec un TCC que le patient viendrait de subir.

Bien qu'il existe un besoin clinique important au niveau de la différenciation des profils neuropsychologiques des personnes atteintes de TCC et des personnes atteintes de DTA, peu d'études à ce jour les ont comparés. De surcroît, les études publiées présentent d'importantes limites méthodologiques telles que l'absence de groupe témoin, l'hétérogénéité de l'âge au sein des groupes à l'étude (c.-à.-d. combinaison d'adultes et de personnes âgées dans le même groupe) ou l'absence de diagnostic précis du TCC et/ou de la DTA. De plus, parmi les études portant sur le développement de la DTA à la suite d'un TCC, la majorité des sujets n'avaient pas de diagnostic médical objectif du TCC, mais une forte fréquence du TCC auto-rapporté, ce qui soulève de nombreuses questions quant à la validité des résultats de prédiction et des profils neuropsychologiques obtenus.

9.1 Étude 1

9.1.1 Objectif. L'objectif de l'étude est d'identifier les caractéristiques liées au TCC qui sont associées au risque de développer une démence de type Alzheimer à partir d'une revue systématique de la littérature. Ainsi, cette étude permettra d'extraire les facteurs de risques et d'identifier les patients TCC à risque de développer la DTA.

9.1.2 Hypothèse. Cette étude pose l'hypothèse que les principaux facteurs de risques de développer la DTA chez les patients atteints de TCC seront une perte de conscience et une durée d'APT plus longues suite au traumatisme et l'obtention d'un résultat plus bas à l'ÉCG (TCC plus sévère).

9.2 Étude 2

9.2.1 Objectif 1. L'objectif de cette étude prospective est de caractériser le profil neuropsychologique d'un groupe de patients TCC âgés et de le comparer aux profils des groupes de patients atteints de la DTA et de personnes âgées sans trouble cognitif (groupe témoin). Les profils neurocognitifs seront définis à l'aide de tests et de questionnaires validés et normalisés.

9.2.2 Hypothèse 1. Nous émettons l'hypothèse que des profils neuropsychologiques uniques et distincts seront observés entre les trois groupes. Bien que cette étude s'avère être davantage exploratoire compte tenu du peu d'études qui existent dans ce domaine, il est néanmoins attendu que les patients atteints de la DTA présenteront davantage de troubles mnésiques (mémoire verbale et visuelle) que les patients du groupe TCC et des participants témoins. Par ailleurs, on prévoit que les deux groupes de patients cliniques (DTA et TCC) auront des performances diminuées dans l'ensemble des autres domaines cognitifs (c.-à.-d. habiletés verbales, fonctions exécutives, mémoire immédiate et mémoire de travail et vitesse de traitement de l'information) relativement au groupe témoin.

9.2.3 Objectif 2. Le deuxième objectif est de déterminer si l'âge et le niveau de scolarisation des patients sont associés aux performances neuropsychologiques des groupes TCC et DTA. De surcroît, pour le groupe TCC, nous examinerons si la sévérité du TCC, mesurée par le résultat à l'ÉCG, ainsi que le nombre de jours à la suite du TCC (mesure du temps de récupération) et le site de la lésion cérébrale traumatique sont associés aux performances neuropsychologiques chez ce groupe de patients.

9.2.4 Hypothèse 2. Nous émettons l'hypothèse que les patients des groupes TCC et DTA qui sont plus âgés et moins scolarisés auront des performances neuropsychologiques plus faibles que les patients plus jeunes et ayant un niveau de scolarité plus élevé. De plus, pour le groupe TCC

seulement, les patients ayant des résultats plus bas à l'ÉCG (TCC plus sévère), ayant vécu un délai plus court entre l'accident et l'évaluation (temps plus court de récupération post TCC) et ayant un scan positif auront des performances plus faibles aux épreuves neuropsychologiques.

Article 1

Does injury severity, loss of consciousness and post-traumatic amnesia related to traumatic brain injury are predictors of the onset of Alzheimer disease? A systematic review

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Abstract

A systematic review of 18 studies was performed to investigate if certain traumatic brain injury (TBI) related variables can predict the risk of developing post-TBI Alzheimer's disease (AD) in adults. For the first time, this paper evaluates and documents the possibility that specific TBI-related variables, such as TBI severity, loss of consciousness (LOC) and post-traumatic amnesia (PTA) could be used as AD development predictors. Inconsistencies regarding the risk of developing AD following a TBI remain in the literature. Indeed, the reasons why certain TBI patients develop AD while others are unaffected by this pathology are still unclear. The goal of this systematic review is to explore the impact of TBI-related variables such as TBI severity, LOC and PTA, which may or may not predict the risk of developing AD. About 55.5% of TBI patients may deteriorate, from their acute post-TBI cognitive deficits, to then meet diagnostic criteria for AD. Whether TBI is a risk factor for AD remains elusive. Failure to establish such a link may be related to methodological problems. Therefore, to shed light on this dilemma, it is of upmost importance that future studies use of a prospective design, define types and severities of TBI as well as use standardized AD and TBI diagnostic criteria. Ultimately, an AD prediction model, based on several variables, would be useful to clinicians in order to acutely detect TBI patients at risk of developing AD.

Key words: Traumatic brain injury, concussion, Alzheimer disease, loss of consciousness, post-traumatic amnesia, Glasgow coma scale score, severity, dementia, outcome, review

TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. TBI severity can be classified according to three levels: mild, moderate and severe. The Glasgow Coma Scale (GCS) score, the duration of the posttraumatic amnesia (PTA) and LOC duration are the main characteristics used to assess TBI severity. Various physical, cognitive (Rabinowitz et Levin, 2014b), emotional and behavioral (Arciniegas et Wortzel, 2014; deGuise et al., 2008) consequences are frequently observed post-TBI, as well as functional difficulties with significant social repercussions (de Guise, LeBlanc, Feyz, et Lamoureux, 2006; Rabinowitz et Levin, 2014b).

TBI severity (GCS score, LOC, PTA) is to be considered to predict outcome in TBI patients (de Guise et al., 2006; Fleminger et al., 2003; McIntyre, Mehta, Janzen, et al., 2013; Ritchie et al., 2011; Utomo, Gabbe, Simpson, et Cameron, 2009). More specifically, TBI severity has an impact on the presence of long term cognitive, psychosocial and functional consequences post-TBI (Rassovsky et al., 2015). Indeed, moderate and severe TBI seem to be associated with more severe and persistent cognitive deficits (Rabinowitz et Levin, 2014b). For example, a study found that a low GCS at admission and a longer length of stay were associated with greater physical disabilities and functional impairments at time of discharge. In general, the link between TBI severity and outcome is approximately linear; the greater the severity, the greater the consequences (Rabinowitz et Levin, 2014b). Thus, GCS and PTA seem to be good predictors of negative outcome post-TBI.

As many as 65% of moderate to severe TBI patients report long-term problems with cognitive functioning (Whiteneck, Gerhart, et Cusick, 2004). Luukinen et al. (1999) and colleagues suggest that the occurrence of major head injury increases the risk of cognitive decline, which is much faster in geriatric-TBI patients than in older individuals without TBI (Mosenthal et al., 2002; Susman et al., 2002). Thus, suffering from a TBI combined with age-related brain changes could exacerbate cognitive decline.

A growing interest has risen in recent decades in understanding and establishing a link between TBI and AD development. It is estimated that 35.6 million people worldwide suffers from AD, the most common form of dementia. However, its etiology is not well understood, and risk factors such as age, family history and genetic factors have been extensively studied. It was recently

evoked that TBI may be a possible AD precipitating factor (Bazarian et al., 2009; Shively et al., 2012; Sivanandam et Thakur, 2012).

Although some studies have challenged the association between AD and TBI (Chandra, Kokmen, Schoenberg, et Beard, 1989; Dams-O'Connor, Spielman, et al., 2013; Fratiglioni, Ahlbom, Viitanen, et Winblad, 1993; Fratiglioni, Paillard-Borg, et Winblad, 2004; Godbolt et al., 2014; Helmes et al., 2011; Li et al., 1992; Mehta et al., 1999). A growing number of studies support the hypothesis of a greater risk of developing AD following moderate and severe TBI (Graves et al., 1990; Guo et al., 2000; Luukinen et al., 2005; Mayeux et al., 1993a; O'Meara et al., 1997; Plassman et al., 2000; Rasmusson, Brandt, Martin, et Folstein, 1995; Salib et Hillier, 1997; Sivanandam et Thakur, 2012; van Duijn et al., 1992). More precisely, evidence appears to favor an increased risk for late-life AD after a single moderate-to-severe TBI involving LOC in early or middle life (Graves et al., 1990; Guo et al., 2000; Johnson, Stewart, et Smith, 2012; Molgaard et al., 1990; O'Meara et al., 1997; Plassman et al., 2000; Schofield et al., 1997). Meta-analyses also support these conclusions (Bazarian et al., 2009; Fleminger et al., 2003; Mortimer et al., 1991). Specifically, some stated that TBI severity may be a factor in explaining the association between TBI and AD. They also specified that post-TBI LOC would be strongly linked to the risk of developing AD (Institute of medicine Committee on Gulf War Health, 2009). Surprisingly, these studies and meta-analysis do not specify which factors, other than LOC, were taken into account when diagnosing a moderate or severe TBI. Furthermore, LOC alone cannot be used in establishing such a diagnosis, as it is not consistent with international TBI diagnostic criteria (Campbell, 2000).

Based on previous studies, the link between TBI occurrence or severity (mild vs. moderate or severe) and the risk of developing AD remains controversial. Can the discrepancies in the criteria used to assess TBI severity across studies partially explain said controversies? Previous studies have shown that variables related to TBI severity, such as presence or duration of LOC, low GCS scores and presence or duration of PTA, have a well known impact on post-TBI outcome (Teasell et al., 2018). These variables may play a role in the development of long-term decline and degenerative processes such as AD, and may have an impact on the risk of developing AD. Surprisingly, previous studies and meta-analyses published in this field have never studied or compared the factors and variables specific to the measurement of TBI severity, such as GCS or

PTA duration. Indeed, only the presence of LOC was considered in a few studies. Since studies are retrospective in nature and were conducted with people who had developed AD, TBI-related criteria are very poorly documented. Similarly, the reviewed meta-analyses have never compared variables related to TBI severity; they only take into account TBI occurrence regardless of its diagnostic features or severity. In short, in the previously published studies, specific TBI-related variables, which are actual risk factors of developing AD, are unknown. Thus, the goal of this specific systematic review is to define TBI-related variables to predict the risk of developing AD following a traumatic brain injury. More specifically, variables related to TBI severity such as LOC, GCS and PTA will be extracted from the selected studies, and the risk of developing AD based on each of these variables will be presented separately.

Methods

A systematic review using the methodology outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of studies evaluating health care interventions. Exploration and elaboration was conducted, and the data was reported following the PRISMA guidelines. The search strategy as well as the review question was decided by the author (Julien) and supervisor (de Guise).

Search Question, Keywords, Population, Inclusion, and Exclusion Criteria

The question posed for the systematic review was to define TBI-related variables (GCS, LOC and PTA) to determine if that can predict post-TBI AD development in the elderly. The primary step was to document the link between TBI and AD as well as to identify TBI-related predictors. The keywords used were: adult, traumatic brain injury, head injury, concussion, mild traumatic brain injury, moderate traumatic brain injury, severe traumatic brain injury, GSC, PTA, LOC, neurodegenerative disease, Alzheimer, long-term, outcome, consequence.

Inclusion criteria were the following: all studies including humans with mild, moderate or severe TBI, adult populations (≥ 18 of age), prospective and retrospective, studies who assessed the relationship between TBI and AD, and studies published between 1985 and 2016. The exclusion

criteria were the following: animal studies, athlete population as well as non-English or non-French studies.

Search Strategy

MEDLINE, EMBASE, PSYINFO and Cochrane Library were searched using the same strategies for each database in May 2016. The search strategy for all databases can be seen in Figure 1. Both electronic and paper publications were searched when available. Finally, a reference list of any review, meta-analysis or systematic review on the link between TBI and AD were reviewed for this study.

Study Selection

Eligibility assessment of all articles was performed independently by 3 reviewers using a two-step evaluation. First, the reviewers independently screened all titles and abstracts of the search strategy results to decide whether they met the inclusion criteria. Second, full texts of the chosen articles were then assessed to confirm whether they met the inclusion criteria, and that the link between TBI and AD was reported in the study. When reviewers initially disagreed they were later able to reach consensus.

Data Collection

Data was extracted from the selected articles and stored in an electronic database. Data fields included the severity of the assessed TBI with LOC, GCS and PTA, number of patients, setting, type of study, long-term post-TBI outcome as well as the link between TBI and AD.

Results

A total of 18 studies such as prospective and retrospective case studies were identified for inclusion in the review. MEDLINE, EMBASE, PSYINFO and Cochrane Library database screening provided a total of 841 citations. Figure 1 indicates the flow of information through the different phases of the systematic review.

Insert Figure 1 about here

All included articles were published between 1985 and 2015. The studies included in the final selection were retrospective (72.22%) and prospective (27.78%) studies published in English or French. While most studies were conducted in the United States (55.56%), one study was done in Canada (5.56%), one in Australia (5.56%) and seven in Europe (38.89%) (Table 1). The included studies involved 743 627 participants with each study including between 60 and 720 933 participants (Table 2).

Insert Tables 1 and 2 about here

Regarding the inclusion criteria, in ten of the selected studies, a lower age limit was used. Therefore, the lower age limit varied between 18 and 70 years old across studies. In eight studies the age was not specified. The mean age of the patients in the studies ranged from 43.1 to 81 years old.

The most frequent exclusion criteria were prevalent neurological disorders, psychiatric diseases and medical disorders. A total of 88.89% (16 studies) used at least one of the previously described exclusion criteria. Previous TBI or a probable/possible AD diagnosis were the main inclusion criteria in all studies. Medical records, interviews, postal questionnaires, physical and neurological exams, databases, as well as neuropsychological batteries were the most frequently used assessment tools. In fact, all studies used at least one of the previously stated measures. Only, 72% of the studies interviewed patients and their family in person.

Criteria used to define TBI as well as TBI severity were not standardized (Table 1) across studies. Self-reported TBI was the criteria used in 66. 67% (n=12) of studies to define TBI. Other criteria such as LOC (four studies), PTA (five studies), GCS score (one study) and neurologic signs of brain injury (one study) were inconsistently used to define TBI. TBI was most frequently defined by LOC (77.78%), but only eight (44.44%) studies specified its duration. TBI severity was defined by the duration of the LOC (38.89% of the studies) or/and the PTA (16.67% of the studies) or/and the GSC score (5.56% of the studies). However, LOC duration is not standardized and mostly self-reported (22.22% of the studies). Only three studies (16.67%) defined TBI severity through medical records and medical interviews. Additionally, the PTA duration was only specified (medical

records and medical interview) in three studies. GCS scores were however described in one study, and the scores ranged between 15 and less than nine (Table 1).

AD diagnosis was also not standardized (Table 1.) In fact, some studies have used the NINCDS/ADRDA criteria (the DSM criteria and the functional neuroimaging techniques such as PET or SPECT) to defined AD, while others used the Diagnostic and Statistical Manual of Mental Disorders (DSM), the ICD-9-CM criteria, the Mini-Mental State Examination (MMSE) or other measures to define AD. Most studies used more than one tool to define AD.

A total of 55, 56% of studies (n=10) found that having suffered a TBI increased the risk of AD (Table 2). More specifically, TBI severity was a predictor of AD for 22.22% (n= 4) of the studies included in this review. In fact, one author found that both moderate (OR= 2.32; CI = 1.04 to 5.17) and severe head injuries (OR= 4.51; CI, 1.77 to 11.47) were associated with an increased risk of developing AD (Plassman et al., 2000). Also, an author found no association between the occurrence of minor head injuries and decline in MMSE scores. A positive relationship was found between the occurrence of major head injuries and a decline in MMSE scores (OR= 3.70; CI 1.25 to 10.9)(Luukinen et al., 1999). Another study however found that mild TBI also increased the risk of AD (OR= 3.26; CI 2.69 to 3.94)(Lee et al., 2013). One more study followed 325 people, 8 of who sustained a TBI and 34 of who developed AD. Mild and moderate brain injuries were associated with younger age at detection of AD (OR= 2.80; CI 1.35 -5.810)(Luukinen et al., 2005). Nonetheless, 11.11% (two studies) of studies found that TBI severity did not increase the risk of AD. Indeed, a study based on 921 individuals with AD found that patients who had self-reported having suffered from a TBI did not have a greater risk of developing AD. Hence, the authors concluded that a TBI could not serve as an AD predictor (Mild TBI: OR= 0.854; CI 0.294-2.2484: moderate-severe TBI: OR = 0.799; CI 0.418-1.525)(Helmes et al., 2011). Another study found no association between mild, moderate and severe TBI and AD among TBI patients (OR= 17.61;CI 0,86-359,90)(Koponen et al., 2004). Importantly, TBI severity was not specified in 72.2% of the studies included in the review (n= 13) and severity criteria were different for all five other studies (Figure 2).

Insert Figure 2 about here

Another TBI outcome associated with increased risk of AD was LOC (see figure 3). In fact, 38.89% (n= 7) of the studies included in this review specified that TBI with LOC was associated with a greater risk of suffering from AD in the future. Findings suggest that self-reported TBI with LOC is a specific risk factor for early AD onset (OR= 1.75; CI 1.47-2.07) (Mendez, Paholpak, Lin, Zhang, et Teng, 2015). Additionally, another study on 649 aging individuals stated that self-reported head injuries with LOC were associated with earlier onset and increased risk of AD but only among men (OR= 1.47; CI 1.03 – 2.09) and not women (OR= 1.18; CI 0.83-1.68). Be that as it may, in 5.55% (n=1) of the included studies a significant AD risk increase was only found for self-reported TBI patients (n=271) with LOC exceeding five minutes (OR= 11.2; CI 2.3-59.8), while a duration of less than four minutes did not increase said risk (OR= 1.7; CI 0.4-7.5)(Schofield et al., 1997). For another study, LOC lasting for more than 30 minutes but less than 24 hours, as well as for more than 24 hours, were respectively moderate (OR= 2.32; CI = 1.04 to 5.17) and severe head injuries (OR= 4.51; CI, 1.77 to 11.47), and were associated with increased risk of AD(Plassman et al., 2000). Another study found that a LOC of less than 30 minutes (mild TBI), and a LOC lasting more than 30 minutes (moderate) were linked to an increased risk of AD (OR= 2.80; CI 1.35 -5.810) (Luukinen et al., 2005). However, 11.11% (n=2) of the included studies reported that TBI with or without LOC was linked to AD. Note that for 22.22% (n=4) of the studies included in the review, LOC was not specified (see figure 3). The Mirage study interviewed 2233 AD patients about a history of TBI with and without LOC. Results suggested that self-reported head injuries with LOC (OR= 9.9; CI 6.5 to 15.1) and self-reported head injuries without LOC (OR= 3.1 CI 2.3-4.0) were related to AD (Guo et al., 2000). Still one more study, comprised of 198 AD patients concluded that self-reported TBI with and without LOC were linked to AD although only in male patients (OR= 2.1; CI 1.1 to 4.1) (Salib et Hillier, 1997). Furthermore, one more study comprised of 6645 self-reported TBI with LOC patients suggested that no increased risk of AD was found for people with a history of head injury with LOC (OR= 0.8; CI 0.4 to 1.9) and multiple head traumas. The time since the head trauma, and the duration of unconsciousness did not significantly influence the risk of AD (Mehta et al., 1999). For one study, regardless of LOC duration, TBI (LOC $\geq$ 1 minutes) didn't increased the risk of AD (OR= 17.61; CI 0,86-359,90) (Koponen et al., 2004). A study based on 921 individuals with AD found that patients who reported losing consciousness following a TBI were not at a greater risk of developing AD. The authors then concluded that the inclusion of head injury with or without LOC information did not improve

the prediction of AD (Mild TBI: OR= 0.854; CI 0.294-2.2484: moderate-severe TBI: OR = 0.799; CI 0.418-1.525)(Helmes et al., 2011). Note that for 22.22% (n=4) of the studies included in the review, LOC was not specified.

Insert Figure 3 about here

PTA was also used in some studies as a predictor of AD (see figure 4). Only 27.78% (n= 5) of the included studies specified the presence and/or the duration of the PTA. 16.67% (n=3) of them used PTA duration to classify TBI severity. In fact, in one study, PTA episodes lasting 1h (mild TBI) and PTA episodes lasting more than 1 hour were linked to an increased AD risk (OR= 2.80; CI 1.35 -5.810) (Luukinen et al., 2005). For another study a PTA episode lasting for more than 30 minutes, but less than 24 hours corresponded to a moderate TBI (OR= 2.32; CI = 1.04 to 5.17) whereas a PTA with a duration greater than 24 hours was indicative of a severe TBI (OR= 4.51; CI, 1.77 to 11.47). This study found that both moderate and severe TBI were associated with increased risk of AD. However, conclusions could not be drawn regarding PTA episodes of less than 30 minutes (mTBI)(Plassman et al., 2000). For one study, regardless of PTA duration (less than 1 day= mild ; 1-24 hours = moderate ; 1 to 7 days = severe ; more than 7 day= very severe) TBI didn't increased the risk of AD (OR= 17.61; CI 0,86-359,90)(Koponen et al., 2004). In two studies (11.1%) the presence of PTA was used as TBI criteria. The time of PTA occurrence was however not specified. The GCS was only used in one study in order to specify TBI severity (see figure 4). This TBI outcome predictor is not specified in all the other studies (94.44%).

Insert Figure 4 about here

Discussion

Our systematic review highlights the lack of information regarding TBI-related variables used to predict the risk of developing AD in the elderly post-TBI. It should be noted that there are important variations of TBI and AD definition and diagnostic criteria used across the reviewed studies. Self-reporting a TBI was the only inclusion criteria used to determine whether a TBI occurred or not in 66. 67% (n=12) of the selected studies. AD was defined by NINCDS/ADRDA

as well as the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria by 38.89% of the included studies. Moreover, TBI-related variables such as LOC, PTA and GCS score were inconsistently used in studies to diagnose the presence and the severity of TBI populations. These TBI-related variables are not systematically used as TBI inclusion criteria to define TBI populations, and there still are inconsistencies about their impact on the risk of developing AD. Thus, the literature reviewed can't provide sufficient evidence supporting that having suffered a traumatic brain injury increased the risk of AD.

Previous studies have shown that TBI severity is an important predictor of post-TBI outcome. As a matter of fact, a more severe TBI may lead to greater negative outcomes (de Guise et al., 2006; Fleminger et al., 2003; McIntyre, Mehta, Janzen, et al., 2013; Ritchie et al., 2011; Utomo et al., 2009). Since TBI severity was inconstantly reported in studies (33.33%), and results were highly heterogeneous, it was not possible to determine if suffering from a traumatic brain injury increases the risk of developing AD. Regarding LOC, it has been known to be especially associated with an increased risk of AD (Health, 2009). Still, this review cannot add evidence. A total of 38.89% of included studies reported that LOC was linked to AD development later in life, but the same percentage fails to demonstrate this association.

TBI severity can also be measured using PTA and GCS, which may also be variables to use when predicting the odds of developing AD. In TBI literature, several previous investigations have suggested that PTA and GCS scores are important outcome predictors for patients with TBI (de Guise et al., 2006; Godfrey, Bishara, Partridge, et Knight, 1993; Toschlog et al., 2003; van der Naalt, 2001). Since only 27.78% and 5.5% of the included studies specified PTA episodes and GCS score respectively, the review cannot provide evidence regarding their predictive value. All stated inconsistencies could be explained by the use of a large variability of TBI and severity criteria. The possibility that using standardized TBI criteria may eliminate discrepancies remains to be investigated.

Age of TBI onset (Goldstein et Levin, 2001; Harris, DiRusso, Sullivan, et Benzil, 2003; LeBlanc et al., 2006; Marquez de la Plata et al., 2008; Mosenthal et al., 2004; Susman et al., 2002; Testa et al., 2005), premorbid factors and patient characteristics (Novack, Bush, Meythaler, et

Canupp, 2001; Rabinowitz et Levin, 2014b) or education (Bonaiuto, Rocca, et Lippli, 1990; Mortimer et al., 1991) should also be incorporated in a predictive model as these variables have a significant impact on post-TBI outcome. Thus, we may hypothesize that these predictive TBI-related outcome variables may play a role in the odds of developing AD.

Some studies have shown that age is an important long-term outcome predictor. The later the TBI occurred, the worse the outcome (Senathi-Raja, Ponsford, et Schonberger, 2010; Spitz, Ponsford, Rudzki, et Maller, 2012; Thompson et al., 2006). However, in this review for the majority of the studies the age of TBI occurrence is unspecified. In fact, the mean patient age in the studies ranged from 43.1 to 81 years old, but we can't claim that the TBI has been experienced later in life.

Another predictive factor was the patients' level of education. More years of education has been shown to be a predictor of long-term outcome (Kesler et al., 2003; Ponsford et al., 2008). However, the literature reviewed can't provide sufficient support that a lower level of education increases the risk of AD. In fact, 55.55% of the studies included in the review didn't provide any information regarding patient educational level. Still, for the articles that do give information about education (44.45%), inconsistencies remain between them. The range of educational years varied between 8 and 15 years of school for all given studies, with and without a significant increased risk of AD. This finding may be explained by the fact that other premorbid variables such as professional occupation, leisure and social activities, head circumference as well as neurologic and psychiatric pre-trauma pathologies, learning disabilities, marital difficulties, lower socio-economic and occupational status increased the risk of cognitive decline, cerebral changes and AD. Accordingly, this reserve indices have been associated with greater risk of decline (Mortimer et al., 2003). However, these variables are rarely specified and taken into account in studies.

In the past decades, the relationship between TBI and AD has been explored using different methodologies such as cross-sectional cohorts of patients with AD and with a history of TBI identified retrospectively. The validity of the autobiographical recall as a methodological procedure to evaluate the risk of developing AD following a TBI, which is recurrently used throughout the reviewed articles (n=13/18), is questionable. In fact, it may be difficult for patients without AD to remember having suffered from PTA or LOC to recall the length of said episodes.

This applies to all patient age groups. Furthermore, patients may be frequently unable to differentiate between PTA and LOC symptoms, and may often confuse the two conditions. Since memory loss follows PTA, patients who suffered from this condition will often be unable to remember whether they lost consciousness or not. Thus, despite having been conscious throughout the PTA episode, many patients will believe that they have suffered a LOC episode. Researchers may reverse the methodology by doing longitudinal studies with TBI patients and follow them as soon as their first emergency room (ER) visit or hospitalization as well as document the ones who developed AD in the latter course of recovery instead of asking patients suffering from dementia to recall past TBI, which may be problematic with AD patients who suffered memory impairments.

Our study has several limitations. First, despite the extensive nature of our search strategy, published literature may be unrepresentative of the population of completed studies due to publication bias, and our systematic review is limited by the methodological quality of studies included. Second, a majority of included studies have missing data related to TBI severity, thus limiting the comparisons among studies. In that sense, variations in inclusion and exclusion criteria and the criteria used for the diagnosis of TBI and AD, were important, and could lead to both under or over diagnosis. Third, the generalizability of our results warrants caution since several studies were conducted in the United-States. We also included French and English studies and we did not cover the grey literature. Despites these limitations, this review used the highest methodological standards to conduct a rigorous systematic review.

To this day, it is still unclear whether TBI is a risk factor for AD, and the inconsistencies found in the literature may be related to methodological problems. Therefore, to clarify this dilemma, it is important that future studies use a prospective design, define types and severity of TBI as well as use standardized AD and TBI diagnostic criteria. The present systematic review mainly targeted the need to be more rigorous in the inclusion and exclusion variables related to TBI in the studies that aim to predict the risk of developing AD. Researchers should better document TBI-related variables in order to better compare the studies among themselves, and ultimately identify which TBI-related variables are the most significant AD predictors.

Ultimately, an AD prediction model based on several variables would be useful to clinicians in order to acutely detect patients at risk of developing AD or other type of dementia. Indeed, early identification of risk factors will allow patients to benefit from closer medical monitoring, early medication start or to participate in a rehabilitation program focused on intervention strategies in order to increase or maintain cognitive reserves following TBI, thus preventing an exacerbated cognitive decline following a traumatic brain injury.

