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L'évaluation du système olfactif suite à un traumatisme craniocérébral léger (TCCL)

Par
Fanny Lecuyer Giguere

Département de psychologie
Faculté des Arts et Sciences

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Présentée par

Fanny Lecuyer Giguere

A été évaluée par un jury composé des personnes suivantes

Miriam Beauchamp

Président-rapporteur

Johannes Frasnelli

Directeur de recherche

Élaine de Guise

Codirectrice

Bruno Gauthier

Membre du jury

Philippe Rombaux

Examinateur externe

RÉSUMÉ

Au cours des deux dernières décennies, plusieurs études ont révélé la présence de troubles olfactifs suite à des traumatismes crâniens (TCC) modérés et sévères. Spécifiquement, les précédents auteurs ont montré que, suite à leur TCC, plusieurs patients présentaient des pertes quantitative (hyposmie, anosmie) et qualitative (parosmie) de leur odorat. Dans le cas des TCC de types modérés et sévères, la présence de tels troubles est généralement causée par l'effet de coup-contre coup provoquant des lésions du nerf olfactif pénétrant dans la lame criblée de l'ethmoïde ainsi que par des contusions et des hémorragies au niveau du bulbe olfactif et des régions corticales traitant les stimuli olfactifs. En effet, puisque ces types de TCC provoquent des lésions assez apparentes, il a été facile de comprendre la nature de tels troubles ainsi que d'identifier les patients à risque de développer des pertes olfactives. Un suivi de ces patients est d'autant plus nécessaire puisque différentes études ont démontré des associations entre les pertes olfactives suite au TCC et la chronicisation de troubles de l'humeur (dépression, anxiété) et cognitifs. En effet, il a été démontré que, les patients développant des troubles olfactifs suite à un TCC modéré/sévère, présentaient davantage de symptômes d'anxiété et de dépression plusieurs semaines suite au trauma, lorsque comparés à des patients n'ayant pas de troubles olfactifs. En revanche, il n'y a que trois études qui ont, jusqu'à aujourd'hui, étudié la présence de troubles olfactifs et leurs conséquences auprès de patients ayant subi un traumatisme craniocérébral léger (TCCL), malgré le fait qu'ils représentent près de 85% des patients TCC. De plus, dû à la présence de plusieurs faiblesses méthodologiques dans les précédentes études (choix d'outils d'évaluation non valides, omission de groupe contrôle) une grande hétérogénéité, en ce qui a trait à la proportions de patient TCCL vivant avec un trouble olfactif, est retrouvée dans la littérature. Ainsi, les études composant le présent ouvrage visent globalement à évaluer, à l'aide d'une méthodologie valide et contrôlée, la réelle proportion de patients ayant subi un TCCL qui développeront un trouble olfactif. De plus, un regard sera posé sur les capacités prédictives de la présence de troubles olfactifs suite au TCCL sur le développement, à long terme, de symptômes anxieux et dépressifs.

La première étude visait à évaluer la présence de troubles olfactifs dans les premières 24 heures et un an suite au TCCL. Les résultats de cette étude transversale, à caractère exploratoire, ont démontré que, en phase aiguë, plus de la moitié des patients ayant subi un TCCL présentaient une perte partielle de leur odorat (hyposmie). En effet, lorsque comparée à un groupe de patient

contrôle, ayant subi une blessure orthopédique, la proportion de patients TCCL ayant un trouble olfactif suite à leur accident s'est révélée significativement plus élevée. Lorsqu'évalués un an suite à leur TCCL, les patients ne présentaient plus de troubles olfactifs et aucune différence significative ne fut retrouvée entre les patients TCCL et orthopédique. Cependant, lorsque nous avons comparé les patients TCCL qui, à l'évaluation initiale, présentaient un trouble olfactif (OD+) à ceux qui n'en présentaient pas (OD-) à l'évaluation initiale, nous avons trouvé que les patients TCCL OD+ rapportaient significativement plus de symptômes anxieux et post-commotionnels, lorsqu'évalués un an suite à leur trauma.

La deuxième étude de cet ouvrage visait à approfondir les résultats de la précédente, à l'aide d'un plus grand groupe de patients, d'un devis longitudinal ainsi que l'implantation de nouveaux outils d'évaluation permettant d'évaluer un plus large spectre de symptômes post-commotionnels. Dans cette étude, l'olfaction et l'humeur des patients ayant subi un TCCL furent évaluées 1 et 6 mois suite au trauma. Les résultats montrent que, lorsque comparé à un groupe de participants contrôles, une proportion significativement élevée de patients TCCL rapporte avoir remarqué une distorsion de leur olfaction (parosmie), 1 et 6 mois suite au trauma. De plus, les analyses de régression hiérarchique indiquent qu'au sein du groupe de patients TCCL, la présence de parosmie au premier temps de mesure (court-terme) augmente significativement la valeur du modèle de prédiction de la présence de symptômes dépressifs et anxieux à long terme.

En somme, ces deux études ont permis de dresser un portrait beaucoup plus précis de la réelle proportion de patients TCCL qui risquent de développer un trouble olfactif. En effet, grâce aux divers contrôles méthodologiques que nous avons appliqués, les présents résultats permettent de peindre un portrait plus réaliste de la présence, à court et long-terme, de troubles olfactifs suite à un TCCL. Ainsi, ces deux projets ont mis en lumière des proportions allant bien au-delà de ce qui est recensé dans le peu de littérature disponible à ce jour. De plus, il semble que la présence initiale de troubles olfactifs suite au TCCL soit un prédicteur significatif du développement des symptômes d'anxiété et de dépression des patients.

Mots-clés : traumatisme craniocérébral léger, commotions cérébrales, olfaction, anosmie, hyposmie, parosmia, anxiété, dépression, qualité de vie, santé générale, longitudinale, transversal

ABSTRACT

Over the last two decades, several studies have revealed the presence of olfactory disorders (OD) following moderate and severe traumatic brain injuries (TBI). Specifically, previous authors have shown that, following a TBI, several patients had quantitative (hyposmia/anosmia) and qualitative (parosmia) loss of sense of smell in important proportions. For moderate and severe TBI, the presence of such disorders, following trauma, is usually due to a coup-contrecoup mechanism responsible for the shearing of olfactory nerves penetrating the cribriform plate or to contusions or secondary hemorrhages within the olfactory bulb and cortical olfactory areas. Since these types of TBI cause obvious lesions, it was relatively simple to understand the nature of such disorders as well as identify the patients at risk of developing olfactory losses. A close follow-up of these patients is necessary since different studies have demonstrated associations between OD following TBI and long-term development of mood (depression, anxiety). Patients developing OD following moderate to severe TBI exhibited more symptoms of anxiety and depression for several weeks following the trauma, when compared to patients without OD. On the other hand, there are only three studies that have investigated the presence of OD and their consequences in patients with mild traumatic brain injury (mTBI), even though they represent nearly 85% of TBI. Moreover, due to the presence of several methodological flaws (choice of invalid evaluation tools, omission of a control group) a great heterogeneity regarding the proportion of mTBI patients who develop OD after the trauma, is found within the literature. So, the studies included in this thesis aim to give, with the establishment of a valid and controlled methodology, the very first idea of the proportion of patients with mTBI who will develop quantitative and qualitative OD. In addition, the predictive value of OD following mTBI on the development of anxiety and depressive symptoms and general health, is also covered in the manuscript.

The first study aimed to assess the presence of olfactory disorders within the first 24 hours and one year after the mTBI. The results of this cross-sectional study demonstrated that, in the acute phase, more than half of the patients with mTBI exhibited a partial loss of their sense of smell (hyposmia). In fact, when compared to an orthopedic control group, the proportion of mTBI patients with OD following their accident was significantly higher. When evaluated one year after their mTBI, the patients did not have OD and no significant difference was found between control and mTBI groups. However, when comparing mTBI patients with OD (OD+) to those who did not

present OD (OD-) at baseline, we found that OD+ mTBI patients reported significantly more anxiety and post-concussion symptoms, when evaluated one year following their trauma.

The second study of this thesis aimed to deepen the results of the previous one, with the help of a larger group of patients, a longitudinal design as well as the implementation of new tools in order to evaluate a broader spectrum of post-concussive symptoms. In this study, olfaction and mood of patients with mTBI were evaluated 1 and 6 months following the trauma. The results show that, when compared to a group of control participants, a significantly high proportion of mTBI patients report a distortion of their olfaction (parosmia), 1 and 6 months following the trauma. In addition, the hierarchical regression analyzes indicate that, within the mTBI group, the presence of baseline parosmia significantly increases the value of the predictive model for the development of depression and anxiety.

In conclusion, these two studies provided a much more accurate picture of the actual proportion of mTBI patients at risk of developing post-traumatic OD. Indeed, due to the numerous methodological controls applied, these results paint a more realistic portrait of the short and long term presence of OD following mTBI. Thus, these two projects have revealed alarming proportions, going far beyond what is recorded in the restricted literature available to date. In addition, it appears that baseline presence of qualitative OD following mTBI is a significant predictor of the development of symptoms of anxiety and depression.

Key words: mild traumatic brain injury, concussion, olfaction, anosmia, hyposmia, parosmia, anxiety, depression, life quality, general health, longitudinal, cross-sectional

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LISTE DES ABRÉVIATIONS

ANOVA	Analysis of variance
APT	Amnésie post-traumatique
BAI	Beck anxiety inventory
BDI	Beck depression inventory
CSMC	Commission de la Santé Mentale du Canada
COF	Cortex orbito-frontal
CT	Tomodensiométrie
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DTI	Imagerie du tenseur de diffusion
ÉCG	Échelle de coma de Glasgow
ESPT	État de Stress Post-Traumatique
FRSQ	Fonds de Recherche en Santé du Québec
HSCM	Hôpital Sacré-Cœur de Montréal
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
TCC	Traumatisme craniocérébral
TCCL	Traumatisme craniocérébral léger
TO	Troubles olfactifs
Spcp	Symptômes post-commotionnels persistants
WAIS	Weschler Adult Intelligence Scale

À ma mère,
qui a toujours été et ne cessera d'être mon plus beau modèle de don de soi et d'entraide

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CHAPITRE 1 – INTRODUCTION GÉNÉRALE

1.1 Le traumatisme craniocérébral (TCC): Définition et classification

Le traumatisme craniocérébral (TCC) se définit par une altération des fonctions cérébrales, ou par la présence de toutes autres pathologies cérébrales ayant été causée par une force externe (Menon, Schwab, Wright, & Maas, 2010). Le TCC peut occasionner des symptômes physiques, mais également un dysfonctionnement ou une altération des fonctions sensorielles, cognitives et comportementales (Gabbe et al., 2016; Iverson & Lange, 2011; Iverson, Lange, Brooks, & Rennison, 2010; Ponsford, Cameron, Fitzgerald, Grant, & Mikocka-Walus, 2011). Ces dysfonctionnements peuvent être d'intensités variables et de durées temporaires ou permanentes, selon la gravité du traumatisme. La classification du TCC comporte trois niveaux de sévérité, soit léger, modéré et sévère. L'échelle de Coma de Glasgow (ÉCG) est l'un des principaux outils utilisés par le corps médical afin de définir sa gravité. En observant l'ouverture des yeux, la réponse aux commandes motrices et aux commandes verbales, un résultat global, issu de ces trois catégories, fournit l'indice de sévérité du TCC. Un TCC sera considéré sévère lorsque le résultat à l'ÉCG est inférieur à 8, modéré s'il se situe entre 9 et 12 et léger si le patient obtient un score entre 13 et 15. De plus, bien qu'ils ne sont pas obligatoires au diagnostic, la durée de l'amnésie post-traumatique (APT) ainsi le la durée de la perte de conscience (si elle est présente) sont deux autres observations fréquemment utilisées afin d'aider à déterminer la sévérité du TCC (Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012; Menon et al., 2010). Ainsi, un patient sera diagnostiqué avec un TCC léger (TCCL), s'il démontre l'une ou plusieurs des caractéristiques suivantes : (1) un résultat à l'ÉCG entre 13 et 15 (à l'arrivée à l'urgence ou 30 minutes après le traumatisme), (2) une perte ou altération de la conscience d'une durée de 0 à 30 minutes, (3) une APT d'une durée variable, mais ne pouvant

dépasser 24 heures, (4) une imagerie cérébrale positive ou négative et (5) la présence ou non de signes neurologiques focaux. Il est à noter que dans le cas des patients TCCL, une précision diagnostique quant à la gravité du trauma peut être émise sur la base du résultat de l'imagerie cérébrale. Précisément, les patients TCCL ayant un scan cérébral positif (présence de lésion ou d'hémorragie) seront appelés TCCL complexe, alors que ceux ayant un scan négatif (sans lésion apparente) seront appelés TCCL simple. Le diagnostic du TCC modéré devrait être basé sur (1) la présence d'une perte ou altération de la conscience d'une durée entre 30 minutes et 6 heures (durée limite de 24 heures), (2) un résultat à l'ÉCG entre 9 et 12 (à l'arrivée à l'urgence ou 30 minutes après le traumatisme), (3) une imagerie cérébrale positive, (4) un examen neurologique positif (signes focaux) et (5) une APT d'une durée variable entre 1 et 14 jours. Finalement, pour poser un diagnostic de TCC sévère, les signes suivants doivent être observés, soit (1) une altération de la conscience d'une durée allant de plus de 24 heures et s'étalant à plusieurs jours (doit obligatoirement être supérieure à 6 heures), (2) un résultat à l'échelle de coma de Glasgow entre 3 et 8 (à l'arrivée à l'urgence ou 30 minutes après le traumatisme), (3) la présence de lésions cérébrales rapportées par un scan cérébral positif, (4) un examen neurologique positif et (5) une APT d'une durée de plusieurs semaines. Par ailleurs, les manifestations du traumatisme ne doivent pas être dues à une intoxication à l'alcool, aux drogues ou à la médication, ni être causées par d'autres blessures ou un traitement, ni résulter d'autres problèmes.

1.2 Épidémiologie

La prévalence élevée du TCC représente un problème majeur dans notre société actuelle. Annuellement, près de 4.4 millions de personnes sont victimes d'un TCC en Amérique du Nord (1299 cas/ 100 000 personnes) (Dewan et al., 2018). De ceux-ci, environ 85% sont considérés comme étant légers (TCCL), lorsque comparé aux formes modérées et sévères (Faul & Coronado, 2015). Au Québec, les plus récentes statistiques indiquent que plus de 17 400 individus ont reçu

un diagnostic de TCC entre 2013 et 2016 (Gonthier, Belcaid, & Truchon, 2019). De plus, les hommes sont deux fois plus à risque que les femmes de subir un TCCL. De surcroit, les enfants en bas âge (0-4 ans), les adolescents (15-19 ans) et les personnes âgées de plus de 65 ans sont ceux qui risquent davantage de recevoir un tel diagnostic. De plus, la présence de troubles neurodégénératifs (ex. Alzheimer et Parkinson) s'est aussi révélée comme étant un facteur de risque de subir un TCCL, causée notamment par l'augmentation significative des risques de chutes retrouvées auprès de cette population spécifique (Faul, Wald, Xu, & Coronado, 2010; Fernando, Fraser, Hendriksen, Kim, & Muir-Hunter, 2017). Mondialement, les accidents de la route ainsi que les chutes représentent les principales causes du TCCL, respectivement auprès des jeunes adultes et des personnes âgées. La survenue d'un TCCL suite à des activités sportives et récréatives occupe aussi une place importante chez l'enfant et chez l'adulte (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007; Janak, Pugh, & Orman, 2015).

1.3 Mécanismes neurophysiologiques et imagerie cérébrale

Le TCC est classifié selon qu'il soit ouvert ou fermé. Le TCC dit « ouvert » (*open head injury*) ou blessure pénétrante au cerveau est la conséquence d'une blessure causée par tout élément pouvant pénétrer le cuir chevelu, la voute crânienne, les méninges et le tissu cérébral (Arbour, 2013). Cette dernière blessure expose la cavité intracrânienne et son contenu à l'environnement externe, ce qui augmente le risque de complications infectieuses. Le TCC dit « fermé » (*closed head injury*) se caractérise par une blessure cérébrale suite à un trauma direct au crâne ou secondaire à un mouvement brusque causant un choc significatif du cerveau sur la boite crânienne (mouvements d'accélération, de décélération ou de rotation). Ces forces diffuses engendrent notamment des étirements de petits vaisseaux sanguins et des axones neuronaux (qui assurent la transmission d'informations au cerveau). Bien que fréquemment retrouvées suite aux TCC

modérés et sévères, les blessures ouvertes sont beaucoup plus rares chez les patients ayant subi un TCCL (McKee & Daneshvar, 2015). Cependant, bien que les blessures soient majoritairement de type fermé, celles-ci entrainent tout de même une cascade complexe d'évènements neurométaboliques. Ces changements métaboliques s'effectuent dès les premiers instants suivant le TCCL et peuvent laisser des traces jusqu'à plusieurs semaines suivant le TCCL (Barkhoudarian, Hovda, & Giza, 2016).

Au cours des deux dernières décennies, une augmentation exponentielle des recherches traitant des structures anatomiques lésées suite à un TCCL a été observée dans la littérature. En effet, le raffinement et l'accessibilité des appareils d'imageries ont favorisé cette effervescence. Ainsi, les efforts provenant de la communauté scientifique ont permis d'identifier et de cartographier avec davantage de précision les structures atteintes à la suite d'un TCCL. Cependant, une grande hétérogénéité, quant à l'identification des structures atteintes suite au TCCL, est apparue dans cette littérature en pleine expansion. Face à cette confusion grandissante, Eierud et ses collaborateurs ont mis sur pieds une excellente méta-analyse comprenant plus d'une centaine d'études (Eierud et al., 2014). En ce sens, à l'aide d'une méthodologie robuste, ces chercheurs ont mis en évidence les principaux patrons d'atteintes corticales et sous-corticales suivant un TCCL. Ainsi, les résultats d'IRMf de cette méta-analyse proposent notamment la présence de marqueurs structurels et fonctionnels post-TCCL. En ce sens, une sensibilité de la région frontale a été identifiée par une diminution du signal, lorsque comparée aux sujets sains. Plus spécifiquement, cette méta-analyse met en évidence des diminutions de l'activité cérébrale dans certaines régions frontales telles qu'au gyrus frontal moyen droit, au cortex cingulaire antérieur ainsi qu'au gyrus précentral droit. Une diminution du signal a aussi été retrouvée au cortex préfrontal dorsolatéral. Ces mêmes auteurs se sont aussi intéressés aux résultats d'études ayant utilisé la technique d'imagerie par diffusion. Cette technique est de plus en plus utilisée dans les études sur le TCCL

puisqu'elle permet d'identifier les différents états de la matière blanche. Il est intéressant de soulever que la totalité des études sur le sujet démontre de manière systématique, des altérations post TCCL au niveau de la matière blanche. Ainsi, la majorité de ces altérations ont été retrouvées aux régions antérieures sous-corticales telles qu'au genu et au splenium du corps calleux, à la corona radiata antérieure et supérieure, à l'hippocampe ainsi qu'au cortex cingulaire. De manière intéressante, des altérations de ces régions sont aussi associées à des troubles des fonctions exécutives, de la cognition et de l'humeur chez une clientèle atteinte d'un TCCL (Hashimoto & Abo, 2009; Lipton et al., 2009; Niogi et al., 2008).

1.4- Récupération et symptômes post-commotionnels persistants (Spcp) suite au TCCL

Bien que les patrons de récupération suite à un TCCL varient grandement d'un patient à l'autre, deux phases distinctes de récupération ont été identifiées par la communauté scientifique. Ainsi, les trois premiers mois suite au TCCL sont considérés comme étant partie intégrante de la phase de récupération aigue. Durant cette première phase, les patients rapportent davantage de symptômes d'ordre physique (céphalées, fatigue, étourdissements) et cognitif (ex. difficultés attentionnelles, trouble de mémoire, ralentissement cognitif) (Lundin, de Boussard, Edman, & Borg, 2006; Paniak et al., 2002). Les auteurs estiment toutefois que, la majorité des patients ayant subi un TCCL ne présenteraient plus de symptômes post-commotionnels persistants (Spcp) après la période de récupération normale, laquelle varie, entre 2 et 12 semaines (Hiploylee et al., 2017; Levin & Diaz-Arrastia, 2015). Précisément, la majorité des auteurs estiment qu'entre 10 et 15% des patients ayant subi un TCCL développeront des Spcp (Alves & Reviews, 1992; Binder, Rohling, & Larrabee, 1997; Broshek, De Marco, & Freeman, 2015). Toutefois, une très grande variabilité, en ce qui a trait aux statistiques de prévalence, est présente dans la littérature.

En effet, un bref survol des articles disponibles à ce jour, indique qu'entre 15 et 52% des patients ayant subi un TCCL ont développé des Spcp, dont notamment, des symptômes dépressifs et anxieux (Almeida-Suhett et al., 2014; Bombardier et al., 2010; Lucas et al., 2016; van der Naalt et al., 2017). Cette hétérogénéité semble principalement causée par le choix des patients constituant les groupes TCCL. En clair, la majorité des études s'étant intéressées au développement de Spcp chez les patients TCCL, ont étudié des populations d'athlètes de haut niveau et de vétérans (Broshek et al., 2015). Conséquemment, il est difficile de transposer ces statistiques aux patients provenant de la population générale, puisque ceux-ci présentent des profils et mécanismes de blessure différents. En effet, les athlètes de haut niveau n'en sont généralement pas à leur premier TCCL lorsqu'ils sont évalués, ce qui augmente le risque de développer des Spcp (Collins et al., 2002; Covassin, Elbin, Kontos, & Larson, 2010; Schatz, Moser, Covassin, & Karpf, 2011). En ce qui a trait à la population de patients vétérans, puisque ceux-ci ont subi leurs TCCL dans le cadre d'une mission, le mécanisme de la blessure traumatique est bien différent de ce qui est recensé dans la population générale, alors qu'ils subissent généralement un TCCL aux suites d'une explosion (*blast injury*). De plus, le TCCL s'accompagne généralement d'un état de stress post-traumatique (ESPT), aussi considéré comme étant un facteur de risque au développement de Spcp (Aase et al., 2018; Dolan et al., 2012). Une récente revue de littérature, s'étant penchée sur la prévalence de Spcp suite à un TCCL dans la population générale, indique que plus de 50% des patients présentaient toujours des déficits cognitifs trois mois suite au trauma (Kerry McInnes, Christopher L Friesen, Diane E MacKenzie, David A Westwood, & Shaun G Boe, 2017b). Les précédentes études ont aussi aidé à mettre en lumière la nature de plusieurs prédicteurs au développement du SPC. Ainsi, au cours des deux dernières décennies, les auteurs ont mis en évidence plusieurs facteurs de risque au développement de Spcp, soit (1) des antécédents de TCC, (2) la présence de maux de tête persistants, (3) la présence de difficultés cognitives et (4) la présence de symptômes

d'anxiété et de dépression pré et post-TCCL ((ONF), 2017; Dischinger, Ryb, Kufera, & Auman, 2009; Kerry McInnes, Christopher L Friesen, Diane E MacKenzie, David A Westwood, & Shaun G Boe, 2017a; Ponsford et al., 2012).

1.5- Symptomatologie

1.5.1- Atteintes physiques

L'apparition de troubles physique est l'un des symptômes les plus fréquemment observés en phase aiguë du TCCL. En effet, les auteurs ont recensé, dans les dernières années, un nombre élevé de symptômes physiques survenant suite au TCCL. Précisément, un récent rapport de l'Institut national d'excellence en santé et en services sociaux (INESSS), basé sur le rapport du Task Force de l'OMS, a identifié les céphalées, la fatigue, les nausées, les étourdissements, la sensibilité aux sons ainsi que les troubles du sommeil comme étant les symptômes les plus fréquemment rapportés dans les jours suivant un TCCL (INESSS, 2018). En ce qui a trait à la persistance et la chronicisation de ces symptômes, les études indiquent que ceux-ci, en comparaison aux atteintes cognitives et émotives, n'ont pas tendance à perdurer au-delà de la phase de récupération normale de trois mois (Marshall et al., 2012; Marshall et al., 2015).