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Table 1

Characteristics of the included studies

Authors	Years	country-setting	Exp. design	Selection dementia (Alzheimer)	Selection TBI	Types of measures
Abner, E. L. & al.	2014	United States	Retrospective study	MCI: at least one observed score of at least 1.5 standard deviations below the expected score for age based on the baseline performance of the entire normal cohort on tests of episodic memory (aMCITB) or language and executive function (mild MCI TB); clinical consensus-based MCI (MCICC) indicates a diagnosis of MCI based on criteria used by the National Alzheimer's Coordinating Center's Uniform Data Set; and dementia indicates a clinical diagnosis of dementia based on DSM-IV criteria	Self report head injury with and without LOC Specify if LOC < 5 minutes LOC > 4 minutes	-Interview -Questionnaires -Autopsy -Clinical Assessment
Amaducci, L. A. & al.	1986	Italy	Retrospective study	Decline of mental function documented by Blessed dementia scale for at lest 6 mouth, at lest two of the following signs or symptoms: memory lost, intellectual impairment, impaired recognition of people, things, or place, personality changes, behavioral disorders, and mood disorders without clear signs of depression; and a score of six or less on three items of the Hamilton depression scale	Self report head injury	Interview
Broe, G .A. & al.	1990	Australia	Retrospective study	NINCDS-ADRDA criteria	Self report head injury	-Assessment Neuropsychological battery test -Interview

Dams-O'Connor, K., Gibbons, L.E., Bowen, J.D., McCurry, S.M., Larson, E.B., & Crane, P.K.	2013	United States	Retrospective study	Criteria Diagnosis : National Institute of neurological and communicative disorders and stroke –AD and related disorders association criteria	Self report head injury With LOC > 5 minutes or chronic deficit	-Structured interview -Medical record -Informant report -Neurological and physical exam
French, L. R. & Al.	1985	United States	Retrospective study	Insidious onset, gradual progression of dementia with intact level of consciousness and absence of focal neurologic signs	Self report head injury	Interview
Guo, Z., Cupples, L. A., Kurz, A., Auerbach, S. H., Volicer, L., Chui, H., & al.	2000	United States, Canada, Germany	Prospective study	1 or 2 on the A axis of the MIRAGE AD rating scale (ADRS) (these ratings correspond to NINCDS/ADRDA criteria for definite or probable AD)	Self report head injury with loss of consciousness. that cause the subject to seek medical care or hospitalization	-Interview -Medical records
Helmes, E. Ostbye, T. Steenhuis, R. E.	2011	Canada	Retrospective study	-Modified Mini-Mental States examination (3MS): score below 78 -DSM-VI-R -NINCDS-ADRDA criteria	Self-reported head injury Mild TBI: no LOC Moderate-Severe: LOC	-Interview -Neuropsychology assessment (tests) -Medical assessment

Koponen, S. & al.	2004	Finland	Retrospective study	DSM-IV criteria Mild Deterioration Battery: classified as normal (0–1 points), mildly impaired (2–4 points), moderately impaired (5–8 points), severely impaired (9–13 points), or very severely impaired (14 points or more) AND MMSE < 24/30	A head trauma severe enough to cause traumatic brain injury and causing neurological symptoms (including headache and nausea) lasting 1) at least 1 week and 2) at least one of the following: loss of consciousness for at least 1 minute, posttraumatic amnesia for at least 30 minutes, neurological symptoms (excluding headache and nausea) during the first 3 days after the injury, or neuroradiological findings suggesting traumatic brain injury (e.g., skull fracture, intracerebral hemorrhage) The severity of traumatic brain injury was classified on the basis of the duration of posttraumatic amnesia as follows: < 1 jour = mild; 1-24 hours = moderate; 1 to 7 days=severe; > 7 day very severe	-Medical records - Neuropsychological evaluation -Cognitive assessment - Dementia Screening Battery -Mild Deterioration Battery
Lee, Y-K. Hou, S-W. Lee, C-C. Hsu, C-Y. Huang, Y-S. Su, Y-C.	2013	United States	Retrospective study	-ICD-9-CM (International Classification of diseases (Ninth Division) Clinical Modification) : Dementia affecting all cognitive functions and skills Includes: deterioration of cognitive functioning as a result of cerebral disease or trauma	-ICD-9-CM (International Classification of diseases (Ninth Division) Clinical Modification)	-Database

Luukinen, H. & al.	2005	Finland	Prospective study	DSM-VI criteria MMSE 24/30 or less Word list and delayed recall (<80% of recall) Clock drawing test (4/6)	Mild TBI: GCS score between 13-15 with LOC lasting < 30 min, or with PTA lasting < 1h or with risk factors associated with intracranial complications (nausea, headache, dizziness, seizures, focal neurologic deficits, skull fracture) Moderate TBI: GCS score of 9-12 on admission, including cases with longer LOC or PTA than described for mild Severe TBI:GCS score of <9 on admission	-Postal questionnaire -medical record -neurologic examination
Luukinen, H., Viramo, P., Koski, K., Laippala, P., & Kivelä, S. L.	1999	Finland	Prospective study	MMSE < 26/30	TBI is define by an injury to the head. Severity of the head injury: ability to rise up without personal assistant and the inpatient care needed after all major head injuries were compared with the corresponding consequences of major injuries affecting other body part	-Postal questionnaire -Assessment of cognitive function
Mayeux, R. & al.	1995	United States	Retrospective study	Autopsy confirmed	Self report head injury with LOC	Interview
Mehta, K.M., Kalmijn, S., Slooter, A.J.C., van Duijn, C.M., Hofman, A., Breteler, M.M.B.	1999	Netherlands	Prospective study	Scoring below 26 on the MMSE or above 0 on the GMS-A Criteria diagnosis: American psychiatric association criteria (DSM-III-R) and NINCDS-ADRDA criteria	Self report head injury with LOC	-Physicians interview -Assessment

Mendez, M. F. Paholpak, P. Lin, A. Zhang, J .Y. Teng, E.	2015	United States	Retrospective study	NINCDS/ADRDA criteria for definite or probable AD	Self report head injury with LOC < 5 minutes or LOC <30 minutes	-NACC-database -Neuropathological database
Nemetz, P. N., Leibson, C., Naessens, J. N., Beard, M., Kokmen, E., Annegers, J. F., & Kurland, L. T.	1999	United States	Retrospective study	-Presence of dementia: previously normal intellectual and social function, progressive decline of intellectual/cognitive/social function that cannot be reversed with medication or psychiatric treatment, memory impairment, dementia sufficient to impair age-/education-/occupation-appropriate lifestyle adjustment In addition, documented evidence of at least two of the following: disorientation, personality/behavioural, problems, dyscalculia, aphasia or apraxia or agnosia, impairment of judgment/abstract thinking Alzheimer: presence of dementia, insidious onset of symptoms of dementia, gradual progression and irreversible course, other potential causes of dementia either not present or occurring definitely after the onset of symptoms of dementia	Loss of consciousness. post-traumatic amnesia, or neurologic signs of brain injury	-Medical record

Plassman, B. L. & al.	2000	United States	Prospective study	TICS-m < 29 IQCODE< 3.27 Dementia questionnaire Clinical assessment using National Institute of neurological and communicative disorders and stroke – AD and related disorders association criteria	Mild TBI: loss of consciousness or PTA for less than 30 minutes, with no skull fracture Moderate TBI: LOC or PTA for more than 30 minutes but less than 24 hours, and/or a skull fracture Severe TBI: loss of consciousness or PTA for more than 24 hours	-Telephone interview for cognitive status (TICS-m) -Informant Questionnaire for Cognitive decline (IQCODE) -Telephone dementia questionnaire (DQ) -Clinical assessment (neuropsychological battery)
Salib, E. Hillier, V.	1997	England	Retrospective study	NINCDS-ADRDA DSM-III ICD9	Self report head trauma With or without LOC	-Questionnaire -Interview -Medical history -Standard physical examination -Laboratory tests -Cognitive functions assessment
Schofield PW, Tang M, Bell K, Dooneief G, Chun M, Sano M, Stern Y, Mayeux R	1997	United States	Retrospective study	-NINCDS criteria -Patient met threshold criteria on neuropsychological evaluation: failed at least 2 memory test and at least 2 test of other cognitive domains and that cognitive problems could not be attributes to an acute state of confusion	Self report head injury TBI LOC or PTA (LOC < 5 minutes or PTA LOC > 4 minutes)	-Assessment (clinical evaluation) -Battery of neuropsychological test

Notes. AD, Alzheimer's disease ; TBI, Traumatic brain injury ; OR, Odds ratio (95%) ; CI, Confidence interval for the odds ratio; GCS, Glasgow Coma scale ; LOC, Loss of conciousness ; PTA, post-traumatic amnesia ; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association ; DSM, Diagnostic and Statistical Manual of Mental Disorders ; MMSE, Mini-Mental States examination;

Table 2

Summary of studies reviewed (OR and TBI-related variables)

Authors	**Years**	**Number of participants**	**OR**	**GSC**	**LOC**	**PTA**
Abner, E. L. & al.	2014	649	Men : 1.47 (95% CI 1.03 – 2.09)* Female : Women : 1.18 (95% CI 0.83-1.68)	---	LOC < 5 minutes LOC > 4 minutes	---
Amaducci, L. A. & al.	1986	329	TBI was not more frequent in AD patients than hospital (p=0.18) and population control (p=0.51)	---	LOC (time not specify)	---
Broe, G .A. & al.	1990	340	1.33 (95% CI 0.46-3.83)	---	---	---
Dams-O'Connor, K., Gibbons, L.E., Bowen, J.D., McCurry, S.M., Larson, E.B., & Crane, P.K.	2013	996	Later onset of dementia for TBI patient (11.46 years) vs no-TBI (10.55 years), p= 0.004	---	LOC > 5 minutes	---
French, L. R. & al.	1985	154	4.50 (95% CI 1.44-15.69)*	---	---	---
Guo, Z., Cupples, L. A., Kurz, A., Auerbach, S. H., Volicer, L., Chui, H., & al.	2000	2233	Head injury with LOC: 9.9 (95% CI 6.5 to 15.1)* Head injury without LOC: 3.1 (95% CI 2.3-4.0)*	---	LOC (time not specify)	---
Helmes, E. Ostbye, T. Steenhuis, R. E.	2011	921	Mild TBI: 0.854 (95% CI 0.294-2.2484) Moderate-severe TBI: 0.799 (95% CI 0.418-1.525)	---	Mild TBI: no LOC Moderate-severe TBI: LOC (time not specified)	---
Koponen, S. & al.	2004	60	17.61 (95% CI 0,86-359,90)	---	LOC ≥ 1 minutes	< 1 jour = mild ; 1-24 hours = moderate ; 1 to 7 days ; severe ; > 7 day very severe
Lee, Y-K. Hou, S-W. Lee, C-C.	2013	720933	Mild TBI : 3.26 (95% CI 2.69-3.94)*	---	---	---

Hsu, C-Y. Huang, Y-S. Su, Y-C.						
Luukinen, H. & al.	2005	152	2.80 (95% CI 1.35 -5.810)*	Mild TBI : GCS score between 13-15 ; Moderate TBI : GCS score of 9-12 ; Severe TBI :GCS score of <9	Mild : LOC lasting < 30 min ; Moderate : 30 minutes <	Mild= PTA lasting < 1h ; Moderate : PTA more than described for mild
Luukinen, H., Viramo, P., Koski, K., Laippala, P., & Kivelä, S. L.	1999	325	Major head injury: 3.70 (95% CI 1.25-10.9)*	---	---	---
Mayeux, R. & al.	1995	236	1.5 (95% CI, 0.5-3.5)	---	LOC (time not specify)	---
Mehta, K.M., Kalmijn, S., Slooter, A.J.C., van Duijn, C.M., Hofman, A., Breteler, M.M.B.	1999	6645	0,8 (95% CI 0,4-1,9)	---	LOC < 16 minutes LOC > 15 minutes	---
Mendez, M. F. Paholpak, P. Lin, A. Zhang, J .Y. Teng, E.	2015	5786	Early onset of AD : 1.75 (95% CI 1.47-2.07)*	---	LOC < 5 minutes or LOC <30 minutes	---
Nemetz, P. N., Leibson, C., Naessens, J. N., Beard, M., Kokmen, E., Annegers, J. F., & Kurland, L. T.	1999	1283	1,2, 95% CI 0,8-1,7)	---	LOC (time not specify)	PTA (time not specify)
Plassman, B. L. & al.	2000	1776	Mild TBI= 1.23 (95% CI 0.28- 5.31) Moderate TBI = 2.32 (CI 1.04-5,17)* Severe TBI= 4.51 CI 1.77-11.47)*	---	Mild TBI : loss of consciousness less than 30 minutes ; Moderate TBI : LOC for more than 30 minutes but less than 24 hours ; Severe TBI : loss	Mild TBI : PTA for less than 30 minutes ; Moderate TBI : PTA for more than 30 minutes but less than 24 hours ; Severe TBI : PTA for more than 24 hours

					of conciousness for more than 24 hours	
Salib, E. Hillier, V.	1997	538	1.52 (95% CI 0.98 -2.35) Men : 2.1 (95% CI 1.1-4.1)* Female : 1.38 (95% CI 0.74-2.60)	---	LOC (time not specify)	---
Schofield PW, Tang M, Bell K, Dooneief G, Chun M, Sano M, Stern Y, Mayeux R	1997	271	TBI with LOC earlier onset of AD : 4.1 (95% CI 1.3-12.7)* TBI with LOC > 4 minutes : 11.2 (95% CI 2.3-59.8)* TBI with LOC < 5 minutes : 1.7 (95% CI 0.4-7.5)	---	LOC < 5 minutes or PTA LOC : 5-29 minutes LOC : 29-59 minutes LOC : 1-24 hours LOC : > 24 hours	PTA (time not specify)

Notes. * Significative values; AD, Alzheimer's disease ; TBI, Traumatic brain injury ; OR, Odds ratio (95%) ; CI, Confidence interval for the odds ratio; GCS, Glasgow Coma scale ; LOC, Loss of conciousness ; PTA, post-traumatic amnesia.

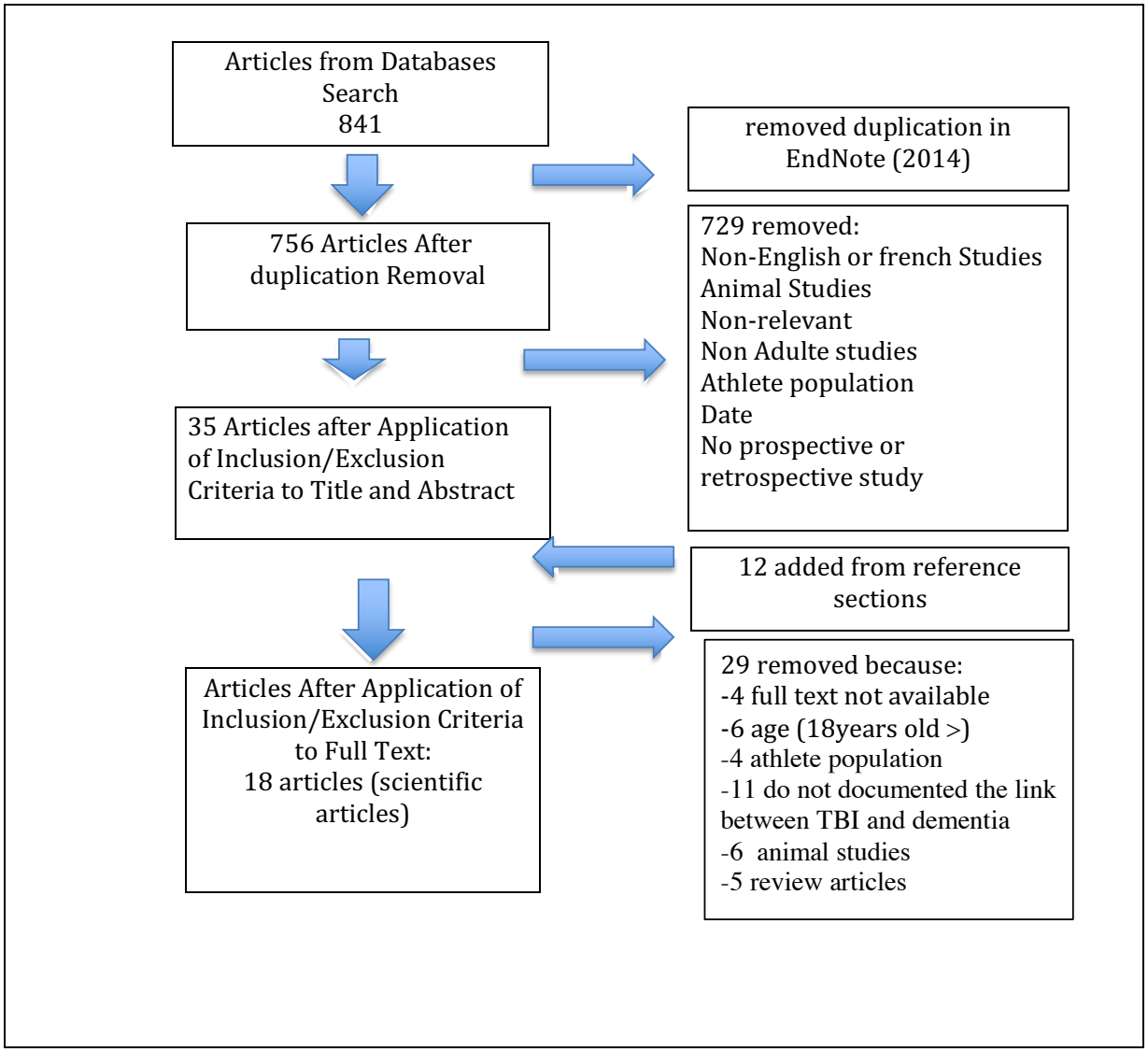

Figure 1. Flow of information through the different phases of the systematic review

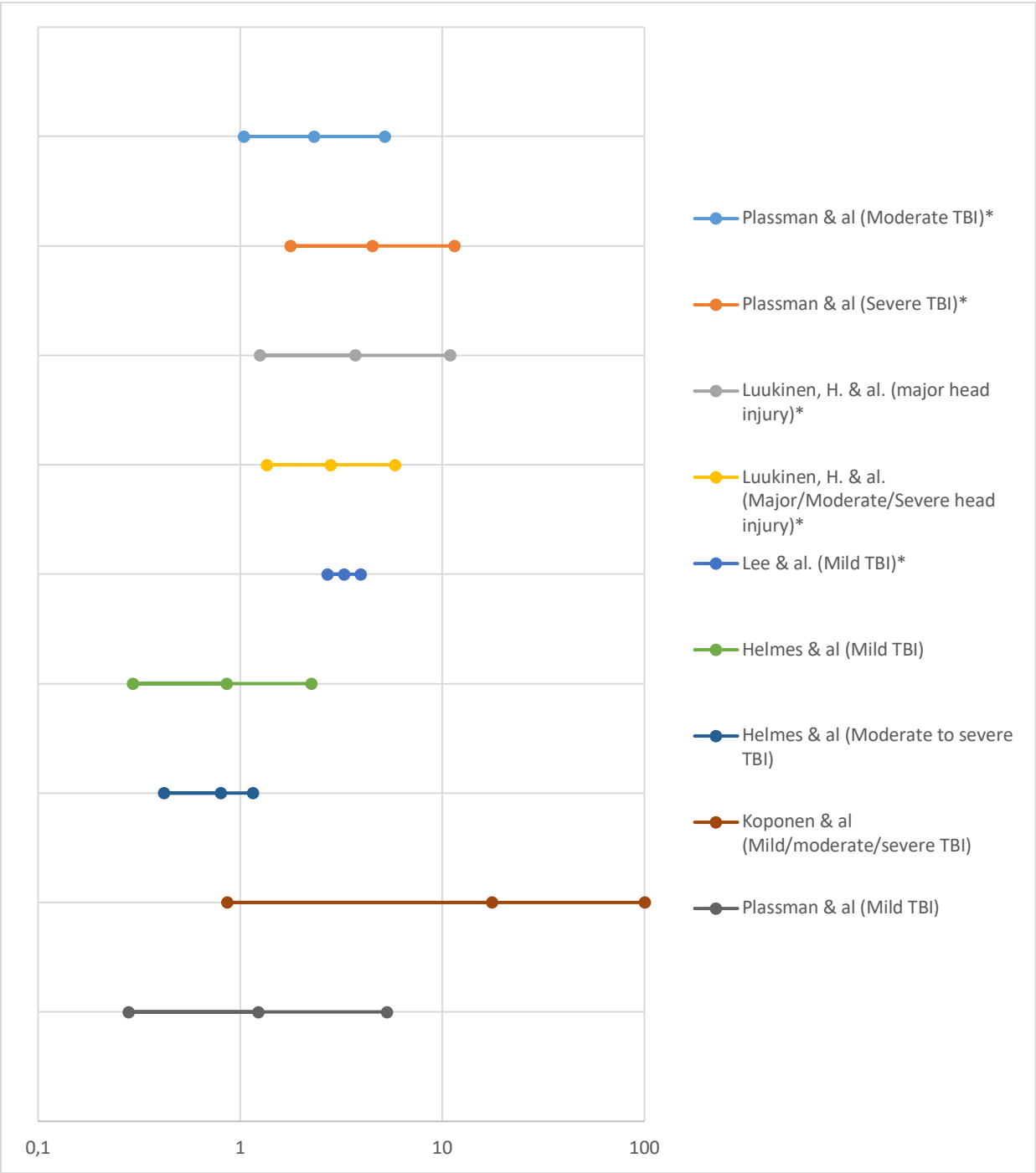

Figure 2. Odd ratios of the TBI severity (95% Confidence interval)

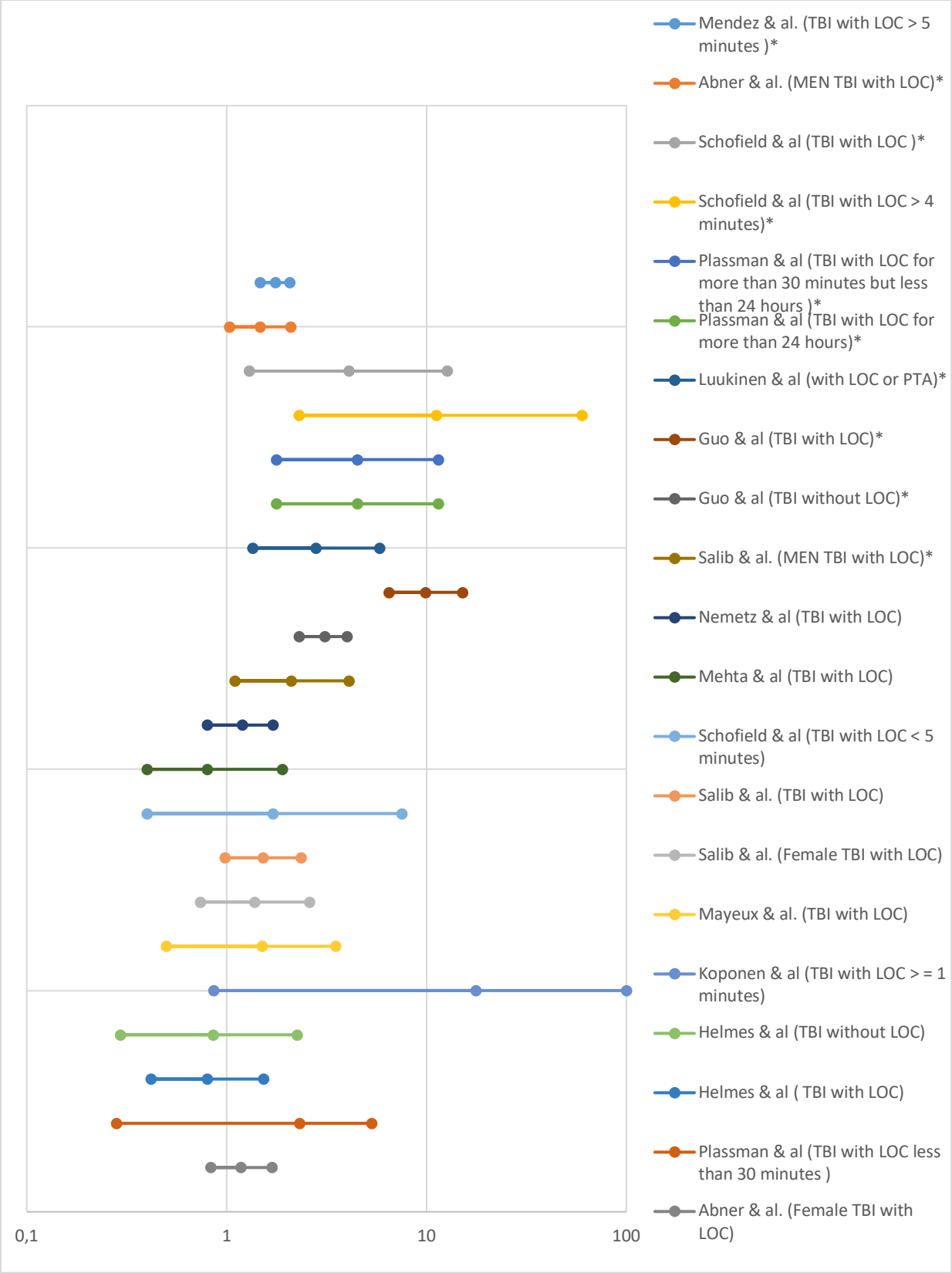

Figure 3. Odd ratios of the LOC (95% confidence interval)

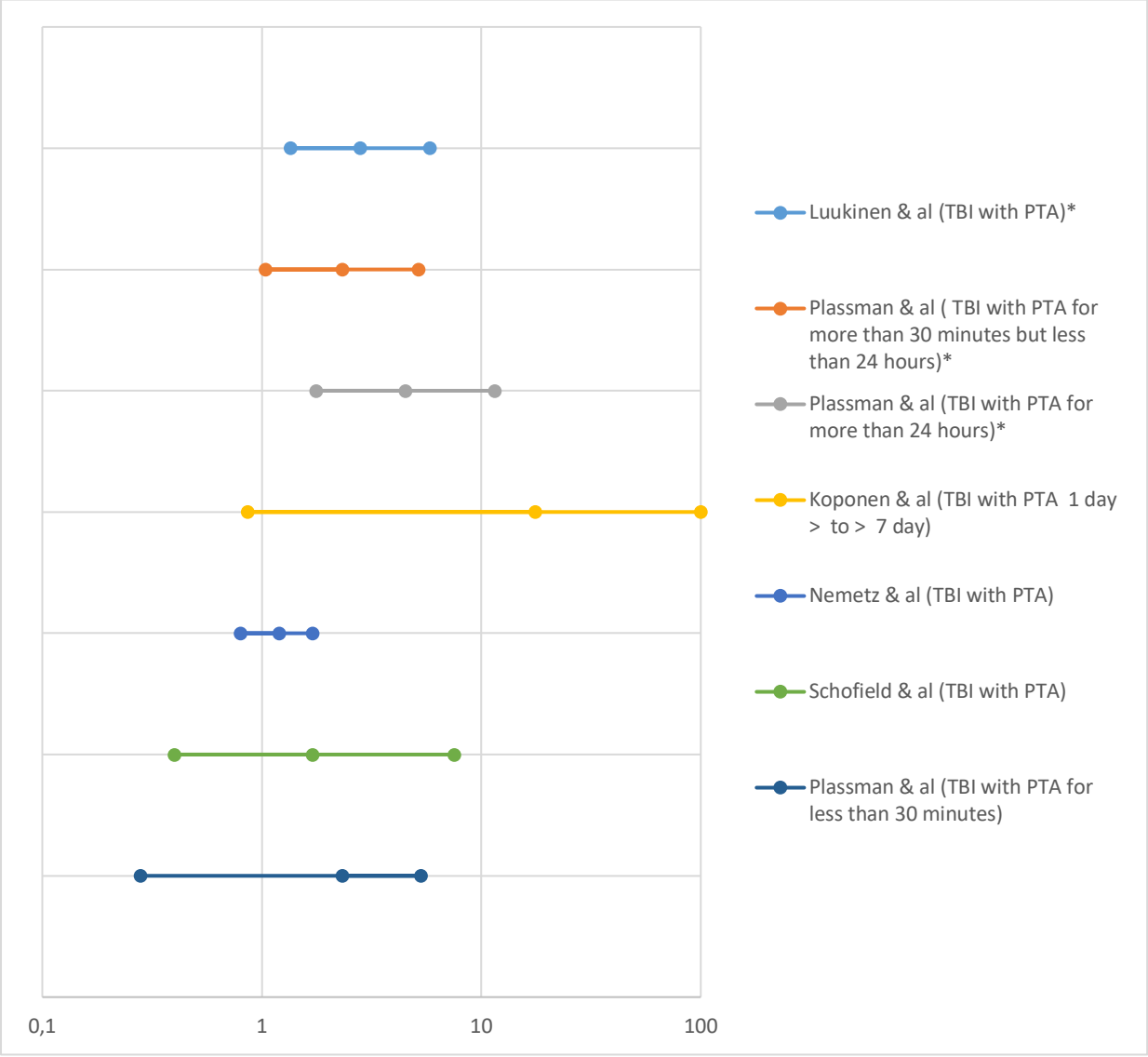

Figure 4. Odd ratios of PTA (95% confidence interval)

Article 2

Comparison of neuropsychological profiles in older adults with traumatic brain injury, Alzheimer's dementia, and with normal cognition

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Abstract

Objective: To assess the differences in neuropsychological profiles of older adults with traumatic brain injuries (TBI) and with Alzheimer's disease (AD). **Method:** In this cross-sectional study, the sample included 76 older adults, aged 60 years old and older, divided into three groups: older adults with TBI (n = 24), older adults with AD (n = 29), and healthy older adults (n = 24). A battery of cognitive tests and questionnaires were administered to all participants in a standardized fashion during a neuropsychological evaluation. Demographic and injury factors were examined as potential predictors of cognitive outcomes. **Results:** Group differences were found across all cognitive functions. More specifically, TBI and AD groups had greater impairments in processing speed, naming, executive functioning and working memory than the control group. AD patients had greater memory problems while TBI patient had more anxiety and depression signs. In the TBI group, neither Glasgow Coma Scale score nor lesion location were associated with cognitive functioning. **Conclusions:** The findings of this study may be helpful to clinicians in the differential diagnosis of TBI versus AD and in the medical decisions for either acute or long-term management.

Key words: Traumatic brain injury; Alzheimer disease; cognitive decline; neuropsychology; outcome

In the last decade, there has been increasing interest in the link between a history of traumatic brain injury (TBI) and increased risk of developing Alzheimer's disease (AD). Although previous studies appear to support such an association (Barnes et al., 2018; Guo et al., 2000; Lye et Shores, 2000; Plassman et al., 2000; Wang et al., 2012), inconsistencies in the literature remain about this relationship (Helmes et al., 2011; Julien, Joubert, et al., 2017). In fact, some studies suggest that TBI do not lead to AD but that it may shows pathological findings similar to AD (Washington, Villapol, Burns, 2016). However, there is accumulating evidence that TBI could lead to an increased risk for dementia similar to AD by a common neuropathological pathway. Specifically, this model suggests that TBI results in greater cerebral beta-amyloid, which in turn increases the probability of neurodegenerative changes later in life (Bird et al., 2017; Gill et al., 2016). It has also been suggested that the presence of the apoE4 allele may have a negative impact on neurological recovery following a TBI (Mayeux, Sano, Chen, Tatemichi, et Stern, 1991) and that TBI occurrence combined with the presence of the apoE4 allele may increase the probability of developing AD later in life (Friedman et al., 1999; Horsburgh, McCarron, White, et Nicoll, 2000; Mayeux et al., 1993b; Samatovicz, 2000).