1.5.2- Atteintes cognitives

Une seconde sphère atteinte suite au TCCL est celle entourant l'ensemble des fonctions cognitives des patients. En effet, les atteintes cognitives suivant un TCCL ont fréquemment été rapportées dans la littérature et varient grandement d'un patient à l'autre. Cependant, puisque le TCCL implique généralement des atteintes frontales (Eierud et al., 2014), la plupart des patients présenteront des atteintes cognitives médiées par cette région. Conséquemment, le rapport de l'INESSS indique que la présence de troubles de mémoire, d'attention ainsi qu'une réduction de la

vitesse de traitement de l'information composent la triade de symptômes cognitifs les plus diagnostiqués au cours des trois premiers mois suivants le TCCL (Truchon, 2018). Il est intéressant de noter que de ceux-ci, les difficultés attentionnelles représentent les symptômes cognitifs les plus fréquemment retrouvés suite au TCCL (Pontifex et al., 2012; Pontifex, O'Connor, Broglio, & Hillman, 2009; Spikman & van Zomeren, 2010). Précisément, l'attention sélective et divisée sont les deux composantes attentionnelles qui semblent les plus atteintes suite au trauma (Blanchet, Paradis-Giroux, Pépin, & Mckerral, 2009; Pontifex et al., 2012). Conséquemment, les plaintes cognitives nommées par les patients réfèrent notamment à des difficultés de concentration, une grande distractibilité et une baisse des capacités à faire deux choses à la fois. Il est aussi très intéressant de noter que la majorité des patients se plaignent de troubles en mémoire à court-terme (Johansson, Berglund, & Rönnbäck, 2009; Mathias, Beall, & Bigler, 2004). Ce type de déficit est souvent associé, par les patients, à des troubles de mémoire purs, alors que des études ont démontré que l'aspect mnésique atteinte était principalement causé par les atteintes attentionnelles, puisque les patients peinent à se concentrer lors de l'encodage des stimuli. En effet, de études ont montré que les difficultés mnésiques suite au TCCL se rapportaient principalement au processus d'encodage et de consolidation, grandement influencé par des difficultés attentionnelles, alors que les processus de récupération d'information restent intacts (Blanchet et al., 2009; Carroll et al., 2004; Fortier-Lebel et al., 2021; L'Ecuyer-Giguère et al., 2018). Ayant collaborée à deux des articles cités ci-haut, ceux-ci ont été placés en annexe de la présente thèse (Annexe 1 et 3). Contrairement aux symptômes physiques, les déficits cognitifs ont davantage tendance à perdurer dans le temps, alors que les résultats d'une récente revue de la littérature indique que près de 50% des patients ayant subi un TCCL présentaient toujours des symptômes cognitifs trois mois suite à l'accident (McInnes et al., 2017a). De plus, lorsque comparés à des patients ayant subi des blessures orthopédiques (sans TCCL), les patients TCCL présentaient des scores significativement moins

élevés aux tâches impliquant de la vitesse de traitement, des capacités attentionnelles et mnésiques (Karr, Areshenkoff, & Garcia-Barrera, 2014; Rabinowitz et al., 2015).

1.5.3- Atteintes psychologiques

De tous les symptômes énumérés ci-haut, l'apparition de troubles de l'humeur représente l'une des affections les plus courantes suite au TCCL. Précisément, de récentes études indiquent qu'entre 15 à 52% des patients ayant subi un TCCL rapporteront des symptômes de dépression au cours de la première année suivant le trauma (Bombardier et al., 2010; Lucas et al., 2016; van der Naalt et al., 2017). Cette prévalence de patients TCCL présentant de symptômes dépressifs est d'autant plus alarmante lorsqu'elle est comparée à celle retrouvée dans la population générale. En effet, les statistiques de la Commission de la Santé Mentale du Canada (Canada, 2013) estiment qu'environ 8% de la population canadienne présentent un trouble dépressif. En plus des études citées ci-haut, le rapport de l'INESSS identifie, à son tour, les symptômes dépressifs comme étant l'une des complications les plus observées en phase chronique suite au TCCL (Truchon, 2018). En ce sens, la présence de symptômes dépressifs a été retrouvée chez plus de 17% des patients TCCL, évalués trois mois suivant leur trauma (Levin et al., 2001). De plus, des associations entre la présence de symptômes dépressifs et l'apparition de Symptômes post-commotionnels persistants (Spcp), ont été trouvées dans le passé. En effet, lorsque comparés à des patients TCCL ne rapportant pas de symptômes dépressifs et a des sujets contrôles, les patients TCCL ayant des symptômes dépressifs rapportaient un nombre significativement plus élevé de symptômes post-commotionnels 8 mois suivant le trauma (Lange, Iverson, & Rose, 2011).

En ce qui a trait à la présence de symptômes anxieux suite au TCCL, il a été démontré que, lorsque comparé à un groupe de sujets sains, un nombre significativement plus élevé de patients

ayant subi un TCCL atteignait le seuil d'anxiété modéré/grave au questionnaire d'anxiété de Beck et que ces symptômes auraient persisté et se seraient même intensifiés au-delà de six semaines suite au trauma (Sung et al., 2016). Des résultats similaires ont d'ailleurs été retrouvés dans une précédente étude, lors de laquelle la présence de symptômes anxieux a été décelée auprès d'un groupe de patients TCCL deux semaines suivant le trauma. Ces mêmes auteurs ont aussi mis en lumière la présence de liens positifs entre l'intensité de symptômes anxieux rapportés et l'intensité des troubles cognitifs et des symptômes post-commotionnels (E. de Guise, LeBlanc, Tinawi, Lamoureux, & Feyz, 2012). De plus, au même titre que les symptômes dépressifs, la présence de symptômes anxieux au cours de la première semaine suite au TCCL a été identifiée comme étant un excellent indicateur de développement de symptômes post-commotionnels, trois mois suite au TCCL (Ponsford et al., 2012). Par ailleurs, la présence de troubles anxieux semble aussi être spécifique au TCC et non pas uniquement à une réaction psychologique suite à un accident. En ce sens, des chercheurs ont comparé des patients ayant subi un TCCL à un groupe de patients ayant subi des blessures orthopédiques (n'impliquant pas la tête). Les résultats indiquent que les patients TCCL rapportaient un nombre significativement plus élevé de symptômes anxieux que les patients victimes de blessures orthopédiques (Lange et al., 2015).

1.5.4- Atteintes sensorielles

Bien que largement moins documentées, les atteintes sensorielles représentent de réels enjeux suite au TCCL. Cependant, dû au nombre assez restreint d'études disponibles sur le sujet, il est plutôt rare que les altérations sensorielles soient considérées comme une sphère à part entière. De façon générale, les auteurs incluront ces atteintes dans la sphère physique, au même titre que les maux de tête et la fatigue, ce qui est aberrant, compte tenu de la gravité et des conséquences à long terme impliquées suite à l'atteinte d'un sens. En effet, il a été largement documenté que la

perte de vision, de l'ouïe et de l'olfaction est fréquemment liée au développement de symptômes d'anxiété et de dépression dans la population générale (Kohli, Soler, Nguyen, Muus, & Schlosser, 2016; Senra et al., 2015; Wayne & Johnsrude, 2015). En ce qui a trait à la présence de telles altérations suite à un TCCL, la grande majorité des études se sont penchées sur la présence et le développement des troubles de la vision et de l'audition. Précisément, certains patients ayant subi un TCCL peuvent développer une vision floue ainsi qu'un ralentissement des saccades et de la poursuite oculaire (Caplan et al., 2016). L'apparition de troubles auditifs, tels que l'acouphène, l'hypersensibilité aux bruits et même une réduction partielle de l'ouïe sont aussi décrits dans la littérature (Karch et al., 2016; Vander Werff, 2012). Au final, bien que l'audition et la vision furent longtemps considérées comme les principaux sens atteints suite au TCCL, des chercheurs ont identifié la présence d'altérations du système olfactif suite au trauma (de Kruijk et al., 2003). Dû au nombre très limité de littératures disponibles sur le sujet, il est, à ce jour, encore très difficile de bien saisir l'ampleur et les impacts des troubles olfactifs suivant un TCCL.

1.6- L'olfaction

1.6.1- La physiologie

Une muqueuse composée de terminaisons nerveuses tapisse le plafond des fosses nasales. Cette muqueuse, nommée épithélium olfactif, est constituée d'une couche de cellules réceptives olfactives (CRO), de cellules de soutien, de cellules basales (cellules de souche) et de cellules glandulaires.. L'humain possède entre 200 et 400 CRO au total. Les molécules volatiles agissent donc sur l'épithélium olfactif dont les CRO possèdent des récepteurs auxquels les odorants se lient de façon réversible grâce à des liaisons de faible énergie. Les récepteurs d'odorants appartiennent à une famille de protéines couplées à des protéines G. Une molécule ne peut activer un récepteur que si elle trouve sur ce récepteur une région avec laquelle elle est en mesure d'échanger des

liaisons physicochimiques adéquates. La transduction olfactive implique une cascade de réactions enzymatiques dont la première étape est l'activation d'une protéine G, créant une dépolarisation et ultimement un influx nerveux. Ensuite, les CRO forment des synapses avec les cellules mitrales, dont le corps cellulaire se retrouve à l'intérieur des glomérules du bulbe olfactif (des renflements situés sous les hémisphères). Le bulbe olfactif est donc la première région du système nerveux central à recevoir les influx nerveux olfactifs en provenance de l'épithélium olfactif (Hawkes & Doty, 2018). Les cellules réceptrices envoient leurs axones dans les glomérules. Ces glomérules sont des lieux de contact synaptiques très denses comportant entre quelques milliers d'axones de cellules réceptrices et quelques dizaines de cellules-relais (cellules mitrales). Puisque les axones des cellules réceptrices convergeant vers un glomérule expriment la même sensibilité, les cellules mitrales transmettent des messages nerveux correspondant exclusivement à cette sensibilité. Les axones des cellules mitrales cheminent dans la bandelette olfactive (ou tractus olfactif) et atteignent les aires du cortex olfactif primaire (Ressler, Sullivan, & Buck, 1994). Chez l'humain, le cortex olfactif primaire comprend les cortex piriforme, entorhinal et le trigone olfactif, qui est une voie d'entrée sur l'hippocampe et le système mnésique ainsi que l'amygdale dont le rôle dans l'affect, l'émotion et le conditionnement est bien établi (Anderson et al., 2003). Le cortex olfactif primaire est à l'origine de projections de troisième ordre vers certaines structures corticales et sous-corticales. Ces projections s'acheminent ainsi vers ce que l'on appelle le cortex olfactif secondaire comprenant, entre autres, le cortex orbitofrontal, impliqué dans la détection et le jugement sur la valeur hédonique des odeurs (Royet et al., 2001). Il est intéressant de noter que ces mécanismes olfactifs de haut niveau ont précédemment été liés à certaines fonctions cognitives de haut niveau. Précisément, une bonne mémoire sémantique et une bonne fluence verbale furent associées avec de meilleures capacités d'identification et de discrimination d'odeurs (Larsson, Nilsson, Olofsson, & Nordin, 2004). Par ailleurs, l'hypothalamus, structure importante pour le contrôle des

comportements motivés, comme la prise alimentaire fait partie de ce cortex secondaire (Holley, 2006; Zatorre, 2002). Il est à noter que l'hypothalamus, inclus dans le système limbique, est aussi responsable des émotions telles que la colère, la joie, le dégout et le contrôle des états dépressifs et anxieux (Meierhenrich, Golebiowski, Fernandez, & Cabrol-Bass, 2005). Finalement, il est important de relever que, contrairement aux autres systèmes sensoriels, le système olfactif est le seul à ne pas avoir de relais thalamique obligatoire.

1.6.2- Principaux troubles olfactifs

Le terme « trouble de l'odorat » (dysosmies) décrit différent trouble de la perception des odeurs. On distingue les troubles quantitatifs et qualitatifs. Les troubles dits quantitatifs de l'olfaction se recoupent sous trois types dont leurs classifications dépendent de l'intensité de l'atteinte olfactive (Brämerson, Johansson, Ek, Nordin, & Bende, 2004). Ainsi, la perte totale du sens de l'odorat s'identifie comme étant une *anosmie*, tandis qu'une perte partielle de ce sens se nomme *hyposmie*. Une troisième affectation quantitative, l'*hyperosmie*, apparait lors d'une exacerbation du sens de l'odorat ou une hypersensibilité aux odeurs. Aussi, les individus ayant un sens de l'odorat tout à fait normal sont désignés comme ayant une normosmie. Pour leurs parts, les troubles dits qualitatifs se répartissent en deux grandes catégories. Tout d'abord, un patient peut souffrir de *parosmie* (Reden, Maroldt, Fritz, Zahnert, & Hummel, 2007), soit une altération de la perception des odeurs en présence d'une source d'odeurs. Dans ce cas-ci, la plupart du temps, les parfums sont perçus comme des odeurs désagréables (p. ex : une rose est identifiée comme étant du caoutchouc brulé). En plus de la parosmie, un deuxième trouble qualitatif s'ajoute au tableau, la *phantosmie* (B N Landis, Konnerth, & Hummel, 2004). Dans certains cas, beaucoup plus rares cependant, des patients peuvent rapporter percevoir des odeurs en l'absence de stimulations. La

phantosmie consiste en une perception d'odeurs, le plus souvent désagréables, en absence d'une source d'odeurs.

1.6.3- Troubles olfactifs et troubles affectifs

Ne bénéficiant que depuis quelques mois seulement d'un engouement public et scientifique, dû à l'arrivée de la pandémie de la COVID-19, puisque près de 60% des patients ayant contracté la COVID-19 ont présenté des signes généralement temporaires d'anosmie et d'hyposmie (Rocke, Hopkins, Philpott, & Kumar, 2020), l'olfaction a longtemps été le parent pauvre de la littérature consacré aux sens. Toutefois, il n'en demeure pas moins que l'olfaction joue un rôle fondamental au quotidien. À titre d'exemple, le système olfactif fut et est toujours garant de notre survie par sa capacité à transmettre divers signaux d'alarme nous permettant d'identifier la nourriture avariée ou la présence de fumée (Temmel et al., 2002). En plus d'assurer notre survie, l'olfaction contribue grandement à nos sensations de plaisir et de bonheur (ex : sentir le parfum d'une fleur ou de notre partenaire de vie). Plusieurs études ont démontré de forts liens entre la présence de différents troubles olfactifs et une diminution de la qualité de vie et de l'humeur (Croy, Nordin, & Hummel, 2014; Frasnelli & Hummel, 2005; Kohli et al., 2016; Seo, Jeon, Hummel, & Min, 2009; Simopoulos et al., 2012). Dans l'ensemble de ces études, les participants souffrant d'anosmie (perte totale de l'odorat) ou d'hyposmie (perte partielle), lorsque comparés aux groupes contrôles (sans troubles olfactifs), rapportaient un nombre significativement plus élevé de symptômes dépressifs. D'autres études ont aussi lié la présence de dysfonctions olfactives au développement de dépressions majeures, et ce, auprès de diverses populations cliniques (Kim, Kim, Hong, Kang, & Choung, 1997; Takeda et al., 2014). D'un autre point de vue, une étude a montré que les patients dépressifs présentaient une réduction en volume de leur bulbe olfactif (Negoias et al., 2010) et que la prise de médicaments antidépresseurs avait comme effet d'améliorer les fonctions olfactives

(Croy & Hummel, 2017). Des liens et résultats similaires ont aussi été retrouvés lors de l'étude des symptômes anxieux et de leurs impacts sur l'olfaction (Burón & Bulbena, 2013; Takahashi et al., 2015). L'un des fondements neurobiologiques proposés par les chercheurs expliquant cette association se base sur le fait que le traitement olfactif prend place, en autres, dans le système limbique, siège du traitement des émotions (amygdale, hippocampe, cortex enthorinal et le cortex cingulaire antérieur) (Heimer, Van Hoesen, Trimble, & Zahm, 2007; Kohli et al., 2016; Krusemark, Novak, Gitelman, & Li, 2013; Soudry, Lemogne, Malinvaud, Consoli, & Bonfils, 2011). En plus de cette association corticale, un autre lien, plus indirect cette fois, semble lier l'olfaction et l'humeur : les individus avec un trouble olfactif sont moins portés à partager des repas et à socialiser durant ceux-ci (commenter le gout de la nourriture), ils ont tendance à développer de l'anxiété/crainte face aux dangers pouvant être décelé à l'aide de l'olfaction (nourriture moisie, feu, fuite de gaz) et certains d'entre eux peuvent être complexés quant à leur hygiène personnelle (Croy et al., 2014; Rolls, 2015).

1.7- Troubles olfactifs et TCC

1.7.1 Prévalence et évolution des troubles olfactifs suite au TCC

Bien qu'il existe plusieurs causes menant au développement de troubles olfactifs, la plupart se présentent majoritairement suite à une infection virale (COVID-19, grippe), à des troubles nasaux (sinusite chronique, polypes nasaux) ainsi qu'à un TCC (Temmel et al., 2002). La pathogenèse des troubles olfactifs post-traumatiques est multiple et serait liée à plusieurs types de mécanismes tels qu'un étirement, une contorsion ou une coupure des nerfs olfactifs, par un impact direct aux régions frontales, à des fractures faciales et de la base du crâne, à un traumatisme direct au tract naso-sinusien (Tao & Shenbagamurthi, 2012), ou encore à une blessure du parenchyme olfactif (de Guise et al., 2015; Sigurdardottir, Jerstad, Andelic, Roe, & Schanke, 2010). La majorité

des données de prévalence disponible à ce jour traitent des troubles olfactifs suite aux TCC modérés et sévères, puisque la plupart des mécanismes cités ci-haut (blessures du nerf olfactif, fractures faciales) sont retrouvés suite à des TCC plus sévères et mènent à des troubles olfactifs plus facilement identifiables (anosmie), comparativement aux impacts documentés suite aux TCC de plus légères intensités.

En ce qui a trait à la prévalence de troubles olfactifs suite au TCC modéré-sévère, une grande hétérogénéité existe dans les résultats publiés à ce jour. Alors que certaines études ont trouvé la présence de troubles olfactifs chez 55 à 65 % de leurs patients TCC modéré-sévère (Callahan & Hinkebein, 2002; Drummond, Douglas, & Olver, 2015; Frasnelli. et al., 2016), d'autres ont trouvé de tels troubles seulement chez 12% de leurs patients (Haxel, Grant, & Mackay-Sim, 2008). Les inconsistances sur la prévalence des troubles de l'olfaction sont en partie liées au fait que la définition d'un trouble olfactif n'est pas consistante d'une étude à l'autre. Ainsi, certaines études identifient un trouble olfactif seulement lorsqu'une perte totale de l'olfaction (anosmie) est objectivée, alors que d'autres parlent d'un trouble olfactif lorsqu'une perte partielle (hyposmie) est identifiée et, dans de plus rares cas, des critères maison sont utilisés. De plus, la population TCC est très variable entre les études. En effet, des variations de sévérité du TCC et de délais d'évaluation post-traumatique font ainsi augmenter la variabilité entre les projets. Au final, certains auteurs expliquent cette grande hétérogénéité dans les statistiques de prévalence par l'absence de contrôles quant à la présence de symptômes cognitifs pouvant influencés certains résultats olfactifs. En effet, un groupe de chercheurs Suédois ont montré l'existence de corrélations positives significatives entre les résultats aux épreuves évaluant la mémoire sémantique et la mémoire de travail et les tâches de discrimination (laquelle des trois odeurs présentées est différente) et d'identification d'odeurs de la batterie Sniffin'Sticks (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010).

Tel que mentionné plus haut, la littérature entourant les troubles olfactifs suite à un TCCL reste, à ce jour, extrêmement circonscrite. Une revue systématique des écrits, publiée en 2016, estimait à dix le nombre d'études totales ayant abordée la question de l'anosmie suite à un TCCL (Proskynitopoulos, Stippler, & Kasper, 2016). Une étude approfondie des études intégrées dans la revue, révèle que la majorité des études sélectionnées (7/10) incorporaient les trois types de TCC et n'ont fait que des analyses de surfaces, tels que des corrélations entre le scores à l'ÉCG et les résultats aux évaluations olfactives, au lieu de séparer les groupes selon leur sévérité et mener des analyses approfondie sur chacun des groupes. Par ailleurs, une telle méthodologie limite grandement les conclusions liées exclusivement au groupe de patients TCCL. Ainsi, outre les articles contenus dans la présente thèse, seulement trois articles ont tenté de chiffrer la prévalence et de comprendre les effets du développement de troubles olfactifs suite au TCCL spécifiquement (Ciofalo et al., 2018; de Kruijk et al., 2003; Ruff, Riechers, Wang, Piero, & Ruff, 2012). Tout comme les TCC d'intensité modérée et sévère, une grande hétérogénéité réside dans le peu de résultats disponibles. Ainsi, les études estiment qu'entre 20 et 51% des patients développent un trouble de l'olfaction suite au TCCL. Tout comme les études traitant des troubles olfactifs auprès des TCC modéré-sévère, la grande variabilité des choix méthodologiques explique cette hétérogénéité (qualité des outils d'évaluation du système olfactif, critères de sélection permettant l'inclusion des patients TCCL, le temps entre le TCCL et l'évaluation olfactive). Cette limitation et hétérogénéité dans la littérature s'explique aussi par le caractère plus subtil des troubles olfactifs documentés suite au TCCL (hyposmie, parosmie), comparativement aux pertes flagrantes et facilement identifiables lors de TCC plus sévères. En effet, alors que des fractures faciales et des ruptures et contorsions des nerfs olfactifs sont documentées suite aux TCC modérés-sévères, les structures lésées suite au TCCL sont beaucoup plus subtiles et disparates. Conséquemment, les

structures corticales lésées suite au TCCL n'ont pas, à ce jour, été clairement liées aux pertes olfactives.

En ce qui a trait aux données disponibles quant à l'évolution des troubles olfactifs suivant le TCC, celles-ci sont aussi assez limitées. De façon générale, les études disponibles à ce jour indiquent que seulement une faible proportion des patients ayant subi un TCC présente une amélioration de leurs capacités olfactives. En effet, les statistiques indiquent qu'entre 15 et 27% des patients TCC modérés-sévères retrouveront, et ce, que partiellement, leurs capacités olfactives, six à douze mois suite au TCC (Caplan et al., 2018; Drummond, Douglas, & Olver, 2017; Welge-Lüssen, Hilgenfeld, Meusel, & Hummel, 2012). En ce qui a trait aux statistiques concernant l'évolution des troubles olfactifs suite aux TCCL, aucune étude n'a, à ce jour, traité de ce sujet.

1.7.2 Liens neuroanatomiques entre les troubles olfactifs et le TCCL

Tel qu'expliqué dans la section précédente, la plupart du traitement olfactif se déroule dans les régions frontales et temporales. Précisément, une étude d'imagerie fonctionnelle a montré l'importance du cortex orbitofrontal (COF) et du cortex préfrontal dans la perception des odeurs (Bersani, Quartini, Ratti, Pagliuca et Gallo, 2013). Cette étude rappelle le lien étroit entre le COF et les modalités sensorielles (Bersani et al., 2013). Des études ont également rapporté le rôle du cortex temporal antérieur (CTA) pour la discrimination et l'identification des odeurs (Tranel et Welsh-Bohmer, 2012). Au plan fonctionnel, une hypoactivation a été observée dans les régions préfrontales ainsi qu'une réduction du métabolisme des régions temporales, auprès de patients présentant des troubles quantitatifs de l'odorat. Une revue de la littérature indique aussi la présence de corrélations négatives entre la sévérité du TCC et le volume du bulbe olfactif (Proskynitopoulos et al., 2016). Dans cette même revue de littérature et dans plusieurs articles publiés dans les dernières années des liens étroits entre la présence de lésions frontale post-traumatique et celle de

développement de TO furent relevés (Savic, Gulyas, Larsson et Roland, 2000; Varney, Pinkston et Wu, 2001; Dade, Zatorre et Jones-Gotman, 2002; Atighechi et al., 2009), alors qu'une réduction de volume de l'insula, du bulbe olfactif ainsi que du cortex cingulaire ont été associés à la présence de parosmie (Bitter et al., 2011; Mueller et al., 2005). Ainsi, tel que relevé dans la méta-analyse présentée en début de chapitre (Eierud et al, 2014), la grande majorité des structures impliquées lors du traitement olfactif sont atteintes suite au TCCL.

1.7.3- La présence de troubles olfactifs post-TCCL comme possible prédicteurs de symptômes anxieux et dépressifs.

La littérature entourant les conséquences à court et long-terme du TCCL, identifie, elle aussi, le développement de symptômes anxio-dépressifs, comme étant l'un des symptômes post-commotionnels les plus rapportés par les patients. En effet, entre 15 et 52% des patients ayant subi un TCCL rapportent des signes cliniques de dépression et d'anxiété durant la première année suivant leurs traumas (Almeida-Suhett et al., 2014; Bombardier et al., 2010; Lucas et al., 2016; van der Naalt et al., 2017), comparativement à environ 8% dans la population générale (Canada, 2013). De plus, 20% des patients ayant subi un TCCL ont développé un épisode de dépression majeur durant les trois premiers mois suite à leurs TCCL (Stein et al., 2019). Bien qu'il ait été largement documenté que la présence de symptômes anxio-dépressifs suite au TCCL est associée à un plus sombre pronostique (Lange et al., 2011; McCauley, Boake, Levin, Contant, & Song, 2001; Terry, Brassil, Iverson, Panenka, & Silverberg, 2018), la littérature traitant des facteurs de risque de développer de tels symptômes aux suite d'un TCCL, reste assez hétérogène. En effet, au cours des années, différents facteurs, tels que (1) la présence pré et post-morbide de troubles anxio-dépressifs, (2) la présence de plusieurs TCC, (3) le niveau d'éducation, (4) l'ethnicité, (5) l'âge ainsi que (6) la durée de l'APT furent documentés comme étant de possibles facteurs de risque au

développement de symptômes dépressifs suite au TCCL (Levin et al., 2005; Rao et al., 2012; Roy et al., 2019; Stein et al., 2019; Wojcik, 2014; Zahniser et al., 2019). Bien que ces différents facteurs donnent aux cliniciens une certaine idée des facteurs à surveiller lors de la prise en charge du patient, ceux-ci demeurent exhaustifs et peu spécifiques à la population générale de patients TCCL. En fait, puisque la majorité des études citées ont travaillé avec une population d'athlètes et de vétérans, il devient assez difficile de généraliser ces facteurs de risque aux patients ayant subi un TCCL dans des conditions plus typiques (ex. chute à vélo, accident de voiture, chute sur la glace). De plus, il est important de mentionner que la grande majorité des études, traitant des facteurs de risque au développement de symptômes affectifs aux suites d'un TCCL, ont évalué les risques de développement de symptômes dépressifs et non d'anxiété.

Les facteurs de risque liés au développement de symptômes anxio-dépressifs suite au TCCL, cités plus haut, n'expliquent pas l'entièreté de la variance quant à la chronicisation de tels troubles suite au TCCL. En scrutant la littérature, certaines études ont récemment émis l'hypothèse d'un lien entre la présence de troubles olfactifs, le développement de troubles de l'humeur et le TCC (Drummond, Douglas, & Olver, 2013; Frasnelli. et al., 2016; Sigurdardottir et al., 2016). Précisément, ceux-ci avancent que la détection des troubles olfactifs suite à un TCC pourrait nous donner de l'information sur l'état du système limbique des patients. Tel que mentionné précédemment, les régions impliquées dans le traitement des stimuli olfactifs sont aussi celles impliquées dans la régulation de l'humeur chez l'être humain (amygdale, hippocampe, cortex cingulaire, COF et insula). De ce fait, les troubles olfactifs et le développement de symptômes anxio-dépressifs seraient les deux conséquences d'une atteinte du système limbique, mais l'un à court et l'autre à long terme. Il est d'autant plus intéressant de rappeler que plusieurs de ces régions (COF, cortex cingulaire, hippocampe et insula) sont altérées suite à un TCCL (Eierud et al., 2014). Bien que certaines études aient commencé à s'intéresser aux liens entre le TCC (tous types

confondus), les troubles olfactifs et de l'humeur, aucune étude n'a évalué de telles hypothèses auprès de patients TCCL. Ainsi, l'évaluation des capacités olfactives post-TCCL nous permettrait d'évaluer l'état du système limbique, ce qui permettrait une prédiction du développement d'un trouble de l'humeur à long terme.

Bien que de telles hypothèses n'aient pas encore été vérifiées auprès d'une population TCCL, un nombre assez restreint de publications explorant des hypothèses similaires auprès d'une population atteint de démences frontales a montré des résultats allant dans le sens de ces hypothèses (Attems, Lintner, & Jellinger, 2005; Kesslak, Nalcioglu, & Cotman, 1991). Ainsi, une étude explorant la perte olfactive auprès de patients atteints d'Alzheimer a démontré que les patients atteints de la maladie d'Alzheimer ayant des troubles olfactifs développaient davantage de troubles dépressifs et anxieux que ceux n'ayant pas de troubles de l'olfaction (Solomon, Petrie, Hart, & Brackin, 1998). Ces premiers résultats donnent donc d'excellentes pistes en ce qui a trait aux inférences pouvant être tirées à partir de simples résultats aux évaluations olfactives.

1.8- Objectifs et hypothèses de recherche

Cette thèse porte en elle deux grands objectifs. Le premier consiste à évaluer, à l'aide de contrôles méthodologiques stricts (composition des groupes, contrôle des données démographiques et de l'impact de la cognition, contrôle temporel strict), la prévalence et l'évolution de troubles olfactifs et affectifs suite à un TCCL. Le deuxième objectif vise à évaluer la valeur prédictive de la présence de troubles olfactifs et affectifs suite au TCCL dans le développement et la chronicisation des symptômes d'anxiété et de dépression à long terme. Bien que plusieurs études aient déjà évalué la prévalence des troubles olfactifs suite au TCC, un nombre extrêmement restreint l'ont fait auprès des patients TCCL spécifiquement, bien qu'ils représentent plus de 85% des patients TCC (Faul & Coronado, 2015). Il est primordial d'évaluer correctement la prévalence

de tels troubles suite au TCCL puisque les conséquences qu'apporte la perte de l'olfaction peuvent se montrer dévastatrices (dépression, suicide et anxiété). De plus, l'identification des troubles olfactifs comme possible facteur de risque à la chronicisation des symptômes anxio-dépressifs suite au TCCL, permettra d'enrichir la littérature, assez limitée, entourant ce sujet et, par le fait même, permettra aussi un dépistage rapide et efficace des patients à risque de développer de tels symptômes.

1.8.1- Article 1 : L'évaluation de l'olfaction, de la cognition et des affects 24 heures et un an suite à un traumatisme craniocérébral léger (TCCL)

Dans ce premier article au devis transversal, l'olfaction, ainsi que l'humeur sont évaluées au cours des premières 24 heures suite à l'hospitalisation de patients ayant subi un TCCL. De plus, une évaluation de la cognition fut intégrée au projet dans le but de contrôler et de nuancer les possibles impacts des symptômes cognitifs sur les résultats aux tâches olfactives. À titre de contrôle, l'ensemble des tests sont aussi administrés à un groupe de patients ayant subi une fracture orthopédique sans TCC. Un an suivant cette première évaluation, un test olfactif et des questionnaires évaluant les affects sont envoyés par la poste aux participants ayant préalablement accepté de participer au suivi. La cognition, elle, n'a pu être évaluée à distance. Considérant les études antérieures ayant évalué l'olfaction auprès d'une population TCCL (Ciofalo et al., 2018; de Guise et al., 2015; de Kruijk et al., 2003; Larsson et al., 2004; Schofield, Moore, & Gardner, 2014), les hypothèses suivantes ont été formulées :

1) Les patients ayant subi un TCCL présenteront un plus haut taux de trouble olfactif et, conséquemment, de plus bas scores aux tâches évaluant les différentes sphères olfactives à

court-terme, lorsque comparés au groupe de patients orthopédiques. De tels résultats ne sont pas attendus à l'évaluation à long-terme.

2) Des corrélations positives sont attendues entre les résultats aux tâches olfactives impliquant un traitement cognitif de plus haut niveau (discrimination et identification) et les résultats aux tâches évaluant la mémoire sémantique et la fluence verbale.
3) Des corrélations négatives sont attendues entre les performances à l'ensemble des tâches olfactives (Sniffin'Sticks) à court-terme et les scores d'anxiété et de dépression (HADS) à long-terme.

1.8.2- Article 2 : La présence précoce de parosmie et de symptômes affectifs comme prédicteurs du développement de symptômes anxio-dépressifs six mois suite à un traumatisme craniocérébral léger (TCCL)

Dans ce deuxième article, les troubles quantitatifs (anosmie et hyposmie) et qualitatifs (parosmie et phantosmie) de l'olfaction ainsi que l'humeur sont évalués à un et six mois suite au TCCL. Contrairement au premier article, des évaluations identiques sont administrées à l'ensemble des participants au deuxième temps de mesure, ce qui permet, pour l'une des premières fois dans le domaine, l'obtention de données longitudinales. De plus, des analyses de régressions hiérarchiques sont menées afin de déterminer la place que peut prendre la présence de troubles olfactifs et de l'humeur dans le modèle de prédiction du développement de symptômes anxieux et dépressifs à long terme. Considérant les études antérieures, les hypothèses suivantes ont été formulées :

1) Lorsque comparés aux participants contrôles, les patients ayant subis un TCCL présenteront davantage de troubles olfactifs et symptômes anxio-dépressifs dans les premières semaines suivant le TCCL.
2) Une amélioration générale des capacités olfactives est attendue entre le premier (2-4 semaines suivant le TCCL) et le deuxième temps de mesure (6 mois suite au TCCL).
3) Nous nous attendons à ce que les symptômes anxio-dépressifs, évalués au premier temps de mesure, soient des prédicteurs significatifs des scores de dépression et d'anxiété à long terme.
4) De plus, nous estimons que les scores olfactifs, récoltés au premier temps de mesure, soient, eux aussi, des prédicteurs significatifs du développement de symptômes anxio-dépressifs six mois suite au TCCL.

CHAPITRE 2 – ARTICLE 1: OLFACTORY, COGNITIVE AND AFFECTIVE DYSFUNCTION ASSESSED 24 HOURS AND ONE YEAR AFTER A MILD TRAUMATIC BRAIN INJURY (MTBI).

Fanny Lecuyer Giguère [1,2,3], Andreas Frasnelli[4], Élaine de Guise[1,2,5] & Johannes Frasnelli [1,3,6]

1. Department of Psychology. University of Montreal, Montreal, Quebec, Canada.
2. Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR), Montreal, Quebec, Canada.
3. Hôpital du Sacré-Cœur de Montréal, Montreal, Quebec, Canada
4. Emergency Department, Spitalzentrum Oberwallis, Visp, Switzerland
5. Research Institute-McGill University Health Centre, Montreal, Quebec, Canada.
6. Department of Anatomy, Université du Québec à Trois-Rivières (UQTR), Trois-Rivières, Quebec, Canada.

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2.1 Abstract

Objective: This cross-sectional study aimed to evaluate olfaction 24 hours (baseline) and one year (follow-up) after a mild traumatic brain injury (TBI). We further evaluated the influence of the cognition and affective state on olfactory function. **Method:** At baseline, olfactory function, neuropsychological and affective state were assessed in 42 patients (20 mild TBI; 22 orthopedic injury). At follow-up, 12 patients with mild TBI and 7 controls could be included and we assessed olfactory function, affective states and post-concussion symptoms. **Results**: At baseline, patients with mild TBI demonstrated significantly reduced olfactory function, compared to controls, with more than 55% of the patients presenting sing of hyposmia. One year later, no significant differences in olfactory scores between cases and controls were observed. However, patients with mild TBI who had exhibited hyposmia at baseline exhibited significantly higher anxiety levels and more post-concussion symptoms than patients with mild TBI with normal olfactory function at baseline. **Conclusions**: In the acute phase of mild TBI a majority of patients has impaired olfactory function. Further patients with olfactory dysfunction are more likely to exhibit post-concussion and anxious symptoms at follow-up. Olfactory testing in the acute phase may therefore serve as a screening tool for long term outcome.

Keywords: Mild traumatic brain injury, olfaction, anxiety, cognition, cross-sectional.

2.2 Introduction

Traumatic brain injury (TBI) is one of the major causes of death and handicap in the Western world. Annually, about 1.4 million people suffer from different degrees of TBI in the United States alone (1). The majority of the studies on the subject reported physical, cognitive, behavioural and affective symptoms after the trauma (2-6). In addition to these symptoms, olfactory dysfunction (OD) occurs regularly among people who have suffered a TBI (7-10). In a systematic review, the majority of 25 articles reported OD following TBI, with OD prevalence ranging between 4 and 66% (11). The heterogeneity of prevalence may be due to the fact that most studies do not differentiate between different degrees of TBI. In fact, based on the Glasgow Coma Scale (GCS) score, TBI can be subdivided into mild (GCS: 13–15), moderate (GCS: 9–12), and severe (GCS: 3–8) TBI. Mild TBI is by far the most prevalent type of TBI, representing more than 85% of TBI in the United States (12). The term "mild" is somehow misleading since mild TBI is also associated with cognitive, behavioral and affective symptoms (2-6). To date, the literature on the impact of mild TBI on olfactory function is very scarce and findings are heterogeneous. This may, at least partly, be explained by inter-study differences in (a) the interval between trauma and testing and (b) the tests used to evaluate olfactory function between different studies.

First, the interval between the trauma and testing varies from two weeks to several years for different reports. This interval, however, appears to be of utmost importance as some longitudinal studies on the effect of TBI on olfactory function suggest changes in olfactory function over time. More specifically, two studies described improvement of olfactory function within the first year after TBI (13, 14), while a third report, found persistent OD in the majority (83%) of patients with severe TBI 12 months after the trauma (15). These studies underline the dynamic of OD following TBI and therefore the importance of testing patients within a well-defined interval after

a trauma. In line with this notion, all studies that evaluated OD after a mild TBI within the first 3 months (16, 17) showed a high prevalence of OD, while mixed results were found in the ones that evaluated olfactory function after longer intervals (18, 19). Second, although valid and reliable methods to evaluate the sense of smell are available (e.g., the Sniffin' Sticks test battery (20), the University of Pennsylvania Smell Identification test (UPSIT) (21), the Brief Smell Identification Test (B-SIT) (22)), clinical studies still often use custom-made olfactory tests for which no normative data are available (23, 24). This renders study-to-study comparisons difficult. In summary, when examining the effects of mild TBI on olfactory function, one has to carefully (a) assess the time elapsed between TBI and olfactory assessment, and (b) select the tools used to evaluate OD.

In order to understand the effects of mild TBI on olfactory function, it is therefore important to evaluate the link at precise intervals after the trauma, with appropriate methods. The present study focused on the evaluation of olfactory function with established tests within 24h after a mild TBI. We compared patients with mild TBI with a control group composed of patients that had an orthopedic trauma without any injury to the brain. We hypothesized that mild TBI patients exhibit higher rates of olfactory dysfunction and lower olfactory scores than the control group. Finally, we used different tools to evaluate olfactory function at baseline and at follow-up. This prevented us to have a true longitudinal study design. Future studies should use the same tool at both baseline and follow-up in order to provide data on the evolution of OD after a mild TBI.

Further, cognitive and affective symptoms are often reported after a mild TBI (2-6). This is interesting since higher order olfactory tasks are linked to cognition. Specifically, better semantic memory and verbal fluency are associated with higher odor identification (25) and odor discrimination scores, but not odor detection (26). Further studies additionally link anxiety to

olfactory function, with higher anxiety levels being associated with reduced olfactory performance (27). We therefore inquired whether olfactory impairment within the first 24 hours after a mild TBI was associated with cognition and/or affective profiles at baseline and follow up. We expected to find positive correlations between scores of higher order olfactory function (odor discrimination and identification) and specific cognitive evaluations (short-term memory, verbal fluency). Further, we hypothesized olfactory performance to be negatively correlated with scores of anxiety and depression.

2.3 Methods

The study took place between December 2016 and February 2018 and was approved by the Ethics Committee of the Commission cantonale d'éthique de la recherche sur l'être humain (#2016-01442).

2.3.1 Participants

A total of 20 (8 women) patients with mild TBI and 22 (13 women) patients with orthopedic trauma, i.e., a fracture of a limb (e.g., hand, arm, foot, ankle) were evaluated 24 hours after their trauma. We collected demographic information, such as age, gender, manual dominance, occupation and years of education, for all patients at baseline and follow-up (Table 1). We further noted dates/ type of accident, site of the impact, post-traumatic amnesia (PTA), GCS score upon administration to the Emergency Room as well as the result of the CT scans results. At follow-up, one year after the trauma, 12 patients with mild TBI and 7 orthopedic controls accepted to participate. We additionally collected information about the presence of any new medical incident and medications.

Table 1. Descriptive statistics of patients with mild TBI and orthopedic controls at baseline and follow-up.

baseline	Mild TBI	Orthopedic	*p*
n	20	22	
Age in years (SD)	33.05 (12.24)	38.68 (13.31)	0.16
Women, n (%)	8 (40)	13 (59)	0.35
Right handers (R), n (%)	19 (95)	20 (90)	0.53
Years of Education (SD)	13.45 (1.70)	14.50 (1.40)	0.03
CT-Scan (+), n (%)	3 (15)		
GCS (SD)	14.85 (0.36)		
PTA (minutes) (SD)	22.65 (40.81)		
LOC (minutes) (SD)	3.46 (4.26)		
Type of accident, n			
Sport	18		
Fall	2		

follow-up	Mild TBI	Orthopedic	*p*
n	12	7	
Age in years (SD)	34.08 (12.44)	39.42 (14.66)	0.40
Women, n (%)	5 (42)	4 (57.)	0.65
Right handers, n (%)	11 (92)	6 (86)	0.53
Years of Education (SD)	13.08 (1.37)	15.00 (1.52)	0.01
CT-Scan (+), n (%)	2 (17)		
GCS at baseline (SD)	14.83 (0.38)		
PTA at baseline (minutes) (SD)	31.91 (51.19)		
LOC at baseline (minutes) (SD)	3.43 (4.85)		
Type of accident, n (%)			
Sport	10		
Fall	2		

Note. SD= Standard Deviation. GCS = Glasgow Coma Scale. PTA = Post-Traumatic Amnesia. LOC= Loss of consciousness.

General inclusion criteria were: (a) age between 18 and 55 years, (b) having completed a minimum of 12 years of education, and (c) having the capacity to understand, talk and write in either French, English or German. Across all patients in the mild TBI group, the majority, 90% (n=18), had a concussion after a sport accident (skiing or biking) while 10% (n=2), suffered from mild TBI after a fall. The diagnosis of mild TBI was based on the criteria of Center for Disease

Control and Prevention (12), was carried out by the physician; the trauma had to have occurred less than 24h before testing. Specifically, diagnostic criteria of mild TBI included one or more of the following: (a) confusion, disorientation and/or loss of consciousness for 30 minutes or less, (b) post-traumatic amnesia for less than 24 hours, and (c) a GCS score between 13 and 15, observed within the first 30 minutes' post trauma or later upon presentation at the ER. In line with Canadian CT head rules (28), the majority (15/20) of the mild TBI patients had a first CT scan done within the first hours following their arrival in the ER. Identification of any cranial or intracranial injury on radiological imaging was used to confirm the presence of complicated mild TBI, which was the case in 3/15 patients. Of them, two had left cerebral lesions (e.g., sub-epidural bleeding) and one had bilateral lesions (e.g., hyperdense formations). Because of the small sample size, we did not analyze this group separately.

Participants in the orthopedic control group suffered from a confirmed fracture of a limb (e.g., hand, arm, foot, ankle) and were also evaluated within the first 24 hours after the accident. The presence of a limb fracture was diagnosed by the physician in charge of the ER. General exclusion criteria were: (a) the presence of any history of TBI, (b) known pre-existing OD, (c) history of psychiatric or neurological disorders, (d) excessive use of recreational drugs (e.g., cannabis; more than one consumption per day) and alcohol (more than three consumption per day) (29), (e) being under the influence of alcohol or recreational drugs during the testing, (f) smoking more than 6 cigarettes a day, (g) medication known to interfere with cognitive abilities (e.g., antidepressants, benzodiazepines, hypnotics). Finally, a specific exclusion criterion for the control group was a related head trauma.

2.3.2 Instruments

2.3.2.1 Evaluation of olfactory function

At baseline, we used the Sniffin' Sticks Inventory Test to evaluate olfactory function. This test is based on felt tip pen-like odor dispensing devices and allows for the evaluation of three different aspects of the olfaction (odor detection threshold, odor discrimination, and odor identification). The exact procedure is described elsewhere (20). In short (a) detection threshold is determined by using 16 different concentrations of phenyl ethanol (rose odor) in an ascending/ descending staircase procedure. The score can vary between 1 (lowest sensitivity) and 16 (highest sensitivity). Next, (b) odor discrimination is assessed by using 16 triplets of pens, two of which contain the same and the third an odd odor. Patients' task is to detect the odd pen. Scores range between 0 and 16. Finally, (c) odor identification is carried out with 16 pens containing different odors. For each odor, patients have to select amongst four choices. Scores can range from 0 to 16. The results of the three subtests can be added up to a composite score (TDI score) for which normative data are available (30). Accordingly, scores below the 10th percentile indicate the presence of hyposmia (partial loss of olfactory function).

Olfactory function at follow-up was assessed by the patients themselves, by using the University of Pennsylvania Smell Identification Test (UPSIT) (21, 22). In short, the UPSIT is comprised of four booklets, each containing 10 microencapsulated (scratch and sniff) odors. Patients choose between four items for each odor. Scores range between 0 and 40 and allow for the distinction of normosmia, hyposmia and anosmia, based on normative data (22)

2.3.2.2 Evaluation of cognitive function

Cognition of all patients was evaluated by the administration of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a screening instrument used to

evaluate general cognitive function. This 30-minutes battery contains 12 cognitive subtests that are transformed into 5 indexes and a total score. Normative data provided age and education corrected indices and subtest standard scores (31). Specifically, we assessed (a) immediate memory with the subtests list learning (number of words correctly recalled) and story memory (number of the story concepts correctly recalled) subtests; (b) visuospatial abilities with the subtests complex figure copying (number of correctly drawn elements of the figure) and judgment of line orientation (number of correctly matched line orientations); (c) language with the subtests picture naming (number of correctly named picture shown) and semantic fluency (number of fruits and vegetables told in one minute); (d) attention with the subtests digit span (correct repeated string of numbers) and coding (number of symbols correctly copied in 90 seconds) subtests; (e) delayed memory with the subtests list recall (number of words correctly recalled 25 minutes after the first lecture), list recognition (number of correctly recognized word from the initial list), and story recall (number of the initial story elements recalled 25 minutes after the first reading) subtests. We then computed a Total Index by summing up the standard scores of all 5 indices.