In addition to the possible neuropathological concomitance between TBI and AD, the precise neuropsychological distinctions between these neurological conditions remain unclear. Some studies have proposed distinct neuropsychological profiles (Breed et al., 2008; Capitani, Rosci, Saetti, et Laiacona, 2009) while others have suggested that TBI mimics the symptoms of true AD, resulting in a similar neuropsychological profile (Hinkebein et al., 2003). Surprisingly, however, very few studies have directly compared the neuropsychological profile of TBI and AD, despite the significant clinical need for differential diagnosis between these both commonly-occurring conditions. In fact, better clinical characterization of these conditions will become increasingly important in coming years, given the aging population and the increasing incidence of TBI in this population.

Post-TBI cognitive and psychosocial sequelae are common in elderly adults (Gardner et al., 2018; Goldstein et Levin, 2001; Graham et al., 2010; Rapoport et al., 2006). Post-TBI deficits often encompass several cognitive functions such as attention, memory, mental processing speed, working memory, visuospatial abilities and executive functioning compared to age-matched

healthy controls (Ashman et al., 2008; Rapoport et al., 2006). Emotional consequences such as depression and anxiety are also very common after TBI in older age (Ashman et al., 2008). Rapoport, McCullagh, Shammi and Feinstein (2005) found that subjects (mild-moderate TBI adult) with depression, compared to those without, were found to have significantly lower scores on measures of working memory, processing speed, verbal memory and executive function. Some studies even suggested that TBI aftereffects in older adults can mimic dementia symptoms (Flanagan et al., 2005). In fact, changes in cognitive functioning after a TBI in older age, especially after a mild TBI, may not start until weeks or months past the injury and may as a result be erroneously attributed to dementia onset (Flanagan et al., 2005). This difficulty in differentiating between the neuropsychological profiles associated with TBI and AD is due to the overlap in cognitive difficulties in both conditions, thus rendering differential diagnosis difficult. For example, in TBI, language difficulties (i.e. word finding, comprehension deficit and semantic paraphrases), memory, processing speed, attention, executive functions, working memory and visuospatial abilities are frequently encountered, which is similar in AD (Baudic et al., 2006; Flanagan et al., 2013; Hinkebein et al., 2003; Weintraub et al., 2012). Consequently, individuals with late-life TBI-related cognitive impairments may be misdiagnosed as having dementia. It is unclear if they mimic or if they stem from AD or TBI aftereffects.

On one hand, some authors argue that, in addition to depleting brain reserve capacity, TBI causes a neuropsychological profile with similar deficits to those seen in AD, and that this pattern of impairment is negatively impacted by age (Hinkebein et al., 2003). They hypothesized that some TBI patients with no evidence of AD, could indeed develop a profile similar to AD patients. To differentiate both pathological processes, neuropsychological profiles of these two clinical populations were compared using data stemming from two different studies which both use the "neuropsychological deficit profile analysis" methodology. The first study included a group of individuals with TBI referred for neuropsychological evaluation (Johnstone et al., 1995), while the second study included a group of individuals diagnosed with probable AD (Johnstone et al., 2002). Based on those two studies, Hinkebein et al. (2003) proposed that TBI yields similar cognitive deficits to those seen in AD, thus mimicking the latter condition. In fact, while TBI and AD profiles were qualitatively similar, AD patients showed greater deficits in the following domains: attention, processing speed, cognitive flexibility, immediate and delayed memory (Hinkebein et al., 2003).

On the other hand, other studies have shown neuropsychological differences between TBI and AD. Breed et al. (2008) compared patterns of cognitive functioning in older participants with self-reported TBI, with AD, and in participants without neurological disorder (ND). The AD group had lower scores than the ND group in most cognitive domains (verbal ability, immediate and delayed verbal memory, immediate and delayed visual memory, processing speed and time set shifting ability), with the notable exception of working memory. The TBI group had lower scores than the ND group on vocabulary, verbal fluency, delayed visual memory and processing speed. Interestingly, the AD group had lower scores than the TBI group on tests of immediate and delayed verbal memory, immediate and delayed visual memory, processing speed and verbal fluency. This study concluded that cognitive impairments were present in older adults with AD and TBI, but that individuals with TBI were better able to learn and retain new information than individuals with AD. In another study, category and letter fluency performances of AD patients and TBI patients was compared. The aim of this study was to explore whether the TBI group would show the reverse profile of what is commonly observed in AD, i.e. preserved category fluency compared to impaired letter fluency in TBI. These results were confirmed. In fact, TBI seems to cause a relatively more severe impairment in letter fluency in comparison with category fluency (Capitani et al., 2009). Nevertheless, these finding suggest that individuals with dementia and a history of TBI may present with a unique profile. To summarize, these studies highlight the differences between TBI and AD-derived cognitive profiles.

In addition to better distinguishing the neuropsychological profiles of patients with TBI and AD, it is also relevant to focus on factors that may influence the individual differences of each of these groups. Accumulating evidence suggests that certain risk factors associated with AD are also relevant in post-TBI outcomes. Individual differences (i.e. age and education) may modulate and highly influence the presence of cognitive and psychosocial TBI impairment (Gardner et al., 2018). In fact, pre-existing factors among TBI older adults tend to complicate recovery. Studies have examined the role of pre-existing conditions and injury factors on post-TBI outcome in this population. Age of TBI onset (Goldstein et Levin, 2001; Marquez de la Plata et al., 2008; Susman et al., 2002) and education level should be considered as variables that have a significant impact on post-TBI outcome. In fact, some studies have shown that age is an important long-term outcome

predictor; the later the TBI occurs, the worse the outcome will be (Senathi-Raja et al., 2010; Spitz et al., 2012; Thompson et al., 2006). Patients' level of education has also been shown to be a predictor of the long-term outcome; individuals with a lower education level may be less able to compensate for the damage that follows TBI (Kesler et al., 2003; Ponsford et al., 2008). Unsurprisingly those same individual factors (age and education) are also relevant and predict outcome in AD (Stern, 2002, 2012). Indeed, it has been shown that the risk of dementia increases in individuals with low education (Stern, 2012; Valenzuela et Sachdev, 2006) and that AD prevalence increases with age. In fact, higher age is a risk factor for AD (Braak et Braak, 1997; Guerreiro et Bras, 2015; Riedel et al., 2016).

It is well known that TBI-related factors such as TBI severity and evidence of cerebral damage can also be relevant in post-TBI outcomes. First, TBI severity has an impact on the presence of long term cognitive, psychosocial and functional consequences post-TBI (de Guise et al., 2006; Fleminger et al., 2003; McIntyre, Mehta, Janzen, et al., 2013; Ritchie et al., 2011; Utomo et al., 2009). For example, a study found that a low GCS at admission and a longer length of stay were associated with greater physical disabilities and functional impairments at time of discharge. In general, the link between TBI severity and outcome is approximately linear; the greater the severity, the greater the consequences (Rassovsky et al., 2015). Secondly, head CT evidence of neurotrauma is also associated with worse outcomes (Brazinova et al., 2010; Mitra, Cameron, Gabbe, Rosenfeld, et Kavar, 2008). Although there is great heterogeneity in the biomechanical profiles of TBI, there is a predominant injury profile that suggests that contusions, or focal damage to the brain's tissue and vasculature structure, are most likely to occur in frontal and temporal regions (Rabinowitz et Levin, 2014b). So, it is not surprising that TBI patients may experience executive and memory deficits. In fact, executive functions such as planning, inhibition and mental flexibility rely heavily on frontal regions. These functions may also influence many everyday cognitive tasks, including learning and memory, decision-making, and social behavior (Lezak et al., 2012; Spitz, Ponsford, Rudzki, & Maller, 2012a). Indeed, learning and memory ability difficulties are common following a TBI (Ariza et al., 2006; McLean, Temkin, Dikmen, et Wyler, 1983) and unsurprisingly those cognitive abilities rely mostly on temporal regions. As mentioned earlier, temporal regions are often damaged as a result of TBI, causing verbal and visual memory dysfunction (Ariza et al., 2006). In general, patients with TBI retain the ability to recognize newly

learned material but have greater difficulty in retrieving information since encoding is often disorganized (Dikmen et al., 2009; Stuss & Alexander 2000). Admittedly, the impact profile of TBI is often heterogeneous and varies from one person to another, so several regions may be involved and influence post-TBI outcomes.

Differentiating TBI and AD-derived cognitive profiles is of crucial importance; it would facilitate differential diagnostic and medical decisions related to acute or long-term patient management as trajectories and intervention plans are different for both conditions. Despite this significant clinical difference, as stated above, few studies have compared the cognitive profile of individuals with TBI and AD. Unfortunately, these studies have significant methodological limitations: lack of control group and wider age groups. More importantly, some studies combined the results of different studies, as shown with the "deficit profile methodology", others employed review methodology and retrospective self-report of a TBI event. The latter of which raises serious doubts regarding the validity of the information reported, especially so for AD patient whose autobiographical memory is often greatly impaired. Therefore, the first objective of this prospective study was to highlight differences in the neuropsychological profiles of patients who sustained a TBI in advanced age and compare them to those of individuals with AD and healthy age-matched controls. To do so, we assessed neuropsychological profiles with validated and standardized cognitive tests and questionnaires. Given the limited literature on the topic, the analyses were exploratory. Nonetheless, it was expected that different neuropsychological profiles would be observed between the three groups. More specifically, it was hypothesized that the AD group would have lower scores than the TBI group on both verbal and visual memory tasks (immediate and delayed recalls). The second objective was to determine if age and education were associated with neuropsychological outcomes in both clinical groups. In addition, we also included injury characteristic such as the Glasgow Coma Scale (GCS) as a measure of TBI severity and the number of days prior to testing (time of recovery) for the TBI group, given that they are usually predictors of TBI outcome. It was expected that TBI and AD patients in more advanced age and with a lower level of education would have poorer cognitive performances (Stern, 2002). For the TBI only group, it was also anticipated that patients with frontal and temporal lesions would have poorer executive and memory abilities than patient without frontal and temporal damage.

Methods

Subjects

The sample included 76 older adults divided in three groups: a mild TBI group (n= 24), an AD group (n= 29), and a group of TBI-AD age-matched healthy participants (n= 24). The flow charts of the TBI and AD patient and normal healthy controls recruitment are present in figures 1 and 2.

Insert Figures 1 and 2 about here

Inclusion criteria for the TBI group were (a) men or women aged between 60 to 85 years; (b) late life mild-TBI, beyond the age of 60, and TBI as defined by one of more of the following criteria: a cranial or intracranial injury on radiological imaging AND/OR one of the following indicators: loss of consciousness, altered state of consciousness (decreased GCS), amnesia of the event and (c) to have French or English as their first language. Only one patient in the TBI group was evaluated in English.

Inclusion criteria for the AD group were; (a) men or women aged between 60 to 85 years; (b) patients referred by specialists at the *Institut Universitaire de Gériatrie de Montréal* (IUGM) where they had been previously assessed and diagnosed by a team of expert neurologists, geriatricians and neuropsychologists. They had received a diagnosis of probable dementia of the Alzheimer's type according to the criteria developed by the National Institute of Neurological and Communication Disorders and stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 2011). All participants had undergone a complete neurological examination and did not show any evidence of other neurological disease or other potential causes of dementia that could account for their condition. AD patients must have had a mild to moderate AD diagnosis (i.e. a score higher than 17/30 on the MMSE) to be included. AD patients had a mean MoCA score of 19.21/30 (*SD* = 4.16); (c) no TBI history and ; (d) to have French or English as their first language.

Inclusion criteria for the control group were (a) men or women aged between 60 to 85 years; (b) scores higher than 26/30 on the MoCA; (c) no TBI history and (d) to have French or English as their first language.

The following exclusion criteria were applied to all participants: (a) history of neurological disorders other than AD and TBI for patients in the AD group and the TBI group respectively; (b) severe psychiatric disorders (except for anxiety and depression disorders if asymptomatic at the time of the study); (c) a history of alcohol or substance abuse and (d) have had general anesthesia in the last six months.

Procedure

Older adults with mild TBI were recruited from the inpatient ward of the Montreal general Hospital, a tertiary trauma center. Between November 2017 and December 2019, a neuropsychologist from the Montreal general hospital approached eligible individuals and obtained their written consent to be contacted by the research coordinator.

Older adults in the AD group were recruited at the IUGM where treating physicians presented the study to potential patients and their family, and obtained their verbal consent (or that of their medical proxies) to be contacted by the research coordinator within the following week. All AD patients had received a general clinical examination as well as neurological and imaging examinations before starting the study.

Individual in the control group were recruited through a pool of healthy participants at IUGM, as well as by advertisements displayed at this same center. In the absence of injury and other neurological conditions, individuals were invited for an assessment as soon as possible.

All participants who gave their consent to participate were individually seen for an evaluation lasting approximately 1 hour and 45 minutes. These meetings took place either at the participant's home or at the IUGM clinic, depending on the participant's preference. A battery of tests and questionnaires were administered to all participants in a standardized fashion. These tests and questionnaires are described in the section below. French and English participants did the same

tests and the same norms were used. Vision problems and audition problems were corrected by the wear of glasses and hearing aids during the evaluation. This study was approved by the IUGM, the McGill University Health Centre and Montreal University ethic board.

Measures

Medical chart

Information obtained from medical charts for TBI participants included the date of the accident, the cause of the accident, the Glasgow coma scale score within 24 hours after the accident and the result of the CT Scans. A radiologist blind to the evaluation analyzed the CT images to describe and localize brain damage, if any. First, he scored scans either as normal or positive if they showed any kind of lesion, for example a contusion or hemorrhage. Second, he looked at each lobe (frontal, temporal, parietal, occipital) separately to see if a lesion was present. Thus, one patient may have lesions at different sites. For the AD participants, MoCA scores were documented from their medical records.

Sociodemographic Questionnaire

This in-house questionnaire provides demographic information such as age, sex and number of years of education.

Verbal Memory

The Rey Auditory Verbal Learning Test (RAVLT) examines the ability to learn new verbal information (encoding, consolidation and retrieval). A list (A) of 15 words is read five times and each time the participant is asked to recall all the words he or she can remember. Then, another list (B) of 15 words is read one time and the participant is asked to report all the words he or she can remember from list B. Recall of list A is assessed immediately after recall of list B (immediate free recall) and a second time after a 30 minute delay (delayed free recall). After, a recognition task is done where participants have to correctly identify the words that were part of list A out of list composed of the words from list A and new words (recognition). Total correct immediate and delayed free recall scores as well as total correct recognition scores were collected. Z-scores were then obtained for each condition by comparing the total raw scores to age and education- matched norms (Strauss, Sherman, et Spreed, 2006).

Visual Memory

The Rey-Osterrieth Complex Figure Test (ROCF) examines the ability to learn new visual information (encoding, consolidation and retrieval) (Rey, 1970). The participant is asked to copy a complex figure. Then, the participant is asked to reproduce the same figure from memory after a delay of three minutes (Immediate recall) and again after a 30-minute delay (Delayed recall). Following the delayed recall, the participant is shown a list of elements and must identify which one were part of the initial figure (Recognition). The total correct immediate and delayed items recall scores were calculated, as well as the total correct recognition scores. Z-scores were obtained for each condition by comparing the total raw scores to age-matched norms (Meyers et Meyers, 1995).

Verbal ability

The Boston naming test short version (BNT) provides 15 images that the participant is asked to name. This tool assesses language and denomination capacities. Only the total correct response provided without any assistance, such as verbal or semantic cues, are marked as correct. A Z score was obtained by comparing the total raw score to age and education-matched norms (Nasreddine et al., 2005).

Executive function

The Trail making test part B measures switching abilities (flexibility). In this test, the participant is asked to link numbers in ascending order and letters in alphabetical order, alternately. The total time to complete the task was collected and a Z-score was obtained by comparing the total raw score to age-matched norms (Reitan, 1955).

Immediate memory and working memory

The Digit span task of the Wechsler Memory Clinical Scale-IV measures immediate and working memory abilities for numbers presented verbally (Weschler, 2001). The individual is first asked to repeat the presented numbers in the same order (digit span forward) and then, asked to repeat the numbers in reversed order (digit span backward). The total score of the digit span forward was used to measure the immediate memory abilities. The total score of the digit span backward

was used to measure working memory abilities. Z-scores were obtained by comparing the total raw scores to age- matched norms.

Processing speed

The Trail making test part A measures the processing speed. In this task, the participant must link numbers in ascending order, without error, as quickly as possible. The total time to complete the part A was collected and a Z-score was obtained by comparing the total raw score to age-matched norms (Reitan, 1955).

Self-reported symptoms of anxiety

Geriatric Anxiety Inventory. The purpose of this questionnaire is to measure self-reported anxiety symptoms in older adults and consists of 20 self-reported agree-not agree questions inquiring about the participant's anxiety over the past week. The total score is taken into account in this study and a total score of 10 and more matches an anxiety disorder (Pachana et al., 2007).

Self-reported symptoms of depression

Geriatric Depression Scale. This questionnaire aims to assess self-reported depressive symptoms in older populations and consists of 30 self-reported yes-no questions inquiring about the participant's mood over the past week. The total score is taken into account in this study. A score between 0 and 9 is normal, a score between 10 and 19 matches a moderate depression and a score between 20 and 30 matches a severe depression (Yesavage, Brink, Rose, et al., 1983).

Statistical Analyses

Group comparisons were conducted on demographic variables (age, sex, education) using analysis of variance (ANOVA) and chi-square tests for categorical variables to ensure that groups were comparable.

The neuropsychological measures analyzed were: the RAVLT (total correct immediate free recall score, the total correct free delayed recall score and the total correct recognition score), the ROCF (total correct immediate score, delayed recall scores were calculated, total correct recognition score), the BNT (total correct responses provided without any assistance), the trail

making test part B (completion time), the digit span task (combined digit span forward and backward score), the trail making test part A (completion time), the geriatric anxiety inventory (total score) and geriatric depression scale (total score). Each neuropsychological measure was entered separately as the dependent variable, with groups (TBI, AD, Control) entered as independent variables. To control for age differences between groups, age-scaled scores were utilized for all neuropsychological measures. All age-scaled scores were put in z-scores for analyses. To investigate group differences in cognitive outcomes, analyses of variance (ANOVA) were performed and non-parametric analysis Kruskal-Wallis tests were conducted when group variance was not equal. The Tukey test (ANOVA) and the pairwise comparisons (Kruskal-Wallis) were used for post hoc analyses.

To construct the multiple regression models and select the variables to include in the exploratory model, correlation analyses were first run across all socio-demographical and accident-related variables and cognitive outcomes. Only variables correlated bivariate to $p<0.01$ were included in the model. Thus, age and education were included in the model for both groups as well as the GCS scores and the time between the accident and the evaluation for the TBI group. Each score from one test representing a cognitive function was used, except for memory where two scores were computed (verbal and visual). To reduce the number of outcomes, only the RAVLT and RCFT delayed recall scores were computed for verbal and visual memory, then the BNT total score for verbal ability, the Trail making test part B completion time for executive functioning, the digit span combined total score for working memory and the Trail making test part A completion time for processing speed. Also, geriatric anxiety inventory for the anxiety symptoms and geriatric depression scale total scores were also used.

As another exploratory analysis, to see if the location of the lesion (frontal injury, temporal injury, parietal injury, occipital injury) influenced cognitive measures, independent t-tests were run across all neuropsychological measures. The same outcome measures as described above were used. Neuropsychological measures were entered as the dependent variable, and groups (positive scan, negative scan) were entered as independent variables.

Tukey corrections were used for all regression models and for independent T-tests analyses (p<.006). An alpha of .05 was used in the other analyses. Effect sizes are reported using partial eta squared for continuous data, and the Cramer's *V* for categorical data. All statistics were performed with SPSS 25.

Results

Participants

Participant demographics and accident-related characteristics are presented in Table 1. As shown, no significant group differences were found across the TBI, AD and control groups in terms of sex, $\chi 2$ (2, N= 77) = 2.54, p = .281, and education, F (2,74) = 0.16, p= .85. Regarding sex, all groups comprised a majority of females (TBI = 66.67%; AD = 58.62%; Control = 79.17%) and had an average of 14 years of education. However, there were age differences between groups at the time of the evaluation, F (2,74) = 6.27, $p < .05$. Post hoc comparisons using the Tukey test indicated that the AD group *(M = 76.14, SD = 7.558)* was significantly older than the TBI group (M = 69.42, SD = 7.19) but no difference in term of age was found between both TBI and AD groups in comparison with the control group (*M = 72.75, SD = 5.61*). Regarding the TBI group, falls were the most frequent cause of trauma (58.33%) followed by car accident (20.80%) and other non-intentional incidents (20.80%). Among the TBI group (GCS from 13 to 15), a total of 87.00% of the cohort had a positive CT scan. Specifically, 57.14% had frontal lobe injury, 52.38% had temporal lobe injury, 42.86% had parietal lobe injury and 47.61% had occipital lobe injury. TBI patients were assessed on average five months after their accident (M = 164.95*,* SD = 94.73).

Insert Table 1

Comparison of neuropsychological profiles among groups.

Comparisons of neuropsychological scores between groups are presented in Table 2.

RAVLT immediate and delayed free recall

Analysis of variance showed that the effect of group was significant for immediate free recall, F (2,73) = 51.56, $p < .05$, and for delayed free recall, F (2,73) = 45.43, $p < .05$. Post hoc

analyses using the Tukey post hoc criterion for significance indicated that the average number of correct responses in the immediate recall condition was significantly lower in the AD (*M= -3.14, SD = 1.12*) than in the other two other groups (TBI and control) (TBI: *M = .14, SD = 1.91*; Control: M = *1.14, SD = 1.66*), and that the two latter groups did not differ between each other. Similarly, the average number of correct responses for delayed free recall was significantly lower for the AD group than the control (*M = .86, SD = 1.50)* and TBI (*M = -.50, SD = 1.46)* groups, suggesting that the AD group has greater difficulties than the two other groups (Control and TBI) to recall verbal information after a longer delay. Furthermore, the TBI group showed a significantly lower score than the control group in terms of delayed free recall. However, the score of the TBI group is in the average of their age group suggesting no difficulty in memory process.

RAVLT recognition recall

Similarly, the Kruskal-Wallis test showed that the effect of group was significant, H (2) = 29.71, $p < .05$). The pairwise comparisons indicated that the average score in the recognition condition for the AD group (*M= -1.43, SD = 1.66*) was significantly lower than the two other groups (TBI (*M= .58, SD= .80*) and control (*M= .38, SD= .87*) (H (2) = -30.05, $p < .05$), H (2) = -26.01, $p < .05$), respectively). No difference was found across the latter two groups, H (2) = 4.04, $p = .529$. These findings suggest that the AD group has difficulty to retain newly learned verbal information over time.

ROCF immediate and delayed free recall

Regarding the performances obtained by the three groups in the ROCF immediate and delayed free recall, a test that measures visual memory, main effects were shown for the ROCF immediate (F (2, 72) = 37.44, $p < .05$) and delayed (F (2,72) = 30.08, $p < .05$) free recall. AD patients (*M= -2.37, SD = 1.59*) had significantly lower average number of correct responses than the control (*M = .35, SD = 1.28)* and the TBI groups (*M = .56, SD = 1.16),* and no differences were found between those two groups. The same pattern was found for the delayed free recall (AD: *M= -3.03, SD = 1.82*; TBI: *M = -.02 SD = 1.61*; Control: *M = .06, SD = 1.46*), indicating that the AD group has more difficulty recalling new visual information after short and long-time lapses.

ROCF recognition recall

The ANOVA showed a significant group effect, F (2,72) = 17.93, $p < .05$. Similarly, to ROCF immediate and delayed recall, the average total correct response score was significantly lower in the AD group (*M= -2.24, SD = 1.57*) than in the other two other groups (TBI and control) (TBI: *M = -.15, SD = 1.62*; Control: *M = .08, SD = 1.44*). Again, no differences were found across the TBI and the control groups. These findings suggest that the AD group has difficulty retaining newly learned information over time, and that TBI patients were able to retain newly acquired information over time as efficiently as uninjured controls.

BNT correct responses

We found a significant main effect of group, H (2) = 16.13, $p < .05$, on main scores. The control group had a significantly higher number of correctly named images (*M= .48, SD= .65*) than the two other groups (TBI (*M= -1.38, SD= 2.34*) and AD (*M= -.79, SD = 1.39*)) (H (2) = -22.63, $p < .05$, H (2) = -21.55, $p < .05$, respectively), thus demonstrating that controls have significantly better verbal abilities. However, the AD and the TBI groups had similar performances, H (2) = 1.08, $p = .861$, suggesting that the two clinical groups have comparable verbal functioning.

TMT part B total completion time (sec.)

Regarding the performances obtained by the three groups in the TMT-B, the ANOVA showed a significant group effect, F (2, 74) = 6.27, $p < .05$. Post-hoc analyses showed that the time to complete the TMT-B was significantly higher in the clinical groups (TBI and AD groups) (AD: *M= -1.24, SD = .85*; TBI: *M = -1.20, SD = 1.33*) than the control group (*M = -.19, SD = 1.36*). Again, TBI and AD groups did not differ among themselves. Similarly, the control group was significantly faster than both clinical groups when completing the TMT-B.

Immediate memory and working memory

The ANOVA performed on the immediate memory showed no group effect *F (2, 74) = 1.62, p = .205.* No difference was found between groups. However, the working memory variable showed a significant group effect, *F (2, 74) = 6.67, p < .05.* Post hoc analyses (Tukey post hoc criterion for significance) indicated that the digit span backward total score was significantly higher in the control group (*M = .14, SD = .87*) than the TBI group (*M= -.14, SD = .94*) and the AD group

(*M = -.67, SD = .63*) suggesting that the control group had a better working memory than the two other groups. No difference was shown between both clinical groups.

TMT part A total completion time (sec.)

An analysis of variance conducted on TMT-A completion time scaled-scores showed a significant group effect, F (2,74) = 12.81, $p < .05$. Similarly to the TMT part B, Tukey post hoc analysis highlighted that the average total completion time was significantly shorter in the control group (*M = .20, SD = .92*) than in the two other groups (TBI and AD) (AD: *M= -76, SD = .65*; TBI: *M = -.73, SD = .70*). However, TBI and AD group did not differ among themselves. These findings suggest that both clinical groups were significantly slower than the control group.

GAI total score

Self-reported symptoms of anxiety measured with the GAI have been shown to be different among groups. In fact, an analysis of variance showed a significant group effect, F (2, 73) = 12.44, $p < .05$. As demonstrated by post hoc analyses, the total score obtained by the TBI group (*M = 9.65, SD = 5.48*) was significantly higher than for the other two other groups (AD and control) (AD: *M= 5.03, SD = 4.26*; Control: *M = 2.88, SD = 4.58*). Both latter groups did not differ among themselves. This finding suggests that the TBI group reports more anxiety symptoms than the control and AD groups. However, when qualitatively analyzed with the ranges provided by the test (Pachana et al., 2007), the total score obtained by the TBI group did not meet the clinical threshold.

GDS total score

The GDS self-reported questionnaire allows us to access mood symptoms. Indeed, we found a significant main effect of group, H (2) = 23.09, $p < .05$, on main scores. Pairwise comparisons indicated that total scores of the TBI (*M= 12.30, SD= 8.80*) group was significantly higher than both other groups (control (*M= 3.48, SD= 4.55*) and AD (*M= 3.46, SD= 2.95*)) (H (2) = 27.44, $p < .05$; H (2) = -24.23, $p < .05$, respectively), the latter of which did not differ among themselves, H (2) = 3.20, p = 595. When qualitatively analyzed with the ranges provided by the test (Yesavage et al., 1983), the TBI group meet the clinical threshold.

Insert Table 2

Prediction of the neuropsychological performances in the TBI and AD groups

Prediction of the TBI group

To explore if age, level of education, GCS score and the post-accident delay were associated with neuropsychological outcomes in the TBI group, multiple regression analyses were conducted, and results can be found in Table 3. As shown in table 3, the model predicted the verbal memory score (R^2= .49, F (4, 23) = 4.51, p < .01). More specifically, the model (i.e. age, level of education, GCS score, number of day since the accident) explains 49% of the variance of the verbal memory performance. The level of education was the only independent variable significantly associated with the verbal memory score (b = .318, t (18) = 3.49, p < .006), suggesting that the higher the level of education, the better a TBI patient will perform in verbal memory task.

Also, the model predicted the working memory performance (R^2= .55, F (4, 22) = 5.50, p < .01). More specifically, together (age, level of education, GCS score, number of day since the accident) explains 55% of the variance of the working memory score. The level of education (b = .18, t (18) = 3.33, p < .006) as well as the post-accident delay (b = .004, t (18) = 2.92, p < .006) were the only independent variables significantly associated with the working memory score. A higher level of education and a higher number of days before cognitive testing after the accident predicted a higher working memory score.

Insert table 3

Since a higher score of psychological symptoms were found in the TBI group some regression were conducted to see how those symptoms predicted neuropsychological outcomes. To construct the multiple regression models and select the variables to include in the exploratory model, correlation analyses were first run across all cognitive outcomes and psychological outcomes (i.e. GDS total score and GAI total score). Only variables correlated bivariate with GDS and GAI total scores to $p < 0.01$ were included in the model. Thus, BNT score and the trail making A test score were the two only variables included in the models. First, the model (i.e. GDS total score and GAI total score) predicted the BNT score (R^2= .39, F (4, 22) = 6.49 p < .01). More specifically, together (GDS score and GAI score) explains 39% of the variance of the BNT performance. However, separately independent variables were not significantly associated with the

BNT score (GDS score: b = -.064, t (18) = -1.01, p = .326; GAI score : b -.192, t (18) = -1.90, p = 0.07). So, lower were both GDS total score and GAI total score, better was the performance in naming ability. Neither GDS score nor GAI score predicted the trail making test part A (R^2= .33, F (4, 22) = 4.88 p < .02).

AD group prediction

To determine if age and level of education were associated with cognitive outcomes in the AD group, multiple regression analyses were conducted, and results are presented in Table 4. The model doesn't explain a significant proportion of variance across all neuropsychological scores. As shown in Table 4, neither age nor education predicted any cognitive or psychological variables in AD patients.

Insert table 4

Influence of lesion location on neuropsychological profiles

To determine if the location of the lesion influenced neuropsychological measures, independent t-tests were run for all cognitive measures for the TBI group only, between lesion-positive patients' vs lesion-negative counterparts. Results are presented in *Mean* and *S.D.* in brackets. Group comparisons for neuropsychological outcomes are presented in Table 5. On average, and after correction for multiple comparisons, lesion-positive patients (frontal, parietal, temporal or occipital) were found to not significantly differ from their lesion-negative counterparts, thus indicating that CT-evidence of brain damage is not a reliable predictor of post-injury cognitive functioning or maybe the lesions were probably small in a group of TBI with a very tight range of GCS scores.

Insert table 5

Discussion

The purpose of this study was to first highlight cognitive profiles of advanced-age TBI patients and compare them to individuals with AD and to healthy age-matched controls. To our knowledge, this is the first study to attempt to compare cognitive performance of AD patients, TBI

patients and healthy age-matched controls in a prospective study. Moreover, we aimed to explore which variables were associated with cognitive and psychological outcomes of both TBI and AD groups.

Neuropsychological differences between groups

Verbal and visual memory

Interestingly, our findings show that older adults with AD had significantly lower performances and more difficulties than the TBI and control groups on tests of memory in visual modality (immediate recall, delayed recall and recognition conditions) and in verbal modality (i.e. immediate recall, delayed recall and recognition). These finding are consistent with those of Breed et al. (2008), Bigler, Rosa, Schultz, Hall, et Harris (1989) and Brooker (1997) who found reduced memory functioning in individuals with AD when compared with individuals with TBI. In fact, individuals with TBI resembled their uninjured peers; they were able to retain new information over time, whereas inability to retain new information characterizes individuals with AD. Again, this memory profiles are consistent with what has been reported by Breed et al. (2008) and Bigler et al. (1989). Nestor, Fryer, et Hodges (2006) hypothesized that impaired episodic memory in AD results from the dysfunction of an integrated network that includes the medial temporal lobe, mamillary bodies, dorsomesial thalamus, posterior cingulate, and the connecting white matter tracts. Associations were found between episodic memory and elements of the limbic–diencephalic network across the spectrum of healthy aging, MCI and AD. For example, impaired verbal episodic memory has been associated with reduced hippocampal volume in AD patients, measured using structural magnetic resonance imaging (MRI) (Choo et al., 2010; Leube et al., 2008; Sexton et al., 2010). The hippocampus is already considerably damaged at the time AD clinical symptoms first appear (Schuff et al., 2009) and plays a central role in memory consolidation (Zhao et al., 2014). The greater memory capacity in the TBI group makes them more receptive to many effective cognitive rehabilitation tools. Because of their ability to retain information, older adults with TBI are likely to learn and understand techniques that are taught, retain information, and be able to apply strategies.

Naming, processing speed, immediate memory, working memory and executive functioning

Consistent with our hypothesis, the 3 groups had different neuropsychological profiles. More specifically, AD and TBI groups did not differ between each other but both showed reduced performance when compared to controls in verbal ability (naming), processing speed, executive function, and working memory. The immediate memory was comparable between the three groups.

Interestingly, naming, processing speed, short-term memory and executive functioning are all frontal lobe functions. In fact, the frontal lobes are no longer considered as a single functional entity and most researchers accept that the frontal lobes have three major divisions: precentral, premotor and prefrontal regions (Lezak et al., 2012). Lesions here result in impairments for several neuropsychological functions such as working memory, set shifting, processing speed and naming. As a matter of fact, many neurological disorders involve the frontal lobes either directly or through frontal-subcortical connexions (Miller et Cummings, 2017). Unsurprisingly, TBIs (Rabinowitz et Levin, 2014a) and AD (Ossenkoppele et al., 2015) are examples of diseases in which the frontal cortex is affected at some point in the course of the illness. AD is characterized by inexorably progressive degenerative nerve cell changes that originate in the entorhinal cortex and hippocampus (temporal lobes) and progress to the prefrontal areas (Lezak et al., 2012). As for TBI, the brain undergoes rapid acceleration-deceleration forces which involves a biomechanical force (i.e translational and rotational acceleration) as well as coup contre-coup damage to the frontal and temporal regions (Rabinowitz et Levin, 2014a). This may explain why the clinical groups in this study did differ from the control group as these diseases tend to disturb the integrity of these areas, causing cognitive difficulties. Hence, within the context of the current study, it is not surprising that performance in some cognitive functions was very similar in TBI and AD. These results are consistent in part with those of Bashore et Ridderinkhof (2002), who found that processing speed is diminished in individuals with TBI and with AD. Impairment in naming in both groups is also mentioned in the study of Capitani et al. (2009). Indeed, in AD there is a general deterioration in the quality and the quantity of speech as semantic knowledge declines and impairment in confrontational naming appears early in the disease process (Delazer, Semenza, Reiner, Hofer, et Benke, 2003; Lezak et al., 2012). Language impairments are also seen in TBI and have been observed in older adults with both mild and moderate TBI, although individuals with TBI benefit from cueing on language tasks in contrast to AD patients who do not (Goldstein et Levin, 2001). It is thus possible that the TBI group may have had better performance in naming if cuing had been

given during the task. In addition, Breed et al. (2008) found similarities between the TBI and the AD groups for working memory and executive functioning.

Self-reported anxiety and depression

Regarding the emotional state, we found that the TBI group had greater psychological distress (anxiety and depression) than both other groups. However, the clinical range with the ranges provided by the test (Pachana et al., 2007), did not reach the clinical threshold for anxiety symptoms and only showed mild-to-moderate depression symptoms. These finding are consistent with those of Dams-O'Connor, Gibbons, et al. (2013) who found more psychological distress in individuals with dementia who reported a history of TBI. In fact, mood and anxiety disorders seem to be a frequent psychiatric complication among patients who sustain a TBI (Bowen, Chamberlain, Tennant, Neumann, et Conner, 1999; Jorge et al., 2004a; Silver, Kramer, Greenwald, et Weissman, 2001). The neuropathological changes produced by the brain injury may lead to deactivation of lateral and dorsal prefrontal cortices and increased activation of ventral limbic and paralimbic structures including the amygdala (Jorge et al., 2004a), which may explain why patients with TBI report a greater number of mood and anxiety symptoms. The analyses of this study also demonstrated that emotional state was associated with the BNT total score, suggesting that lower psychological distress predicted better naming performance. Unsurprisingly, Beaudreau and O'Hara (2009) suggested that co-existing anxiety and depressive symptoms was associated with deficit in naming and verbal fluency in the older adult's population. Some authors proposed that preoccupation (internal and external threats) coupled with age-related cognitive change could lead to reduction of available attention resources to performed tasks (Eysenck, Derakshann, Santo and Clavo, 2007). In contrast, the AD group did not report significant emotional symptoms, which may be due to the phase of the disease. It is possible that individuals with AD may be less likely to recognize and identify those feelings and responses adequately on the self-reported questionnaire. Nevertheless, psychological distress in patients with TBI and AD need to be addressed in the evaluation and the treatment as it can interfere with outcome.

Prediction of the neuropsychological performance in the TBI and AD groups

The second aim of the study was to determine if age and education level were associated with neuropsychological outcomes in both clinical groups. We thus examined these demographic

characteristics as predictive variables. Our hypothesis was partially confirmed for the TBI group but not confirmed for the AD group.

TBI population

The present findings suggest that education level seems to affect performance differently across cognitive domains. Indeed, more educated participants were found to perform better in verbal and working memory tasks. No other link was established between education and other cognitive domains. The results are thus partially in line with the 'Cognitive reserve theory' according to which a greater level of education (a greater cognitive reserve) has a protective effect on overall cognitive performance (Stern, 2009). This theory has been supported by many studies reporting that participants with high cognitive reserve displayed better cognitive performances (Opdebeeck, Martyr, et Clare, 2016; Ritchie, Bates, et Deary, 2015; Roldan-Tapia, Garcia, Canovas, et Leon, 2012). However, in line with the current study (although in healthy older adults), Lavrencic, Churches, et Keage (2018) and Ritchie, Bates, Der, Starr, et Deary (2013) found that benefits afforded by high cognitive reserve were not generalized through all cognitive spheres. Indeed, Lavrencic et al. (2018) found that the level of education was associated with better attention, executive functions, verbal and working memory, and orientation. In contrast, it was not significantly related to emotional perception, processing speed, or motor performance. While previous work has studied the link between cognitive reserve and overall cognitive performance, to our knowledge no other study has examined the influence of cognitive reserve on individual cognitive spheres in aged patients with TBI. Interestingly, if cognitive reserve is associated with specific cognitive domains, it could entail that these domains are potentially more malleable to lifetime experiences and could be targeted in interventions.

Age was not a significant predictor of cognitive outcomes in the present study, which partially contrasts with previous studies that have established that older adults with TBI have on average higher mortality, slower rates of functional and cognitive recovery compared to their younger counterparts (Senathi-Raja et al., 2010; Spitz et al., 2012; Thompson et al., 2006). In fact, a meta-analysis examined the effect of age on cognitive function, overall, the mean effects were relatively small but significant, indicating that younger people have slightly better post-TBI outcomes (Mathias et Wheaton, 2015). However, this same meta-analysis argued that age-related

changes in cognition are commonly observed in healthy adults, which may partially explain their findings. In the present study, the use of scaled scores allows us to control age-related deficits in cognition, which could explain the lack of association between age and cognition. Also, all samples were older people and the majority of the sample sustained mild TBI which are likely to cause relatively subtle deficits and small variability, making it harder to detect age-related differences in outcomes. It highlights the need for additional research that controls for normal age-related changes when examining the impact of age on post-TBI outcomes. Literature also proved that a substantial number of older adults with TBI may recover well including some with severe TBI (Bhullar, Roberts, Brown, et Lipei, 2010; Flaada et al., 2007; Kristman, Brison, Bedard, Reguly, et Chisholm, 2016). So, it is possible that the majority of our sample have recovered relatively well cognitively.

Like age, neither the GSC score nor the location of the lesion were associated with the neuropsychological measures. The GCS, although the most widely used clinical assessment to determine TBI severity at the time of initial presentation, may lack the nuance required to accurately assign TBI severity and adequately captured the patient's real condition (Gardner et al., 2017). Indeed, older adults with pre-existing dementia may have an abnormal GCS at baseline (Bloch, 2016), others may have comorbid medical conditions that may complicate diagnosis (Papa, Mendes, et Braga, 2012). Furthermore, TBI evolution may not be adequately captured by the initial GCS score (Kehoe, Rennie, et Smith, 2015). Some authors even suggested that GCS score alone, without considering other indices may underestimate injury severity in older adults (Goldstein et Levin, 2001) and that classification criteria may need revision since injured elders with a field GCS of 14 would have worse clinical outcomes than nonelderly adults with a field GCS of 13 (Caterino, Raubenolt, et Cudnik, 2011). For example, studies have demonstrated that older adults are at risk for delayed complications and as a result, the presence of focal brain lesions may be a stronger indication of severity than the initial GCS score (Goldstein et Levin, 2001). It is safe to say that the GCS may be inappropriate to capture TBI severity in elderly adults, therefore making it difficult to find a relationship between this traditional injury severity index and cognitive functioning. Furthermore, the majority of the sample have a GCS score between 14 and 15 (*M= 14.58, SD = 0.77*), showing a lack of variability in the score analyzed, making it harder to detect related differences in outcomes.

Like the GCS score, head CT is a diagnostic tool wildly used in acute evaluation, management, and outcome prediction for patients across the age spectrum (Gardner et al., 2018). Conventional CT is more available and cost-effective, requires shorter imaging time and is easier to perform on patients who are on ventilator support, in traction, or agitated. However, CT is limited in its ability in detecting discrete abnormalities like axonal injury, small areas of contusion, subtle neuronal damage and deeper brain structure injuries (brainstem, basal ganglia, and thalami) (Lee et Newberg, 2005). Studies have shown that CT missed approximately 10–20% of abnormalities seen on MRI (Doezema, King, Tandberg, Espinosa, et Orrison, 1991; Mittl et al., 1994). In the present study, CT scans may have missed injuries and decreased the likeliness to detect related differences in outcomes. Furthermore, the presence of microlesions were not taken into account in this study as well as diffuse axonal injury (Hammoud et Wasserman, 2002; Mittl et al., 1994). It is known that these types of cerebral damages correlate with poorer outcomes (Levin et al., 1989). This is a limitation of our study. The use of MRI could be useful in detecting damages in older patients since it is generally more sensitive than CT scan findings (Lee et Newberg, 2005). However and more importantly, there is an urgent need for objective biomarkers to aid in the diagnosis, management decisions, and recovery monitoring of older adults with TBI, particularly those with pre-existing medical or neurological conditions.

Greater number of days since accident also predict a better working memory score, suggesting that TBI patients who were assessed later post-accident had better performance. In fact, working memory seems to improve with time. The TBI patients of our cohort has sustained a mild TBI and previous studies have shown that most individuals recover following an mTBI over the course of weeks to several months after the trauma. However, 10–15% of patients will continue to experience atypical and persisting symptoms (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, et Pepin, 2004; Cassidy et al., 2014; Hibbard et al., 2004). One of the most common post-TBI reported symptoms are cognitive impairments (Chamelian et Feinstein, 2006; K. R. Marshall et al., 2012). When study results are sorted into neuropsychological domains, deficits over time seem to differ within cognitive areas (Frencham, Fox, et Maybery, 2005; Kwok, Lee, Leung, et Poon, 2008; Schretlen et Shapiro, 2003). For example, Kwok et al. (2008) indicated that patients performed significantly more poorly in information processing, divided attention, sustained

attention, verbal recognition and verbal fluency immediately post-injury. While information processing and divided attention in mild TBI patients improved after one month and returned to normal after three months post-injury, their sustained attention remained significantly poorer over the 3-month period. Similar to our study, digit span total scores, which are used to evaluate working memory, improved after 1 month and returned to normal 3 months post-injury. It may be possible that working memory is more sensitive to recovery with time than other cognitive functions. In fact, working memory impairments in TBI seems to be associated with alterations in functional cerebral activity. However, studies have shown recovery or compensatory cerebral activity mechanisms during the short post-injury period (Chen et al., 2012). This phenomenon explains why working memory improves with time and consequently why TBI patients who were assessed later post-accident had better performance.

AD population

Surprisingly, none of the demographic measures predicted neuropsychological outcomes in the AD group. Advanced age is known to influence cognitive functions. In fact higher age is a risk factor for cognitive deficits (Edwards et al., 2002; Fried et al., 2000; Salthouse, 2012). However, effects of age could not be replicated in the current study given use of scaled score. The lack of association between education and cognitive functioning is inconsistent with the findings of several authors (Stern, 2002, 2012). In contrast to the TBI group, the standard deviation from the level of education was much smaller, making it harder to detect related differences in outcomes. All stated inconsistencies could be explained by the lack of variability in the scores analyzed and the small simple size. The majority of the sample were university level, which makes it possible that all individuals had a similar cognitive reserve and therefore a similar cognitive deficit profile.

Limitations

A number of methodological limitations must be considered when interpreting the current results. First, neuropsychological results are limited by the modest sample size and the lack of variability in the sample. Recruitment of TBI elderly patients and AD patients is challenging. Despite all the help from professionals, 50% of the TBI group and 21% of the AD group screened were not eligible or un reachable or refused to participate. Of note, this study is one of the first to document neuropsychological profiles in these two clinical populations (TBI and AD) using an

objective TBI and AD medical criteria diagnosis. Second, we acknowledge the limitations of the GCS use in reporting TBI severity. Although frequently used, the GCS score alone may under-estimate brain injury severity for individuals aged 60 years or more (Rothweiler et al., 1998). Nevertheless, not many severity measures have been validated with elderly persons (Gardner et al., 2018). Third, we did not assess multiple lesions, diffuse axonal injury and brain activation patterns, which had previously been identified as a predictor of outcomes (Hammoud et Wasserman, 2002; Levin et al., 1989; Mittl et al., 1994). Fourth, composite scores were not used to measure each function, which is known to have greater consistency, reliability and validity of the cognitive concept measured (Alwin, 2015). Despite these limitations, this study brings a significant contribution by documenting neuropsychological profiles of TBI and AD diagnoses and their predictors.

Conclusions

Both AD and TBI groups were slower, had greater naming, executive and working memory impairments than healthy elderly adults. Within the clinical groups, individuals with AD had greater memory problems while individuals with TBI had more anxious and depressive symptoms. Effects of age and education were not conclusive in this clinical population. The present findings are helpful to clinicians confronted with cognitive impairments in elderly individuals with TBI. This study better delineates the cause of the cognitive deficits related to the TBI versus AD and assists clinicians in medical decisions for acute or long-term services.

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Table 1

Participants characteristics

	TBI *M* (SD)	AD *M* (SD)	Control *M* (SD)	F/x^2	*P*	n^2 /*V*
N	24	29	24			
Demographic characteristics						
Age	69.42 (7.19)	76.14 (7.56)	72.75 (5.61)	6.27	**.003***	.15
Sex (female), *n* (%)	16 (66.67)	17 (58.62)	19 (79.17)	3.04	.22	.28
Years of education	14.33 (2.67)	14.69 (1.93)	14.50 (2.28)	.16	.85	.00
Injury characteristics						
Causes of trauma, *n* (%)						
Car accident	5 (20.80)	-	-			
Fall	14 (58.33)	-	-			
Other non-intentional incidents	5 (20.80)	-	-			
GSC score	14.58 (0.77)	-	-			
CT Scan findings, *n* (%)		-	-			
Positive CT scan	21 (87.00)	-	-			
Frontal injury	12 (57.14)	-	-			
Temporal injury	11 (52.38)	-	-			
Parietal injury	9 (42.86)	-	-			
Occipital injury	10 (47.61)	-	-			
Normal CT scan	3 (13.00)	-	-			
Time since injury (days)	164.95 (94.73)	-	-			

Note. GCS = Glasgow Coma Scale; CT = Computed tomography.
* $p < .05$.

Table 2

Comparisons of cognitive functions and psychological status across the three groups

	AD *M* (SD)	TBI *M* (SD)	Control *M* (SD)	*F/H*	*p*	n^2	*Post-hoc*
RAVLT							
Immediate free recall	-3.04 (1.3)	.14(1.9)	1.14 (1.66)	51.56	.000*	.59	AD < TBI = C
Delayed free recall	-2.70 (1.15)	-.50(1.46)	.86(1.50)	45.43	.000*	.56	AD < TBI < C
Recognition recall	-1.43(1.66)	.58(.80)	.38(.87)	29.71†	.000*	.37	AD < TBI = C
ROCF							
Immediate free recall	-2.37 (1.59)	.56 (1.16)	.35 (1.28)	37.44	.000*	.51	AD < TBI = C
Delayed free recall	-3.03 (1.82)	-.02(1.61)	0.06(1.46)	30.08	.000*	.46	AD < TBI = C
Recognition recall	-2.24 (1.57)	-.15(1.62)	.081 (1.44)	17.93	.000*	.33	AD < TBI = C
BNT							
Correct responses	-.79(1.39)	-1.38 (2.34)	.48(.65)	16.13†	.000*	.20	AD = TBI < C
TMT part B							
Total completion time (sec)	-1.24 (.85)	-1.20 (1.33)	-.19(1.36)	6.27	.003*	.15	AD = TBI < C
Immediate memory							
Total score of the digit span forward	-.58 (.94)	-.31 (.70)	-.17(.87)	1.62	.205	.72	AD = TBI = C
Working memory							
Total score of the digit span backward	-.67 (.63)	-.08 (.99)	.14 (.88)	6.57	.002*	.70	AD = TBI < C
TMT part A							
Total completion time (sec)	-.76 (.56)	-.73 (.70)	.20 (.92)	12.81	.000*	.26	AD = TBI < C
GAI							
Total score	5.03(4.26)	9.65(5.48)	2.88 (4.58)	12.44	.000*	.25	TBI < AD = C
GDS							
Total score	3.46(2.95)	12.30(8.80)	3.48(4.55)	23.09†	.000*	.29	TBI < AD = C

Note. RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure Test; BNT = Boston naming Test; TMT = Trail making Test; GAI = Geriatric Anxiety Inventory; GDS = Geriatric Depression Scale; C = Control. .

† = non-parametric tests were carried out due to non-normal distribution of sample (Kruskal-Wallis tests)

* $p < .05$.

Table 3

Regression analyses predicting neuropsychological outcomes in TBI patients

	Criterion			
Model	R^2	*Adjusted* R^2	ΔR^2	F/β
RAVLT	.49	3.8	.49	**4.51***
Age at the time of the injury				-.08
Education				**.318****
GCS score				.07
Number of days since the accident				-.00
ROCF	.26	.11	.26	1.70
Age at the time of the injury				.02
Education				.25
GCS score				-.43
Number of days since the accident				.00
BNT	.37	.23	.37	2.8
Age at the time of the injury				-.01
Education				.25
GCS score				1.67
Number of day since the accident				-.00
TMT part B	.19	.02	.19	1,10
Age at the time of the injury				.02
Education				-.81
GCS score				.11
Number of day since the accident				.01
Digit span	.55	.45	.55	**5.50****
Age at the time of the injury				-.03
Education				**.18****
GCS score				.28
Number of day since the accident				**.00****
TMT part A	.11	-.08	.11	.60
Age at the time of the injury				.01
Education				.00
GCS score				.29
Number of day since the accident				.00
GAI	.26	.10	.26	1,59
Age at the time of the injury				-.24
Education				-.47
GCS score				-2.70
Number of day since the accident				-.01

GDS	.36	.22	.36	2.57
Age at the time of the injury				-.23
Education				-.77
GCS score				-6.37
Number of day since the accident				-.02

Note. RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure Test; BNT = Boston naming Test; TMT = Trail making Test; GAI = Geriatric Anxiety Inventory; GDS = Geriatric Depression Scale.

* $p < .01$. ** $p < .006$.

Table 4

Regression analyses predicting cognitive and mood outcomes for the AD group

	Criterion			
Model	R^2	*Adjusted* R^2	ΔR^2	F/β
RAVLT	.03	-.04	.03	.46
Age at the time of the injury				.02
Education				-.09
ROCF	.02	-.06	.02	.25
Age at the time of the injury				.01
Education				.11
BNT	.15	.08	.15	2.21
Age at the time of the injury				-.07
Education				.213
TMT part B	.12	.06	.12	1,84
Age at the time of the injury				.01
Education				.15
Digit span	.01	-.08	.01	.07
Age at the time of the injury				.01
Education				.02
TMT part A	.13	.07	.13	1.97
Age at the time of the injury				.03
Education				.03
GAI	.01	-.07	.01	.06
Age at the time of the injury				-.03
Education				.14
GDS	.03	-.05	.03	.40
Age at the time of the injury				-.04
Education				-.19

Note. RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure Test; BNT = Boston naming Test; TMT = Trail making Test; GAI = Geriatric Anxiety Inventory; GDS = Geriatric Depression Scale.

Table 5

Comparisons of cognitive functions and psychological status across the different lesion sites in TBI patients

	Positive scan *M* (SD)	Normal scan *M* (SD)	*t*	*p*
Frontal lobe (*N*)	12	12		
RAVLT	-.84 (1.50)	-.15 (1.39)	1.16	.26
ROCF	-.16 (2.09)	.13 (1.00)	.43	.67
BNT	-1.36 (2.39)	-1.39 (2.39)	-.03	.98
TMT part B	-1.10 (1.80)	-1.29 (.67)	-.35	.73
Digit span	-.12 (.98)	-.47 (.69)	-1.01	.33
TMT part A	-.40 (.68)	-1.07 (.56)	-4.10	.02
GAI	8.09 (6.17)	11.08 (4.56)	1.33	.19
GDS	13.63 (12.10)	11.08 (4.29)	-.66	.52
Temporal lobe (*N*)	11	14		
RAVLT	-.15 (1.38)	-.74 (1.52)	-.97	.34
ROCF	-.14 (1.63)	.07 (1.65)	.31	.76
BNT	-1.54 (2.95)	-1.26 (1.90)	.260	.80
TMT part B	-1.56 (1.79)	-.94 (.87)	1.13	.27
Digit span	-.17 (.93)	-.41 (.76)	-.68	.50
TMT part A	-.78 (.75)	-.70 (.69)	.29	.78
GAI	10.00 (5.22)	9.43(5.83)	-.24	.81
GDS	12.11 (8.48)	12.43 (9.32)	.08	.94
Parietal lobe (*N*)	9	15		
RAVLT	-1.20 (1.43)	-.07 (1.35)	1.94	.07
ROCF	-.92 (1.95)	.53 (1.12)	2.34	.03
BNT	-1.06 (2.33)	-1.57 (2.40)	-.51	.62
TMT part B	-1.37 (2.01)	-1.09 (.76)	.49	.63
Digit span	-.33 (1.11)	-.29 (.70)	.12	.91
TMT part A	-.58 (.76)	-.83 (.67)	-.84	.41
GAI	8.75 (6.34)	10.13 (5.14)	.57	.58
GDS	10.50 (8.83)	13.27 (8.94)	.71	.47
Occipital lobe (N*)*	10	14		
RAVLT	-.74 (1.66)	-.32 (1.34)	.68	.51
ROCF	.27 (1.75)	-.22 (1.54)	-.72	.48
BNT	-1.51 (2.28)	-1.28 (2.46)	.23	.82
TMT part B	-1.09 (.41)	-1.27 (1.73)	-.33	,74
Digit span	-.50 (.69)	-.15 (.94)	.98	.34
TMT part A	-.93 (.63)	-.60 (.74)	1.14	.27
GAI	11.22 (5.07)	8.64 (5.68)	-1.11	.28
GDS	11.67 (6.91)	12.71 (10.06)	.27	.79

Note. RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure Test; BNT = Boston naming Test; TMT = Trail making Test; GAI = Geriatric Anxiety Inventory; GDS = Geriatric Depression Scale

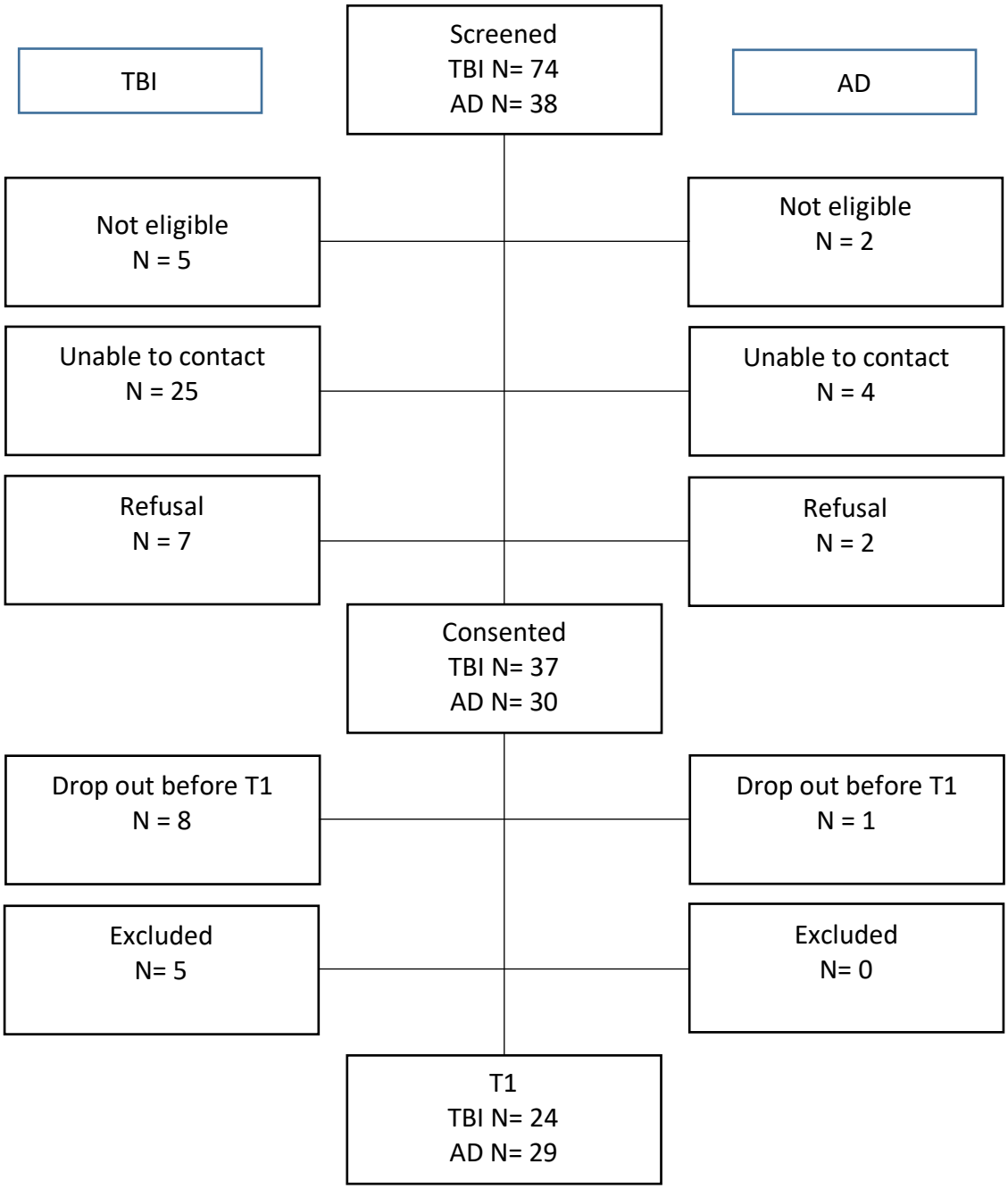

Figure 1. Recruitment flowchart for TBI and AD groups

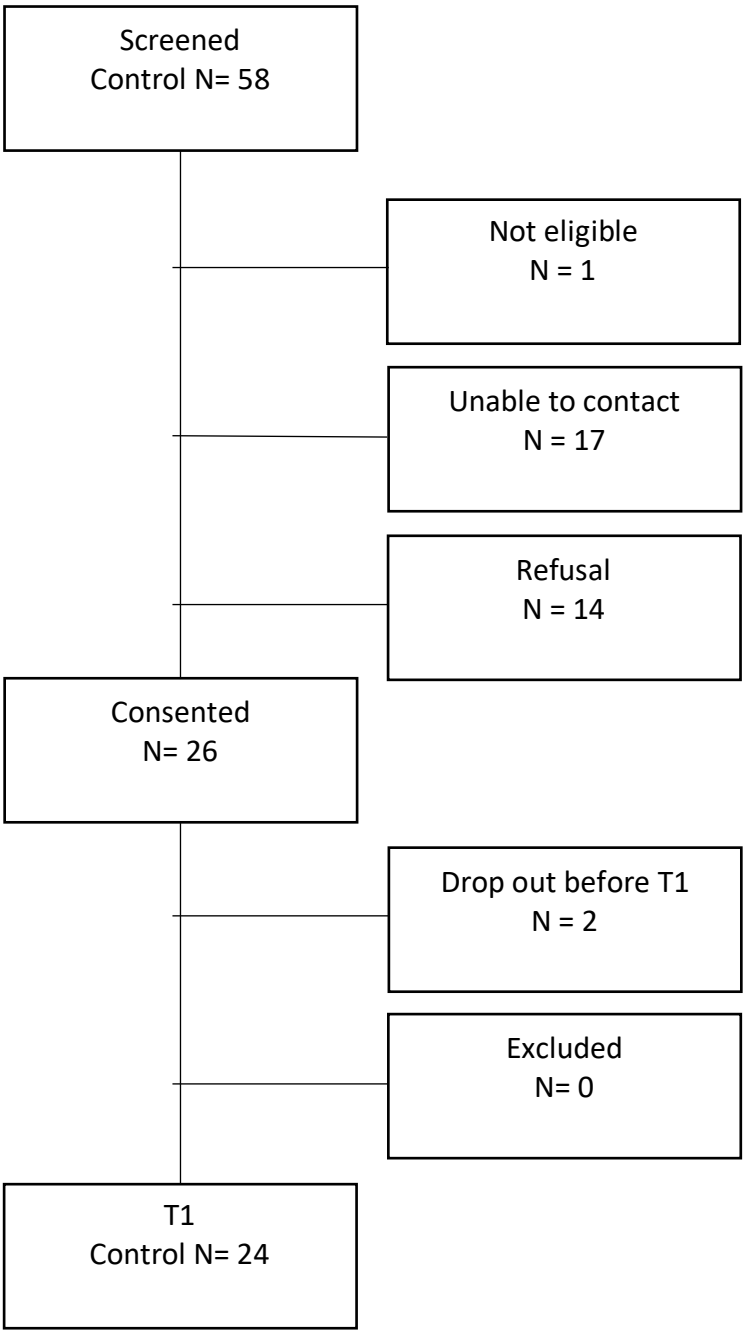

Figure 2. Recruitment flowchart for the control group

Discussion générale

1.0 Synthèse des objectifs et des résultats des articles de la thèse

Le vieillissement de la population accompagné par une forte prévalence de TCC (Yokobori et al., 2016) et de la maladie d'Alzheimer (MA) chez les personnes âgées (Pouryamout et al., 2012) oblige les cliniciens à se questionner sur les liens entre ces deux conditions, notamment au niveau du risque de développer une démence de type DTA suivant un TCC ainsi que sur les diagnostics différentiels neuropsychologiques spécifiques à ces deux conditions neurologiques. Cette thèse a été initialement élaborée à partir de questionnements cliniques très pragmatiques issus d'observations sur le terrain et des demandes formulées à l'endroit des neuropsychologues exerçant dans les milieux de traumatologie ou de réadaptation et ce, autant de la part des patients, des familles, des équipes de soins que des gestionnaires de programmes. Les deux grandes questions qui ont émergé étaient les suivantes : 1) Quels sont les patients TCC à risque de développer la DTA ? et 2) Existe-t-il des différences sur le plan des profils neuropsychologiques entre les patients TCC et les patients ayant une DTA ? Les réponses à ces deux questions auront pour conséquence une meilleure planification des soins et orientation des patients vers des services appropriés et ciblés en fonction de leurs besoins. Pour tenter de répondre à ces deux questions, une revue systématique de la littérature et un article empirique ont été réalisés. Dans les sections suivantes, les résultats de la thèse seront résumés et discutés en lien avec la littérature existante. Les principales limites des études seront exposées et les implications cliniques et les avenues de recherche futures seront, enfin, abordées.