2.3.2.3 Evaluation of executive function

We further evaluated executive function. To do so, we first evaluated the participants' processing speed, cognitive flexibility and switching abilities by the use of the Delis-Kaplan Executive Function System (DKEFS) Color-Word interference test (32). In this 10-minutes test, patients were presented four different tasks, namely (a) colors reading (processing speed), (b) words reading (processing speed), (c) inhibition (cognitive flexibility), and (d) switching. Here, the time and the number or errors of all four subtasks were collected. Next, patients' visual attention and switching abilities were evaluated by the Trail Making Test (Trails A and B) (33).

The time that participants took to complete each of the two tests were noted (34). Finally, we assessed working memory by the use of the Digit Span task of the WAIS-IV (34). We only used the "backward" subtask of the Digit Span WAIS-IV task, since the "forward" subtask was already included in the RBANS battery (Digit Span task). So, in this 10-minutes test, patients are read a sequence of numbers and have to recall the sequence backward. Here, an adequately recalled sequence is worth one point and the test ends when the participant missed two sequences in a row. A total score of all adequately recalled sequences was compiled. All raw scores were standardized and converted into z-scores by using the appropriate demographic normative data for the respective test manuals (31, 32, 34, 35), correcting for age, sex and education.

2.3.2.4 Evaluation of affective status

All patients completed the Hospital Anxiety and Depression Scale (HADS). This fourteen items scale generates two scores, one for depression (7 items) and the other for anxiety (7 items) (36). Scores range from 0 to 3 for each item, giving a maximum score of 21 for each domain (anxiety or depression). Based on the normative data (36), the absence of pathology is reflected by scores between 0-7, borderline cases are the ones who obtain scores between 8-10 and abnormal (pathological) cases are the ones who scored between 11-21.

2.3.2.5 Evaluation of post-concussion symptoms

We used the Rivermead post-concussion symptoms questionnaire (37) to evaluate post-concussion symptoms. This questionnaire is a self-report measures of post-concussion symptoms following mild TBI. It consists of 16 post-concussion symptoms that patients are asked to rate from 0 (not a problem) to 4 (severe problem since the injury). Scores for each item are summed

to a score with a maximum of 64 (36). This test was only applied at follow up because according to the test manual it can only be administered at least 24 hours after a TBI.

2.3.3 Procedure

2.3.3.1 Baseline

Patients in both groups (mild TBI, orthopedic) were recruited at their admission at the Visp hospital (VS, Switzerland).

After the confirmation of the diagnosis (mild TBI or orthopedic), a semi-structured interview was carried out to verify the presence of inclusion and exclusion factors. Afterwards, the consent forms were explained and signed by all of the patients and olfactory, affective and cognitive evaluations were carried out at bedside by a trained neuropsychology PhD candidate (FLG).

2.3.3.2 Follow-up

One year after the first evaluation, an email was sent to all the patients. We were able to contact 38/42 patients. Nineteen (19) of them accepted to do the follow-up investigation (12 patients with mild TBI, 7 controls) and received, by post, an envelope, containing a self-administered olfactory test and a link leading to an online survey containing several affective and post-concussion questionnaires.

2.3.4 Statistical Analysis

All variables followed a normal distribution (Kolmogorov-Smirnov test for normality, all $p>0.05$) unless stated otherwise. All patients were classified, using the Sniffin' Sticks' global TDI scores, as presenting (OD+) or not (OD –) clinical sing of OD (a score <30.3). The proportion of

OD+ and OD- patients in both groups were compared by using a chi square analysis. Next, group comparisons for olfactory function were carried out by a repeated measures ANOVA, with condition (2 levels: mild TBI; orthopedic control) as the between subject factor and task (three levels: threshold score; discrimination score; identification score) as within subject factor. Next, we carried out three separate rm ANOVA to compare group scores for (a) cognitive (z-scores of the five RBANS index), (b) executive (z-score for TMT A & B, 4 Color-words subtests and the backward Digit Span) and (c) affective scores (raw scores of the anxiety and depression HADS subscales). Subsequently, we evaluated the association between cognitive ((a) Total RBANS Index and 5 subscores, (b) two TMT subtests, (c) four Color-Word (DKEFS) subtests, and (d) the backward digit Span), affective (HADS depression and anxiety subtests) scores, and olfactory scores (Spearman's rank correlation coefficient).

Scores of olfactory testing at follow-up data were not normally distributed and therefore analyzed using individual nonparametric Mann-Withney U-tests. Finally, we compared patients with mild TBI and OD (mTBI +) and patients with mild TBI and normosmia (mTBI -) at baseline, on affective, cognitive and post-concussion symptoms (Mann-Whitney U-test).

Bonferroni correction was applied for multiple comparisons and statistical significance was defined as $p<0.01$.

2.4 Results

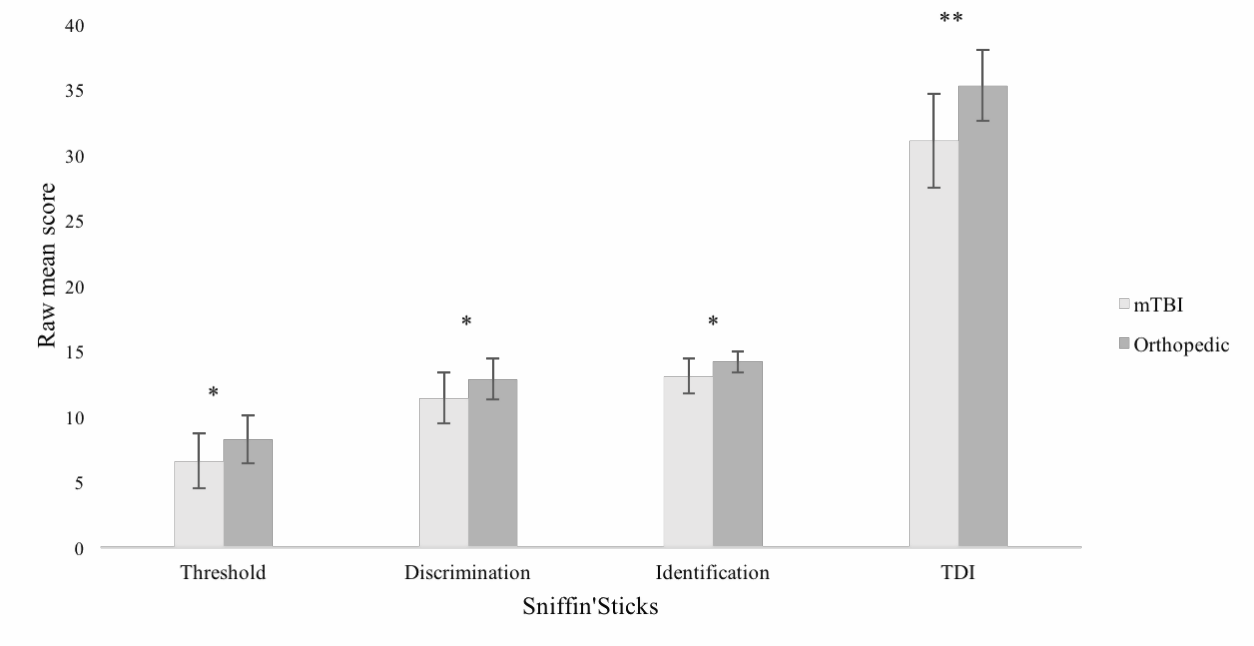
2.4.1 Olfactory function

At baseline, patients with mild TBI (M=31.1, SD= 3.6) had lower TDI scores than controls (M=35.3, SD= 2.7) ($t(40) = - 4.290$, $p < .001$,Hedges' g = 1,32). Based on normative data (Hummel, 2007), 55% of the patients with mild TBI (n=11) reached the clinical threshold for hyposmia (TDI score <30.3). In comparison, only one patient (4.5%) in the orthopedic group

exhibited hyposmia. Consequently, there was a significant association between the condition of the patients and the presence of olfactory dysfunction $\chi 2$ (1) = 13.06, $p < .001$. The odds of exhibiting olfactory dysfunction were 30.5 times higher if the patients had sustained mild TBI than if they had an orthopedic injury. None of three patients with complicated mTBI (i.e., positive CT) had clinical sing of olfactory dysfunction, based on their Sniffin'Sticks composite score (TDI > 10th percentile).

To investigate olfactory function more closely, we computed a repeated measures (rm) ANOVA and observed a significant effect of condition ($F(1, 40) = 18.404$, $p < .001$). Post hoc t-tests showed that patients with mild TBI had significantly lower scores on the threshold ($t(40) = -2.732$, $p = .009$), identification ($t(40) = -3.228$, $p = .002$) and discrimination ($t(40) = -2.676$, $p = .011$). We further found a significant effect of task ($F(1,40) = 182.776$, $p< .001$), indicating that the three tasks yielded different average results, but no significant interaction between task and condition ($F(1,40) = .370$, $p= .692$). Figure 1 shows the performance scores (group mean and standard deviation) on the three subtests of the Sniffin' Sticks test and the composite score (TDI).

Figure 1 Sniffin'Sticks mean raw scores of the three subtasks and composite index.



For the follow-up, nonparametric Mann-Withney U-tests revealed no significant group difference for the UPSIT score (mild TBI: M=34.00, SD= 2.86; Ortho: M=34.14, SD= 3.38; t(17) = -,098 p = .923). Further, normative data showed that 42% (n=5/12) of the patients in the mild TBI group presented clinical sing of hyposmia at follow up, compared to 29% (n=2/7) in the orthopedic group. This distribution was not significantly different between both groups ($\chi 2$ (1) = .326, p = .568).

2.4.2 Cognitive function and association with olfaction

With regards to cognition, patients with mild TBI scored significantly lower on the Total Index of the RBANS (t(40) = -3.727, p = .001) than controls. To investigate this further, we computed a rm ANOVA on the five RBANS indices. We observed a significant effect of condition F(1, 40)= 12.869, p = .001), in line with the previous findings. We further found a significant effect of task (F(1,40) = 5.781, p= .001), indicating that the five RBANS indexes

yielded different average results. Finally, we found a significant interaction between task and condition ($F(1,40) = 3.674$, $p = .011$). Post hoc t-tests showed that patients with mild TBI had significantly lower indices for immediate memory ($t(40) = -3.031$, $p = .005$), delayed memory ($t(40) = -4.167$, $p < .001$) and language ($t(40) = -4.074$, $p < .001$), but no difference on the visuospatial and attention indexes. Average test scores are presented in Table 2.

There was no correlation between cognitive scores and olfactory function in patients with mild TBI.

Tables 2. Demographically adjusted performances z-scores of the cognitive and executive domains.

	Mild TBI Mean (SD)	Orthopedic Mean (SD)	*p*
Cognition			
RBANS			
Immediate Memory Index	-.50 (1.13)	.42 (.75)	**>.001**
Visuospatial Index	-.45 (.82)	-.21 (.85)	.35
Attention Index	-.61 (1.02)	-.43 (1.03)	.57
Language Index	-.42 (.71)	.48 (.72)	**>.001**
Delayed Memory Index	-1.20 (1,07)	-.05 (.63)	**>.001**
Total Index	-.89 (.75)	.05 (.76)	**>.001**
Executive Function			
TMT A	-.04 (1.26)	.02 (.83)	.87
TMT B	-.17 (1.36)	.24 (.79)	.23
Stroop 1	-.17 (.67)	-.22 (.94)	.83
Stroop 2	.38 (.49)	.01 (.76)	.07
Stroop 3	.14 (.85)	.40 (.82)	.32
Stroop 4	.05 (.57)	.48 (.87)	.06
WAIS-IV Digit Span	-.93 (.75)	-1.04 (.63)	.58

Note. Stroop 1= DKEFS Color Reading subtask. Stroop 2= DKEFS Word Reading subtask. Stroop 3= DKEFS Inhibition subtask. Stroop 4= DKEFS Switching subtask. TMT A= Trail Making Test A. TMT B = Trail Making Test B.

2.4.3 Executive function and association with olfaction

Next, we investigated executive function (z-scores of the TMT A and B, 4 Color-Word interference tasks and WAIS-IV backward Digit Span task). We did not observe any effect of condition, nor interactions between conditions and task for any of the tests; all $P > 0.05$). Further, there was no correlation between scores of executive function and olfaction in patients with mild TBI.

2.4.4 Affective status and association with olfaction

Finally, we evaluated the patients' affective state. We did not observe any effect of condition ($F(1, 40) = .270$, $p = .606$) or task ($F(1, 40) = .024$, $p = .877$), but a significant interaction between task and condition ($F(1, 40) = 14.072$, $p = .001$). Post hoc t-tests showed that mild TBI patients significantly reported more anxiety symptoms than controls within the first 24 hours after the concussion ($t(40) = 2.590$, $p = .013$), but no difference for depression. However, at follow up and thus in groups with a smaller sample size, no such difference was observed ($t(16) = -1.255$, $p = .227$).

Tables 3. Raw scores, at baseline and follow-up, of the Hospital Anxiety and Depression Scale.

	Mild TBI Mean (SD)	Orthopedic Mean (SD)	*p*
HADS (Baseline)			
Anxiety symptoms scale	4.85 (3.66)	2.27 (2.76)	**>.00**
Depression symptoms scale	2.80 (3.44)	4.50 (3.30)	.82
HADS (Follow-up)			
Anxiety symptoms scale	3.27 (2.90)	5.42 (4.42)	.32
Depression symptoms scale	2.90 (3.56)	2.42 (3.20)	.26

Note. HADS= Hospital Anxiety and Depression Scale. SD= Standard deviation.

There was no correlation between anxiety/ depression ratings and olfactory scores in patients with mild TBI after correction multiple comparisons.

2.4.5 Olfactory function at baseline and symptoms at follow-up

We investigated if patients with mild TBI and hyposmia at baseline (TBI+; of 11 patients at baseline, 5 could be included at follow up) differed in any way from the patients with mild TBI and normal olfactory function at baseline (TBI-; of 9 patients at baseline, 7 could be included at follow up). TBI+ reported more anxiety symptoms at baseline ($p = .020$) and at follow up ($p = .009$). They also showed significantly more post-concussion symptoms (Rivermead questionnaire) at follow-up ($p = .008$) (Table 4). This measure could not be assessed at baseline.

Tables 4. mTBI+ and mTBI- raw scores (mean and SD) up at the HADS (baseline and follow-up) and the Rivermead post-concussion symptoms questionnaire (follow-up).

	mTBI + Mean (SD)	mTBI - Mean (SD)	*p*
HADS (Baseline)			
Anxious symptoms scale	6.54 (3.26)	2.77 (3.11)	**.01**
Depression symptoms scale	3.09 (3.01)	2.44 (4.06)	.68
HADS (Follow-up)			
Anxious symptoms scale	5.33 (2.16)	.80 (1.09)	**.00**
Depression symptoms scale	4.00 (4.24)	1.60 (2.30)	.28
Rivermead (Follow-up)	24.20 (5.44)	3.80 (1.78)	**.00**

Note. HADS= Hospital Anxiety and Depression Scale (HADS). SD= Standard deviation.

2.5 Discussion

2.5.1 Olfactory function 24 hours and one-year after a mild TBI

The main objective of this study was to evaluate olfactory impairment within the first 24 hours and at one year after a mild TBI, by using valid and reliable olfactory measures. As

hypothesized, olfactory function is significantly reduced within the first 24-hour after a mild TBI. Indeed, clinical sing of hyposmia were found in 55% (11/20) of the mild TBI group, while only 1/20 control patient exhibited hyposmia. Moreover, olfactory impairment was observed on all three subtasks of the Sniffin' Sticks test. At follow up we did not find any significant difference between the two groups. The follow-up investigation was carried out on a portion of the original patients and with a different olfactory tool and therefore has to be interpreted with caution.

The available literature on olfactory impairment following mild TBI is relatively limited, especially during its acute phase. Earlier publications consistently report significant olfactory impairment following mild TBI. For instance, in 2003, De Krujik (17), found that 26% (28/111) of mild TBI patients presented clinical sing of reduced olfactory function, two weeks after their trauma. However, these results were obtained by the use of the Hyposmia Utility Kit (Olfacto-labs, El Cerrito, US), for which the only normative data were published 40 ago on only 50 healthy individuals (38), limiting the interpretation of the results and conclusions. More recently, a group of researchers used the Sniffin' Sticks test to evaluate olfactory function in patients with mild TBI (16). They found that, of the 352 mild TBI patients evaluated, 118 (33%) presented olfactory loss. However, they did not include a control group and, even more importantly, they did not record the time elapsed between trauma and olfactory evaluation which renders the interpretation of the conclusions again difficult. By using a valid test and by limiting the time frame to the first 24h after the trauma, we observed that the majority of patients with mild TBI exhibit OD within the first 24 hours after the trauma. By comparing them to a group of patients with traumatic orthopedic fractures, we could show that olfactory dysfunction is not due to a trauma in general, but rather to a trauma to the brain.

Also, even with a limited sample size and the absence of a longitudinal design, the present study provides exploratory data on olfactory function one year after a mild TBI. The data

suggests that mild TBI patients' olfactory function is not significantly affected one year after the trauma as no significant group difference was found using the UPSIT. Still 5/12 mild TBI patients (42%) exhibited clinical signs of hyposmia. Although this is the first study on the effects of mild TBI on olfactory function one year after the trauma, this result is, at least partially, in line a previous study on the evolution of OD on severe TBI, six months after the trauma (15). Here the majority (37/45) of patients showed OD, but 32/45 showed improved olfactory function compared to baseline, mostly from anosmia to hyposmia. Together, these and our results suggest that recovery takes place in the early months after a TBI but seems to be limited to the first 6 months, as only 10% (10/99) of TBI patients exhibited improvement of olfactory function from, on average, 18 months to 30 months after the trauma (39).

2.5.2 Cognitive, executive and affective function

Patients with mild TBI had lower performances in measures of language as well of immediate and delayed memory, in comparison with a control group. This is in line with the literature (2, 4, 6, 40-42). However, reports present great variability in the delays between trauma and cognitive evaluation, as cognition was evaluated from one week to several years after the mild TBI. Most studies on acute TBI focus on athletes and only two studies evaluated cognition of non-athletes with mild TBI within the first hours after the trauma and found impairments of immediate and delayed memory (43, 44). However, since we evaluated several cognitive domains rather than only memory, we additionally found that patients with mild TBI present lower language skills, a cognitive domain that is largely unexplored in mild TBI. However, the few studies published to date are in line with our findings, suggesting that patients with mild TBI demonstrate lower performances, when compared to controls, on naming and verbal fluency tasks (40). Moreover, the present study included only first-time mild TBI patient, in contrast to the

great majority of previous reports. This is important as other studies found significant differences in the neuropsychological performances between first-time mild TBI patients and multiple mild TBI patients (45, 46). Indeed, a previous meta-analysis revealed that multiple self-reported mild TBI was associated with poorer neuropsychological performance (executive function, memory), compared to patients with a single mild TBI (47). Also, for the interpretation of our results it is important to point out that, although the patients with mild TBI presented significantly lower cognitive scores than controls, their mean values were still in the average or low average ranges (between -1.33 and +.33 SD) (31, 32, 34, 35).

We did not observe any significant correlations between cognition and olfactory scores, in contrast to previous reports. This lack of association may appear surprising, since the relationship between cognition and olfactory performance is well established. Precisely, two studies found that healthy participants' executive function and semantic memory to be related to odor discrimination and identification (25, 26). However, it is important to mention that the previous results were found on older adults (mean age between 58 and 68 years) compared to our sample that was 20 to 30 years younger. It is therefore conceivable that the patients in our study had better cognitive skills, as cognitive abilities decline with age (48, 49), especially after the age of 50 (4, 50, 51). Furthermore, the strongest cognitive loss is seen in working and episodic memory, two of the main cognitive domains previously found to be correlating with olfactory performances (25, 26, 48, 49, 51). Indeed, as mentioned above, even if the patients with mild TBI had lower scores on three cognitive domains, when compared to the orthopedic patients, their results were still within one standard deviation from the mean. This implies that compared to previous studies on more severe TBI or in older participants (7, 25, 26), we tested young mild TBI patients with generally well-preserved cognitive functions.

In addition, compared to the control group, patients with mild TBI reported significantly more anxiety symptoms. These results are consistent with the majority of the studies carried out in the past years (6, 52-54). However, in these earlier reports, the delays between trauma and testing varied a lot, ranging from two weeks to several years. We therefore show that anxiety symptoms, although subclinical, are present from day 1 after the trauma, which is potentially useful for clinicians. Interestingly, scores on the anxiety questionnaire were not correlated with olfactory function; only with odor discrimination we observed a negative correlation before correction for multiple comparisons (rho = - 0.507, P = 0.023). Other studies have reported a link between anxiety and olfactory function, but typically for odor identification (55). However, one has to keep in mind that previous results investigated patients with clinically diagnosed anxiety disorders (e.g., post-traumatic stress disorders, general anxiety disorder), whereas the patients with mild TBI in our study did not meet the criteria for a high and significant number of anxiety symptoms.

2.5.3 Hyposmia at baseline may be a predictor of anxiety and post-concussive symptoms

We found that patients with mild TBI and hyposmia at baseline (TBI+) reported significantly more anxiety symptoms than patients with mild TBI without hyposmia at baseline (TBI-). This was true for the baseline, 24 hours after the trauma, and follow-up, one year after the trauma. Further, TBI+ patients reported significantly more post-concussion symptoms, one year after the trauma. The Rivermead post-concussion symptoms questionnaire cannot be used within 24h after the trauma, so this could not be evaluated at baseline. However, the mean number of post-concussive symptoms reported by TBI+ was 8 times higher than in the TBI- group. This implies that, compared to TBI-, TBI+ have more somatic, cognitive and affective complaints, one year after a mild TBI. However, these results must be taken as preliminary as they were obtained

on data from 12 individuals. Future studies should further investigate the predictive power of hyposmia in the early phase of mild TBI.

2.5.4 Study limitations and future directions

A cross-sectional quasi-experimental design as the present one does not establish any causal link between variables since subjects are not randomly distributed. Further, the small number of patients that accepted to participate to the follow-up limits the interpretation of the findings. Future studies should include a larger sample to examine the association between anxiety and olfaction. Another limitation is related to the tool used to evaluate the patients' cognitive profile, since the RBANS is a screening tools rather than a comprehensive cognitive battery, as for example the WAIS-IV (34). Further, since they were evaluated at distance, we could not carry out any cognitive evaluation at follow-up. Future studies should perform thorough cognitive evaluations at baseline and at follow up to gain information in the cognitive development after a mild TBI. Finally, we used different tools to evaluate olfactory function at baseline and at follow-up. This prevented us to have a true longitudinal study design. Future studies should use the same tool at both baseline and follow-up in order to provide data on the evolution of OD after a mild TBI.

2.6 Conclusion

Even mild TBI leads to significant loss of olfactory function within the first 24 hours. Compared to a control patient population, patients with mild TBI show lower cognitive (immediate, delayed memory and language) and affective (anxiety) scores. Patients with olfactory dysfunction within 24h after mild TBI may have more anxiety and post-concussion symptoms on the long run.

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2.8 Disclosure of interest

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CHAPITRE 3 – ARTICLE 2: EARLY PAROSMIA SIGNS AND AFFECTIVE STATES PREDICTS DEPRESSION AND ANXIETY SYMPTOMS SIX MONTHS AFTER A MILD TRAUMATIC BRAIN INJURY

Fanny Lecuyer Giguere[1,2,3], Benoit Jobin[1,3], Joëlle Robert[4], Laurianne Bastien [1,3], Jean-François Giguère[3], Louis De Beaumont[3, 5], Elaine de Guise[1,2,6] & Johannes Frasnelli [1,3,7]

1. Department of Psychology, University of Montréal, Montréal, Québec, Canada.
2. Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR), Montréal, Québec, Canada.
3. Research Center, (CIUSSS-NIM), Montréal, Québec, Canada.
4. Department of Psychology, University of Sherbrooke, Sherbrooke, Québec, Canada
5. Department of Surgery, University of Montréal, Montréal, Québec, Canada.
6. Research Institute-McGill University Health Centre, Montreal, Quebec, Canada.
7. Department of Anatomy, University of Québec in Trois-Rivières (UQTR), Trois-Rivières, Québec, Canada

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3.1 Abstract

This longitudinal study aimed to evaluate qualitative (parosmia) and quantitative (hyposmia/anosmia) olfaction 2-4 weeks (baseline) and six months (follow-up) after a mild traumatic brain injury (mTBI). We further evaluated the predictive value of baseline depression, anxiety and olfaction scores on depression and anxiety at follow-up. At baseline, olfactory function and affective state were assessed in 107 participants (53 patients with mild TBI; 54 healthy controls). At follow-up, data were collected on 71 participants (32 patients, 39 controls). Both at baseline and follow-up, patients with mild TBI showed more signs of parosmia, depression and anxiety, compared to controls. However, patients did not, neither at baseline nor follow-up, show quantitative olfactory impairment. Moreover, while baseline scores of depression and anxiety helped predict the development of symptoms of depression and anxiety at follow up, adding parosmia scores to the prediction model significantly increased the amount of explained variances. Clinicians should implement affective and olfactory evaluation to predict patients' affective outcome.

Mild traumatic brain injury, olfaction, depression, anxiety, longitudinal

3.2 Introduction

Traumatic brain injury (TBI) is one of the leading causes of dysfunction and disability in North America. Approximately 4.4 million new cases of TBI occur each year in the United States and Canada (1299 cases per 100,000) (Dewan et al. 2018). Of these, about 85% are considered mild TBI (Faul and Coronado 2015), as opposed to moderate and severe forms. While most patients recover fully within the first 3 months after mild TBI, approximately 10-15 % of patients have persistent physical, behavioural, cognitive and affective symptoms, known as the post-concussion symptoms (PCS) (Alves and Reviews 1992; Binder et al. 1997). Of these symptoms, the onset and development of symptoms of depression and anxiety are amongst the most common and persistent issues following a concussion. In fact, 15-52% of mild TBI patients reported clinical signs of depression and anxiety within the first-year after the trauma (Almeida-Suhett et al. 2014; Bombardier et al. 2010; Lucas et al. 2016; van der Naalt et al. 2017), compared to approximately 8% in the general population (Canada 2013). Further, 17% of patients with mild TBI developed a major depressive episode within 3 months after the trauma (Levin et al. 2001). Finally, mild TBI patients with significant depression reported significantly more and intense post-concussion symptoms than both healthy controls and mild TBI patients without depressive symptoms, further strengthening the link between depression symptoms and PCS (Lange et al. 2011).

While it is now widely documented that symptoms of anxiety and depression after mild TBI are associated with worse prognosis (Lange et al. 2011; McCauley et al. 2001; Terry et al. 2018), there is a need to better understand the factors that determine the risk to develop persistent symptoms of anxiety and/or depression after mild TBI. Such knowledge could facilitate selective therapeutic options and reduce negative outcomes after mild TBI. To date, only four studies evaluated potential risk factors to developing long-term depression symptoms after a mild TBI

(Levin et al. 2005; Rao et al. 2012; Wojcik 2014; Zahniser et al. 2019). Furthermore, most of these papers only evaluated predictors of depression symptoms, leaving anxiety symptoms relatively neglected. Results from these four studies revealed the strongest markers of long-term symptoms of depression after mild TBI to be (1) the presence of depression symptoms within the first weeks after the mild TBI and (2) older age (Carroll et al. 2004; Levin et al. 2005). However, it is difficult to compare the results between these studies since they all present different methodologies. Precisely, studies differed regarding (1) the tools selected to evaluate depression (generic vs disorder-specific instruments), (2) the time frame chosen between the evaluations (ranging from 1 months to 4 years) and (3) the definition of depression symptoms themselves (some studies evaluated major depression, others the presence of depression symptoms). In summary, there is a lack of longitudinal studies with a controlled time frame that use valid and reliable methods to evaluate affective status, which is however needed to detect the risk factors for a later development of symptoms of anxiety and/or depression.

Another interesting avenue is the presence of olfactory dysfunction (OD) as OD, depression symptoms and TBI are associated (Drummond et al. 2013; Sigurdardottir et al. 2016). Specifically, olfactory function can be impaired quantitatively (anosmia: complete absence of olfactory perception; hyposmia: reduced olfactory perception) or qualitatively (parosmia: smells are perceived differently than they are supposed to smell; phantosmia: the perception of smells in the absence of an odor source) (Doty 2015). First, OD is common in TBI; both parosmia (37-40%) (Doty et al. 1997b; Frasnelli et al. 2016) and anosmia/hyposmia (37-61%) are highly prevalent in moderate to severe TBI (Schofield et al. 2014). However, only few studies evaluated the presence of OD in mild TBI – which is by far the most common form of TBI – and reported heterogeneous prevalence rates ranging from 20–55% (Ciofalo et al. 2018; de Kruijk et al. 2003;

Lecuyer Giguère et al. 2019; Schofield et al. 2014). This heterogeneity may be explained by the fact that the interval between the trauma and the evaluation of olfactory function varied strongly between studies, from hours to years, and that non-validated tools were used in some of the studies to evaluate olfactory function. Second, OD and depression are linked. OD is commonly found in depression (Kohli et al. 2016), patients with depression exhibit smaller olfactory bulbs (Negoias et al. 2010), and anti-depressive treatment leads to improved olfactory function (Croy and Hummel 2017). Inversely, a high proportion of patients with OD often show signs of mild-moderate depression (Frasnelli and Hummel 2005; Jung et al. 2014; Temmel et al. 2002). One of the proposed neurobiological underpinning of this association may be the fact that olfactory processing takes place in the limbic system (amygdala, hippocampus, anterior cingulate, entorhinal cortex) (Heimer et al. 2007; Kohli et al. 2016; Krusemark et al. 2013; Soudry et al. 2011). In addition to this possible association, there is also an indirect link connecting olfactory dysfunction with symptoms of depression and/or anxiety: individuals with OD tend to be more anxious to expose themselves to dangers such as spoiled food, fire, or gas leaks (Croy et al. 2014), they are less inclined to socialize over meals (Rolls 2015) and they may develop complexes regarding personal hygiene (Croy et al. 2014).

The present study thus aimed at evaluating the possible predictors leading to the development of symptoms of depression and/or anxiety 6 months after a mild TBI. To do so, we assessed olfactory function and symptoms of depression and anxiety on two occasions, namely (1) 2-4 weeks after the trauma (baseline) and (2) 6 months after the trauma (follow up). We compared patients with a matched control group without any history of TBI. We hypothesized that (1) patients exhibit higher rates of OD, and more symptoms of depression and/or anxiety than controls at baseline, and that (2) patients' olfactory function significantly improves between

baseline and follow up. We also expected (3) symptoms of depression and/or anxiety at baseline to be significant predictors of anxiety and depression scores at follow up. Finally, we hypothesized (4) baseline olfactory scores to be significant predictors of anxiety-depression scores at follow up.

3.3 Methods

Data acquisition for this study took place between April 2015 and July 2018 and was approved by the local Ethics Board (CIUSSS-NIM #2014-1016). This study complies with the Declaration of Helsinki for Medical Research involving Human Subjects and all participants gave their written informed consent.

3.3.1 Participants

A total of 53 (30 men) patients with mild TBI and 54 (27 men) healthy controls were evaluated at baseline, between 2 and 4 weeks after the trauma. We collected demographic information, such as age, gender, manual dominance and years of education, for all participants. For the patients, we further noted type of accident, presence of loss of consciousness (LOC), presence of post-traumatic amnesia (PTA), Glasgow Coma Scale (GCS) upon admittance to the Emergency Room (ER) as well as the result of the CT scans (positive [presence of blood clots, hemorrhages or skull fractures] or negative [no abnormalities]). At follow-up, six months after baseline, 32 patients with mild TBI (16 men) and 39 (22 men) healthy controls accepted to return for the follow up (Table 1).

Table 1

Descriptive statistics of patients with mild TBI and controls at baseline and follow-up

Baseline	Controls	Mild TBI	*p*
n	54	53	
Age in years (SD)	31.3 (9.19)	38.7 (13.31)	.36
Women, n (%)	27 (50)	23 (43)	.50
Years of Education (SD)	15.6 (2.49)	14.5 (1.40)	.61
CT-Scan (+), n (%)		8 (24)	
GCS (SD)		14.85 (0.36)	
PTA (yes), n (%)		36 (68)	
LOC (yes), n (%)		24 (45)	
follow-up	Controls	Mild TBI	*p*
n	39	32	
Age in years (SD)	31.6 (9.72)	34.8 (13.44)	.40
Women, n (%)	17 (44)	16 (50)	.60
Years of Education (SD)	15.1 (2.44)	15.0 (1.52)	.28
CT-Scan (+), n (%)		5 (15)	
GCS at baseline (SD)		14.96 (0.21)	
PTA at baseline (yes), n (%)		21 (66)	
LOC at baseline (yes), n (%)		12 (38)	

General inclusion criteria were: (1) age between 18 and 55 years, (2) having completed a minimum of 12 years of education, and (3) having the capacity to understand, talk and write in either French or English. The most common causes of mild TBI were (1) falls (38%, n=20), (2)

sport accident (30%, n=16), (3) car accident (19%, n=10), and (4) assaults (6%, n=3). For the remainder (7%, n=4) the cause was unknown. The diagnosis of mild TBI, based on the criteria of Center for Disease Control and Prevention (Faul and Coronado 2015), was carried out by the physician. Specifically, diagnostic criteria of mild TBI included one or more of the following: (a) confusion, disorientation and/or loss of consciousness for 30 minutes or less, (b) post-traumatic amnesia for less than 24 hours, and (c) GCS between 13 and 15, observed within the first 30 minutes after the trauma or upon presentation at the ER. In line with Canadian CT head rules (Stiell et al. 2001), the majority (34/53) of patients had a CT scan done within the first hours following their arrival in the ER. Identification of any cranial or intracranial injury on radiological imaging was used to confirm the presence of complicated mild TBI, which was the case in 8/34 patients. Of them, five had right cerebral lesions (sub-epidural bleeding, signs of petechiae) while the other three had occipital lesions with unspecified laterality. Because of the small sample size, we did not analyze the CT-positive group separately.

Participants in the control group were healthy subjects. General exclusion criteria for both groups were: (1) the presence of any history of TBI, (2) known pre-existing OD, (3) history of psychiatric or neurological disorders, (4) excessive use of recreational drugs (cannabis: >1 consumption/d; alcohol: >3 consumptions/d) (CCSA 2012), (5) being under the influence of alcohol or recreational drugs during the testing and (6) medication known to interfere with cognitive abilities (antidepressants, benzodiazepines, hypnotics).

3.3.2 Instruments

3.3.2.1 Evaluation of olfaction

We used the Sniffin' Sticks Inventory Test to evaluate the quantitative olfactory function of all participants. This test is based on felt tip pen-like odor dispensing devices and allows for the

evaluation of three different aspects of the olfaction (odor detection threshold, odor discrimination, and odor identification). The exact procedure is described elsewhere (Hummel et al. 1997). In short (1) detection threshold was determined by using 16 different concentrations of phenyl ethanol (rose odor) in an ascending/ descending staircase procedure. The score can vary between 1 (lowest sensitivity) and 16 (highest sensitivity). Next, (2) odor discrimination was assessed by using 16 triplets of pens, two of which contain the same and the third an odd odor. Participants' task was to detect the odd pen. Scores range between 0 and 16. Finally, (3) odor identification was carried out with 16 pens containing different odors. For each odor, participants have to select amongst four choices. Scores can range from 0 to 16. The results of the three subtests can be added up to a composite score (TDI score) for which normative data are available (Hummel et al. 2007). Accordingly, scores below the 10th percentile indicate the presence of hyposmia (partial loss of olfactory function) and participants were classified as hyposmia positive (H+), otherwise as H-. To evaluate qualitative olfactory dysfunction, i.e., the presence of parosmia/phantosmia. we used a standardized four-items questionnaire (Landis et al. 2010). The questionnaire inquires on (1) altered food perception, (2) phantom smells, the (3) presence and the (4) severity of altered smell perception. For each item, participants indicate, on a 4-point scale (I agree: 3 points to I disagree: 0 points) the presence of the four parosmia-related symptoms. To interpret the results, we used two different approaches. First, we counted the total score (parosmia score). Second, if a participant indicated at least one parosmia sign, i.e., had a parosmia score >0, we classified him/her as parosmia positive (P+), otherwise as parosmia negative (P-). This more liberal approach is accordance with previous reports (Frasnelli et al. 2004; Frasnelli. et al. 2016; Malaty and Malaty 2013).

3.3.2.2 Affect evaluation

All participants completed the second version of the Beck Depression Inventory (BDI-II) (Beck et al. 1996). This 21-item inventory assesses the degree of depression symptoms. Each item is rated on a 0-3 scale with summary scores ranging between 0 and 63. Revised norms (Dozois et al. 1998) set the clinical threshold for depression (D+) at scores >12; otherwise we considered participants as D-.

Symptoms of anxiety were evaluated by the use of the Beck Anxiety Inventory (BAI) (Beck et al. 1988), a 21-item self-report measure of anxiety, where each item is rated on a 0-3 scale with summary scores ranging between 0-63. Based on norms (Beck and Steer 1990), we considered a participant to present anxiety symptoms (A+) when scoring > 8, otherwise as A-.

3.3.3 Procedure

3.3.3.1 Baseline

Patients were recruited by phone within two to four weeks following their admission at our tertiary care clinic. Patients in the control group were recruited in the community by ads on university campus and on internet sites. First, we carried out a semi-structured phone interview out to verify the presence of inclusion and exclusion criteria. Then, participants were invited to the laboratory. During this first meeting, participants provided informed consent. Next, we carried out olfactory and affective evaluations. Controls and patients were matched with regards to sex, age and education.

3.3.3.2 Follow-up

Six months after the first evaluation, all participants were contacted by phone and/or by email. Of the 107 initial participants, 71 accepted to do the follow-up investigation (31 patients, 39 controls). We observed no significant difference regarding age, sex, education, anxiety-depression and parosmia scores, between the participants who returned for follow-up and participants who did return (t-tests, all $p < .05$). This was true for both controls and the mTBI group. Once at the lab, they underwent the exact same procedure as at baseline. In addition, participants filled out an additional questionnaire on potential additional health issues that may have appeared since the baseline measurement. Since no participant reported new health issues, this information was not included in the present study.

3.3.4 Statistical Analysis

All data analyses were performed with SPSS v.24 for Mac (IBM Inc., Chicago, IL). Group averages are reported as mean values (standard deviation). Both at baseline and follow-up, most of the variables did not follow a normal distribution (Kolmogorov-Smirnov, $p<0.05$). So, we used non-parametric tests for group comparisons and correlations. However, since there is no non-parametric equivalent to mixed ANOVA and hierarchical regression analysis, we used ANOVA and regression, which are relatively robust to deviation from non-normality. Post hoc tests were, however, again non-parametric. Bonferroni correction was applied for multiple comparisons and statistical significance was defined as $p<0.05$.

3.3.4.1 Baseline

We first compared the proportion of hyposmia (H+/H-), parosmia (P+/P-), depression (D+/D-), and anxiety (A+/A-) between groups (patients vs controls) with chi-square tests. Then, we

compared groups for average TDI scores (quantitative OD), parosmia scores (qualitative OD), BDI-II scores (depression) and BAI scores (anxiety) by means of Mann-Whitney U-tests.

3.3.4.2 Follow-up

First, we compared the proportions of hyposmia (H+/H-), parosmia (P+/P-), depression (D+/D-), and anxiety (A+/A-) between both groups (patients vs controls) at follow up by chi square tests. Then we evaluated the evolution of symptoms with separate repeated measures ANOVA. To do so, we evaluated the effect of condition (2 levels: patients, controls; between subjects) and time (2 levels: baseline, follow up; within subjects) on TDI scores (quantitative OD), parosmia scores (qualitative OD), BDI-II scores (depression) and BAI scores (anxiety).

3.3.4.3 Olfactory function at baseline and symptoms at follow-up

Within the group of patients, we compared P+ vs P- at baseline on scores at follow-up for BAI and BDI-II (Mann-Whitney U-test).

3.3.4.4 Predicting the development of symptoms of depression and/or anxiety

We used a hierarchical regression analysis with backward selection to develop a prognostic model. Variables that had an association (Spearman rank; $p<.003$) with outcomes were included in the backward selection in the multivariable hierarchical regression analyses. For the outcome variables follow up scores for (1) BDI-II and (2) BAI, the following variables fulfilled this criterion: baseline scores for GCS, age, sex, years of education, BDI-II, BAI and parosmia scores (Table 2). After selecting the significant variables, two two-stage hierarchical multiple regressions were conducted with follow up scores for (1) BDI-II and (2) BAI as the dependent

variables. Baseline scores for BAI and BDI-II were entered at Stage I of the regressions followed by baseline parosmia score at stage II.

Table 2

Intercorrelations between demographic, psychometric and olfactive data of patients with mild TBI and controls at baseline and follow-up

	BAI	BDI T2	Parosmia score	QOD T2
Measure	T2		T2	
Age	-.12	.001	.04	-.01
Years of Education	-.21	.001	-.05	-.02
GCS	.16	.15	.19	.18
BAI T1	.55**	.58**	.36*	.18
BDI T1	.34*	.61**	.44**	.22
Parosmia score T1	.32*	.40**	.67**	.41**

Note. GCS = Glasgow Coma Scale. BAI = Beck Anxiety Inventory. BDI-II = Beck Depression Inventory.
* $p < .03$
** $p < .001$

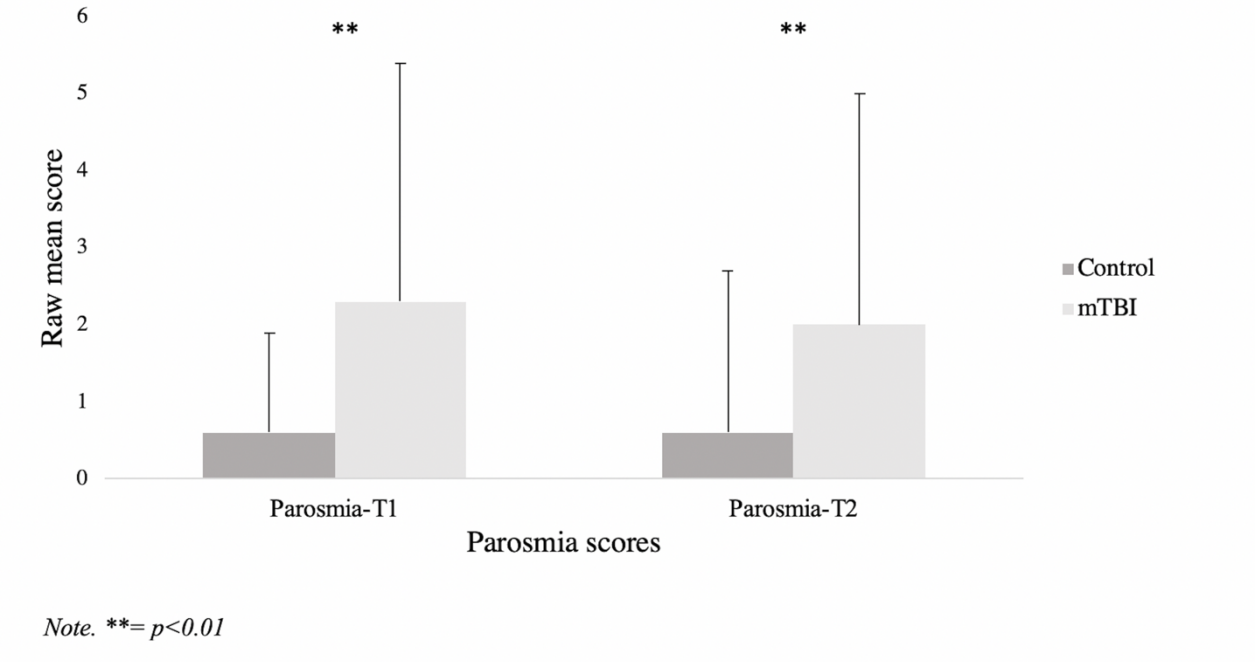
3.4 Results

3.4.1 Baseline

At baseline, significantly more patients (49%, 26/53) than controls (20%, 11/54) showed signs of parosmia (χ^2 (1) =9.730, p=.002). In contrast, 22% (12/53) of the patients and 9% (5/54) of controls exhibited hyposmia; this failed to reach significance (χ^2 (1) =3.584, p=.061). With regards to affective symptoms, significantly more patients than controls reached the clinical threshold for depression (patients: 36%, 19/53; controls: 13%, 7/54; χ^2 (1) =7.616, p=.005) and anxiety (patients: 53%, 28/53; controls: 26%, 14/54, χ^2 (1) =8.120, p=.004).

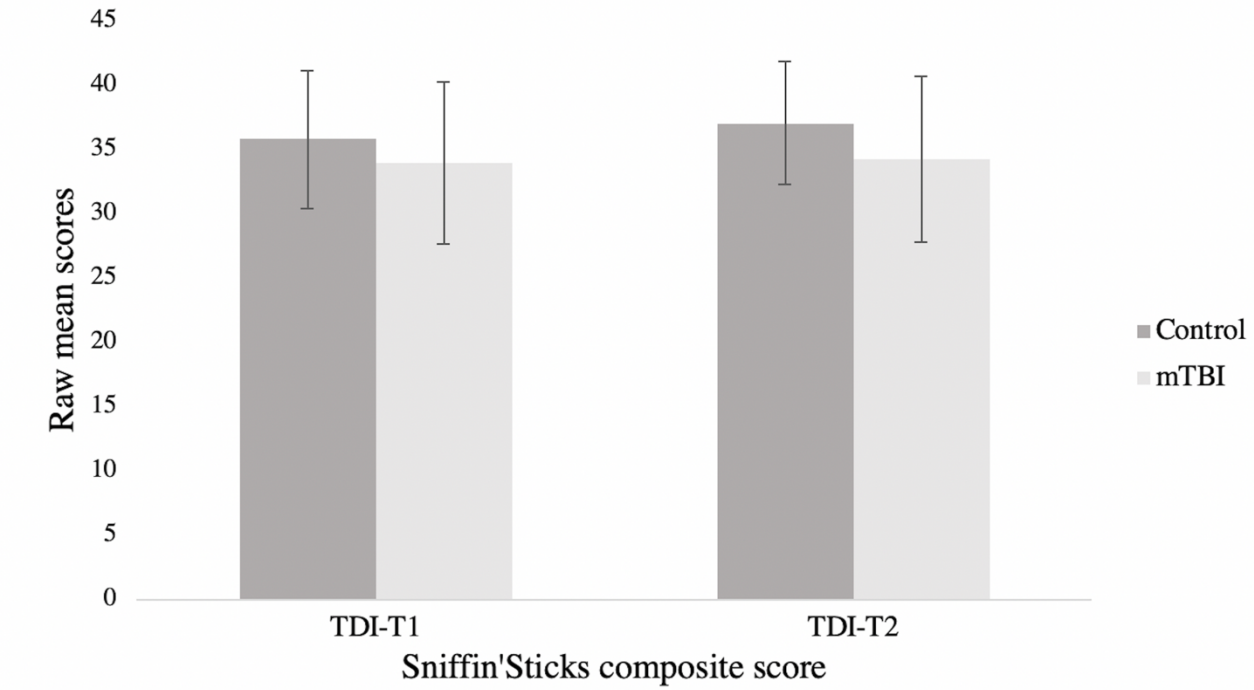
There was a significant group difference for scores of qualitative olfactory dysfunction (parosmia score; patients: 2.3 (SD: 3.16); controls: .6 (SD: 1.39); U=967.50, Z=-3.406, p=.001; Figure 1) but not for quantitative olfactory function (TDI score; patients: 33.9 (SD: 6.4) points; controls: 35.8 (SD: 5.5) points; U=1194.5, Z=-1.474, p=.140; Figure 2).