2.0 Objectif et synthèse des résultats de l'étude 1

Le premier article de la thèse avait pour objectif d'identifier les facteurs de risques de développer la DTA suivant un TCC. Plus spécifiquement, ce premier article, basé sur une revue systématique de la littérature, visait à examiner les facteurs de risques liés à la sévérité du TCC. Une revue de littérature apparaissait comme la meilleure méthodologie pour extraire les données de plusieurs études antérieures et pour tenter de synthétiser et conclure sur les liens entre la sévérité du TCC et les risques de développer la DTA. En résumé, est-ce qu'un résultat à l'ÉCG plus faible (TCC plus sévère), la présence d'APT ou une plus longue durée de celle-ci, et/ou la perte de conscience post-accident et une plus longue période d'inconscience seraient associés à davantage

de risque de développer une DTA ? Basée sur les études antérieures, l'étude 1 de la présente thèse a tenté de répondre à ces questions.

Un nombre croissant d'études suggèrent que le TCC serait un facteur de risques de développer la DTA et ce, même suite aux formes les plus légères de TCC (Barnes et al., 2018; Fleminger et al., 2003; Guo et al., 2000; Lye et Shores, 2000; Mortimer et al., 1991; O'Meara et al., 1997; Plassman et al., 2000; Schofield et al., 1997). Néanmoins, des incohérences persistent encore quant à l'existence d'un tel lien et aux facteurs de risques de développer la DTA à la suite d'un TCC (Helmes et al., 2011; Mehta et al., 1999). Ces contradictions émanent sans doute des différences méthodologiques et limites perceptibles d'une étude à l'autre. Elles sont majoritairement basées sur des TCC auto-rapportés par les participants eux-mêmes, les dossiers médicaux sont rarement disponibles pour consultation, les variables démographiques des patients telles que l'âge ou le niveau d'éducation sont irrégulièrement rapportées, elles arrivent difficilement à contrôler les vulnérabilités prémorbides, le temps entre l'accident et l'évaluation varie énormément d'une étude à l'autre et la sévérité du TCC est variable d'une étude à l'autre. En plus, les critères diagnostiques tant pour le TCC que pour la DTA varient d'une étude à l'autre, rendant parfois difficile de comparer les études entre elles. Il convient de mentionner qu'une seule étude empirique pourrait difficilement pallier toutes ces limites, c'est pourquoi il est intéressant d'explorer une variable importante dans la littérature sur le TCC, soit la sévérité de la blessure en question. En ce sens, cette première étude de thèse avait pour objectif de synthétiser les résultats des recherches antérieures en utilisant une méthodologie de revue systématique afin d'identifier les facteurs de risques reliés à la sévérité du TCC qui pourraient augmenter la probabilité de développer la DTA en âge avancé.

2.1 La prévalence du lien entre TCC et DTA : un lien fragile

Concernant la prévalence ou le risque de développer la DTA à la suite d'un TCC, notre revue systématique a permis d'identifier un total de 10 études sur 18, soit 55% des études, qui ont démontré une relation significative entre la présence antérieure d'un TCC et le développement de la DTA. Donc, ce résultat amène à conclure que le lien entre ces deux conditions n'est pas aussi évident, ou sans équivoque, qu'on aurait pu le croire. En effet, seulement la moitié des études recensées arrive à cette conclusion. En somme, l'étude ne permet pas de répondre clairement à la

question posée sur le risque de développer une DTA à la suite d'un TCC. À ce jour, il semble n'y avoir aucun consensus sur cette question, de sorte qu'il paraît important de poursuivre la recherche dans ce sens. Il est donc recommandé aux cliniciens de demeurer prudents et nuancés avant de se prononcer sur cette question.

2.2 Problématiques comparatives liées à la définition et la sévérité du TCC et de la DTA

Parmi les études appuyant le lien entre le TCC et la DTA, la question pertinente à poser concerne l'impact de la sévérité du TCC sur le risque de développer une DTA. Encore ici, la revue systématique n'est pas concluante. En ce sens, aucune tendance significative portant sur la sévérité du TCC n'est ressortie de cette analyse : ni la sévérité mesurée par l'ÉCG ni la perte de conscience ni l'APT n'ont été identifiées comme facteurs pronostiques importants. Au total, 4 articles sur 18, soit 22.22% des articles recensés, ont démontré un lien entre la sévérité du TCC et le risque de développer une DTA.

Par ailleurs, la littérature supporte clairement l'hypothèse que la sévérité est un facteur déterminant dans la prédiction des conséquences fonctionnelles et de l'autonomie suivant un TCC tous âges confondus, un TCC plus sévère étant associé à un niveau fonctionnel moins élevé et une moins bonne autonomie (de Guise et al., 2006; Fleminger et al., 2003; McIntyre, Mehta, Janzen, et al., 2013; Ritchie et al., 2011; Utomo et al., 2009). L'étude 1 de la thèse ne nous permet toutefois pas de conclure sur les liens effectifs entre la sévérité du TCC et le risque de développer une DTA. Le problème majeur rencontré dans cette revue systématique était le manque de données précises, valides et standardisées à cet effet dans les articles récoltés. À titre de rappel, 66.67% des études incluaient des diagnostics de TCC auto-rapportés par les participants. De plus, 77.78% des études ont posé un diagnostic de TCC en se basant uniquement sur la présence ou non d'une perte de conscience, ou encore de la durée de celle-ci, alors que la perte de conscience n'est pas requise ou essentielle pour poser un diagnostic de TCC (Ministère de la Santé et des Services Sociaux, 2010; Marshall, Bayley, McCullagh, Velikonja, et Berrigan, 2012; Teasell et al., 2018). La présence d'une APT a été considérée dans seulement 16.67% des études et le résultat à l'ÉCG, dans 5.56% d'entre elles. L'étude de Luukinen et al. (2005) est certainement celle où la sévérité du TCC est la mieux documentée (résultat à l'ÉCG, l'ATP et durée de la perte de conscience), et conclut à l'augmentation du risque de développer la DTA suivant un TCC léger à modéré en âge avancé. Si

l'on se réfère principalement à cette étude, le résultat à l'ÉCG, la durée de l'APT et la durée de la perte de l'état de conscience semblent être ensemble de bons prédicteurs du risque de développer la DTA, mais des études futures seront essentielles pour confirmer ces résultats. En ce sens, on peut ainsi penser qu'une meilleure définition de la sévérité du TCC permettrait une prédiction plus fiable du risque de développer la DTA. Par ailleurs, l'étude de Lilley et al. (2016) suggère que le résultat à l'ÉCG ne serait pas le seul marqueur pronostique à considérer et qu'une certaine réserve devrait être émise à l'égard de ce critère. En effet, les auteurs Goldstein et Levin (2015) ont avancé que, chez la personne âgée plus spécifiquement, le résultat à l'ÉCG seul, sans tenir compte d'autres indices, pourrait conduire à sous-estimer la gravité des blessures et ne serait pas un bon indicateur de la sévérité du TCC. Les personnes âgées seraient plus vulnérables aux lésions intracrâniennes, moins symptomatiques pour l'ÉCG, mais entraînant des complications à retardement ou une réponse pathophysiologique différente que chez les individus plus jeunes (Goldstein et Levin, 2001). Les lésions intracrâniennes devraient donc être prises en compte comme mesures de sévérité du TCC et être incluses dans les modèles de prédiction du risque de développer une DTA suite à un TCC en âge avancé.

Enfin, en plus de la définition et de la sévérité du TCC qui ont été jugées problématiques dans la revue systématique, il apparaît essentiel de souligner les diverses définitions du concept prédit, soit la DTA. Certaines études ont utilisé les critères du NINCDS/ADRDA, d'autres ceux du Diagnostic and Statistical Manual of Mental Disorders (DSM), certains du ICD-9-CM et enfin d'autres se sont appuyées sur le Mini-Mental State Examination (MMSE). Ces différents critères diagnostiques rendent la comparaison entre les cas de DTA difficile : est-ce que le patient est réellement atteint de DTA et si oui, quelle est la sévérité de la démence.

2.3 Conclusions de l'étude 1

Les résultats de la première étude de revue systématique de cette thèse ne permettent donc pas de conclure qu'un TCC augmenterait le risque de développer la DTA. Toutefois, cette étude met de l'avant plusieurs obstacles méthodologiques fréquemment rencontrés par les chercheurs, ces limites ayant possiblement nui en partie à la possibilité d'identifier des facteurs de risques de développer une DTA à la suite d'un TCC. Ces obstacles seront ainsi invoqués dans la section

suivante afin d'émettre des recommandations pour les études futures qui se pencheront sur ce problème.

2.4 Recommandations théoriques et cliniques de l'étude 1

Les résultats de l'étude 1 mettent en évidence la complexité pour un clinicien de déterminer si le patient est à risque de développer la DTA suivant son TCC. L'établissement d'un modèle pronostique fiable devient donc nécessaire pour cette catégorie de patients, de plus en plus nombreux dans nos établissements de santé. À la lumière de la littérature exposée dans cette thèse, notamment en introduction et dans l'article 1, il serait important qu'un futur modèle pronostique de la DTA suivant un TCC puisse inclure des variables telles que : la sévérité du TCC prenant en compte l'ensemble des variables qui lui sont associées, l'âge au moment de la blessure, le niveau d'éducation et possiblement les comorbidités médicales. Dans la littérature portant sur le TCC, deux modèles pronostiques ont été à ce jour proposés. D'une part, il y a le modèle pronostique « *Corticosteroid Randomization After Significant Head injury* (CRASH-CT) » qui tente de prédire la mortalité 14 jours post-accident et les conséquences post-TCC six mois suivants l'accident. Ce modèle inclut âge, le résultat à l'ÉCG, la réactivité des pupilles lors de l'arrivée à l'urgence et les lésions extra et intracrâniennes visualisées à la tomodensitométrie cérébrale (Perel et al., 2008). Ce modèle est toutefois critiqué puisqu'il n'inclut pas les comorbidités et le fonctionnement pré-accidentel du patient. De plus, il semble surestimer les risques de mortalité et les conséquences cognitives (Roe, Skandsen, Manskow, Ader, et Anke, 2015). D'autre part, le modèle pronostique IMPACT tente de prédire la mortalité et les conséquences post-TCC six mois suivant l'accident (Roozenbeek et al., 2012; Steyerberg et al., 2008). Pour sa part, ce modèle plus exhaustif inclut l'âge, le résultat à l'ÉCG, la réactivité des pupilles à l'arrivée à l'urgence, la présence d'hypoxie et d'hypotension post-accident, la présence de lésions intracrâniennes visualisées à la tomodensitométrie cérébrale, le glucose et le taux d'hémoglobine. Les mêmes critiques sont apportées à ce modèle, soit qu'il n'inclut pas les comorbidités et le fonctionnement pré-accidentel. Contrairement au modèle précédent, celui-ci semble sous-estimer les risques de mortalité et les conséquences à plus long terme (Staples, Wang, Zaros, Jurkovich, et Rivara, 2016). En somme, il est recommandé de développer des modèles ou des algorithmes prenant également en compte les comorbidités médicales (conditions médicales et pharmacologiques) et le fonctionnement post-accident ainsi que d'autres caractéristiques du patient telles que son niveau d'éducation. D'ici

l'établissement d'un tel modèle, l'anamnèse devient particulièrement importante chez cette clientèle afin de brosser un portrait complet pré et post-accident et d'intégrer ces variables dans le jugement clinique pronostique.

Pour développer un modèle pronostique fonctionnel, il va de soi que les chercheurs devront utiliser des variables fiables et bien définies, notamment en se basant sur les critères diagnostiques reconnus du TCC (résultat à l'ÉCG, durée du LOC et durée de l'APT) et de la DTA, et favoriser des études prospectives et longitudinales. Tel que mentionné précédemment, le problème méthodologique le plus important des articles recensés dans l'étude 1 était le caractère auto-rapporté du TCC, et le manque d'informations quant au statut pré-accidentel de la personne. Il aurait ainsi été important de se questionner sur la validité des informations rapportées par les patients. De surcroît, la majorité de ces études n'interrogeait pas non plus le fonctionnement cognitif pré-accidentel de ces patients. Or, les études ne tenaient pas compte du fait que peut-être certains patients présentaient un déclin cognitif préexistant à l'accident (Gardner et al., 2018). De manière intéressante, certains membres de la communauté scientifique proposent une hypothèse de « causalité inverse » entre les deux pathologies, soit la démence et le TCC. Plus spécifiquement, l'individu âgé chuterait et subirait un TCC en raison d'une condition neurodégénérative sous-jacente prodromale plutôt que l'inverse. Par exemple, l'étude de Rugbjerg, Ritz, Korbo, Martinussen, et Olsen (2008) s'est penchée sur le lien entre le TCC et la maladie de Parkinson (MP). Les chercheurs rapportent une association significative entre la MP et le TCC seulement chez les patients âgés ayant reçu un diagnostic de MP entre un et trois mois suivant le TCC. Les auteurs proposent que la chute causant le TCC ait été possiblement provoquée par les premiers symptômes de la maladie découverte au moment de l'hospitalisation. La personne âgée qui présente des conditions médicales chroniques ou des effets secondaires d'une polypharmacologie serait plus vulnérable sur le plan fonctionnel (c-à-d. étant sujette à des problèmes de vision, des difficultés cognitives et des difficultés d'équilibre ou de démarche) et ainsi plus susceptible de chuter. Par conséquent, les risques de subir un TCC seraient considérablement plus élevés (Coronado et al., 2005; M. Faul et al., 2010; Shumway-Cook et al., 2009).

En somme, les études futures se doivent d'adopter des méthodologies prospectives longitudinales afin de suivre l'évolution des symptômes (c.-à.-d. de l'accident jusqu'à la mort de

l'individu). De plus, une telle méthodologie permettrait de mieux documenter les variables reliées au TCC (c.-à.-d. sévérité, CT scan, etc.) et à l'individu (c.-à.-d. âge, éducation, comorbidité, etc.) afin de bien identifier leurs impacts sur le risque de développer la DTA. Un modèle pronostique valide et fiable pourrait soutenir les cliniciens afin qu'ils puissent prévoir avec davantage de certitudes les risques encourus par leur patient TCC de développer la DTA au cours des années suivant l'événement traumatique.

3.0 Objectif et synthèse des résultats de l'étude 2

La seconde étude de cette thèse avait pour objectif d'offrir des outils aux neuropsychologues afin de les aider à poser un diagnostic différentiel entre ce qui relève du TCC et ce qui relève davantage de la DTA. Cet objectif est particulièrement pertinent, notamment en lien avec l'hypothèse de « causalité inverse » entre ces deux pathologies présentée précédemment. L'objectif de cette seconde étude n'était pas de confirmer cette hypothèse de « causalité inverse », mais de montrer que cette dernière s'avère utile dans la démarche réflexive de diagnostic différentiel à laquelle les cliniciens sont confrontés dans leur pratique. À la suite d'un TCC, est-ce que le patient présenterait une condition prodromale de la DTA pré-traumatique ? Est-ce que le tableau neurocognitif observé est davantage attribuable à un TCC ou des indices neuropsychologiques permettent de croire à la présence d'une DTA sous-jacente ? Les effets délétères des TCC sur le fonctionnement cognitif de la personne âgée commencent tout juste à être rapportés dans la littérature (An and Monette, 2018). La recherche demeure néanmoins limitée quant au partage de ce qui relève davantage d'une vulnérabilité prémorbide et ce qui fait partie des impacts secondaires typiques du TCC.

Plus spécifiquement, le second article de la thèse avait pour objectif de distinguer les profils neuropsychologiques du TCC (6 mois post-accident) et de la DTA, et de déterminer les variables susceptibles d'influencer ces profils. En ce sens, cette étude, basée sur la comparaison de profils entre trois groupes (TCCL, DTA stade 1, témoins sains), a permis de conclure que la mémoire et les symptômes anxio-dépressifs sont les meilleurs indicateurs pour départager les profils neuropsychologiques entre les deux conditions neurologiques. La mémoire épisodique était plus affectée chez les patients présentant une DTA que chez les patients TCCL ; en revanche, des affects anxio-dépressifs plus importants étaient rapportés par les patients TCCL que chez les patients DTA.

Les résultats de cette thèse appuient ainsi l'hypothèse que les profils neuropsychologiques des patients TCCL et DTA se distinguent sur certaines fonctions cognitives et symptômes psychologiques (Breed et al., 2008).

Par ailleurs, les résultats concernant les variables d'influence des profils cognitifs (c.-à.-d. l'âge, le niveau de scolarité, le résultat de sévérité à l'ÉCG, le délai de récupération, le site de la lésion cérébrale) chez chacun de ces deux groupes cliniques demeurent peu concluants. Chez le groupe TCCL, seul le niveau de scolarité s'est révélé être un prédicteur significatif de la mémoire verbale et de la mémoire de travail, cette dernière étant également influencée par le délai de récupération. En outre, l'âge d'apparition de la DTA et le niveau de scolarité ne se sont pas montrés de bons prédicteurs de la performance neuropsychologique chez les patients DTA. Les prochaines sections de la thèse seront consacrées, dans un premier temps, à présenter de manière plus détaillée les profils neuropsychologiques des patients TCCL en âge avancé, pour ensuite présenter celui des patients DTA. Une réflexion concernant le profil neuropsychologique des deux conditions présentées de manière simultanée sera exposée, avant de conclure sur les approches d'intervention à privilégier.

3.1 Profil neuropsychologique des patients TCC en âge avancé

La présente thèse ajoute aux données probantes, notamment présentées de manière détaillée dans l'étude 2, soutenant que les fonctions langagières expressives (c.-à.-d. manque du mot), les fonctions exécutives (c.-à.-d. flexibilité mentale) et la vitesse de traitement de l'information (Tracé A du TMT*)* sont majoritairement affectées suivant un TCC en âge avancé (An and Monette, 2018) et ce, en plus des symptômes d'anxiété et de dépression rapportés par ce groupe. Comme l'a montré notre deuxième étude, les résultats obtenus par les patients TCCL à l'examen de ces différentes tâches cognitives oscillent effectivement entre la zone limite et la moyenne faible, ce qui démontre que les gens âgés sont spécialement vulnérables au TCC, et particulièrement dans le cas présent, même suite à un TCC de niveau léger (résultat à l'ÉCG : moyenne de 14.5) (Ferrell et Tanev, 2002). Néanmoins, la mémoire de travail (empan de chiffres) de même que la mémoire à long terme verbale (RAVLT) et visuelle (ROCF) se situent quant à elles dans les normes. Ainsi, les patients TCCL âgés de l'étude 2 sont en mesure d'encoder, de consolider et de récupérer l'information verbale et visuelle au fil du temps (c.-à.-d. rappels immédiats, rappels différés et

reconnaissances), de même que de manipuler des informations sur une courte période de temps en conformité avec la norme des gens de leur âge. Au même titre que les personnes âgées saines, ils sont capables d'apprendre de nouvelles informations et de les mémoriser sur une longue période de temps.

De manière importante, mais aussi préoccupante, le profil neuropsychologique des patients âgés TCCL est aussi caractérisé par une détresse psychologique. En ce sens, les résultats du deuxième article abondent dans le sens de la littérature soutenant que l'anxiété et la dépression sont des complications fréquentes chez les patients âgés qui ont vécu un TCC (Albrecht et al., 2015; Goldstein, Levin, Goldman, Clark, et Altonen, 2001; Levin et Goldstein, 1995; Rapoport et al., 2006; Yi et Dams-O'Connor, 2013). Le TCC entraînerait une désactivation des cortex préfrontaux latéraux et dorsaux, ainsi qu'une activation accrue des structures limbiques et paralympiques ventrales, y compris l'amygdale (Jorge et al., 2004a). Ces changements cérébraux expliqueraient possiblement pourquoi les patients ayant eu un TCC rapportent des symptômes anxieux et dépressifs. De plus, une augmentation des symptômes de détresse psychologique est associée à une diminution des performances verbales (c-à-d. capacité de nommer une image). En ce sens, plusieurs auteurs rapportent en effet que la présence de symptômes psychologiques affecte les fonctions cognitives chez la clientèle âgée (Beaudreau et O'Hara, 2009; Eysenck et al., 2007.) et possiblement de même chez la clientèle âgée TCC. Il demeure ainsi essentiel d'adresser ces symptômes.

Les performances en mémoire épisodique était plus faibles chez les patients présentant une DTA que chez les patients TCCL ; en revanche, des affects anxio-dépressifs plus importants étaient rapportés par les patients TCCL que chez les patients DTA. En somme, et dans une optique de diagnostic différentiel, les symptômes anxieux et dépressifs, au même titre que les fonctions mnésiques, pourraient aider les neuropsychologues à poser un diagnostic différentiel plus précis. Il serait ainsi important pour ces derniers de s'assurer d'administrer des questionnaires à même de mesurer les symptômes anxieux et dépressifs, de même que de faire passer des épreuves de mémoires verbale et visuelle. Ces résultats viennent s'ajouter à ceux de Dams-O'Connor, Gibbons, et al. (2013), qui constatent aussi davantage de détresse psychologique chez les patients DTA ayant un historique de TCC que chez les patients DTA sans historique de TCC. Le clinicien doit néanmoins demeurer prudent puisque ces résultats sont basés sur des questionnaires auto-rapportés.

Certaines études mentionnent que ce type de mesure, lorsqu'utilisé auprès d'une clientèle ayant une démence, ne serait pas toujours optimal, c'est-à-dire ne serait pas le reflet de l'état émotif réel vécu par la personne (Harper, Kotik-Harper, et Kirby, 1990; Lichtenberg, Marcopulos, Steiner, et Tabscott, 1992). Or, il est possible que les symptômes psychologiques aient été sous-estimés chez les patients DTA. Plusieurs auteurs rapportent que les patients DTA ont de la difficulté à identifier leurs symptômes adéquatement, ce qui aurait pour effet de minimiser leurs résultats (Harper, Kotik-Harper, et Kirby, 1990; Lichtenberg, Marcopulos, Steiner, et Tabscott, 1992). Il est donc possible que la clientèle DTA présente des symptômes psychologiques (anxiété et symptômes dépressifs) et que les questionnaires utilisés dans cette étude ne soient pas suffisamment sensibles pour les détecter. Par ailleurs, 25% à 70% des patients DTA seraient sujets à vivre des symptômes dépressifs et/ou anxieux (Ferretti, McCurry, Logsdon, Gibbons, et Teri, 2001; Holtzer et al., 2005; Porter et al., 2003; Teri et al., 1999). À la lumière de ces résultats, il demeure essentiel de mener une anamnèse exhaustive en incluant la famille et les proches, et, même si les résultats de l'étude 2 sont pertinents pour le diagnostic différentiel, il importe aux cliniciens de demeurer prudents lors de l'utilisation de ces outils auprès de cette clientèle.

3.2 Profil neuropsychologique des patients DTA

Le profil neuropsychologique reconstitué par le deuxième article abonde en partie dans le même sens que la littérature déjà présente sur ce sujet, soit que l'ensemble des fonctions mnésiques évaluées seraient touchées (Joubert et al., 2007), à l'exception de la mémoire de travail. Les résultats se situent dans la zone déficitaire pour la mémoire à long terme épisodique verbale et visuelle. De plus, les résultats sont à la frontière de la zone limite et la moyenne faible pour la flexibilité mentale évaluée à l'aide du tracé B du *Trail Making test*. Le processus de dénomination (BNT) et la vitesse de traitement (Tracé A du *Trail Making Test*) se trouvent quant à eux dans la moyenne faible chez notre groupe de patient DTA.

Les mémoires épisodiques verbale et visuelle sont particulièrement touchées dans le profil neuropsychologique des patients DTA de l'étude 2, ce constat étant supporté par la littérature actuelle sur ce sujet (Becker, 1988; Goldstein et Levin, 2001; Salmon et Bondi, 2009). L'hypothèse de la perte de cellules neuronales dans les régions entorhinale et de l'hippocampe ainsi que dans

les régions préfrontales qui servent de support aux fonctions mnésiques à plus long terme (Lezak et al., 2012) est sans doute la plus pertinente pour expliquer les résultats obtenus dans cette thèse.

L'hypothèse de la perte cellulaire au niveau des régions préfrontales (Lezak et al., 2012) pourrait aussi être valable pour expliquer les difficultés obtenues par le groupe DTA de l'étude 2 lors de la tâche de flexibilité mentale. Bien que les fonctions exécutives ne permettent pas de distinguer les patients DTA des patients TCC dans notre étude, plusieurs auteurs ont documenté ces difficultés chez la clientèle DTA. Par exemple, Baudic et ses collègues (2006) ont mis en évidence des déficits de flexibilité mentale observés dans les tâches du *Stroop* (c.-à.-d. condition 4) et du Tracé B du *TMT* (Baudic et al., 2006) chez la DTA.

Contrairement à nos hypothèses, les patients DTA de notre étude n'ont pas montré de difficultés ni même de déficits sur le plan de l'expression orale, plus spécifiquement de la dénomination, en comparaison avec le groupe TCCL. Des études antérieures ont démontré que le manque du mot demeure une difficulté perceptible indicative des débuts de la DTA qui serait causée par la combinaison des difficultés d'accès lexical et de mémoire sémantique (Joubert et al., 2007). En outre, ces patients pourraient aussi présenter une diminution de la quantité du discours, mais avec une organisation du langage, soit la syntaxe et la structure lexicale, relativement intacte dans le début de la maladie (Joubert et al., 2007). Il est possible que le haut niveau de scolarité du groupe de patients DTA ait pu compenser pour ce déficit en début de DTA. De fait, des études ont mis en relation le niveau de scolarité et l'accès au lexique chez les patients concernés : les personnes ayant un plus haut niveau de scolarité réaliseraient effectivement des performances plus élevées dans les tâches de dénomination (Albert, Heller, et Milberg, 1988). Il est enfin possible que la taille modeste de l'échantillon vienne limiter les observations.

Concernant la mémoire de travail, la littérature demeure à ce jour contradictoire. Certaines études rapportent que ce ne sont pas tous les patients atteints de DTA (c.-à.-d. léger à modéré) qui ont des difficultés à retenir et à manipuler une quantité d'informations sur une courte période de temps (c.-à.-d. mémoire de travail) (Belleville, Peretz, et Malenfant, 1996; Mortamais et al., 2017). À l'instar des résultats de notre étude 2, plusieurs études ont noté que certains patients arriveraient à mémoriser une séquence de chiffres et à se la rappeler à l'envers (c.-à.-d. sous-test séquence de

chiffres en ordre inverse du WAIS), tout comme la moyenne des gens de leur âge (Breed et al., 2008; Mortamais et al., 2017). Il est également possible que la performance en mémoire de travail diffère d'un individu à l'autre. En ce sens, on remarque une grande hétérogénéité dans l'évolution des difficultés cognitives, et ce particulièrement sur le plan de la mémoire de travail (Joubert et al., 2007), ce qui expliquerait possiblement l'absence de consensus entre les études. En somme, de futures études sur le sujet permettraient assurément d'y voir plus clair.

3.3 Profil neuropsychologique des patients TCC-DTA

Au cours des prochaines années, et comme nous l'avons mentionné à plusieurs reprises dans cette thèse, les neuropsychologues seront de plus en plus fréquemment appelés à intervenir et à poser des diagnostics différentiels auprès de patients TCC en âge avancé, qui présenteront un déclin cognitif de type DTA pré-TCC. Réaliser une étude qui tente de déterminer le profil typique neuropsychologique du TCC et le profil DTA auprès de deux clientèles cliniques distinctes (TCC et DTA), telle que s'y est employée l'étude 2 de cette thèse, est un moyen pour identifier des différences et des similarités entre les deux conditions neurologiques. Toutefois, force est d'admettre que cette thèse ne répond pas directement à la question de ce que pourrait être le profil neuropsychologique des patients qui présenteraient les deux diagnostics puisqu'aucun groupe de patients TCC atteints également de DTA n'a été évalué. Au cours du travail mené dans le cadre de cette thèse, la difficulté à recruter ces clientèles particulièrement vulnérables a été un obstacle important. Il avait été initialement prévu, à partir d'une base de données existante et issue de la RAMQ, de réunir un groupe de patients TCC hospitalisés en centre tertiaire de traumatologie et qui avaient développé, plusieurs années plus tard, une DTA. Quelques patients ont été contactés, mais plusieurs d'entre eux avaient été admis en centre de soins de longue durée, étaient non joignables ou encore ils étaient décédés depuis. Malgré tout, en se basant sur les résultats de l'étude 2, il est possible d'émettre l'hypothèse qu'un individu atteint des deux pathologies présenterait des déficits dans l'ensemble des domaines cognitifs évalués au vu de la complémentarité des profils obtenus. À notre connaissance, la seule étude actuelle qui s'est penchée sur cette question a inclus des patients avec DTA qui rapportaient avoir subi un TCC dans le passé (Dams-O'Connor, Spielman, et al., 2013). Les patients TCC-DTA présentaient un ralentissement psychomoteur plus important (c.-à.-d. objectivé par le « *TMT* »), consommaient davantage de médicaments, présentaient un plus grand nombre de problèmes cardiovasculaires et cérébraux vasculaires, ainsi

qu'une plus grande prévalence de dépression que les patients touchés de DTA uniquement. Ces mêmes patients TCC-DTA performaient de manière comparable aux patients DTA aux examens visant à mesurer l'accès lexical (c.-à.-d. la dénomination), les fonctions exécutives (c.-à.-d. évaluées par le *TMT B*), la mémoire de travail (c.-à.-d. évaluée par le sous-test empan de chiffre à l'endroit et à l'envers) et les tâches évaluant l'attention (c.-à.-d. évaluées par le test de repérage de symboles de Wechsler). Malgré les obstacles liés au recrutement de cette population très vulnérable, des études futures seront nécessaires afin de confirmer ces conclusions. Des suivis longitudinaux multisites de groupes de patients TCC en âge avancé seraient à considérer dans un tel contexte.

3.4 Variables d'influence des performances neuropsychologiques à la suite d'un TCC et d'une DTA

Cette section de thèse sera plus brève dans la mesure où les variables identifiées préalablement n'ont pas été démontrées comme étant de bons prédicteurs du devenir cognitif chez les deux groupes de patients, nos hypothèses n'ayant été confirmées qu'en partie. Tel qu'indiqué précédemment, seul le niveau de scolarité a été associé aux compétences en mémoire verbale et en mémoire de travail, cette dernière étant aussi liée au délai de récupération. Chez le groupe avec DTA, ni l'âge ni la scolarité n'a montré une corrélation avec les performances neuropsychologiques. Le manque de diversité inter-individuelle pour l'âge (69 ans pour le groupe TCC et 76 ans pour le groupe DTA, avec un ET de 7) explique peut-être en partie cette absence de valeur pronostique. L'inclusion de patients plus jeunes ou plus âgés aurait peut-être permis à cette variable d'atteindre un seuil significatif. Le même constat s'applique pour le niveau de scolarité, la majorité ayant en moyenne 14 ans de scolarité chez les deux groupes, ce qui est élevé. En outre, la sévérité chez le groupe TCC ne se révèle pas non plus un bon prédicteur de la performance cognitive. Notons que la majorité des patients avaient obtenu des résultats à l'ÉCG entre 13 et 15, ce qui a limité la variabilité en termes de sévérité du TCC subi. De plus, tel que mentionné précédemment, le résultat à l'ÉCG n'est sans doute pas le meilleur outil pour mesurer la sévérité du TCC chez une clientèle âgée. Les résultats montrent en effet que 87% des patients TCCL de l'étude présentaient une ou des lésions cérébrales, malgré un résultat à l'ÉCG de 14,58. L'inclusion de patients ayant obtenu des TCC modérés et sévères, la prise en compte des caractéristiques préaccidentelles et la prise en compte d'autres critères que le résultat à l'ÉCG auraient été idéales,

mais le recrutement de cette clientèle est encore plus difficile puisque qu'elle est souvent admise en centre de réadaptation ou en centre de soins de longue durée. En outre, le délai post-accident associé au délai de récupération, déterminé à 6 mois post TCC, limite aussi la variabilité. Le recrutement de patients TCC vus par exemple à 3, 6 ou 12 mois aurait peut-être permis d'observer une évolution de la récupération des fonctions chez ce groupe. Enfin, la présence de lésions cérébrales observées au CT scan ne s'est pas montrée un bon indicateur de la performance cognitive à la suite du TCC. Enfin, aucune lésion cérébrale objectivée au CT Scan n'a été associée au fonctionnement neuropsychologique à la suite d'un TCC en âge avancé. Ces résultats sont étonnants puisque des études ont montré qu'à la suite d'un TCC, les régions les plus vulnérables sont les aires frontales et temporales (Rabinowitz & Levin, 2014), lesquelles sont responsables de médier les fonctions cognitives telles que les fonctions exécutives et la mémoire (Lezak et al., 2012; Spitz, Ponsford, Rudzki, et Maller, 2012; Ariza et al., 2006; McLean, Temkin, Dikmen, et Wyler, 1983). L'absence de liens entre la présence de lésions cérébrales et la cognition dans l'étude 2 pourrait être expliquée en partie par le fait que les patients évalués présentaient un trouble de sévérité légère et il s'était passé plus de 6 mois depuis l'accident. Il est donc probable que les saignements initiaux aient été moins importants ou graves, et que ces derniers se soient résorbés lors de la rencontre d'évaluation effectuée 6 mois post-accident. Il est également possible que l'atrophie cérébrale associée au cerveau vieillissant permette à la personne âgée de tolérer un plus grand volume de sang lors d'une hémorragie intracrânienne contrairement aux adultes plus jeunes (Beedham, Peck, Richarsdson, Tsang, Fertkeman, & Sphipway, 2019). Les études rapportent des volumes cérébraux globaux plus faibles (Driscoll et al., 2009; Seidler et al., 2010a), une épaisseur corticale réduite (Salat et al., 2004) et une expansion du système ventriculaire (Scahill et al., 2003) dans le cerveau des personnes âgées, ce qui permet une plus grosse accumulation de sang dans les espaces libres et donc une meilleure tolérance aux hémorragies intracrâniennes. Possiblement que le saignement était trop léger pour observer un impact cognitif et fonctionnel.

3.4.1 Le niveau d'éducation et l'hypothèse de la réserve cognitive à la suite d'un TCC. L'étude 2 de cette thèse propose qu'un plus haut niveau éducation serait associé à de meilleurs résultats dans certains domaines cognitifs tels que les capacités mnésiques verbales et la mémoire de travail, et ce particulièrement chez la clientèle TCC, ce qui concorde avec la littérature déjà existante. L'hypothèse de la RC, présentée en introduction de la thèse, pourrait être appropriée dans

ce contexte. Par exemple, il a été démontré que la RC estimée par le niveau éducation pouvait agir comme facteur de protection des fonctions cognitives (c.-à.-d. la vitesse de traitement de l'information, la mémoire de travail et la mémoire épisodique) après un TCC modéré-sévère (Bigler et Stern, 2015; Sumowski, Chiaravalloti, Krch, Paxton, et Deluca, 2013). De surcroît, Fernandez-Cabello et al. (2016) ont démontré – cependant chez des individus âgés sains – qu'un haut niveau d'éducation serait associé à de meilleures performances dans les tâches de mémoire de travail. Toujours selon cette étude, les patients les plus éduqués chez qui des dommages à la matière blanche ont été identifiés recouraient à l'activation de zones cérébrales supplémentaires afin d'obtenir la même performance que les sujets sans dommage cérébral. L'activation de zones cérébrales supplémentaires lors de tâches chez les patients TCC a aussi été démontrée par Stern et ses collaborateurs (2013). Or, on constate également dans la présente thèse qu'un haut niveau d'éducation semble être un bon facteur de protection suivant un TCC. En ce sens, il est possible que les patients du groupe TCC de la présente étude, ayant en moyenne 14,3 années d'étude, aient recouru à l'activation de zones cérébrales supplémentaires afin d'obtenir des performances dans la moyenne générale du point de vue de la mémoire épisodique et de la mémoire de travail.

4.0 Les interventions et la réadaptation à la suite d'un TCC en âge avancé et d'une DTA

En raison de l'accroissement de la population vieillissante et de la plus grande complexité des cas admis dans nos établissements d'une part, et des ressources de réadaptation parfois limitées d'autre part, il s'avère essentiel d'identifier les interventions optimales et spécifiques à la clientèle TCC en âge avancé, de même que chez ceux présentant un déclin cognitif. Bien que la thèse n'ait pas évalué les effets des interventions auprès des patients TCC et DTA, les résultats de l'article 2 permettront de mieux informer les équipes d'intervention et de réadaptation puisqu'ils ont permis d'identifier les difficultés neuropsychologiques à cibler pour offrir des interventions adaptées à ces clientèles. Tel que mentionné tout au long de cette thèse, peu de données existent sur le fonctionnement neuropsychologique spécifique à la suite d'un TCC en âge avancé et encore moins d'études portent sur les interventions à privilégier afin d'améliorer la cognition et le fonctionnement suivant l'accident. En ce sens, les résultats de notre étude 2 permettront de perfectionner les programmes de réadaptation en regard aux conditions plus spécifiques et ciblées en fonction des patients ayant subi un TCC en âge avancé et de ceux présentant une DTA. Afin d'optimiser le succès des interventions auprès de la personne âgée, certains auteurs tels que

(Uomoto, 2008) et Fenn et al. (1993) s'entendent pour dire qu'il est nécessaire d'éliminer dans un premier temps ce qu'ils nomment « l'excès d'invalidité ». Pour ces auteurs, l'excès d'invalidité est défini comme un moyen de décrire la perte fonctionnelle qui n'est pas expliquée par le processus de la maladie et se produit lorsque le fonctionnement du patient décline plus rapidement que prévu sur la base de la pathologie cérébrale seulement. Les troubles de l'humeur et du sommeil, les douleurs aiguës et chroniques, la poly pharmacologie, le manque de soutien social, les conditions médicales concomitantes, la perte de vision et d'audition, la fatigue et le déconditionnement représentent certains des facteurs qui contribuent à l'excès d'invalidité. En ce sens, avant d'agir directement sur le déficit cognitif, ils recommandent d'abord de traiter la dépression, les difficultés de sommeil, les problèmes de douleurs chroniques, et suggèrent également de renforcer le soutien social de la personne. Agir de manière prioritaire sur ces difficultés est essentiel puisque ces dernières ont des impacts directs sur le fonctionnement cognitif (Uomoto, 2008) et interfèrent avec la réalisation des tâches de la vie quotidienne nécessitant l'intégration de multiples compétences cognitives, comportementales et émotionnelles (Dams-O'Connor et Gordon, 2013).

En ce qui concerne plus spécifiquement la population TCCL en âge avancé, et tel que démontré dans l'article 2 de cette thèse, des suivis psychothérapeutiques s'avèrent essentiels afin de traiter les affects anxieux et dépressifs de ces patients, et cela, le but premier est de répondre au principe « d'excès d'invalidité ». De surcroît, l'intégrité des fonctions mnésiques à court et long terme offre l'opportunité pour la personne d'apprendre de nombreuses techniques de réadaptation cognitive et d'appliquer ces stratégies de réadaptation au quotidien. En effet, les adultes plus âgés atteints d'un TCC semblent susceptibles d'apprendre et de comprendre les techniques enseignées, de conserver les informations lors des séances de traitement et d'être en mesure d'appliquer ces stratégies dans tous les contextes (Abrams, 2003). L'utilisation d'interventions de type « *top down* » (c.-à.-d. résolution de problèmes, technique auto-indicée et discours interne) devient donc particulièrement intéressante puisque celles-ci enseignent un principe directeur ou une règle générale sur la façon d'accomplir une tâche qui peut être appliquée dans divers contextes (Dams-O'Connor et Gordon, 2013). Généralement, ces stratégies reposent sur des routines comportementales et sur la mentalisation. L'objectif est d'aborder les difficultés cognitives qui sont principalement exécutives. Par exemple, cela peut impliquer la reconnaissance et la définition d'un problème, l'identification et le choix entre des solutions possibles, l'énumération des étapes

nécessaires à la mise en œuvre de la solution choisie et l'évaluation du résultat. Bref, en apprenant un ensemble de principes directeurs qui peuvent être appliqués à toutes les situations, l'individu est capable de répondre de manière adaptative aux demandes situationnelles à mesure qu'elles se présentent. Des stratégies « compensatoires » peuvent aussi être enseignées comme l'utilisation d'aide-mémoires, d'un calendrier, d'un cahier de notes, etc. (Dams-O'Connor et Gordon, 2013; Rees et al., 2007).

Concernant les interventions à privilégier pour les patients avec DTA, les résultats de notre second article permettent de confirmer le fait que les personnes atteintes de DTA éprouvent des difficultés à apprendre de nouvelles informations et à les conserver sur une longue période de temps. À cet égard, elles seraient moins susceptibles de bénéficier de programmes d'intervention de type « *top down* » qui nécessitent une mémoire explicite ou déclarative. En contrepartie, il est possible qu'elles puissent bénéficier d'une intervention basée sur la notion d'apprentissage procédural intensif tout en permettent de compenser les déficits en mémoire déclarative. En d'autres mots, ce type d'entraînement permet à l'individu d'exploiter des stratégies basées sur des processus cognitifs préservés dans la maladie. En conséquence, cela pourrait possiblement permettre de compenser en partie leurs déficits en mémoire déclarative. Il existe plusieurs techniques telles que l'apprentissage sans erreur (Callahan et Anderson, 2017), la récupération espacée (Creighton, Van der Ploeg, et O'Connor, 2013) et l'estompage (Haslam, Moss et Hodder, 2010) qui visent à exploiter les processus mnésiques implicites et automatiques et qui permettront de favoriser de nouveaux apprentissages. Bref, les stratégies à privilégier pour les patients DTA sont davantage axées sur le maintien et la compensation du fonctionnement cognitif et fonctionnel.

5.0 Limites du projet de thèse

Tel que mentionné dans la discussion de chacun des articles, cette thèse présente des limites méthodologiques qui doivent être considérées dans l'interprétation des résultats. Ces limites seront donc présentées dans cette section et seront accompagnées de recommandations en prévision des études futures.

Tout d'abord, la petite taille de l'échantillon de l'étude deux vient certainement diminuer la puissance statistique et limiter les effets observés. Tel que mentionné précédemment, le

recrutement des participants TCC et DTA en âge avancé, qui représentent des clientèles âgées et vulnérables, s'est avéré un réel défi lors de cette thèse. Ces patients avec comorbidités et complications médicales et fonctionnelles recevaient des services de réadaptation, de même que plusieurs suivis médicaux. Il est également pertinent de mentionner que la généralisation des résultats pour le groupe TCCL doit se faire avec prudence puisque ces patients ont tous été hospitalisés au départ pour leur blessure traumatique ; ces derniers représentent donc un groupe dont le TCC aurait possiblement été plus sévère que ceux qui, par exemple, n'auraient jamais été hospitalisés pour leur blessure. Il serait donc intéressant d'examiner les performances neuropsychologiques de patients TCC dont les sévérités sont très légères (c.-à.-d. commotions cérébrales) ou encore ceux avec des TCC de plus grande gravité, tels les cas modérés ou graves, et ce, en utilisant des critères catégoriels autres que ceux basés uniquement sur le résultat à l'ÉCG, ce dernier n'étant sans doute pas le meilleur outil pour catégoriser la sévérité du trouble chez une clientèle en âge avancé.

La généralisation des résultats pour les deux groupes cliniques et le groupe témoin devrait aussi être prudemment effectuée puisque, il est essentiel de le mentionner, nos groupes étaient très éduqués, la majorité des individus ayant une formation de niveau universitaire. Cela représente donc également un biais d'échantillonnage et a sans doute haussé les moyennes des performances cognitives chez nos trois groupes. Comme mentionné précédemment à l'occasion de l'hypothèse de la RC, le niveau d'éducation aurait un impact sur le fonctionnement cognitif (Dik et al., 2003; Manly et al., 2005; Mortimer et al., 2003; Stern, 2012; Wilson et al., 2003). De plus, il a été démontré que la RC estimée par le niveau d'éducation pouvait agir comme facteur de protection des fonctions cognitives à la suite d'un TCC (c.-à.-d. vitesse de traitement de l'information, la mémoire de travail et la mémoire épisodique) (Bigler et Stern, 2015; Sumowski et al., 2013). Il serait ainsi intéressant d'explorer le fonctionnement cognitif de ces deux groupes cliniques mais avec une plus grande diversité sur le plan des caractéristiques sociodémographiques ; ainsi, la prise en compte d'un échantillon plus diversifié serait plus représentatif des cas rencontrés par les neuropsychologues dans leur pratique.

Toujours pour le groupe TCC, la majorité des patients du groupe, soit 87%, présentait des lésions cérébrales objectivées au CT Scan. Ces lésions ne se sont pas révélées de bons prédicteurs

du fonctionnement cognitif. En ce sens, la technique d'imagerie cérébrale utilisée (CT Scan), quoique la plus utilisée dans les milieux cliniques, n'est pas la plus performante pour détecter des microlésions ou encore des lésions axonales diffuses, et n'offre aucune indication sur le fonctionnement des réseaux d'activation cérébrale. Les études futures auront avantage à utiliser des méthodes d'imagerie plus sensibles comme l'imagerie par résonance magnétique (IRM) afin de détecter un plus grand éventail de dommages cérébraux (Lee et Newberg, 2005).

Une autre limite importante de cette thèse est le nombre restreint de données recueillies et ce, tant pour l'étude 1 que l'étude 2. Pour l'étude 1, la revue de littérature était limitée puisque la recherche n'a pas inclus la littérature grise, négligeant ainsi les résultats intéressants provenant par exemple de thèses de doctorat ou de mémoires de maîtrise. D'autres facteurs d'exclusion ont été appliqués à cette revue, tels les types d'études (c.-à.-d. étude de cas, cas multiples, revues), la langue et la provenance – les articles récoltés étaient majoritairement issus des États-Unis –, de sorte que le spectre de généralisation de nos résultants s'avère restreint. Concernant l'étude 2, les outils neuropsychologiques employés ont été limités, notamment en raison de l'endurance de nos patients pour de longues évaluations. En outre, seulement quelques épreuves cognitives ont été administrées et considérées comme étant représentatives de la fonction étudiée. Cette approche est très restreinte et l'ajout d'autres outils standardisés et validés permettraient de mesurer la mémoire, les fonctions exécutives, le langage ou les fonctions instrumentales auraient été essentielles pour l'obtention d'un profil neuropsychologique compréhensif. De plus, la distribution de questionnaires mesurant le fonctionnement, l'autonomie ou la participation sociale, et remplis par les proches, aurait été instructif et nécessaire pour la constitution d'un profil représentatif de ces populations cliniques. Finalement, notre étude 2 ne permet pas d'observer le suivi de la récupération des patients TCC, ni l'évolution de ceux présentant une DTA. Une approche longitudinale et des suivis de réévaluation réguliers auraient été utiles afin de mieux documenter l'évolution des symptômes cognitifs et psychologiques chez les deux groupes. En outre, et pour faire le pont avec l'étude 1, ils auraient aidé à reconnaître le développement d'une DTA à la suite du TCC chez un patient en âge avancé. Les chercheurs sont encouragés à utiliser d'autres outils dans les études futures afin de compléter le profil des similarités et des différences entre les patients TCC et DTA en âge avancé. Il est recommandé également d'adopter des paradigmes de recherche longitudinaux.

Enfin, il est important de reconnaître que d'autres facteurs que ceux utilisés/contrôlés dans la présente thèse ont pu influencer le fonctionnent cognitif des individus des trois groupes. Il importe donc d'envisager la possibilité que les profils cognitifs obtenus dans le deuxième article aient été influencés par une autre condition médicale comme un fardeau vasculaire (e.g. l'obésité, l'hypercholestérolémie, les problèmes cardiaques tels que l'arythmie, l'hypertension, le diabète de type II, etc.), ou encore par la prise de médicaments. Bien que, dans cette étude, les individus avec des antécédents de troubles neurologiques, psychiatriques ou d'abus de substances aient été exclus afin d'isoler au maximum les effets du TCC et de la DTA, d'autres conditions pouvant possiblement influencer les résultats aux différentes tâches exécutées devront être considérées dans le futur. De fait, comme mentionné précédemment, les conditions médicales préexistantes et la prise de médicaments sont très fréquentes chez la personne âgée en général (Gardner et al., 2018). À titre d'exemple, les effets de l'hypertension, surtout lorsque non-traitée, sur les fonctions cognitives doivent être pris en considération lors de l'évaluation neuropsychologique des patients TCC et DTA (Gorelick et al., 2011). La littérature est bien documentée à ce sujet, cette maladie serait associée à une réduction du raisonnement abstrait, un ralentissement de la vitesse de traitement de l'information ou parfois à des difficultés mnésiques (Gasecki, Kwarciany, Nyka, et Narkiewicz, 2013; Gorelick et al., 2011). De la même manière, certains auteurs proposent que le diabète de type II aurait un impact sur le fonctionnement cognitif (Mayeda, Whitmer, et Yaffe, 2015). Il apparaît également important d'explorer le rôle de la poly pharmacologie lors d'un TCC chez la personne âgée ou lors de la présence d'une DTA. L'abondante littérature sur le sujet montre bien que la consommation simultanée de plusieurs médicaments est de plus en plus fréquente chez la personne âgée (Wastesson, Morin, Tan, et Johnell, 2018), ce qui sous-entend que la poly pharmacologie pourrait être associée à une augmentation du risque de chute ou de mortalité (Fried et al., 2014; Gutierrez-Valencia et al., 2018; Leelakanok, Holcombe, Lund, Gu, et Schweizer, 2017) ainsi qu'à une diminution des fonctions cognitives (Niikawa et al., 2017; Vetrano et al., 2018). Dans un contexte de poly pharmacologie et d'évaluation de la cognition, il est aussi très important de considérer le type de médication : par exemple, les psychotropes et les médicaments aux propriétés anticholinergiques sont connus pour avoir des effets négatifs sur la cognition (Park, Park, Song, Sohn, et Kwon, 2017; Vetrano et al., 2018). En somme, considérant les études qui suggèrent l'influence de plusieurs conditions médicales (c.-à.-d. diabète, hypertension, etc.) et de la poly

pharmacologie sur la cognition, et que celles-ci soient particulièrement prévalentes chez la personne âgée, il est important de souligner la nécessité de continuer à considérer ces facteurs en pratique clinique adaptée à une clientèle âgée.

6.0 Conclusion

Cette thèse avait pour but de répondre à deux questions fréquemment posées aux neuropsychologues travaillant auprès d'une clientèle TCC en âge avancé ou présentant une DTA. La première question était la suivante : Quels sont les patients TCC à risque de développer une DTA ? Les démarches visant à répondre à cette première interrogation ne se sont pas avérées très concluantes puisque les résultats de cette thèse ne permettent actuellement pas aux cliniciens de statuer sur les risques de développer une DTA à la suite d'un TCC en âge avancé. De plus, les lacunes méthodologiques et l'hétérogénéité des variables à l'étude permettent encore moins d'identifier les variables liées au TCC pouvant être incluses dans un algorithme déterminant le risque de développer ou non une DTA. Il est ainsi recommandé aux cliniciens de demeurer prudents lors de la communication des informations aux patients, à leur famille et à leurs proches concernant ce potentiel risque. Les chercheurs sont toutefois encouragés à prendre en considération ces limites et les recommandations soulevées dans cette thèse afin de bonifier leurs protocoles de recherche.

La seconde question fréquemment posée aux neuropsychologues, et qui a fait l'objet d'analyses dans le cadre de cette thèse, était la suivante : existe-t-il des différences de profils neuropsychologiques entre les patients TCC et les patients ayant une DTA ? Les résultats de cette thèse appuient l'hypothèse selon laquelle les profils neuropsychologiques des patients TCCL et DTA sont différents. La mémoire épisodique est plus affectée chez les patients présentant une DTA que chez les patients TCCL, alors que les symptômes anxio-dépressifs sont plus importants chez les patients TCCL que chez les patients DTA. Les résultats de cette thèse apportent ainsi une meilleure compréhension des profils neuropsychologiques associés à ces deux conditions neurologiques et offrent des pistes pour dissocier les deux pathologies avec pour objectif d'obtenir un meilleur diagnostic différentiel.

Enfin, les travaux liés à cette étude ont permis de constater que, contrairement à la littérature s'intéressant à une clientèle plus jeune, les études réalisées à partir d'une population en âge avancé

sont moins nombreuses, notamment en ce qui a trait aux approches de prévention, d'intervention et de réadaptation. Compte tenu du vieillissement de la population, mais aussi des facteurs de risques et des comorbidités fréquentes chez ces clientèles vulnérables, les neuropsychologues, mais aussi tous les intervenants en santé seront de plus en plus confrontés à la nécessité d'offrir des soins de qualité. En ce sens, un changement dans la société sur la façon dont sont prises en charge les personnes les plus vulnérables devra être adopté, et des ressources tant financières qu'humaines devront être déployées afin d'améliorer la qualité de vie de ces personnes.

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Annexe A

Article 3

Highlighting the differences in post-traumatic symptoms between complicated and uncomplicated mild traumatic brain injury patient groups and injured controls

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Julien, J., Tinawi, S., Anderson, K., Frenette, L. C., Audrit, H., Ferland, M. C., . . . De Guise, E. (2017). Highlighting the differences in post-traumatic symptoms between patients with complicated and uncomplicated mild traumatic brain injury and injured controls. *Brain Injury*, 1-10. doi:10.1080/02699052.2017.1346289

Abstract

Objective: The goal of the current study is to explore the difference in acute post-concussive symptoms (PCS), headaches, sleep and mood complaints between groups of complicated and uncomplicated mTBI patients and a comparable group of injured controls. Interactions between the following five factors were studied: presence of (1) PCS; (2) headaches; (3) sleep disorders (4), and psychological status (5). Methods: A total of 198 patients, followed at the outpatient mild traumatic brain injury clinic of the MUHC-MGH, completed questionnaires and a brief neurological assessment two weeks post-trauma. Results: Whether they had a TBI or not, all patients presented PCS, headaches, sleep and mood complaints. No significant differences between groups in terms of reported symptoms were found. Variables such as depression and anxiety symptoms as well as sleep difficulties and headaches, were found to correlate with PCS. The high rate of PCS in trauma patients was observed independently of traumatic brain injury status. This study has also shown that patient with complicated mTBI were more likely to have vestibular impairment after their injury. Conclusion: Vestibular function should be assessed systematically after a complicated mTBI. Furthermore, mTBI diagnosis should be based on operational criteria, and not on reported symptoms.

Key words: Traumatic brain injury, concussion, headaches, sleep, mood, injured controls, post-traumatic symptoms.

The incidence of traumatic brain injury (TBI) is estimated to be over 1 million cases per year in North America (Cassidy et al., 2014; Iverson, 2010), and the prevalence of TBI in Canada is near 600 in 100 000 (Cassidy et al., 2004). This constitutes a substantial number, which creates significant pressure on the health system, as considerable time and resources are devoted to the assessment and management of TBI patients. On average, 70-90% of all TBI are mild traumatic brain injuries (mTBI), and previous studies have shown that most individuals recover following a mTBI over the course of weeks to several months after the trauma. However, 10-15% of patients will continue to experience atypical and persisting symptoms (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Cassidy et al., 2014; Hibbard, Uysal, Kepler, Bogdany, et Silver, 1998), which can impact on work reintegration and quality of life (Dikmen, Machamer, Fann, et Temkin, 2010). Post-concussive syndrome includes physical, cognitive and emotional symptoms that some patients experience after a mTBI or concussion. The most common post-TBI reported symptoms are headaches, blurred vision, dizziness, subjective memory problems and other cognitive impairments as well as sleep and mood problems (Chamelian et Feinstein, 2006; Kreutzer, Seel, et Gourley, 2001; S. Marshall et al., 2012; Ponsford et al., 2000).