Figure 1. Parosmia mean raw scores and SD at baseline and follow-up



Note. **= $p<0.01$

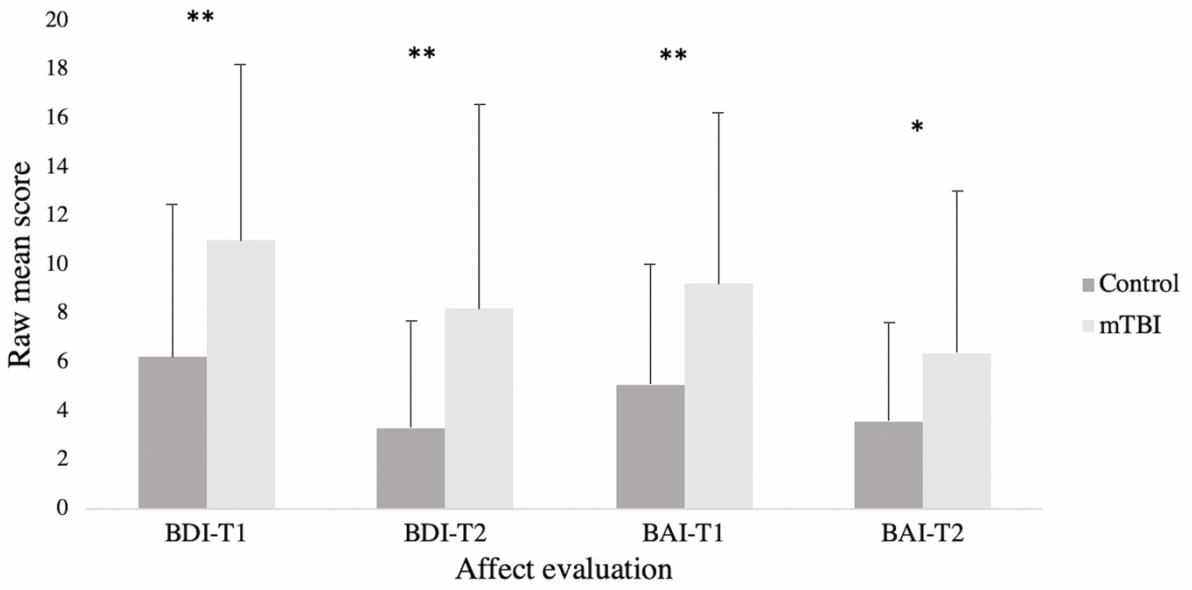
Figure 2. Sniffin'Sticks mean raw scores and SD of baseline and follow-up composite index



Note. TDI= Composite score of Threshold, Discrimination and Identification subtasks. * = p< .05. **= p<0.01*

Compared to controls, patients reported significantly more severe symptoms of depression (BDI-II score; patients: 11.0 (SD: 7.2) points; controls: 6.2 (SD: 6.3) points; U=825.50, p=.001) and more anxiety symptoms (BAI score; patients; 9.2 (SD: 7.0) points; controls: 5.14 (SD: 4.98); U=910.50, Z=-3.25, p=.001) (Figure 3).

Figure 3. Depression and anxiety mean raw scores and SD at baseline and follow-up



*Note. BDI= Beck Depression Inventory. BAI= Beck Anxiety Inventory. * = p< .02. **= p<0.01*

3.4.2 Follow-up

At follow up, significantly more patients (50%; 16/32) than controls (14%; 5/37) reported parosmia (χ^2 (1) =10.79, p =.001). In contrast, no such difference could be observed with regards to quantitative olfactory dysfunction (hyposmia rate: patients (19%, 6/32); controls (13%; 5/39); not significant; (χ^2 (1) =.472, p =.492). With regards to affect, we did not observe any group difference for both depression (patients: 25%, 8/32; controls: 7%, 3/39; not significant, (χ^2 (1) =4.022, p =.045) and anxiety rates (patients: 22%, 7/32; controls: 18%, 7/39; not significant after correction for multiple comparisons, (χ^2 (1) =.171, p =679).

With regards to the parosmia score, we observed a significant effect of condition (F (1, 67) =8.241, p=.005). Patients reported significantly more parosmia symptoms than controls both at

baseline (patients: 2.3 (SD: 3.1) points; controls: .6, (SD: 1.3) points) and follow-up (patients: 2.0, (SD: 3.0) points; controls: .6, (SD: 2.1) points). We did not observe a significant interaction of condition and time (F (1, 67) =.032, p=.859), nor any effect of time (F (1, 67) =.831, p=.365). There was a statistically significant interaction between the condition and time for quantitative olfactory function (TDI score: F (1,69)=4.730, p=.033, partial η^2=.064), but no significant effect of time (F(1, 69)=.121, p=.729) or condition (F(1, 69)=1.909, p=.172) alone. TDI scores of controls improved from baseline (35.7 (SD: .8) points) to follow-up (37.0 (SD: .9) points), patients' scores slightly worsened (from 35.2 (SD: .8) points to 34.2, (SD: .9) points).
With regard to depression scores, we found a significant main effect of condition (F (1, 69) =11.290, p=.001, partial η^2=.141), where patients (9.4 (SD: 1.0) points) reported significantly more severe symptoms than controls (4.7 (SD: .9) points). Further, we observed a significant main effect of time (F (1,69) =12.130, p=.001, partial η^2=.150). Depression scores were significantly higher at baseline (8.4 (SD: .8) points) than at follow-up (5.7 (SD: .7) points). However, we did not observe any significant interaction between condition and time (F (1,69) =.035, p=.851) (Figure 3).

For anxiety scores, we observed a significant main effect of condition (F (1,69) =14.125, p<.001, partial η^2=.170), where patients (8.1 (SD: .8) points) reported more severe symptoms than controls (4.0 (SD: .7) points). Next, there was a significant effect of time (F (1,69) =9.018, p=.004, partial η^2=.116) with a reduction of anxiety symptoms from baseline (7.1, (SD: .6) points) to follow-up (5.1 (SD: .6) points). Finally, we observed a significant interaction between condition and time (F (1,69) =3.987, p=.050, partial η^2 =.055). Even if both groups saw a reduction of severity of anxiety symptoms between baseline (patients: 9.2 (SD: 7.0); controls: 5.1

(SD: 4.9)) and follow-up (patient: 6.4 (SD: 6.6); controls: 3.6 (SD: 4.0), the improvement was more accentuated for patients (Figure 3).

3.4.3 Olfactory function at baseline and symptoms at follow-up

We investigated if patients with parosmia at baseline (P+; of 26 patients at baseline, 15 could be included at follow up) differed, on reported anxiety and depression symptoms, from the patients with normal olfactory function at baseline (P-; of 27 patients at baseline, 17 could be included at follow up). Compared to the 17 P-, the 15 P+ reported more depression symptoms (BDI-II score; TBI+: 11.9 (SD: 10.4) points; TBI-: 4.8 (4.3) points; U=65.00, p=.018) at follow-up. No significant difference was found for anxiety (BAI score; TBI+: 8.8 (SD: 8.6) points; TBI-: 4.3 (3.1) points; U=86.50, p=.119).

3.4.4 Predicting depression and anxiety at follow-up with baseline scores

We next computed several hierarchical multiple regressions to determine the predictive values of scores for depression (BDI-II), anxiety (BAI), and parosmia at baseline for (1) depression (BDI-II) and (2) anxiety (BAI) scores at follow up. First, baseline BDI-II and BAI scores significantly predicted follow-up BDI-II scores (Model 1; R2=.511, F (2, 29) =15.128, p <.001, adjusted R2 =.478). The addition of baseline parosmia scores predicted BDI-II at follow-up significantly better than Model 1 alone (Model 2: R2 increase=.079; F (2, 29) =13.444, p=.028). Second, baseline BDI-II and BAI scores significantly predicted follow-up BAI scores (Model 1: R2=.364, F (2, 29) =8.306, p=.001, adjusted R2=.320). The addition of baseline parosmia scores significantly increased the explained variance of the follow-up BAI score (Model 2: R2 increase=.203; F (2, 29) =13.167, p<.001).

Table 3

Summary of Hierarchical Regression Analysis for Variables predicting long-term (1) BDI and (2) BAI.

Model 1: BDI-T2	B	*t*	*p*	R	R^2	ΔR^2
Step 1				.715	.511	.511
BDI T1	**.647**	**3.592**	**.001**			
BAI T1	.358	1.794	.083			
Step 2					.590	
Parosmia scores T1	**1.071**	**2.323**	**.028**	.768		.079

Model 2: BAI-T2	B	t	p	R	R2	ΔR2
Step 1				.603	.364	.364
BDI T1	.320	1.990	.056			
BAI T1	.368	2.067	.048			
Step 2				.753	.568	.203
Parosmia scores T1	**1.344**	**3.629**	**.001**			

Note. BAI = Beck Anxiety Inventory. BDI-II = Beck Depression Inventory. Bold = significant model

3.5 Discussion

This study suggests that symptoms of depression, anxiety, and parosmia within 2-4 weeks after a mild TBI predict the persistence of symptoms of depression and/or anxiety. They do so significantly better than age, GCS scores or years of education. Furthermore, our results show that parosmia scores significantly increase the proportion of explained variance for symptoms of both anxiety and depression. However, these findings have to be considered as preliminary as they were obtained on a limited number of patients.

These results are partly in line with a previous study where a model that included symptoms of depression one week after a mild TBI, older age and positive CT scans, predicted the development of an episode of major depression, within 3 months after the trauma (Levin et al. 2005). We did not observe any effect of age, but it is worth mentioning that we only included participants aged between 18-55 years old. Moreover, unlike the previous study, which specifically evaluated major depression, we included all, i.e., even subclinical, symptoms of depression. We did so because only a small proportion of patients with mild TBI exhibit major depression (Carroll et al. 2014), but most develop symptoms of depression without reaching clinical thresholds of major depression. The evolution of symptoms of depression and anxiety after a mild TBI was to date only evaluated in one study (Zahniser et al. 2019). Here, the presence of symptoms of depression and/or anxiety within two weeks after a mild TBI correlated with scores collected three months later. Unfortunately, the authors evaluated symptoms of depression and/or anxiety with a generic questionnaire, the Brief Symptoms Inventory (BSI), rather than a disorder-specific instrument such as BDI-II or BAI. A recent study showed that well-validated and disorder-specific tools yield the most precise assessment (de Beurs et al. 2019).

In addition to the predictive value of baseline anxiety and depression scores, parosmia scores significantly increased the proportion of explained variance for both anxiety and depression symptoms, based on a small sample of patients. In other words, assessing parosmia within one month following a mild TBI helps to predict the severity and long-term outcome of affective symptoms.

The link between OD and depression is in line with previous work, in which 35% of OD patients exhibited high depression scores (Deems et al. 1991). Moreover, a recent study showed that patients with mild TBI who exhibited OD within 24h following the trauma reported significantly more affective and post-concussive symptoms one year after the injury when compared to patients without OD (Lecuyer Giguère et al. 2019). In fact, parosmia has a profound negative impact on the patient's overall quality of life and alters life quality, decreases appetite leading to weight change (loss or gain) and/or changes psychological well-being (Bonfils et al. 2005). Here we report that parosmia is linked to the development and persistence of affective symptoms in a TBI context.

Previous research reports the prevalence of parosmia after mild to severe TBI to be in the range of 40% (Doty et al. 1997a; Frasnelli et al. 2016), which is close to the 49% we observed. This suggests that independent of its severity, TBI can affect qualitative olfactory function. On the other hand, we observed hyposmia in 19% of the patients which compares well to both the control group and published data on the general population (Brämerson et al. 2004) but is well below the numbers in moderate to severe TBI (50-60%) (Drummond et al. 2015; Sigurdardottir et al. 2016). Nevertheless, our result is in contrast to our recent publication on a different cohort of mild TBI patients tested within 24h after the trauma, where 55% of patients exhibited hyposmia

(Lecuyer Giguère et al. 2019). The discrepancy may be an indicator that quantitative OD resorbs rapidly, within few days/weeks after a trauma, but that qualitative OD, which was not assessed in the previous study, persists or develops over the first weeks. In line with this notion, the same study reported no difference in hyposmia rates between patients and controls one year after the trauma. One may thus speculate that parosmia persists more than hyposmia/anosmia, as it has been shown in one study on acute rhinitis (Faulcon et al. 1999), but more support exists to the contrary, as quantitative OD generally tend to persist (Caplan et al. 2018; Drummond et al. 2017; Uecker et al. 2017) and qualitative symptoms usually decrease with time (Frasnelli et al. 2004; Leopold 2002). When qualitative and quantitative OD are associated, the onset of parosmia is seen as an indicator of a changing olfactory system (Frasnelli et al. 2004). Unfortunately, due to the restricted literature, no other study has compared trajectories of qualitative and quantitative OD; this should be included in future studies.

Parosmia is not yet well understood. Two possible pathomechanisms have been put forward. The peripheral hypothesis proposes that a reduced repertoire of olfactory receptor neurons leads to the inability to form a complete neuronal image of the odorant. The central hypothesis on the other hand, proposes that impairment of the integrative/interpretive centers in the brain leads to the formation a distorted odor percept (Leopold 2002; Leopold and Meyerrose 1994). Recent neuroimaging studies support the latter hypothesis, as patients with parosmia exhibit profound volume loss in the right anterior insula, the cingulate cortex, the hippocampus and the medial orbitofrontal cortex (Bitter et al. 2011). It is interesting to note that most of these areas are typically affected by mild TBI (Eierud et al. 2014). This neuroanatomical finding may represent the neurobiological underpinning of the link between parosmia and anxiety/ depression, as these symptoms are linked to hippocampal and orbitofrontal atrophies (Hudak et al. 2011; Terpstra et

al. 2017). One may therefore hypothesize that parosmia and affective symptoms are due to persisting alterations of frontotemporal structures as the hippocampus and the orbitofrontal cortex. As a consequence, presence of parosmia within 4 weeks after a mild TBI may serve as a predictor of anxiety/ depression. Future studies should use neuroimaging techniques such as MRI to investigate the link between olfactory dysfunction and anxiety/depression as well as cerebral deformation.

Interestingly, the percentage of mild TBI patients with either quantitative or qualitative olfactory dysfunction did not change between baseline and follow up in the present study. This is in line with the finding that 74-84% of patients exhibit hyposmia six to 12 months after moderate to severe TBI (Caplan et al. 2018; Drummond et al. 2017). Regarding the evolution of parosmia after TBI, the only available study reports that the majority patients did not exhibit parosmia after an 8-year period (Doty et al. 1997b).

As limitations for the present study, even with longitudinal data, a quasi-experimental design cannot establish a causal link between the variables. Further, a considerable portion of patients (40%) opted to not return to the follow-up session, as they returned home after the baseline examination and lived across the province. These losses limit the interpretability of the hierarchical regression, as we only performed the analysis on 15 patients with mTBI. Moreover, the small sample size may contribute to the disparity between the results of the present study and previous ones, regarding the proportion and development of both quantitative and qualitative OD after TBI. We did not carry out a formal sample size calculation, also due to the very limited number of available studies on mild TBI. Another limitation is related to the four questions used to evaluate the participants' parosmia/phantosmia symptoms. The limitation comes from the lack

of validation of the tool on a TBI population combined to the lack of a unified rating procedure. We decided to base our classification procedure on previous studies, where participants were classified as parosmic when a score >1 was found. This classification can be perceived as liberal and could have possibly led to the inclusion of some false positive cases. However, we still are confident with our findings as the baseline total parosmia scores correlated significantly with follow-up scores of depression ($p= 0.003$) and anxiety ($p= 0.01$), within our mTBI group. Finally, we were not able to gather information about the site of impact and did not have access to MRI scans. Future studies should address these issues.

3.6 Conclusion

Compared to controls, patients with mild TBI showed more signs of anxiety, depression and parosmia one and six months after the trauma. Also, baseline depression, anxiety and parosmia scores significantly predicted symptoms of depression and/or anxiety symptoms six months after a mild TBI. Finally, in addition to the baseline depression and anxiety scores, baseline parosmia scores significantly added explained variance to the severity of both long-term depression and anxiety symptoms.

3.7 Disclosure of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper. The present study was supported by the Chercheur Boursier program of FRSQ and by the Research Center of Sacré-Coeur hospital.

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CHAPITRE 4 DISCUSSION GÉNÉRALE

4.1 Sommaire

Le premier objectif de cette thèse était de dresser un portrait réaliste, à l'aide de contrôles méthodologiques stricts, de la prévalence et de l'évolution des troubles qualitatifs et quantitatifs de l'olfaction suite à un TCCL. Le choix de ce premier objectif relevait de trois motivations spécifiques. Premièrement, la littérature traitant des capacités olfactives suite à un TCCL spécifiquement est quasiment inexistante (Ciofalo et al., 2018; de Kruijk et al., 2003) et aucune donnée n'est disponible concernant les troubles qualitatifs (parosmie, phantosmie), bien que ces patients représentent près de 80% des cas de TCC (Faul & Coronado, 2015). De plus, l'évaluation et l'identification de tels symptômes suite à un TCCL nous est apparue comme un sujet de thèse intéressant puisque, du au nombre extrêmement limité de données probantes, les pertes et distorsions olfactives suivant un TCCL ne sont pas des symptômes couramment questionnés et évalués lors du séjour des patients aux urgences (Proskynitopoulos et al., 2016; Xydakis et al., 2015), bien que celui-ci [le TCC] soit l'une des principales causes des pertes olfactives (Temmel et al., 2002). Finalement, il nous a semblé primordial d'orienter nos recherches vers une meilleure compréhension des troubles olfactifs suite au TCCL afin de sensibiliser le personnel médical à la présence de tels troubles suivant un TCCL et, par le fait même, de fournir une description des différents outils d'évaluation adaptés au contexte hospitalier. Il est d'autant plus important de sensibiliser le personnel médical à la présence précoce de troubles olfactifs suite à un TCCL, puisqu'il a été maintes fois démontré que la majorité des patients présentant des troubles olfactifs post-traumatiques ne sont pas conscients de la présence de ceux-ci (Callahan & Hinkebein, 2002; Drummond et al., 2015; Fortin, Lefebvre, & Ptito, 2010). Ainsi, puisque les troubles olfactifs sont difficilement identifiables par les patients eux-mêmes, ceux-ci passent généralement sous silence puisque ni le clinicien ni le patient n'ont le réflexe d'investiguer la présence de tels symptômes,

bien que plusieurs études aient mis en évidence que les pertes olfactives, mêmes mineures, peuvent avoir des conséquences importantes sur la santé mentale et le bien-être des individus (Drummond et al., 2013; Soudry et al., 2011). Pour l'ensemble de ces raisons, il s'est donc avéré nécessaire de dresser un profil juste de la proportion de patients TCCL développant des troubles de l'olfaction en phase aiguë et, par le fait même, de déterminer le profil évolutif des symptômes. De façon générale, les résultats indiquent, qu'au cours des premières 24 heures suivant un TCCL, plus de la moitié des patients présentent un trouble quantitatif de l'odorat (hyposmie), alors que lorsqu'évalués dans les deux à quatre semaines suivant le TCCL, le trouble prendrait davantage la forme qualitative (parosmie). De façon générale, alors que les troubles quantitatifs de l'olfaction semblent partiellement se résorber plusieurs mois suite au TCCL, ceux de type qualitatif tendent à persister. Les résultats seront discutés en profondeur dans les prochaines sections.

Le second objectif de cette thèse fut de mieux saisir l'implication du développement de troubles olfactifs en phase aiguë d'un TCCL dans la chronicisation des symptômes d'anxiété et de dépression à long-terme. L'orientation de ce second objectif de thèse se base sur deux principaux facteurs. Le premier provient de la grande hétérogénéité et du nombre restreint de littérature traitant de la prévalence et des facteurs de risque entourant le développement de symptômes de dépression et d'anxiété auprès de patients ayant subi leur tout premier TCCL dans des conditions autres qu'en contexte sportif ou de guerre. En effet, bien que certains facteurs, tels que la présence pré morbide des troubles affectifs ainsi que le fait d'être une femme (Dischinger et al., 2009; McInnes et al., 2017a; Ponsford et al., 2012), aient été identifiés comme étant les principaux facteurs de risque à la chronicisation des symptômes anxio-dépressifs, ils n'expliquent pas l'entièreté de la variance. Dans ce contexte, nous trouvions intéressant de contribuer à l'approfondissement de cette littérature par l'évaluation d'une toute nouvelle variable, n'ayant jamais été incluse dans les modèles de prédiction du développement de symptômes anxio-dépressifs suite au TCCL.

Puisqu'encore méconnue dans le domaine du TCCL, la présence de troubles olfactifs n'a toujours pas été considérée comme un possible facteur de risque à la chronicisation des troubles de l'humeur, bien que ceux-ci partagent des substrats neuroanatomiques identiques et que la présence de ceux-ci [les troubles olfactifs] a été maintes fois liée au développement de symptômes dépressifs dans la population générale présentant des troubles olfactifs (Kohli et al., 2016). C'est donc sur ces similarités corticales que se base notre second argument inhérent au deuxième objectif de thèse. Ainsi, il a été démontré que des atteintes des principales structures liées à la régulation des affects (amygdales, hippocampes, insula, cortex orbitofrontal, cortex cingulaire) affectent, du même coup, les capacités olfactives (Oral et al., 2013). De plus, les associations contraires ont aussi été largement documentées, statuant que la présence de troubles de l'olfaction semblait mener à des altérations des structures liées à la gestion des émotions (Croy et al., 2014). Pour ces raisons, nous avons jugé nécessaire d'évaluer l'impact du développement des troubles olfactifs dans la chronicisation des symptômes anxio-dépressifs chez les patients ayant subi un TCCL. De façon générale, les résultats indiquent que la présence en phase aiguë de troubles qualitatifs de l'olfaction augmente, de façon significative, la force de prédiction des patients étant à risques de voir leurs symptômes anxio-dépressifs se chroniciser au-delà de la phase de récupération normale. Une discussion approfondie de ces résultats sera présentée dans les prochaines sections.