The most common TBI-related psychiatric after-effects include depression and anxiety (Whelan-Goodinson, Ponsford, Johnston, et Grant, 2009). The prevalence of post-TBI depression is very high, and estimated to be between 25% and 60% (Gould, Ponsford, Johnston, et Schonberger, 2011) whereas the prevalence of anxiety is estimated at 60% (Whelan-Goodinson et al., 2009). mTBI patients often report fatigue and irritability as well as anxiety (Meares et al., 2006). Several studies that have followed individuals for 1 year or more after injury have found that anxiety and depression are the most commonly reported symptoms by these individuals (Hart et al., 2012; Whelan-Goodinson et al., 2009). Furthermore, some studies point out that depression, anxiety and post-concussive stress reactions are greater in mTBI participants with post-concussive symptoms than those without the latter symptoms (King, 1996; Meares et al., 2006). As a matter of fact, concurrent anxiety, depression and post-traumatic stress may contribute to acute post-traumatic symptoms so called ‘’post-concussive symptoms’’ (Bryant, 2008; Hoge et al., 2008; Stulemeijer, van der Werf, Borm, et Vos, 2008). Indeed, the postconcussional model of Hou (Hou et al., 2012) explained that the combination of predisposing factors, precipitating factors (TBI) and perpetuating factors such as cognitive, behavioural and emotional reactions to the head injury may

contribute to PCS. Therefore, anxiety and depression are important predictors for PCS. Also, it at been observed that a strongest effect for acute post-concussive symptoms was a previous affective or anxiety disorder (OR 5.76, 95% CI 2.19 to 15.0) (Meares et al., 2008). Besides, other studies report that acute depression is more associated with biological mechanisms (Jorge et al., 2004b) and chronic depression is more related to psychosocial factors (Hibbard et al., 2004). The literature suggests that factors such as pre-existing psychiatric or depressive disorders (Bombardier et al., 2010; Jorge et al., 2004b), female gender (Whelan-Goodinson et al., 2009), increasing age (Levin et al., 2005), lower education level (Dikmen, Bombardier, Machamer, Fann, et Temkin, 2004; Holsinger et al., 2002; Whelan-Goodinson et al., 2009), unemployment (Dikmen et al., 2004; Franulic, Carbonell, Pinto, et Sepulveda, 2004; Seel et al., 2003), pain (Hibbard et al., 2004; Whelan-Goodinson et al., 2009), and substance abuse (Bombardier et al., 2010; Dikmen et al., 2004; Hart et al., 2012) may play roles in the development of depression after TBI.

The prevalence of post-TBI sleep impairments is estimated between 30% and 84% (Castriotta et al., 2007; Rao et Rollings, 2002). Sleep disturbances, including a decline in sleep quality, longer sleep-onset latency, reduced sleep efficiency, excessive daytime sleepiness, and diagnosed sleep disorders are reported by a significant proportion of individuals with TBI (Baumann, Werth, Stocker, Ludwig, et Bassetti, 2007; Castriotta et al., 2007; Kempf, Werth, Kaiser, Bassetti, et Baumann, 2010; Parcell, Ponsford, Rajaratnam, et Redman, 2006; Rao et Rollings, 2002). Indeed, traumatic brain injuries may cause or intensify symptoms or co-morbid disorders, such as depression, anxiety, irritability, fatigue, cognitive deficits, pain, and functional impairments (Fichtenberg, Millis, Mann, Zafonte, et Millard, 2000; Zeitzer, Friedman, et O'Hara, 2009). 30-60% of TBI patients presented with either insomnia symptoms or insomnia disorder. Some studies state that mTBI patients have more insomnia-related complaints than severe TBI patients (Mathias et Alvaro, 2012; Ouellet, Savard, et Morin, 2004). This finding could possibly be explained by increased symptom-awareness in mTBI patients (Mahmood, Rapport, Hanks, et Fichtenberg, 2004; Ouellet, Beaulieu-Bonneau, et Morin, 2006; Parcell, Ponsford, Redman, et Rajaratnam, 2008). Sleep disturbances may also be explained by trauma-induced physical injuries (Zeitzer et al., 2009), comorbid conditions (depression) (Ouellet et Morin, 2006) or injury related sleep problems, such as pain (Silver, McAllister, et Yudofsky, 2005). Indeed, the wide variability

of sleep disturbance definitions, criteria, types of measures and sources of information (Zeitzer et al., 2009) makes it difficult to assess TBI contributions in sleep difficulties.

In addition, other injuries as well as pain and medication use may also contribute to post-concussive symptom development (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Fleminger et Ponsford, 2005; Meares et al., 2006). It is in fact quite common for those who had a head injury to also present comorbid pain issues. A study examining the prevalence of chronic pain (i.e., still present after 3 months) following TBI, found that it was a very common complication (Nampiaparampil, 2008). It is especially common in the mTBI population, corroborated by the findings of Uomoto and Esselman (1993), who reported that 95% of individuals who had sustained a mTBI reported chronic pain while only 22% of those having suffered a moderate- to-severe TBI did so. Pain and headaches were associated with acute post-concussive symptoms in mTBI (Meares et al., 2006; Ponsford et al., 2000). Post-traumatic headaches are very common in the mTBI population, with a prevalence ranging from 30-90% depending on the type of measurement instrument administered to patients (Alves, Macciocchi, et Barth, 1993). Post-traumatic headaches may persist long after the traumatic brain injury, with 18% to 22% of post-concussive headache sufferers still experiencing symptoms one year after their accident (Lew et al., 2006). In fact, the WHO Task Force found the presence of spine and head-related pain to be significant determinants of recovery after mTBI (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004).

Post-concussive syndrome is a complex consequence of mild TBI, and contradictions in the literature regarding this syndrome remain. This can be partly explained because PCS-associated symptoms are non-specific, and can be found in other clinical conditions and in the general population (Iverson, Zasler, et Lange, 2006; Mittenberg, DiGiulio, Perrin, et al, 1992). Therefore, many factors may play a role in presence of post-concussive symptoms following mTBI. Head injury alone may not explain post-injury depression, anxiety, fatigue and post-concussive stress. There is inconsistent evidence in the literature regarding acute neuropsychological and psychological differences between m TBI patients with PCS symptoms and controls (Landre, Poppe, Davis, Schmaus, et Hobbs, 2006; McMillan et Glucksman, 1993; Meares et al., 2008; Ponsford et al., 2000). Some studies have reported that mTBI subjects performed significantly

lower on all cognitive measures (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Landre et al., 2006; Ponsford et al., 2000). Others found few differences in memory tasks between controls and TBI patients (McMillan et Glucksman, 1993; Newcombe, Rabbitt, et Briggs, 1994). Discrepancies are also present in studies comparing mild complicated versus mild uncomplicated TBI patients. Some studies have shown that mTBI patients with CT-scan visible focal brain lesions (complicated mTBI) presented with diminished cognitive abilities in the days or weeks following their injury compared to uncomplicated mTBI (no cerebral injuries on CT-Scan) (Iverson et al., 2006; Lange, Iverson, et Franzen, 2009; Williams, Levin, et Eisenberg, 1990). Other studies failed to show such a difference (Hughes et al., 2004; Sadowski-Cron et al., 2006).

Intrinsic mTBI and control group characteristics, as well as failure to adequately screen for potentially confounding pre-existing conditions (McLean et al., 1983) may play a major role in explaining inconsistencies found in previous research. In order to evaluate the relative contribution of trauma after-effects and then to identify which factors are associated with mTBI. To better assess mTBI-specific symptoms, a non-TBI injured control group was used instead of a community control group, since the former shared a trauma experience with mTBI patients (Babikian et al., 2011). Therefore, the aims of the present study are threefold. First, (1) PCS two weeks post-TBI will be described. Second, (2) headaches, sleep disturbances and psychological symptoms as well as acute post traumatic symptoms: ‘’post concussive symptoms’’ will be assessed while differentiating both the injured control group’s pre-existing condition and accident related characteristics, and mild and uncomplicated TBI groups. Third, (3) interactions between headaches, sleep disorders, psychological status and PCS will be studied. We hypothesize that complicated mTBI patients will present with more symptoms than the uncomplicated mild ones, and that the injured control group will present with less symptoms than the two previous groups. On the basis of previous studies, we also hypothesize that the presence of headaches, sleep disorders, and psychological distress will be positively associated with the severity and presence of PCS.

Method

Participants

A total of 198 patients followed at the outpatient mild traumatic brain injury clinic of the McGill University Health Center (MUHC) between October 1st 2013 and April 1st 2014 were assessed through a standardized evaluation protocol. All trauma symptomatic patients were referred from the Emergency Department within the first two weeks following their accident. The data of this cohort was retrospectively collected and analyzed. The MUCH research ethics board granted approval for this retrospective study.

MTBI participants

The mTBI group is comprised of one hundred and fifty-seven mTBI patients. In addition to a history of recent head trauma, mTBI-identification was confirmed by a physician, and is based on the WHO Task Force Criteria (Borg et al., 2004; Holm, Cassidy, Carroll, et Borg, 2005). Operational criteria for clinical identification include one or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, posttraumatic amnesia for less than 24 hours and other transient neurological abnormalities such as focal signs, seizure, and intracranial lesions not requiring surgery. To be classified as mTBI, patients must score between 13 and 15 on the Glasgow Coma scale (GCS) for a minimum of thirty minutes post-injury. All admitted patients first underwent a CT-scan as soon as possible after their arrival in the emergency room. The CT scans were carried out according to the existing trauma protocol, and included brain parenchyma and bone windows. The cuts were 5mm in thickness for the supratentorial compartment and 2,5mm in thickness for the posterior fossa. A staff neuroradiologist read all CT scans, and the results were recorded in medical charts. Out of a total of 157 patients, 115 were classified in the uncomplicated mTBI group and 43 were classified in the complicated mTBI group.

Injured control group

Forty-one participants with traumatic injuries were included in the injured control group. They met the following criteria: over 18 years of age, no loss of consciousness, no PTA, no intracranial injury and a normal CT (if performed). Furthermore, it has been suggested that people in the injured control group have suffered a physical trauma, and have been through the emergency

department experience, making their general trauma context similar to that of mTBI patients. The injured control group includes patients who suffered from a traumatic fracture or any traumatic orthopedic injury, and still complain about symptoms two weeks following their accident.

Patients who were non-English or French speakers, who were in a litigation process, who were under the effects of a narcotic or those who were assessed at the mTBI clinic more than two weeks post-accident were excluded from this study.

Measures

Data was collected from medical charts and from patient, family members or family physician interviews. The variables considered were: age at trauma, Glasgow Coma Scale Scores (GCS)**,** gender, education, marital status, employment status, history of alcohol or drug abuse, psychological, neurological and TBI history.

A neurological assessment was performed within the first two weeks post-TBI by an experienced physician specialized in physical and rehabilitation medicine. The examination included the classical neurological exam of cranial nerves, motor and sensation exams, cerebellar function, reflexes and pronator drift examination. An in depth and thorough assessment of cranial nerve VIII components was done, including simple auditory testing by finger rubbing, the Dix-Hallpike test or the Nylen-Barany test, a diagnostic maneuver used to identify benign paroxysmal positional vertigo (BPPV). While performing the test, the examiner looks for rotational nystagmus. The finding of classic rotatory nystagmus with latency and limited duration is considered pathognomonic (Dix et Hallpike, 1952). Finally, based on DSM-5 criteria, patients were evaluated for the presence of an acute stress disorder, an adjustment disorder or a post-traumatic stress disorder.

Measures (at two weeks)

Symptom assessment was performed using the Rivermead Post-Concussion Questionnaire (RPQ) (King, Crawford, Wenden, Moss, et Wade, 1995). This widely used tool consists of a list of 16 post-concussive symptoms that are ranked by the patient from 0 (not experienced at all) to 4 (severe problem).

Headache assessment was performed using the The Headache Impact Test (HIT) (HIT-6 Scoring Interpretation English Version 1.1, 2001).The Hit-6 is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. This tool contains six questions; each answer being ranked by the patient from Never to Always. The cut-offs used are the following: 60 or more: Your headaches are having a very severe impact on your life; 56-59: Your headaches are having a substantial impact on your life; 50-55: Your headaches are having some impact on your life; 49 or less: Your headaches seem to be little to no impact on your life.

Sleep assessment was the perfomed by using the MOS Sleep Scale–Revised (MOS Sleep–R) (Allen, Kosinski, Hill-Zabala, et Calloway, 2009). MOS is a brief, self-administered assessment designed to measure, in both general and clinical populations, key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity. The MOS contains 12 questions, each answer (question 3 to 12) being scored on a scale value of 1 (all of the time) to 6 (none of the time). For question one, answer is being scored on a scale value of 1 (0-15 minutes) to 5 (more than 60 minutes) and question two is being answer by the total amout of hours sleep at night. T scores of 45 or greater are at or above the U.S. general population norm. The cut-offs used are the following : less than 45 : sleep problems; more than 45 : no sleep problem.

Psychological assessment included a test, the Beck Depression Scale-II (BDI-II), which measures depression levels (Beck, Ward, Mendelson, Mock, et Erbaugh, 1961). The BDI-II contains 21 questions, where each answer is attributed a score between 0 and 3. The scores are then compiled to provide a total score reflecting one's depression index. The cut-offs used are the following: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms. The Beck Anxiety Inventory (BAI) (Beck et Steer, 1990), created by Dr. Aaron T. Beck and other colleagues, is a 21-question multiple-choice self-report inventory used for measuring the severity of an individual's anxiety. The BAI has a maximum score of 63. (0-7: minimal level of anxiety; 8-15: mild anxiety; 16-25: moderate anxiety; 26-63: severe anxiety).

Statistical analyses

Descriptive statistics for baseline characteristics and all outcome variables were computed. Baseline characteristics of the large sample were presented as percentage for the categorical variables and mean for the continuous variables. To access the difference of baseline characteristics and all outcome variables of patients between groups, simple group comparisons were performed using ANOVAs (for numerical variables in large groups) and non-parametric chi-square tests (for nominal variables). To investigated the link between outcomes variables; associations between numerical variables were assessed using Pearson correlation coefficients, and associations involving ordinal variables were assessed using Spearman rank correlation coefficients. Considering the large number of association measures computed in this study and its exploratory nature, we opted for a level of significance of $p < 0.01$ with the mention of the need for further investigation when the level of significance was found to be between 0.01 and 0.05. Adjustments for multiple comparisons (Bonferroni) were performed, and all statistical tests used an alpha level of 0.01. All analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL).

Results

Demographics, pre-injury and injury characteristics

Patient characteristics and group comparisons for patients with complicated mTBI, uncomplicated mTBI and the injured control group are reported in table 1. There were no significant group differences between the three groups across all variables (sex, age, marital status, years of education, employment, alcohol abuse before the trauma, drug abuse before the trauma, previous TBI, neurological pre-existing condition, previous mental health problems, post-traumatic stress after the accident, Glasgow Coma Scale (GSC) and alcohol intoxication at admission). Regarding gender, the majority of the sample were women (58.08%) and overall sample had a university education (60%). The average age was 40.37 (± 17.5), ranging from 13 to 90 years of age. Overall, 33% were single, 31.3% married, 5.55% were divorced while others were widowers or had an unknown marital status. Falls (29.0%) or motor vehicle crashes (21.6%) caused most traumas. Other causes included the following: moving vehicles hitting pedestrians or cyclists (8.0%), assaults (9.9%), suicide attempts (8.6%), sports injuries (0.6%) and others not otherwise classified or having no reported etiology (22.2%). Thirty-six subjects (18.1%) had a history of

alcohol abuse prior to their trauma, fifteen subjects (7.58%) had a history of drug abuse before the trauma and 53 patients (26.77%) had a history of TBI. The majority of the sample had no neurological pre-existing conditions (90.9%) and no previous mental health issues (67.68%). There were some missing values for most outcome measures considered in this sample.

Insert Table 1 about here

Acute Post-traumatic symptoms: '' post-concussive symptoms (PCS)''

For the variables shown in table 2, there were no significant differences between groups in terms of reported post-concussive symptoms (PCS). Whether they had a TBI or not, patients all presented with PCS. The outcome measures we considered were the Rivermead post-concussion symptoms (n=198), the Hit-6 (n=119), the MOS Index (n=106), the Beck anxiety inventory (n=83), and the Beck depression inventory (n=105).

Insert Table 2 about here

No significant differences were observed across each group's Rivermead post-concussive scores, ($F_{(2,195)} = 1.763$, $p = 0.174$). Total Rivermead post-concussive scores varied between 0-64, had an average of 27.18(±15.462) and 27.44(±14.210) for uncomplicated and complicated mTBI groups respectively. The injured control group had an average score of 32.34(±16.683). It is thus possible to state that individuals from all injury categories (uncomplicated TBI, complicated TBI, and no TBI) reported having post-concussive symptoms (See table 2).

In addition, there was no significant difference in Hit-6 questionnaire scores across all three experimental groups (uncomplicated TBI, complicated TBI or injured control) ($F_{(2,116)} = 2.014$, $p = 0.138$) (see table 2). The Hit-6 scores varied between 30 and 78. The control, uncomplicated TBI and complicated TBI groups had respective average scores of: 61.00(±9.965), 57.78(±11.055) and 54.71(±12.17). Using the HIT-6 suggested cut-off (50 or higher), it is possible to conclude that a majority of patients from all three groups reported having headaches. Indeed, 76.47%, 64.52% and 89.47% of patients from the uncomplicated mTBI, complicated mTBI and no TBI patient groups respectively presented with headaches that impact their quality of life (See table 3).

Moreover, no significant differences were found across experimental groups for all MOS Index items (see table 3). Indeed, sleep problems, including sleep disturbances, which measure the ability to fall asleep and maintain restful sleep (X^2 = 10.346, p = 0.411; X^2= 11.633, p = 0.476; X^2= 13.104, p = 0.36; X^2= 4.097, p = 0.982), sleep adequacy, which assesses whether the amount of hours slept are sufficient to restore wakefulness (X^2= 13.785, p = 0.315; X^2= 16.628, p = 0.164), sleep quantity, which reflects the hours slept per night ($F_{(2,116)}$ = 0.012, p = 0.988), somnolence, which reflects daytime drowsiness or sleepiness (X^2= 11.406, p = 0.494; X^2= 7.457, p = 0.826; X^2= 2.361, p = 0.999), snoring (X^2= 5.990, p = 0.0917), and shortness of breath, or headache (X^2= 8.894, p = 0.712) were equivalent for all patient groups (see table 2). The mean scores for questions Q1 and Q3-Q12 varied between 3.20-4.4, indicating that sleep disturbances occur «some of the time and a good bit of the time». Using the MOS suggested cut-off (less than 45), both the TBI groups and the control group presented with sleep difficulties. In fact, 84.06% uncomplicated mTBI, 62.96% complicated mTBI and 73.33% non-TBI patients have a score inferior to 45, which is below the U.S. norm and indicates sleep issues (Allen et al., 2009). The reported amount of sleep was of about 7.22(± 2.661) hours for all groups, which lies in the recommended range (See table 3).

Also, no significant differences were found in the BAI scores across all three groups, ($F_{(2,80)}$ = 0.350, p = 0.706) (see table 2). The total BAI scores varied between 0-60. Averages of 17.47(±17.759), 15.59(±12.276) and 14.04(±10.227) were reported for the control, uncomplicated mTBI and complicated mTBI groups respectively. All participants, with and without TBI, showed mild to moderate anxiety symptoms. More specifically, mild anxiety symptoms were present in at least 54.76%, 56.52% and 41.18% of patients in the control, uncomplicated TBI and complicated mTBI groups respectively (see table 3). There was no significant difference in the BDI scores across all three groups ($F_{(2,102)}$ = 1,132 p = 0,326) (see table 2).Total BDI scores varied between 0-55, with an average of 18.94(±14.671) for the control group, 16.27(±11.708) for the uncomplicated mTBI group and 13.38(±9.904) for the complicated mTBI group. Using the BDI suggested cut-off, patients from all groups presented with mild depressive symptoms. Such symptoms were present in, 50.79%, 44.00% and 50.00% of patients in the uncomplicated, complicated and control group respectively (see table 3).

Insert Table 3 about here

Thirty-two patients (16.16%) had benign paroxysmal positional vertigo (BPPV) after trauma. There was a significant difference in the presence of BPPV or vestibular problems between groups ($X^2 = 11.130$, $p = .004$) (see table 2). Indeed, in the complicated TBI group, a significantly higher percentage of patients presented with vestibular impairment after the accident (50%) compared to the percentage of uncomplicated TBI (14.14%) and control (11.4%) patients. Further analyses were done to highlight differences between individuals with and without vestibular impairment (table 4). No differences were found between groups across all variables (age, education, employment, pre-injury alcohol abuse, pre-injury drug abuse, previous TBI, neurological pre-existing condition, pre-injury mental health, post-traumatic stress, GSC score, Rivermead post-concussion questionnaire score, Beck depression scale-II score, the Beck anxiety inventory, the Headache Impact Test™ and MOS sleep scale score).

Insert Table 4 about here

Variables interactions

The correlation matrix for the 5 measures is reported in table 5. The MOS index 1 negatively correlated with all other measures due to its inverse scale where problem "infrequency" was granted a higher score as opposed to the other four measures in which a higher score indicates more problems. The correlation matrix indicated strong correlations and significant associations between the Rivermead scores, the BDI scores ($r = 0.686$, $p<.001$), BAI scores ($r= 0.589$, $p<.001$), HIT-6 scores ($r= 0.615$, $p<.001$) as well as the MOS Index scores ($r= -.342$, $p<.001$).

Insert Table 5 about here

Discussion

The purpose of this study was to determine if patients from a complicated TBI group, an uncomplicated TBI group and a non-TBI injured control group, matched in terms of pre-existing condition and accident-relation characteristics, differed with respect to the presence and

presentation of acute post traumatic symptoms, so called post-concussive symptoms (PCS), headaches, sleep disorders and psychological status. Furthermore, the presence of a link between PCS and headaches, sleep disorders, and psychological status was studied. Contrary to our hypothesis, no differences were found between groups in term of post-concussive symptoms (PCS), mood, sleep disorders and headaches. All groups of individuals, with and without mTBI, experienced post-traumatic symptoms acutely and consistent with expectation all outcomes variables, such as depression and anxiety symptoms, sleep difficulties and headache, correlated with PCS (Bryant, 2008; Hoge et al., 2008; Stulemeijer et al., 2008). The groups only differed with respect to vestibular impairment (VPPB), present in the complicated mTBI group only.

At two weeks post-accident, all groups experienced mild depressive symptoms, mild to moderate anxiety symptoms, reported post-traumatic symptoms, sleep problems and headaches. More specifically, about 40% to 50% of patients from the mTBI groups and 50% of patients from the injured control group experienced at least mild depressive symptoms. Mild to moderated anxiety was reported in at least 54% of mTBI patients (uncomplicated and complicated) and 41% of the injured-control patients. 76% of uncomplicated mTBI, 64% of complicated mTBI and 89% of injured control patients also experienced headaches. All groups considered their headaches severe enough to impact their life. All groups stated having sleep issues. Indeed, respectively 84%, 63% and 73% of the groups' patients considered having some sleep difficulties «some of the time and a good bit of the time», and all groups experienced a high rate of PCS. Consistent with our expectations, high rates of acute PCS were found in mTBI and no-TBI injured trauma patients (Meares et al., 2008; Meares et al., 2011; Mittenberg et al., 1992; Ponsford et al., 2000). In fact, PCS have been reported in the normal population (Kashluba, Casey, et Paniak, 2006; Luis, Vanderploeg, et Curtiss, 2003), in non-brain injury trauma patients (Landre et al., 2006; McCauley, Boake, Levin, Contant, et Song, 2001; Meares et al., 2008) and in other clinical groups (Meares et al., 2008). These findings provide further evidence that PCS are not mTBI-exclusive.

Thus, it could be argued that PCS are not specific to mTBI patients, but are common to trauma patients who were involved in a traumatic accident and who sustained traumatic injuries (head or otherwise). In fact, many TBI after effects, especially in mild injury cases, are not specific to TBI; making it important to control for potential confounds in order identify TBI-related

consequences (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Meares et al., 2008). Recently, even orthopedic control group use for mTBI studies has been challenging (Hanten et al., 2013; McCauley et al., 2014). Since self-reported post-concussion symptoms are not considered exclusive to head injuries per se (e.g. orthopedic injuries report similar post-concussive symptoms as mTBI), the International Collaboration on Mild Traumatic Brain Injury Prognosis has recommended the use of the term "post-traumatic symptoms" instead of "post-concussion syndrome" (Cassidy et al., 2014). However, an appropriate comparison group is needed to determine whether factors are mTBI-specific (Kristman et al., 2014). The lack of which may play a major role in the inconsistencies found in previous research. Orthopedic trauma (injured-control) patients have long been considered to better control for these confounding variables due to their demographic and psychological similarities to TBI groups (e.g. young males engaged in risk-taking activities, involvement in drug and alcohol, hospitalization, injury-related pain and medication use, injury-related stress) (De Monte, Geffen, May, et McFarland, 2010; Dikmen et Levin, 1993; Milders, Ietswaart, Crawford, et Currie, 2006; Rieger et Gauggel, 2002; Satz, 2001; Satz et al., 1997; Satz et al., 1999; Scheibel et al., 2009; Statistics., 2008). Adding a community comparison group could allow the assessment of trauma-related after effects and identification of mTBI-specific factors (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Ettenhofer et Barry, 2012; Satz, 2001; Satz et al., 1999). On the other hand, Mathias and colleagues (Mathias, Dennington, Bowden, et Bigler, 2013) argued that these two control groups are comparable across all variables, and that the use of an orthopaedic control group does not provide any clear advantage over the use of a community control group. It is possible to hypothesize that there are differences between the injured control groups used in our study and in previous studies. Indeed, patients may develop atypical symptoms, as was observed amongst our group while others may present with very few to no symptoms as was seen in the Mathias (Mathias et al., 2013) study where very few differences were noted between an injured patient group and an uninjured control group. To be classified under 'injured control', a patient must have sustained a traumatic injury. Patients with a non-traumatic injury such as a laceration or sprain must be excluded from said group as such an injury may lead to completely different symptoms.

The fact that all groups in the present study experienced PCS may reflect the contribution of several factors. A number of factors may contribute to PCS-like symptom development (Carroll,

Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Ponsford et al., 2000). Indeed, PCS are associated psychological outcome (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Ponsford et al., 2000) as stated in the postconcussional syndrome model of Hou (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Ponsford et al., 2000). In fact, predisposing factor (personality trait of anxiety), precipitating factors (TBI or accident trigger initial symptoms) and precipitating factors such as cognitive (illness perception; perceived stress), emotion (anxiety; depression) and behavior (all or nothing behavior; limiting behavior) contribute to the persistence and the severity of the PCS in injured patients. For instance, the accidents may provide a basis for the injured patients beliefs/conviction that they have a condition outside their control and consequently individuals' may attribute their non-specific pre-existing complaints to the injury, misinterpreting these as negative consequences of the injury (de Guise et al., 2010). The presence of anxiety and depression symptoms may explain the PCS-like symptoms in all groups. That is, PCS are associated psychological outcome (Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, Pepin, et al., 2004; Ponsford et al., 2000). In a prospective study, where mTBI patients and non-TBI trauma controls were compared, the presence of pre-existing depressive or anxiety disorders as well as acute posttraumatic stress five days post-injury were found to be significant predictors of PCS development (Meares et al., 2011). McCauley and colleagues (McCauley et al., 2001) reported that being female, having poor social support and reporting depressive symptoms one month post-injury significantly increased the risk of experiencing PCS. Thus, the fact that mTBI patients and non-TBI trauma patients were found to both experience anxiety and depression post-trauma could contribute to acute PCS onset. Both mTBI and non-TBI patients experienced a similar injury-related trauma mechanism. In fact, the significant correlations found across all outcome measures in the present study support this assumption.

The use of subjective self-report questionnaires, relying of patient perception, may have influenced the results of the present study and that of other studies, which used similar tools to assess post-accident symptoms. Thus, it can be said that benign paroxysmal positional vertigo (BPPV) assessment, done with the Dix-Hallpike test or the Nylen-Barany test, a diagnostic maneuver used to identify BPPV, was the sole objective outcome measure evaluated in the present study. The current results are of significant interest since they demonstrated that the presence of

vestibular impairment differs between groups depending on whether or not a brain lesion is observed on the CT scan. Complicated mTBI patients, with CT scan visible brain lesions (CT-positive), had more frequent vestibular impairment than the CT-negative uncomplicated mTBI group. A positive CT scan is thus the only factor found to impact vestibular impairment. These findings would suggest that vestibular function should be systematically assessed following a mTBI, particularly so if the CT scan is positive and if patients present with vertigo complaints. It is probable that a higher trauma impact (intracranial bleed) caused the vestibular impairment among complicated mTBI patients. Those findings are consistent with a study in which (de Guise et al., 2010), vestibular impairment was found to be more frequent when the cerebral injury was observed on CT scan.

A limitation of the current study is the large proportion (58.08%) of females in the experimental sample, comprised of a total of 198 participants. Indeed, females formed the majority of the sample in each group. Group gender disparities may be problematic since females are more prone to developing PCS than males. This may explain the prevalence of PCS across all groups. (McCauley et al., 2001; Meares et al., 2008; Ponsford et al., 2000). Furthermore, hospitalized patients were not included in the present study. It is possible that the assessed complicated mTBI cases were less severe than those warranting hospitalization. The lack of difference between uncomplicated and complicated mTBI groups could thus be due to the fact the latter group did not differ enough from the former in terms of injury severity. Excluding hospitalized mTBI population entails that, the conclusions of this study may be not generalized to this patient population. On the other hand, the injured control group, who need a follow-up with a physician specialized in physical rehabilitation, may have sustained more severe or complex orthopedic injuries that required a medical follow-up and care than the ones who do not need a medical follow-up in a specialized trauma clinic. These symptomatic patients may be at greater risk of developing concomitant, atypical or more persistent pain issues than the ones seen only in the emergency or who were followed-up by their family physicians. Medical complications may be a factor that increases the risk of developing other symptoms, such as cognitive, psychological, headache or sleep problems.