4.1.1 Évaluation des troubles de l'olfaction en phase aiguë d'un TCCL

L'évaluation des troubles olfactifs suite à un TCCL représente l'un des grands piliers de cette thèse. En effet, avant d'évaluer l'évolution ou la force pronostique de ceux-ci, fallait-il déterminer s'ils étaient réellement présents suite au TCCL. Ainsi, l'absence d'étude évaluant les troubles de l'olfaction dans les premières heures suite au TCCL, a guidé les objectifs du premier article présenté dans cette thèse. Nous avons donc débuté nos recherches par l'évaluation de la

possible présence des troubles olfactifs au cours des premières 24 heures suivant un TCCL. Dans cette première tentative, l'olfaction d'une trentaine de patients, ayant reçu un diagnostic de TCCL, a été évaluée à l'aide d'outils standardisés et comparée à celle de patients ayant subi une blessure orthopédique, sans TCCL. Ces résultats, que nous jugeons préliminaires, dus au nombre assez restreint de patients évalués, indiquent que 55% des patients ayant subis un TCCL présentaient des pertes cliniquement significatives de leurs capacités olfactives quantitatives (hyposmie), alors que seulement 5% des patients du groupe contrôle présentaient de tels symptômes. De plus, une diminution des capacités olfactives a été observée à l'ensemble des modalités olfactives évaluées. Précisément, les patients présentaient une réduction de leurs capacités à identifier et discriminer les odeurs présentées, en plus de voir leurs seuils de détection d'odeurs significativement réduit, lorsque comparés aux participants contrôles. Il est aussi intéressant de mentionner que ces altérations olfactives ne semblent pas avoir été influencées par la présence de symptômes cognitifs puisqu'aucune corrélation significative ne fut retrouvée entre les résultats aux évaluations cognitives et les tâches olfactives. Bien que cette étude soit la toute première à évaluer les symptômes olfactifs au cours des premières heures suite au TCCL, les statistiques retrouvées sont beaucoup plus élevées que celles retrouvées lorsque les patients sont évalués quelques semaines suite au trauma. En effet, les deux études disponibles indiquent qu'entre 25 et 33% des patients TCCL présenteraient une réduction quantitative de leur olfaction dans les premières semaines suivant le trauma (Ciofalo et al., 2018; de Kruijk et al., 2003). Les données recueillies dans ce premier article supposent donc que les troubles olfactifs quantitatifs seraient présents dès les premières heures suivant un TCCL et en plus grande proportion que lorsqu'ils sont évalués quelques semaines plus tard.

Suite à l'acquisition de ces données préliminaires saisissantes, nous avons mis sur pieds la deuxième étude de la présente thèse, dans laquelle nous avons à la fois exploré l'évaluation de

l'olfaction quantitative, mais aussi qualitative, domaine de l'olfaction qui n'a jamais été évalué auprès de patients TCCL. Ainsi, l'olfaction d'une cinquantaine de patients a été évaluée entre deux et quatre semaines suite au TCCL. Ce choix temporel, entre le trauma et l'évaluation, s'est fait dans le but d'en apprendre davantage sur l'évolution des troubles de l'olfaction entre les premières heures (article 1) et les premières semaines suite au TCCL. Ainsi, les résultats suggèrent que dans les deux à quatre premières semaines suivant un TCCL, 22% des patients présentent des signes d'hyposmie, alors que près de la moitié (49%) présentent des signes de parosmie. À titre de comparaison, 9% des participants contrôles présentaient des signes d'hyposmie et 20% des signes de parosmie. Lorsque comparée aux proportions de parosmie relevées dans la population générale jusqu'à ce jour (environ 4%), la statistique trouvée dans cette étude (20% des patients contrôles) est assez surprenante (Nordin, Brämerson, Millqvist, & Bende, 2007; Sjölund, Larsson, Olofsson, Seubert, & Laukka, 2017). Cette disparité entre les proportions retrouvées précédemment et celles retrouvées dans note étude, peut notamment être causée par l'utilisation d'outils différents entre ces études et la nôtre. En effet, les deux seules études ayant estimé, à ce jour, la proportion de troubles qualitatifs dans la population générale, l'ont fait sur la base d'une seule question et/ou d'entrevues avec les patients, alors que nous avons utilisé un questionnaire comprenant plusieurs questions liées à l'évaluation des troubles qualitatifs. De plus, le manque flagrant de données disponibles à ce jour rend très difficile l'estimation de la réelle proportion de parosmie dans la population générale. Toutefois, les résultats retrouvés dans le groupe de patients TCCL concordent avec de précédentes études ayant évalué la proportion des troubles qualitatifs de l'olfaction suite à des TCC légers à sévères, alors que plus de 40% des patients rapportaient la présence de tels troubles (Doty et al., 1997; Frasnelli. et al., 2016).

Lorsque nous comparons les résultats des articles 1 et 2, nous constatons une frappante disparité entre la proportion de patients présentant une hyposmie dans les premières heures suite

au TCCL et la proportion lorsque l'hyposmie est évaluée deux à quatre semaines suite au TCCL. Alors que plus de la moitié des patients présentaient des signes d'hyposmie dans les premières 24 heures suivant le TCCL, cette statistique s'abaisse à 22% lorsque nous évaluons les patients dans les deux à quatre semaines suivant le trauma. Ce changement de proportion, bien qu'il semble drastique, se rapproche toutefois de ce qui a été trouvé dans les précédentes études ayant évalué la présence d'hyposmie chez les patients TCCL dans les premières semaines suite au trauma (25% des patients présentaient des signes d'hyposmie) (de Kruijk et al., 2003). Ainsi, le patron d'évolution retrouvé, lorsque nous observons l'évolution des troubles quantitatifs de l'olfaction entre la première et la deuxième étude, indique que ce type de troubles olfactifs semble partiellement se résorber en phase aiguë du TCCL (dans les quatre premières semaines suite au trauma). De plus, une disparité entre les scores totaux moyens à l'échelle du Sniffin'Sticks est aussi relevée entre les deux études, puisque lorsqu'évalué à quatre semaines les résultats olfactifs globaux sont comparables entre les deux groupes étudiés (contrôles et TCCL) et se situent dans le spectre de la normosmie, comparativement à ce qui a été retrouvé à l'évaluation dans les premières 24 heures ou des différences significatives entre les deux groupes furent retrouvées. Ces données fournissent donc un second appuie à l'hypothèse selon laquelle les troubles olfactifs quantitatifs auraient tendance à se résorber dans les premières semaines suite à l'accident.

Bien qu'une réduction de la proportion des patients présentant un trouble quantitatif de l'olfaction semble s'exercer en phase aiguë du TCCL, nous notons la présence d'un patron tout à fait inverse lorsque nous observons l'évolution des troubles de l'olfaction de type qualitatifs (parosmie, phantosmie). Précisément, alors que les troubles quantitatifs de l'odorat semblent s'effacer graduellement, nous avons observé que ceux-ci semblent laisser leur place aux troubles qualitatifs, puisque 49% des patients ayant subi un TCCL rapportent la présence de parosmie au

cours des deux à quatre premières semaines suivant le TCCL. Les troubles qualitatifs de l'olfaction restent à ce jour très peu documentés et peu connus de la communauté scientifique et médicale. En effet, outre la présente étude, il n'y a que deux autres articles traitant des troubles qualitatifs de l'olfaction suite à un TCC. Bien que ces deux autres études aient évalué la présence de ces troubles olfactifs auprès de patients ayant subis des TCC d'intensités variées (léger à sévère), les résultats de ces deux seules autres études se rapprochent grandement des résultats que nous avons trouvé dans l'étude 2 de la présente thèse. Ainsi, ces deux études ont retrouvé la présence de troubles olfactifs qualitatifs chez plus de 40% des patients, alors que ceux-ci étaient évalués dans les premières semaines suite à leur TCC (Doty et al., 1997; Frasnelli. et al., 2016).

Il est toutefois très important de noter que cette hypothèse, quant au remplacement des troubles quantitatifs par les troubles qualitatifs en phase aiguë d'un TCCL reste assez spéculative. Précisément, cette hypothèse reste au stade embryonnaire, puisqu'il nous a été impossible de récolter des données, quant à la présence de trouble qualitatifs de l'olfaction, dans l'étude 1 de la présente thèse, soit dans les premières heures suivant le TCCL. Par ailleurs, il est relativement impossible, pour n'importe lequel chercheur ou clinicien de récolter de telles données dans les premiers jours suivant un TCCL, puisque ce très court laps de temps ne permet pas aux patients d'identifier la présence de modifications subjectives de leur odorat. Conséquemment, plusieurs chercheurs ont précédemment relevé le fait que les changements qualitatifs de l'odorat ne sont perçus par les patients que lorsqu'ils retournent à la maison et non en contexte hospitalier (Thomas Hummel et al., 2017). Ainsi, puisqu'il nous a été impossible de récolter des informations quant à la réelle proportion des troubles qualitatifs de l'olfaction dans les premières 24h suite au TCCL, l'appréciation de l'évolution, en phase aiguë, de ce type de troubles s'est donc vue limité qu'aux premières semaines suite au TCCL, contrairement aux troubles quantitatifs. Il est donc possible

que les troubles qualitatifs soient présents dès les premiers instants suite au trauma, mais qu'il est impossible pour les patients et le personnel soignant de les percevoir.

Alors que nous avons maintenant une toute première idée de la proportion et de l'évolution des troubles qualitatifs et quantitatifs de l'olfaction dans les premières heures et les premières semaines suite au TCCL (phase aiguë), nous traiterons, dans la prochaine section de l'évolution de ceux-ci à long-terme, soit six et 12 mois suite au trauma.

4.1.2 Évolution à long-terme des troubles olfactifs suite à un TCCL

Alors que nous savons maintenant que la présence de troubles olfactifs est une problématique bien réelle en phase aiguë d'un TCCL, il est maintenant temps d'explorer l'évolution de ceux-ci au-delà de la phase de récupération normale. Les toutes premières données ayant exploré l'évolution des troubles olfactifs suite au TCCL proviennent de l'article 1 de la présente thèse. Les conclusions préliminaires de ce premier article pointent vers une amélioration des capacités quantitatives de l'olfaction (hyposmie), un an suite au TCCL, alors que le pourcentage de patients présentant des troubles quantitatifs de l'olfaction passe de 55 à 42%. De plus, aucune différence significative, entre le groupe de patients ayant subi un TCCL et le groupe de patients contrôle, ne fut relevée au deuxième temps de mesure. Toutefois, bien qu'une réduction du pourcentage de patients présentant des signes d'hyposmie fût observée et qu'aucune différence significative ne fut retrouvée entre les deux groupes au second temps de mesure, ces données sont aussi à prendre avec grande précaution. En effet, bien qu'une amélioration des troubles olfactifs quantitatifs s'aligne avec ce qui a été trouvé auprès de patients ayant subi des TCC modérés et sévères (Drummond et al., 2017), certaines complications méthodologiques limitent l'interprétation de ces résultats préliminaires. Précisément, il nous a été impossible d'évaluer les capacités olfactives des patients à l'aide des mêmes outils aux deux temps de mesures, puisqu'au

deuxième temps de mesure les patients avaient depuis longtemps quitté l'hôpital et résidaient dans différents pays. Il nous était donc impossible de voyager dans tous ces pays afin d'évaluer l'olfaction des patients et avons donc choisi d'envoyer par la poste une évaluation olfactive différente, limitant ainsi le devis à un devis transversal. Sans un devis longitudinal, les présentes données restent hautement spéculatives. De plus, les données de ce premier article restent grandement préliminaires du, notamment, au très petit nombre de participants ayant accepté de participer au deuxième temps de mesure (moins de 10 participants dans chacun des groupes).

Ainsi, le second article de la présente thèse fut mis sur pied dans le but de pallier les précédentes failles méthodologiques et de recueillir des données longitudinales sur l'évolution des troubles olfactifs à la fois quantitatifs et qualitatifs. Les données de ce deuxième article suggèrent que les troubles qualitatifs de l'olfaction auraient tendance à perdurer suite au TCCL, alors que 50% (16/32) des patients ayant subi un TCCL rapportent toujours la présence de parosmie six mois suite au trauma, comparé à 14% dans le groupe contrôle. Il est intéressant de noter que de ces 16 patients rapportant des signes de parosmie six mois suite au TCCL, 12 en rapportaient déjà au premier temps de mesure (75%) et quatre patients (25%) ont développé des symptômes au cours des six premiers mois suivants le TCCL. De plus, nous notons que des 15 patients ayant participé aux deux temps de mesures et ayant rapporté des symptômes de parosmie au premier temps de mesure, seulement trois (20%) ont vu leurs symptômes se résorber à 100%. Ainsi, il est possible de constater que les troubles qualitatifs de l'olfaction semblent persister au-delà de la phase de récupération normale, comparativement aux troubles quantitatifs de l'olfaction. Ces résultats correspondent à ce qui a été recensé auprès de patients ayant subi des TCC d'intensité léger-sévère (40%), évalués entre six mois et plusieurs années suite à leur TCC (Doty et al., 1997). En ce qui a trait aux troubles quantitatifs de l'olfaction, une légère baisse du pourcentage, chez les patients, est notée entre les deux temps de mesure (de 22 à 19%). Alors que ce pourcentage dévie grandement

de ce qui a été retrouvé auprès de patients ayant subi des TCC d'intensités modéré-sévère (50-60% présentent toujours des troubles olfactifs plusieurs mois suivant le trauma) (Drummond et al., 2015; Sigurdardottir et al., 2016), celui-ci est comparable à ce qui fut retrouvé dans le groupe contrôle (13%) et à la représentation des troubles olfactifs dans la population générale (Brämerson et al., 2004). Ainsi, l'analyse de ces données laisse croire qu'il existerait un patron d'évolution des troubles olfactifs propre aux patients ayant précisément subi un TCCL, dans lequel les troubles qualitatifs de l'olfaction persisteraient plus longtemps que les troubles quantitatifs. Nous relevons le fait que ce patron serait unique à cette population, puisque, dans les études précédentes effectuées auprès de patients ayant subi des TCC d'intensités modéré-sévère, c'est majoritairement les troubles quantitatifs de l'olfaction qui auraient tendance à perdurer (Caplan et al., 2018; Doty et al., 1997; Drummond et al., 2017), alors que les troubles qualitatifs s'estomperaient avec le passage du temps (Frasnelli. et al., 2016; Donald Leopold, 2002). Une seule étude, ayant évalué la présence et l'évolution de troubles quantitatifs et qualitatifs de l'olfaction auprès de patients ayant subi une rhinite a, à notre connaissance, trouvé un patron d'évolution similaire à ce que nous avons retrouvé dans les études présentées dans la présente thèse (Faulcon, Portier, Biacabe, & Bonfils, 1999). Précisément, une évolution de 59% à 75% des patients rapportant la présence de parosmie fut enregistrée entre le premier (quelques jours suite à l'infection) et le second (trois ans suite à l'infection) temps de mesure, comparativement à une évolution de 71% à 50% en ce qui a trait à la présence d'anosmie.

Puisqu'aucune étude, mise à part celle présentée dans la présente thèse, n'a été menée dans le but d'évaluer les troubles qualitatifs de l'olfaction auprès de patient TCCL, il est assez difficile de comparer les présentes données et, par le fait même, d'estimer si celles-ci correspondent à ce qui a été précédemment recensé.

4.1.3 L'olfaction et le développement de symptômes affectifs post-TCCL

À partir du moment où nous avons une meilleure idée de la proportion et du patron d'évolution des troubles olfactifs suite au TCCL, nous pouvons alors nous pencher sur le deuxième grand objectif de cette thèse, à savoir si la présence de tels troubles olfactifs pourrait être un facteur de risque au développement de symptômes anxio-dépressifs au-delà de la phase de récupération normale. Ainsi, les résultats retrouvés dans la première étude de cette thèse montrent que les patients ayant subis un TCCL et présentant des symptômes d'hyposmie dans les premières 24h suivant le trauma, présentaient davantage de symptômes anxieux et de symptômes post-commotionnels que les patients ne présentant pas d'hyposmie dans les premières 24h, lorsqu'évalués un an suite au TCCL. Bien que ces résultats concordent avec l'hypothèse que les troubles olfactifs pourraient jouer un rôle significatif dans la persistance des symptômes post-commotionnels à long terme, il est important de rappeler que ces premiers résultats sont grandement préliminaires, puisqu'ils ont été retrouvés à l'aide d'analyse sur 12 patients seulement. De plus, le nombre restreint de données ayant pu être récoltées lors de cette première étude a grandement limité les types d'analyses statistiques pouvant être exécutées sur celles-ci. Cependant, ces premiers résultats encourageants ont permis de forger la structure de la deuxième étude présentée dans cette thèse. Précisément, nous nous sommes afféré, dans cette deuxième étude, à récolter des données sur un nombre beaucoup plus élevé de patients, dans le but de faire des analyses statistiques plus poussées, allant au-delà de la simple comparaison de groupe et davantage vers des analyses permettant la mise en place de modèle de prédiction (régression hiérarchique).

Dans cette deuxième étude nous avons donc réussi à créer deux modèles de prédiction, l'un pour le développement des symptômes anxieux et l'autre pour le développement des symptômes dépressifs, dans lesquels nous avons évalué l'apport statistique de l'âge, le GCS, les années d'éducation, les résultats aux échelles d'anxiété, de dépression et, bien sûr, de parosmie à

l'évaluation initiale. Les résultats retrouvés dans cette deuxième étude suggèrent que les symptômes de dépression, d'anxiété et de parosmie dans les premières 2-4 semaines suivant le TCCL permettent de prédirent la persistance des symptômes d'anxiété et de dépression six mois suivants le trauma. Par ailleurs, ceux-ci prédisent la persistance des symptômes affectifs significativement mieux que l'âge, le score du GCS et l'éducation des patients. De plus, nous avons observé que l'ajout du score de parosmie augmentait, de façon significative, le pourcentage de variance expliquée dans les deux modèles proposés (depression : augmentation de 8% de variance expliquée et anxiété : augmentation de 20% de variance expliquée). Les présents résultats sont partiellement en lien avec ce qui a été précédemment retrouvé dans le peu de littérature disponible à ce jour. Ainsi, la présence de symptômes affectifs lors de l'évaluation de base (*baseline*) est l'un des prédicteurs les plus couramment documentés dans la littérature disponible (Levin et al., 2005; Terry et al., 2018; Wojcik, 2014). L'âge des participants est aussi l'un des facteurs prenant une place significative dans les modèles présentés. De notre côté, nous n'avons pas trouvé de tels liens, mais expliquons ceci par le fait que nous n'ayons recruté des patients âgés entre 18 et 55 ans, contrairement aux autres études ayant inclus des patients de tous âges, incluant la population gériatrique. Un tel contrôle d'âge fut nécessaire, puisque les capacités olfactives tendent à s'atténuer au-delà de 55 ans (T. Hummel, Kobal, Gudziol, & Mackay-Sim, 2007). Ces résultats sont aussi les tout premiers à évaluer la présence de symptômes d'anxiété et de dépression, comparativement aux autres études ayant construit leurs modèles de prédiction basé sur la présence ou non d'un diagnostic formel de dépression ou de troubles anxieux. Cette inclusion faite dans la présente étude reflète, selon nous, une réalité plus juste des symptômes affectifs post-commotionnels suite au TCCL, alors que moins de patients auront un diagnostic de dépression majeure, mais présenteront toutefois des symptômes de celle-ci, ce qui s'avère aussi accaparant. De plus, cette étude est l'une des toutes premières à évaluer l'évolution des symptômes anxieux

suite au TCCL. En fait, une seule étude a tenté d'évaluer l'évolution de tels symptômes trois mois suite au TCCL. Les résultats retrouvés concordent avec ce qui est retrouvé dans la présente étude, alors que les scores d'anxiété dans les deux premières semaines corrélaient avec ceux retrouvés trois mois suite au trauma (Zahniser et al., 2019).

Un autre élément novateur dans les résultats présentés dans la deuxième étude est, bien entendu, l'apport significatif des symptômes de parosmie dans l'explication du modèle de prédiction des symptômes d'anxiété et de dépression. En effet, jamais auparavant les troubles olfactifs n'avaient été inclus dans les modèles de prédiction, et ce, autant auprès des patients ayant subis un TCC modéré-sévère que léger. Les liens entre la présence de troubles olfactifs et le développement de symptômes anxio-dépressifs ne sont toutefois pas une grande surprise à nos yeux, alors que plusieurs études ont grandement documenté les impacts de l'apparition des troubles olfactifs sur le développement de symptômes anxio-dépressifs (Deems et al., 1991; Kohli et al., 2016). Bien que plusieurs études aient documenté l'impact des troubles quantitatifs de l'olfaction sur le développement des troubles de l'humeur, celles ayant évalué l'impact des troubles qualitatifs, comme nous l'avons fait dans l'étude 2, sont extrêmement rares. La seule autre étude que nous ayons trouvée indique que la présence de parosmie diminuait significativement la qualité de vie de plus de 50% des patients présentant de tels symptômes (Bonfils, Avan, Faulcon, & Malinvaud, 2005).

La parosmie et les troubles qualitatifs de l'olfaction en général restent à ce jour très peu connus et assez mal compris. À ce jour deux mécanismes neuroanatomiques, l'un périphérique et l'autre central, ont été mis de l'avant dans le but d'expliquer ce qui peut causer l'apparition de tels troubles. La première hypothèse propose que l'apparition des symptômes de parosmie soit causée par une réduction du répertoire des récepteurs neuronaux olfactifs ce qui mènerait ainsi à la difficulté à former une image neuronale complète de l'odeur présentée. Il faut rappeler que la

parosmie se définit par une distorsion olfactive des odeurs présentées. L'hypothèse dite centrale propose de son côté que la perception distordue des odeurs soit causée par une altération des structures cérébrales impliquées dans l'intégration et l'interprétation des odeurs (Donald Leopold, 2002; Donald Leopold & Meyerrose, 1994). Précisément, une étude de neuroimagerie ont démontré la présence d'une profonde perte altération de matière grise, prenant la forme d'une réduction significative des volumes de l'insula antérieur droit, du cortex cingulaire, de l'hippocampe ainsi que du cortex médial orbitofrontal, chez les patients rapportant des symptômes de parosmie (Bitter et al., 2011). Il est intéressant de noter que la plupart de ces structures ont été identifiées, dans une récente méta-analyse, comme étant les plus affectées suite à un TCCL (Eierud et al., 2014). Ainsi, ces découvertes neuroanatomiques pourraient aussi permettre d'expliquer les liens entre la présence de parosmie et le développement de troubles de l'humeur puisque tous deux sont intrinsèquement liés par la présence d'atrophie de l'hippocampe et du cortex orbitofrontal (Hudak et al., 2011; Terpstra, Girard, Colella, & Green, 2017). Basé sur ces patrons similaires d'atteintes neuroanatomiques, il est possible d'émettre l'hypothèse que la parosmie et les symptômes d'anxiété et de dépression pourraient provenir d'une altération persistante des structures frontotemporales tels que l'hippocampe et le cortex orbitofrontal. Ainsi, il est donc logique que l'évaluation de la parosmie dans les premières semaines suivant le TCCL permette de prédire la persistance des symptômes d'anxiété et de dépression plusieurs mois suite au TCCL, puisque la présence de parosmie est indicatrice de profondes altérations anatomiques du système limbique. Nous sommes toutefois conscients que ces hypothèses restent au stade embryonnaire et se doivent d'être proprement évaluées dans de futures études impliquant des techniques d'imagerie par résonance magnétique (IRM).

4.1.4 Outils de dépistage des troubles olfactifs

Alors que nous venons tout juste de mettre en lumière, qu'en plus d'être présents dès les premières heures suite au TCCL, les troubles de l'olfaction post-TCCL joueraient un rôle important dans le développement des symptômes d'anxiété et de dépression, nous tenions à fournir un aperçue des quelques outils de dépistage olfactifs disponibles. En effet, nous sommes conscients qu'en contexte hospitalier il s'avère impossible d'évaluer complètement le système olfactif, dû au temps considérable qu'une évaluation complète demande au professionnel (plus de 30 minutes). Ainsi, en ce qui a trait à l'évaluation rapide des troubles qualitatifs (parosmie et phantosmie) de l'olfaction, le professionnel peut administrer le court *Questionnaire of Olfactory Dysfunction* (QOD), qui se compose seulement de quatre questions (Basile N Landis, Frasnelli, Croy, & Hummel, 2010). En ce qui a trait au dépistage des troubles quantitatifs de l'odorat, le professionnel peut se tourner vers le *12 items Cross-Cultural Smell Identification Test* ou encore le *12-item identification adaptation of the Sniffin'Sticks test* (Hummel, Rosenheim, Konnerth, & Kobal, 2001). Ces deux évaluations prennent moins cinq minutes à administrer et permettent ainsi un dépistage rapide des patients présentant un trouble olfactif suite au TCCL. Ainsi, les patients chez qui un trouble olfactif aura été identifié pourraient bénéficier d'un suivi téléphonique du personnel médical, dans le but de documenter l'évolution des troubles olfactifs et d'orienter rapidement les patients vers des services de santé mentale adaptés, si les troubles persistent et que le professionnel note la persistance des symptômes anxio-dépressifs.