The lack of differences between all three experimental groups raises important questions regarding the sensitivity of PCS assessment tools. The low sensitivity of some measures used to

assess cognition, psychological, physical and behavioral status may explain the absence of between-group differences. Insufficient sensitivity could incorrectly identify post-traumatic symptoms in individual. This study also highlights major pitfalls in the widespread use of self-reported questionnaires. Indeed such tools rely on a patient's own perception of his or her symptoms, and are not objective measures. It is possible that objective measures such as neuropsychological and medical evaluations yield different clinical profiles? Thus can the discrepancy between self-reported results and objective evaluations explain the lack of difference? Regardless, self-reports should not be used as diagnostic or prognostic tools. Indeed, performing a more in-depth evaluation aimed at identifying TBI-specific symptoms and developing more probing questionnaires would help shed light on the differences between the two groups. Using questionnaires aimed at family members for instance, might be useful in providing corroborating diagnostic evidence.

In conclusion, the high PCS prevalence in trauma patients was observed independently of traumatic brain injury status. In the present study, PCS was not specific to mTBI, but correlations were shown among PCS for all mild TBI and injured patients. This study has shown that patients with complicated mTBI were more likely to have vestibular impairments following their traumatic brain injury. This finding provides a significant contributed to the literature by providing evidence that vestibular function must be systematically assessed following a complicated mTBI. If patients, even non-TBI patients, complain about vertigo or dizziness, it is suggested that they should be taken over or at least monitored for psychological factors, sleep difficulties and pain following their accident. All practitioners should consider a phone follow-up or a follow-up at the trauma clinic. Furthermore, adding a healthy control group, and using more sensitive measures could enable researchers to pinpoint which symptoms are mTBI-specific amongst the varied trauma-induced symptoms. Finally, clinicians should always base their mTBI diagnosis on operational criteria, and not patient reported symptoms, as the latter may lead to a false mTBI diagnosis.

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Table 1

Demographic, pre-injury and injury statistics by groups

Variable	N	M (SD)	χ2 or F	p	Injured controls	Uncomplicated mTBI	Complicated mTBI
Gender							
Females	115	-	**χ2 = 3.123**	**0.21**	26	69	20
Males	83	-	-	-	15	45	23
Age							
Injured control	41	38,15 (16,234))	**F = 0.771**	**0.464**	-	-	-
Uncomplicated mTBI	114	40,15 (16,885))	-	-	-	-	-
Complicated mTBI	43	42,81 (19,527)	-	-	-	-	-
Marital status							
Single	66	-	**χ2 = 3.372**	**0.909**	16	39	11
Married	62	-	-	-	12	40	10
Divorced/separated	11	-	-	-	1	8	2
Widower	4	-	-	-	0	3	1
Unknown	7	-	-	-	1	4	2
Years of education							
1 to 6 yrs	2	-	**χ2 = 2.005**	**0.735**	0	2	0
7 to 13 yrs	28	-	-	-	4	17	7
14 and more	119	-	-	-	24	71	24
Employment							
Manuel work	13	-	**χ2 = 6.168**	**0,801**	2	10	1
Service/Technique	62	-	-	-	11	37	14
Management/ Teacher	52	-	-	-	10	30	12
Student	30	-	-	-	7	17	6
Unemployed	12	-	-	-	3	4	5
Retired	15	-	-	-	3	8	4
Alcohol abuse before the trauma							
No	158	-	**χ2 = 5.186**	**0.075**	34	94	30
Yes	36	-	-	-	5	18	13
Drug abuse before the trauma							
No	177	-	**χ2 = 2.482**	**0.289**	38	102	37
Yes	15	-	-	-	1	9	5

Previous TBI							
No	143	-	**χ2 = 0.703**	**0.704**	32	82	29
Yes	53	-	-	-	9	32	19
Neurological pre-existing condition							
No	180	-	**χ2 = 0.135**	**0.935**	38	104	38
Yes	17	-	-	-	3	10	4
Previous psychological issues							
No	134	-	**χ2 = 0.050**	**0.975**	28	77	29
Yes	61	-	-	-	12	36	13
Variables related to the accident							
Post-traumatic stress							
None	160	-	**χ2 = 5.280**	**0.508**	30	93	37
Acute stress disorder	11	-	-	-	3	6	2
Adjustment disorder	12	-	-	-	5	6	1
Posttraumatic stress disorder	3	-	-	-	0	2	1
Glasgow Coma Scale (GCS)							
7	1	-	**χ2 = 10.479**	**0,4**	0	0	1
8	1	-	-	-	0	1	0
11	2	-	-	-	0	1	1
13	1	-	-	-	0	0	1
14	7	-	-	-	0	4	3
15	37	-	-	-	11	18	8
Alcohol intoxication upon admission							
No	175	-	**χ2 = 2.647**	**0.266**	38	102	35
Yes	16	-	-	-	1	10	5

Note. mTBI= mild traumatic brain injury; M = Means; SD= Standard erreur; N = Number of person

Table 2

Outcomes (means) comparison between uncomplicated TBI, complicated TBI and injured controls

	Numerical variables of outcome					
Outcome measure	M no TBI	M uncomplicated TBI	M complicated TBI	M total (SD)	F or X^2	P
Rivermead Post-Concussion Questionnaire	32.34 (16.683)	27.18 (15.462)	27.44 (14.210)	28.31 (15.523)	1.763	0.174
The Headache Impact Test™	61,00 (9.965)	57.78 (11.055)	54.71 (12.174)	57.55 (11.275)	2.014	0.138
MOS Sleep Scale						
Q1 Sleep latency	3.32 (1.644)	3.14 (1.402)	2.84 (1.393)	3.09 (1.444)	10.346	0.411
Q2 Total hours sleep	7.14 (2.798)	7.22 (2.701)	7.26 (2.352)	7.22 (2.611)	0.012	0.988
Q3 Sleep not quiet	3.32 (1.974)	3.36 (1.693)	3.75 (1.430)	3.46 (1.676)	11.633	0.476
Q4 Get enough sleep	4.05 (1.649)	3.85 (1.506)	3.93 (1.412)	3.90 (1.497)	13.785	0.315
Q5 Awaken short of breath or headache	3.74 (1.910)	4.10 (1.709)	4.50 (1.347)	4.14 (1.664)	8.894	0.712
Q6 Drowsy or sleepy during the day	3,05 (1,268)	3,07 (1,582)	3.57 (1.345)	3.20 (1.476)	11.406	0.494
Q7 Trouble falling asleep	3.11 (1.663)	2.98 (1.578)	3.89 (1.524)	3.24 (1.610)	13.104	0.362
Q8 Awaken during sleep time	3.32 (1.455)	3.28 (1.541)	3.64 (1.393)	3.38 (1.484)	4.097	0.982
Q9 Trouble staying awake	4.37 (1.606)	3.92 (1.465)	4.22 (1.423)	4.08 (1.478)	7.457	0.826

Q10 Snoring	4.35 (1.618)	4.50 (1.777)	4.29 (1.761)	4.41 (1.731)	5.990	0.0917
Q11 Naps (≥5 minutes)	3.56 (1.756)	3.47 (1.780)	3.75 (1.602)	3.56 (1.719)	2.361	0.999
Q12 Get amount sleep	3.47 (1.736)	3.75 (1.578)	3.33 (1.519)	3.59 (1.584)	16.628	0.164
Beck Depression Scale-II	18,94 (14,671)	16,27 (11,708)	13.38 (9.904)	16.07 (11.887)	1,132	0,326
Beck Anxiety Inventory	17.47 (17.759)	15.59 (12.276)	14.04 (10.227)	15.59 (13.126)	0.350	0.706
Vestibular Impairment (presence vs absence)	4/39 vs 35/39	14/113 vs 99/113	14/42 vs 28/42	---	11.130	0.004*

Note: M= means; SD = standard deviation; TBI = traumatic brain injury.
*p <.01

Table 3

Number of uncomplicated, complicated and injured-controls patients by categories in headache, sleep and mood questionnaires

HIT-6	Uncomplicated mTBI	Complicated mTBI	Injured-controls	Total
49 or less	16	11	2	29
50-55	9	2	5	16
56-59	4	4	3	11
60 and more	39	14	9	62
Total	68	31	19	118

MOS Q1 + Q3 to 12	Uncomplicated mTBI	Complicated mTBI	Injured-controls	Total
Less than 40	40	9	7	56
40-44	18	8	4	30
45 and more	11	10	4	25
Total	69	27	15	111

MOS Q2	Uncomplicated mTBI	Complicated mTBI	Injured-controls	Total
Less than 7 h	33	13	7	53
Between 7 h and 8 h	17	9	7	33
More than 8 h	18	9	5	32
Total	68	31	19	118

Beck Depression Inventory	Uncomplicated mTBI	Complicated mTBI	Injured-controls	Total
0-13 (minimal)	31	14	8	53
14-19 (mild)	10	4	3	17
20-28 (moderate)	12	4	2	18
29-63 (severe)	10	3	3	16
Total	63	25	16	104

Beck Anxiety Inventory	Uncomplicated mTBI	Complicated mTBI	Injured-controls	Total
0-9 (minimal)	19	10	10	39

10-16 (mild)	3	4	0	7
17-29 (moderate)	15	8	3	26
30-63 (severe)	5	1	4	10
Total	42	23	17	82

Table 4

Comparisons between patients who suffered or not of a vestibular impairment post-accident

Variable	**Numerical variables**	
	F ou X^2	**P**
Age	2.185	.141
Education (years)	.964	.617
Employment	9.075	.106
Pre-injury alcohol abuse	3.371	.066
Pre-injury drug abuse	1.156	.282
Previous TBI	.046	.830
Neurological pre-existing condition	1.468	.226
Pre-injury mental health issue	.038	.845
Variables related to the accident		
Post-traumatic stress	1.340	.720
Glasgow Coma Scale score	2.601	.761
Rivermead Post-Concussion Questionnaire	.221	.639
The Headache Impact Test™	3.378	.069
MOS Sleep Scale		
Q1	9.684	.085
Q2	.340	.561
Q3	4.251	.643
Q4	7.618	.267
Q5	12.628	.049
Q6	9.379	.153
Q7	10.699	.098
Q8	1.571	.955
Q9	2.400	.880
Q10	2.178	.903
Q11	7.257	.298
Q12	6.676	.352
Beck Depression Scale-II	1.772	.187
Beck Anxiety Inventory	3.113	.081

*p <.01

Table 5

Correlation matrix for outcome measures

	Beck Anxiety	Beck Depression	HIT-6 Total	MOS Index 1
Beck Anxiety				
Beck Depression	0.658**			
HIT-6 total	0.607**	0.566**		
MOS Index 1	-0.347*	-0.450**	-0.292*	
Rivermead Total	0.589**	0.686**	0.615**	-0.342**

** $p < 0.001$
* $p < 0.01$

Annexe B

Article 4

Antithrombotic agents intake prior to injury does not affect outcome after a traumatic brain injury in hospitalized elderly patients

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Abstract

Background: The purpose of this study is to investigate the effect of risk factors including international normalized ratio (INR) as well as the Partial thromboplastin time (PTT) scores on several outcomes, including hospital length of stay (LOS) and The Extended Glasgow Outcome Scale (GOSE) following TBI in the elderly population. **Methods:** Data were retrospectively collected on patients (n = 982) aged 65 and above who were admitted post TBI to the McGill University Health Centre-Montreal General Hospital from 2000 to 2011. Age, Injury Severity Score (ISS), Glasgow Coma Scale score (GCS), type of trauma (isolated TBI vs polytrauma including TBI), initial CT scan results according to the Marshall classification and the INR and PTT scores and prescriptions of antiplatelet or anticoagulant agents (AP/AC) were collected. **Results:** Results also indicated that age, ISS and GSC score have an effect on the GOSE score. We also found that taking AC/AP has an effect on GOSE outcome, but that this effects depends on PTT, with lower odds of a worse outcome for those taking AC/AP agents as the PTT value goes up. However, this effect only becomes significant as the PTT value reaches 60 and above. **Conclusion:** Age and injury severity rather than antithrombotic agent intake are associated with adverse acute outcome such as GOSE in hospitalized elderly TBI patients.

Key words: Traumatic brain injury, older age, aging, Level 1 trauma center, outcome.

In 2011 in Canada, individuals aged 65 years old and over accounted for 15% of the population. By 2031, it is projected that they will account for one quarter of Canada's entire population (Statistics Canada, 2011). The tendency is comparable to the United States where approximately one in five individual is expected to be 65 years or older in 2030 (Bruns et Hauser, 2003). The elderly population is at greater risk of sustaining traumatic brain injury (TBI), with approximately 30% of people aged 65 years or older falling each year, and one fifth of the falls requiring medical care (Gillespie et al., 2003). In Canada, falls are the leading cause of injury for individuals in this age bracket and also contribute to a significant burden on the health care system. Direct health care costs for falls are estimated at $2 billion annually (Parachute, 2014). In a previous study, falling was found to be the main cause of hospitalized TBI patients over 70 years old (52%), followed by vehicle accidents (32.7%) and work accidents (10.3%) (de Guise et al., 2015).

Anticoagulants are frequently used in seniors (Sachdev, Ohlrogge, et Johnson, 1999) and with the aging of the population, clinicians will see more and more patients using anticoagulants. But this class of medication in the context of TBI may cause difficult dilemma for clinicians who have to balance the risk of intracranial bleed with the risk of thrombo-embolic complications. Benefits of chronic anticoagulation have been documented in some clinical population (Hart, Benavente, McBride, et Pearce, 1999; van Walraven et al., 2002) but there is still a lack of consensus regarding the risks of this medication in TBI patients. There are some studies which suggested that mortality and morbidity in elderly patients taking anticoagulation medication is worse than without this pharmacological treatment before trauma (Ferrera et Bartfield, 1999; Lavoie et al., 2004). A recent study has demonstrated that normalization of international normalized ratio (INR) was associated with decreased mortality in isolated TBI patients with acute traumatic anticoagulopathy (Epstein, Mitra, Cameron, Fitzgerald, et Rosenfeld, 2016). Moreover, therapeutic anticoagulation with warfarin, rather than warfarin use itself, is associated with adverse outcomes after TBI in elderly patients (Pieracci, Eachempati, Shou, Hydo, et Barie, 2007). Previous studies have also shown that anticoagulation is associated with a higher risk of bleeding after TBI, a higher frequency of isolated head trauma, a higher risk of intracranial hemorrhage, and a higher mortality rate (Gittleman, Ortiz, Keating, et Katz, 2005; Karni et al., 2001). Being on anticoagulant

also significantly increases the mortality of a traumatic intracranial bleed (Cohen, Rinker, et Wilberger, 2006; Mina et al., 2002).

However, controversial outcomes were reported from studies in the anticoagulated TBI population (Cull et al., 2015; Kennedy, Cipolle, Pasquale, et Wasser, 2000; Lavoie et al., 2004; Wojcik, Cipolle, Seislove, Wasser, et Pasquale, 2001). In some studies, no increase in mortality is reported in anticoagulated trauma patients when controlling for the GCS and ISS (Cull et al., 2015; Kennedy et al., 2000; Wojcik et al., 2001). The controversies may be caused by several factors not systematically controlled in all studies, such as the sample size, the age and the severity of the TBI or the absence of INR upon admission to confirm anticoagulation (Wojcik et al., 2001). For example, a systematic review done recently has revealed that the incidence of delayed intracranial hemorrhage is low among patients on warfarin with minor head injuries (Miller et al., 2015). They also suggested that differences in the risk of delayed intracranial hemorrhage were related to the difference among age groups (Miller et al., 2015). Moreover, age differences among groups were present in studies that compared TBI patients using warfarin with nonusers (Franko, Kish, O'Connell, Subramanian, et Yuschak, 2006) as well as differences in comorbidities (Lavoie et al., 2004; Wojcik et al., 2001) and mechanisms of injury (Karni et al., 2001; Lavoie et al., 2004). These differences led Pieracci and colleagues (Pieracci et al., 2007) to suggest that all these variables account for a worse outcome instead of the anticoagulation effect per se.

In light of previous studies, larger studies are necessary to refine the evaluation of outcomes, especially with regards to the level of anticoagulation. In addition, using the patients' admission international normalized ratio (INR) as well as the Partial thromboplastin time (PTT) scores values to document anticoagulation is robust and innovative. The objective of this study is to investigate the effect of risk factors including INR and PTT scores on outcome following TBI. We hypothesized that higher levels of INR and PTT combined with the use of antithrombotic agents will be associated with longer length of stay in acute care setting and a worse outcome following acute care hospitalization, when controlling for age and TBI severity.

Methods

Participants

All patients aged 65 and above with a diagnosis of TBI admitted to the McGill University Health Centre - Montreal General Hospital (MUHC-MGH) between 2000 and 2011 were included in this study. They were identified using the Trauma Registry and the TBI program database. Patients not admitted or seen only at the emergency department were not included in this study. In this study, we were interested to the outcome of hospitalized patients. We performed a retrospective study of all charts (in-patient hospital charts) and excluded patients where 1) charts were missing or were incomplete after multiple attempts to locate them 2) no outcome information was collected. The institutional research ethics board approved this retrospective study.

Variables measured

Demographic characteristics

Gender and age were collected from the medical charts.

Medical and accident related characteristics

The Glasgow Coma Scale score (GCS) upon admission to the emergency room was used to determine TBI severity. A GCS score of 13-15 indicates a mild TBI, 9-12 a moderate TBI, while a score of 3-8 a severe TBI. Also, the Injury Severity Scores (ISS) was obtained from patient charts. The type of trauma was also collected in the medical charts (isolated TBI vs polytrauma including TBI which correspond to at least three injury sites) as well as the presence or absence of traumatic intracranial hemorrhage (TICH). Initial CT scan results were classified according to the Marshall classification by a neurosurgeon blind to the testing procedure as part of the clinical evaluation. This classification includes (1) no visible intracranial pathology; (2) cisterns present; midline shift: 0-5 mm and/or lesion densities present; no high/mixed density lesions >25ml; (3) cisterns compressed or absent; midline shift:0-5 mm; no high/mixed density lesions >25ml; (4) midline shift >5 mm; no high/ mixed density lesions >25ml; (5) evacuated mass lesion (any lesion surgically evacuated) (6) non evacuated mass lesion (high/mixed density lesions >25ml, not surgically evacuated (Marshall, Marshall, et Klauber, 1999). Qualitative information regarding the type (intracerebral, subarachnoid and skull base fracture) and the sites of cerebral injuries were obtained: (1) basal-frontal, (2) prefrontal, (3) non-basal frontal (dorsolateral), (4) left and (5) right temporal, (6) occipital. The International Normalized Ratio (INR) as well as the Partial

Thromboplastin Time (PTT) were collected as well as prescriptions of antiplatelet or anticoagulant agents (AP/AC).

Outcome variables

Length of Stay (LOS)

LOS was defined as the number of days the patient remained hospitalized in the acute care setting from admission to discharge.

The Extended Glasgow Outcome Scale (GOSE)

The GOSE assesses global outcome (Jennett, Snoek, Bond, et Brooks, 1981). For analysis, the values of this scale were collapse and reverse-coded from best to worse outcome into five categories, (1) scores of 7 or 8 correspond to good recovery referring to normal participation in social, vocational and physical life. (2) Scores of 5 or 6 indicate moderate disability describing the patient as independent but physically or cognitively disabled and requiring an altered physical, social, psychological or vocational environment for participation.(3) Patients with severe disabilities receive scores of 3 or 4 and are totally dependent in managing a normal or modified environment whereas (4) a score of 2 corresponds to a vegetative state reflecting total dependency with no awareness of the environment. (5) Patients who died receive a score of 1. The multidisciplinary team rated each patient on this scale at the time of his or her discharge.

Statistical analysis

Descriptive statistics are presented as means and standard deviations for variables in an interval scale when we had evidence that the values follow an approximately Normal distribution; otherwise medians and inter-quartile range (IQR) are reported. For categorical variables we report counts and percentages.

To investigate the marginal effect of the risk factors gender, age, ISS, GCS, TICH, Marshall classification scores. INR, PTT and AP/AC agents variables on the GOSE scores, we used the proportional odds, or cumulative logits, regression model to take into account the ordinal nature of the coding for this outcome. Results for these analyses are reported as odds ratios (OR) and 95% confidence intervals (CI). To investigate the marginal effect of the same risk factors on hospital

LOS we used regression models for competing risks. Considering death during hospitalization and other discharge destinations as mutually exclusive events, they can be treated as competing risks. These models allow to take into account information on those who die at the hospital and those who are eventually discharged alive, as analyzing only those who are discharged alive will create estimates of LOS in a hypothetical situation where patients will not die (Taylor, 1997). We used two approaches for this analysis (Latouche, Allignol, Beyersmann, Labopin, et Fine, 2013): a cause-specific hazards model (Proportional-hazards Cox model) and a direct model for the cumulative incidence functions (proportional sub-distribution-hazards Fine-Gray model) (Latouche et al., 2013). Results for these analyses are reported as hazard ratios and 95% CI.

All statistical tests of hypothesis were two-sided and carried out at the level of significance of 0.05. All analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient population

A total of 982 patients aged 65 years or more with a diagnosis of TBI were admitted to the Traumatic Brain Injury Program of the MUHC-MGH during this period. The cohort included patients with mild, moderate and severe TBI. The demographic, medical and accident related characteristics are presented in Table 1.

Insert Table 1 about here

Antithrombotic agents and coagulation status:

A total of 439 patients were taking an antithrombotic agent at the time of their admission, which represents 44.7% of the sample. Six hundred and ninety-two patients (70.4%) had an INR below 1.3 and another 78 (7.9%) had an INR below 1.5. Only 114 patients (11.6%) had an INR higher than 2.0, and 21 of those (2.1% of the total sample) had an INR above 3.0 with the maximal value seen at 4.89. There was no association between the presence of AC or AP at the time of admission and the Marshall grade score.

Outcome results

Table 2 shows descriptions of patient outcomes, the GOSE, discharge destination and LOS. The minimum LOS was 1 day and the maximum 187 days. Of these 968, a total of 162 (16.7%) died in the hospital, their minimum LOS was 1 day and their maximum 105 days. For those discharged (n=806) the minimum LOS was 1 day and the maximum 121 days. Regarding the GOSE scores, the great proportion of the cohort had moderate disabilities (52.3%) or even severe disabilities (26.3%).

Insert Table 2 about here

Glasgow Outcome Scale-Extended (GOSE)

Table 3 shows the results of a cumulative-logit model for the reverse-ordered categories of GOSE scores, as described in the *Outcome variables* section. The regression models the probability of being in a worse outcome category for GOSE scores. Results indicated that age, ISS and GSC score have an effect on the GOSE score. As age increases, the odds of having a worse outcome also increase (OR 1.10, 95%CI (1.08, 1.12)). The odds also increase as ISS increases (OR 1.03, 95%CI (1.01, 1.05)). However, odds of a worse outcome decrease with increased GCS score (OR 0.75, 95%CI (0.72, 0.78).

Insert Table 3 about here

We also found an interaction effect between PTT and the use of antiplatelet or anticoagulant agents (AP/AC) ($p = 0.01$). Results suggest that taking AC/AP has an effect on GOSE outcome, but that this effects depends on PTT, with lower odds of a worse outcome for those taking AC/AP agents as the PTT value goes up. However, this effect only becomes significant as the PTT value reaches 60 and above. Table 4 shows odds ratios for a worse outcome category for the reverse-coded GOSE scores comparing those taking AC/AP agents to those not taking AC/AP agents for different arbitrarily chosen PTT values in 10-year increments.

Insert Table 4 about here

Discussion

This study on post-TBI outcome in the elderly population included patients who required admission for their traumatic injury. It showed that age, GCS and ISS had significant impacts on the outcome (GOSE). These findings correlate with published literature on the subject on elderly patients (Cull et al., 2015; de Guise et al., 2015; McIntyre, Mehta, Janzen, et al., 2013; Ritchie, Cameron, Ugoni, et Kaye, 2000; Utomo et al., 2009).

Contrary to our hypothesis, the use of antithrombotic agents at the time of the traumatic event did not correlate with a prolonged length of stay. Likewise, the INR value did not correlate with outcome either. Only a high value of PTT correlated with a worse outcome, in the absence of antithrombotic agents. The later finding can probably be explained by a traumatic induced coagulopathy that is not secondary to anticoagulant intake or antiplatelet effect. Traumatic coagulopathy is usually seen in the presence of blood loss leading to hypoperfusion, and in significant tissue injury. Traumatic coagulopathy is strongly associated with mortality (Cardenas, Wade, et Holcomb, 2014; Davenport, 2014; White, 2013).

However, how could the use of antithrombotic agents not affect outcome? Possibly, by selecting for the study only admitted patients, we only see the tip of the iceberg. Patients with a traumatic event not on antithrombotic agents may be seen in the emergency department, have brain imaging but suffer only form a minor injury, requiring no admission to the hospital. While those on antithrombotic therapy tend to have a more severe injury and abnormal findings on CT and more often require admission. The present study was not designed to capture that eventuality. The finding that a large proportion of the patients in the present cohort (44.7%) were using antithrombotic agents could support this hypothesis. The exact rate of antithrombotic use in the general population aged 65 and above is not currently known. One study form Poland estimated the use of acid acetyl salicylic at 33.1% for the population aged 65 and over (Labuz-Roszak, Pierzchala, Skrzypek, Swiech, et Machowska-Majchrzak, 2012). Our findings suggest that anticoagulation or antiplatelet therapy did not alter the outcome once a traumatic brain injured patient was admitted to the hospital.

This retrospective study may have missed relevant patients who were not entered into the trauma database or were excluded because of missing data. In particular, it did not include patients seen in the emergency department only, without admission. Another limitation of the retrospective nature of this study is our inability to assess the patient's preinjury status. Many patients brought to most trauma centers do not receive regular care at that institution, and comorbidity and medication histories taken during resuscitation are either unavailable or unreliable. It is also possible that having an elevated INR may be associated with unmeasured comorbidities thereby introducing bias into our association between anticoagulation and mortality.

In conclusion, age and injury severity rather than antithrombotic agents intake are associated with adverse acute outcome in hospitalized elderly TBI patients.

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Disclosure

The authors report no conflicts of interest.

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Table 1

Demographic and clinical characteristics of the patients studied (N=982)*

Variable	
Age (years)	79.4 (72.6-84.8)
Gender (F)	427 (43.5)
Marshall Classification	
Diffuse Injury I	92 (9.4)
Diffuse Injury II	263 (26.8)
Diffuse injury III	197 (20.1)
Diffuse Injury IV	127 (12.9)
Evacuated mass lesion V	211 (21.5)
Non evacuated mass lesion VI	92 (9.4)
Presence of traumatic intracranial hemorrhage (TICH)	430 (43.8)
Type of trauma**	
Isolated traumatic brain injury	387 (57.4)
Polytrauma including traumatic brain injury	287 (42.6)
GCS	14 (13-15)
ISS***	25 (17-26)
INR	1.2 (1.1-1.4)
PTT	33.8 (30.3-39.0)

*Results are reported as or n (%) or median (IQR).
Legend: IQR=Interquartile range (25% percentile – 75% percentile); F: female;
GCS: Glasgow Coma Scale score; ISS: Injury Severity score; INR: International Normalized Ratio;
PTT: Partial Thromboplastin Time
**Data available on 674 patients
*** Data available on 952 patients

Table 2

Outcome results of the patients studied (N=982)*

Variable	
GOSE**	
7-8	13 (1.3)
5-6	508 (52.3)
3-4	256 (26.3)
2	31 (3.2)
1	162 (16.7)
LOS (days)	11 (5-22)

*Results are reported as or n (%) or median (IQR).
Legend: IQR: interquartile range (25% percentile – 75% percentile)
GOSE: Extended Glasgow outcome scale score; LOS: Length of stay
**Data available on 970 patients

Table 3

Results of the ordered logistic regression with inversed collapsed Glasgow outcome Scale-Extended GOSE scores (N=931)

Variable	OR (95% CI)	*p* value
Gender	0.87 (0.66, 1.14)	0.31
Age	1.10 (1.08, 1.12)	<0.0001*
ISS	1.03 (1.01, 1.05)	0.001*
GCS	0.75 (0.72, 0.78)	<0.0001*
INR	0.80 (0.61, 1.05)	0.11
PTT	1.00 (0.99, 1.02)	0.75
MC (vs. 6)		
1	0.84 (0.44, 1.58)	0.72
2	0.76 (0.46, 1.25)	0.18
3	0.85 (0.50, 1.44)	0.69
4	1.05 (0.60, 1.84)	0.36
5	0.95 (0.57, 1.58)	0.73
TICH	0.72 (0.54, 0.96)	0.03
AP/AC	1.09 (0.83, 1.43)	0.56

Legend: OR: Odds ratio; CI: confidence interval; ISS: Injury Severity Score; GCS: Glasgow Coma scale score; INR: International Normalized Ratio; PTT: Partial Thromboplastin Time; MC: Marshall Classification; TICH: Traumatic Intracranial Hemorrhage; AP/AC: presence of anticoagulant or antiplatelet at admission.

Table 4

Odds ratios for worse outcome category in GOSE scores for AC/AP agent by PTT

PTT	OR (95% CI)
10	2.59 (1.20, 5.57)
20	1.83 (1.09, 3.05)
30	1.29 (0.95, 1.77)
40	0.91 (0.68, 1.23)
50	0.65 (0.4, 1.05)
60	0.46 (0.22, 0.96)
70	0.32 (0.12, 0.88)
80	0.23 (0.06, 0.82)
90	0.16 (0.03, 0.76)
100	0.11 (0.02, 0.71)

Legend: PTT: Partial Thromboplastin Time; OR: Odds ratio; CI: confidence interval