4.2 Limites et avenues futures

Les études décrites dans cette thèse présentent quelques limites à prendre en compte dans l'interprétation des résultats ainsi que dans la mise en place de nouvelles études évaluant les troubles olfactifs et leurs conséquences auprès d'une population ayant subi un TCCL. La première

grande limite, retrouvée dans la première étude, fait référence au nombre de participants inclus dans celle-ci. En effet, seulement 30 patients ayant subi un TCCL ont pu être évalués lors de cette première étude. Ainsi, ce nombre restreint de participants a limité la qualité d'interprétation des données, puisqu'il ne permet pas une représentation juste de l'ensemble des patients ayant subi un TCCL. De plus, un nombre considérable de patients (près de 40%) ont pris la décision de ne pas participer au suivi, limitant, encore une fois, la portée des résultats obtenus dans cette étude. Par ailleurs, le nombre limité de participants ayant participé au suivi limite la qualité d'interprétation des analyses statistiques effectuées. Face à ces différentes limites, provoquées par le nombre restreint de participants, nous nous sommes afféré, dans notre seconde étude, à recruter un nombre beaucoup plus important de participants, ce qui nous a permis de sélectionner des analyses statistiques fournissant des données novatrices et une analyse en profondeur des troubles olfactifs suite à un TCCL.

Une seconde grande limite, qui est aussi retrouvée dans les deux études cette fois, réfère au manque de données d'imagerie cérébrale ou minimalement des informations quant au site d'impact suite du TCCL. De telles données auraient fourni une compréhension beaucoup plus globale des troubles olfactifs suite au TCCL. En effet, des données quant au site d'impact auraient permis de déterminer si certains sites sont plus prompts au développement de troubles olfactifs suite au TCCL, quel que démontré dans de précédentes études portant sur les patients ayant subi des TCC modéré-sévère (Gudziol et al., 2014). De plus l'acquisition de données sur la nature des scans de tomodensitométrie (positif ou négatif) aurait permis de classifier les patients selon leurs types de TCCL, soit simple (CT scan négatif) et complexe (CT scan positif) et, par le fait même, déterminer si les patients ayant un TCCL complexe sont plus à risque de développer des troubles olfactifs suite à leur trauma. Par ailleurs, la récolte de données d'imagerie par résonance magnétique aurait aussi été particulièrement intéressante dans le contexte ou la majorité des altérations cérébrales suite à

un TCCL ne sont perceptibles qu'avec cette technique (Eierud et al., 2014). L'acquisition des données d'IRM aurait aussi permis de vérifier l'hypothèse neuroanatomique présentée plus haut expliquant les liens entre la parosmie, le TCCL et le développement de symptômes anxio-dépressifs. Ainsi, il serait extrêmement pertinent pour les prochains chercheurs s'intéressant au développement de troubles de l'olfaction et de symptômes anxio-dépressifs suite au TCCL d'intégrer des données d'imagerie dans leur devis de recherche.

Finalement, la dernière limite, propre à la seconde étude, réfère au choix d'outils et à son système de classification lors de l'évaluation des troubles qualitatifs (parosmie et phantosmie) de l'olfaction. Précisément, il n'existe qu'un outil validé à ce jour et celui-ci présente des failles méthodologiques importantes. En effet, bien qu'il soit facile et très rapide à administrer, le *Questionnaire of Olfactory Dysfunction (QOD)*, ne comporte seulement que quatre questions et classe les participants comme présentant un trouble qualitatif de l'olfaction lorsque le participant obtient un score au questionnaire au-dessus de 1 point. Bien que cette classification puisse sembler libérale, nous avons basé notre choix sur les précédentes études ayant utilisé cet outil. De plus, nous estimons que la présence de parosmie est quelque chose de si peu commun dans le quotidien d'une personne, que si de tels signes sont rapportés par le patient, et ce, même si celui-ci a répondu positif à une seule question, nous jugeons adapté de le classifier comme présentant un trouble qualitatif de l'olfaction.

4.3 Conclusion

En somme, la présente thèse dresse le tout premier portrait de la proportion et de l'évolution des troubles olfactifs qualitatifs et quantitatifs auprès de patients ayant subi leur tout premier TCCL. Ainsi, il a été démontré que les troubles quantitatifs de l'olfaction (hyposmie) étaient présents dès les premières heures suite au TCCL et que ceux-ci tendent à se résorber partiellement

au cours des premières semaines suite au trauma. De plus, les résultats suggèrent que les troubles quantitatifs de l'olfaction semblent laisser leur place aux troubles qualitatifs dans les deux à quatre premières semaines suivant le TCCL, alors que près de 50% des patients rapportent des symptômes de parosmie. De plus, le devis longitudinal de la seconde étude nous a permis de dresser le tout premier portrait de l'évolution des troubles olfactifs six mois suite à un TCCL. Ainsi, alors que les troubles quantitatifs de l'olfaction tendent à se résorber et se stabiliser dans les premières semaines, les troubles qualitatifs tendent à persister plusieurs mois suite à l'accident. En effet, nous ne notons aucun changement dans la proportion des patients rapportant des symptômes de parosmie entre l'évaluation de base et celle de suivi (près de 50% dans les deux cas).

Le second grand objectif de cette thèse portait vers l'évaluation du possible apport des troubles olfactifs dans le modèle de prédiction du développement des symptômes anxio-dépressifs plusieurs mois suite au TCCL. Les résultats présentés dans cette thèse montrent, pour la toute première fois, que les symptômes de parosmie, rapportés dans les premières semaines suivant le TCCL, permettent d'expliquer une part significative de variance dans les modèles de développement des symptômes anxio-dépressifs à long terme, et ce au même titre que la présence initiale de symptômes d'anxiété et de dépression. Il est toutefois important de rappeler que ces résultats sont préliminaires et des études futures doivent tenter de les reproduire avec un nombre beaucoup plus élevé de participants. Toutefois, ces tout premiers résultats, concernant l'impact et de la présence des troubles olfactifs qualitatifs suite au TCCL, mettent en lumière la nécessité alarmante de sensibiliser le personnel hospitalier à cette nouvelle réalité. En effet, s'il n'y a qu'une chose à retenir de cette thèse c'est que les troubles de l'olfaction sont beaucoup plus présents suite au TCCL que personne n'aurait imaginé. En effet, le manque criant de connaissance dans les milieux hospitalier et scientifique se reflète par l'absence de suivi et de ressources disponibles dans notre système de santé à ce jour. Par ailleurs, alors que les offres de réadaptation olfactive sont

couramment proposées aux patients aux prises avec des troubles de l'olfaction dans plusieurs pays d'Europe, aucun type de suivi n'est malheureusement offert aux patients du Québec et même d'Amérique de Nord en général. Ainsi, nous espérons profondément que la présente thèse sensibilisera les différents professionnels, impliqués auprès de patients ayant subi un TCCL, au réel fléau qu'est l'apparition des troubles olfactifs qualitatifs et quantitatifs suite au TCC, et ce, aussi léger soit-il.

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ANNEXE

ARTICLE 1: VISUAL MEMORY PERFORMANCE FOLLOWING MILD TRAUMATIC BRAIN INJURY AND ITS RELATIONSHIP WITH INTELLECTUAL FUNCTIONING

Fanny Lecuyer Giguere[A,B], Selma Greffou[C], Sabrina Tabet[A,B], Lucie C. Frenette[A,B], Simon Tinawi[D], Mitra Feyz[D], and Elaine de Guise[A,B,E]

A. Department of Psychology, University of Montréal, Montréal, Québec, Canada.
B. Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR), Montréal, Québec, Canada.
C. Department of Neurology and Neurosurgery, Mc Gill University, Montreal, Quebec, Canada.
D. Mc Gill University Health Center-Montreal General Hospital, Montreal, Quebec, Canada
E. Research Institute-McGill University Health Centre, Montreal, Quebec, Canada.

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Abstract

Objective: To compare the visual memory performance of uncomplicated and complicated mild TBI (mTBI) groups with that of a control group on the Rey complex Figure test (RCFT). We also aimed to explore the influence of factors such as age, gender, education, occupation and intellectual functioning on visual memory in individuals with mTBI. Method: The RCFT and the Wechsler Abbreviated Scale of Intelligence (WASI-II) were administered to 138 participants (90 uncomplicated mTBI patients, 19 complicated mTBI patients and 29 controls). Results: mTBI patients demonstrated significantly lower scores than control participants on both immediate and delayed RCFT recall conditions, with performance in the low average and borderline range. However, there was no difference in performance between the two mTBI groups on the recall conditions. In addition, no significant differences were observed across the three groups on the recognition condition. The WASI-II Performance and Verbal IQ scales explained most of the variance in the immediate and delayed RCFT recall conditions but were not associated with performance on the recognition condition. Conclusions: In contrast with the recognition processes involved in visual memory, recall processes seem to be more vulnerable following mTBI and both verbal and performance IQ seem to be related to visual memory performance.

Keywords: Concussion, Mild traumatic brain injury, Rey Complex Figure Test, visual memory, intelligence

Introduction

It is well known that mild traumatic brain injuries (mTBI) can cause multiple physical, cognitive, behavioral or emotional symptoms (Arciniegas, Anderson, Topkoff, & McAllister, 2005; Carroll, Cassidy, Holm, Kraus, & Coronado, 2004; de Guise, LeBlanc, Tinawi, Lamoureux, & Feyz, 2012; Ponsford et al., 2000; Van der Horn et al., 2013). In the vast majority of cases, people who experience mTBI no longer exhibit symptoms after the expected period of spontaneous recovery, which varies from 2 to 12 weeks (Hiploylee et al., 2017; Karr, Areshenkoff, & Garcia-Barrera, 2014; Levin & Diaz-Arrastia, 2015). However, studies have shown that 10 to 20% of mTBI sufferers experience persistent post-concussive symptoms, which were found to have a direct impact on their reintegration into society and on their quality of life (Carroll et al., 2014; Cassidy et al., 2014; Levin et al., 2015; Harmon et al., 2013). Nevertheless, this symptomatic subsample of patients has remained largely unexplored to date (Karr et al., 2014). For patients with persistent post-concussive symptoms, a comprehensive neuropsychological assessment may be recommended as well as cognitive intervention to gradually reintegrate patients back to work, school or leisure activities.

To provide optimal rehabilitation intervention, specific cognitive difficulties must be targeted. A meta-analysis reported that, despite some variability in the results due in part to differences in the classification of cognitive domains (i.e., categorizing the same neuropsychological tests into different cognitive domains), visual and verbal memory processes are two of the most severely impaired cognitive functions following a mTBI (Karr et al., 2014). Furthermore, distinct effect sizes for verbal paired memory (large effect size), story memory (small effect size), list memory (small effect size), and figure memory tests (small effect size) have been reported. The present study focused on the exploration of visual memory skills, which

has been studied less frequently in the mTBI population, in contrast with other cognitive domains such as verbal memory, processing speed or executive functioning (Dikmen et al, 2009; Draper & Ponsford, 2008; Senathi-Raja, Ponsford, & Schonberger, 2010).

With respect to verbal and visual memory processes following TBI, multimodal memory impairments have been found in patients when assessed with the Wechsler Memory Scale (WMS-III) (Fisher, Ledbetter, Cohen, Marmor, & Tulsky, 2000). Furthermore, these results were used to discriminate between control participants, mTBI and moderate-to-severe TBI groups. Indeed, on measures of immediate verbal memory, visual delayed memory, and general memory (global score), mTBI patients showed lower mean verbal and visual memory index scores compared to normal control participants, but higher scores compared to patients with moderate/severe TBI (Fisher et al., 2000). Ponsford and colleagues (2011) also showed that mTBI patients performed more poorly than control participants on a visual memory task (ImPACT) at one week and three months post-injury.

While the presence of post-mTBI memory deficits is generally agreed upon, findings concerning the nature of these memory impairments are inconsistent. It is not clear whether the problem results from impaired recall or recognition processes (Carlesimo, Sabbadini, Loasses, & Caltagirone, 1997; DeLuca, Schultheis, Madigan, Christodoulou, & Averill, 2000; Hart, 1994; Vanderploeg, Crowell, & Curtiss, 2001). The recall task involved remembering details that had been previously presented and familiarity based-recognition involved simply recognizing that an item was presented without recalling exactly the learning episode. Some authors have suggested that recollection depends on the hippocampus and that familiarity depends on the adjacent medial temporal cortex (Brown & Aggleton 2001; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002). Several case studies and group studies have demonstrated relatively preserved recognition

performance in amnesic patients with selective hippocampal lesions, in the context of severe recall deficits (Baddeley, Vargha-Khadem, & Mishkin, 2001; Mayes et al., 2002; Bastin et al., 2010). One specific test that can help distinguish between different visual memory processes is the Rey Complex Figure test (RCFT). In fact, this test identifies and measures three different visual memory processes; (1) immediate recall, (2) delayed recall and (3) recognition. Despite the RCFT being a test that is commonly used in clinical practice, only a few studies have used it to evaluate visual memory functions in the TBI population. Based on the limited research, results show that mTBI patients have short- and long-term visual memory impairments on the RCFT during the long-term recovery phase from 1 to 22 months post- injury (Leininger, Gramling, Farrel, Kreutzer, & Peck, 1990). However, preservation of visual recognition functions was found in the mTBI group. Furthermore, a recent study that investigated deployed veterans who had a mTBI found visual memory impairment on all of the RCFT measures several months following their injuries. Specifically, lower scores compared to healthy controls were found on the immediate and delayed recall and the recognition tasks (Gaines, Soper, & Benrenji, 2016).

One question that emerges from these mixed findings is whether confounding variables, related to mTBI, may influence performance on the RCFT. For example, some studies have suggested that poor neuropsychological performance in patients with mTBI may be accounted for by low effort rather than low ability (Green, Iverson, & Allen, 1999; Flaro, Green, & Robertson 2007). Furthermore, the severity of the mTBI, as defined by the presence or not of cerebral lesions observed in neuroimaging, may be considered as another confounding variable. A complicated mild TBI is defined as the presence of a cerebral lesion, and the absence of cerebral lesions is considered an uncomplicated mild TBI (Iverson, 2006). Some studies have shown lower cognitive performance in patients with complicated mTBI compared to those with an

uncomplicated mTBI (Iverson, 2006; Lange, Iverson, Zakrzewski, Ethel-King, & Franzen, 2005). More recently, Iverson and colleagues (2012) compared two groups of patients with mTBI (complicated and uncomplicated) but found no difference on the neuropsychological measures administered (i.e. the Rey Auditory Verbal Learning Test, Phonemic Fluency, Animal Naming total, Trail-making and Stroop Color-Word) and directly related to the present study, no difference among mTBI groups (complicated vs uncomplicated) were shown in the RCFT (Iverson, Lange, Wäljas & al. 2012). However, there are still controversies regarding the cognitive impact of a positive finding on the CT scan.

Some cognitive variables may also influence performance on the RCFT. Although the RCFT is designed to assess patients' perceptual organization skills and visual memory it does involve several other cognitive functions, such as global IQ and processing speed. In fact, intellectual skills have been related to performance on the RCFT. The relationship between RCFT performance and intelligence was shown by Fujii, Lloyd, and Miyamoto (2000). Better performance demonstrated by better organization skills on the copy condition of the RCFT were observed in individuals with higher intelligence. It is widely accepted that a better copy of the figure is more likely to be encoded in memory. Thus, it is relevant to include this variable when exploring performance on the RCFT. In fact, Gallagher and Burke (2007) found strong positive correlations between RCFT copy, immediate and delayed recall and the estimated IQ score (determined by the vocabulary subtest of the WAIS-R) in a healthy population. Meyers and Meyers (1995) also performed similar analyses but used the full IQ scale that includes scores for the Performance IQ and the Verbal IQ scales. Unlike the previous study, Meyers and Meyers found that the copy and the two recall tasks were not correlated with Verbal IQ, but were correlated with Performance IQ, which involves organization skills, visual scanning and

attention. In an aim to better understand the variables that influence RCFT performance following TBI, Ashton, Donders, & Hoffman (2005) investigated the variables that predicted RCFT performance in a clinical population including mild, moderate and severe TBI patients. After including factors such as cerebral injury characteristics (length of coma), education, perceptual organization skills, and information processing speed in their hierarchical regression analyses, they found that within the first year after a TBI, RCFT performance is affected by perceptual organization skills to a greater extent than by injury severity characteristics, level of education, and processing speed. Thus, that study was one of the first to include the recognition task of the RCFT. By including the recognition condition, it was possible to distinguish between recall and recognition processes, leading to the finding that memory impairment was limited to immediate and delayed recall, and not to recognition (Ashton et al., 2005).

To our knowledge, despite some significant findings that show visual memory impairments several months or years post mild, moderate and severe TBI, there is still a gap in the literature regarding the evaluation and understanding of visual memory processes following mTBI in the post-acute phase (between one to three months post-accident). Our first goal was to evaluate the visual memory capacities of mTBI patients suffering from post-acute persistent symptoms and to determine which process (es) (i.e., recall and/or recognition) may be impaired. The second goal of this study was to explore which demographic and intellectual (IQ) or accident-related variables are associated with any observed impairments. We hypothesized that mTBI patients would demonstrate significantly lower scores across all RCFT components compared to healthy control participants, but we expected no differences in performance between the two mTBI groups (uncomplicated vs complicated). We also expected to find associations between Performance IQ and RCFT performance in mTBI patients.

Method

Participants

A total of 109 patients with mTBI (90 uncomplicated mTBI (normal CT scan) and 19 complicated mTBI (positive CT scan)) and 29 healthy control participants were included in this cross-sectional study. As shown in Table 1, of the 109 participants in the uncomplicated (n=90) and complicated (n=19) mTBI groups and 29 participants in the control group, 90.5% of participants were right-handed and 61.6% were female. ANOVAs were used to compare age and years of education between the three groups; no significant differences were found for education ($F(2, 131) = .001$, $p = .999$) nor for gender ($F(2, 135) = .961$, $p = .385$). However, a significant difference was found for age ($F(2, 136) = 4.58$, $p = .012$). A post-hoc Bonferroni test showed that complicated mTBI patients were significantly older than those of the control group. All other comparisons were not significant.

Table 1. *Descriptive characteristics of uncomplicated and complicated mTBI and control groups*

Characteristic	Uncomplicated (n=90)	Complicated (n=19)	Controls (n=29)
Age in years (range)	33.47 (16.00-70.00)	40.9 (17.00-72.00)	29.17 (19.00-48.00)
Gender (F), n (%)	58 (64.40)	9 (47.40)	18 (62.06)
Years of Education (range)	14.81 (9.00-24.00)	14.79 (9.00-21.00)	14.79 (9.00-22.00)
Occupation, n (%)			
Manual labor	11 (12.50)	5 (29.40)	6 (20)
Technical	17 (19.30)	0	7 (23.30)
Professional	23 (26.10)	7 (41.20)	6 (20)
Student	35 (39.80)	2 (11.80)	10 (33.30)
Retired	1 (1.10)	2 (11.80)	0 (0)
Unemployed	1 (1.10)	1 (5.90)	0 (0)

Across the two patient groups, thirty-four percent (n = 37) were involved in road accidents, 30% (n = 33) in falls, 11% (n=12) in sports accidents, 5% (n = 6) in an assault and 19% (n=21) experienced another type of accident. For the patients who were diagnosed with a complicated mTBI, 36% (n=7) had right cerebral lesions (i.e., cortical hemorrhage), 15% (n=3) had left cerebral lesions and 47 % (n=9) had a bilateral lesion.

Following their accident, patients were seen at the emergency room (ER) at the McGill University Health Centre – Montreal General Hospital (MUHC-MGH), an urban tertiary trauma-center. Operational criteria for clinical identification of an mTBI included one or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours and other transient neurological abnormalities such as focal signs, seizures, and intracranial lesions not requiring surgery. The other inclusion criterion was a Glasgow Coma Scale score (GCS) between 13 and 15 observed within the first thirty minutes post injury, or upon presentation at the ER. The diagnosis of mTBI was confirmed by a physician and was based on the Centers for Disease Control and prevention (2015). Based on the Canadian CT head rule (Stiell et al., 2001), patients had a first CT scan done soon after their arrival in the ER. The identification of a cranial or intracranial injury on radiological imaging was used to confirm the presence of a complicated mTBI. Following this, patients were referred to the MUHC-MGH out-patient clinic where they were thoroughly assessed by a physician. Demographic variables and accident-related variables were collected from medical charts and through interviews with the physician and neuropsychologist. The semi-structured interviews were carried out with the goal of obtaining the most valid information possible from the patient or a relative.

Patients were referred to the mTBI clinic if they complained of any post-concussive symptoms during their visit to the ER. Following their first visit to the out-patient clinic, patients with a score of more than 12 on the Rivermead post-concussive Questionnaire (RPQ) (King et al., 1995; Potter et al., 2006) were subsequently referred for the cognitive assessment included in the current investigation. All cognitive assessment tools were administered within the first three months post-injury (Mean= 62 days; SD= 15.1). There was no difference (p=.14) in the delay of evaluation (numbers of days between accident and assessment) between the mild uncomplicated group (M=80.05;SD=45.22) and the mild complicated group (M=56.84; SD=40.13) and the number of days between accident and assessment were not related to the copy condition (p=.95), the immediate recall condition (p=.14), the delayed recall condition (p=.12) or the recognition condition (p=.91).

Participants in the control group (n=29) were recruited from ads posted at the University, at the hospital and in shopping centers. A semi-structured screening interview was completed by phone to verify the eligibility of potential participants for inclusion in the study. Eligible participants visited the university, or the hospital and testing comprised signing the consent form and completing the cognitive assessment. The patient and control groups were comprised of participants who 1) were between 18 and 50 years of age, 2) in the case of patients, did not sustain more than one mTBI.

Participants were excluded if they 1) had a previous history of psychiatric or neurological disorders, 2) had previously been diagnosed with a mTBI in the control group, 3) were excessive drug users (daily drug consumption in the month before the accident, National Institute on Drug Abuse, 2005), 4) engaged in excessive alcohol consumption defined as more than 7 drinks per week during the month preceding the TBI for a women and 14 drinks per week for men

(Corrigan, Borgner, & Lamb-Hart, 2005), 5) were currently taking medication known to interfere with cognitive abilities (e.g., antidepressants, benzodiazepines, hypnotics) or 6) were in litigation or exhibited financial compensation-seeking behaviours. Regarding the latter criteria, patients were excluded when the experienced neuropsychologist had a reason to think that the patient was in litigation with an insurance company (vehicle crash or work accident) and did not deploy enough effort in the tests (e.g. lack of participation in testing, low motivation). The study took place between November 2014 and August 2015 and was approved by the ethics committee of the McGill University Health Centre.

A total of 195 mTBI patients were referred to the out-patient clinic from the ER of the MUHC-MGH. Among this cohort, a total of 69 patients with mTBI showed good recovery of their post-concussive symptoms (less than 12 on the RPQ) and were discharged from the out-patient clinic. A total of 126 patients with persistent symptoms (more than 12 on the RPQ) were then referred for the cognitive assessment and 17 were excluded based on the exclusions criteria. A total of 109 patients with mTBI completed the study.

Procedure

Demographic, medical and accident-related variables

Age, gender and years of education were collected from patients' medical records. The date of accident and of the assessment were also collected, as was the accident-related medical data of all mTBI patients. Accident-related data included the mechanism of the accident (road accident, fall, sport, assault, other), the Glasgow Coma Scale score (GCS) upon admission to the hospital, and the presence and site of a cerebral injury observed on the CT scan.

Instruments

All assessments were performed in a standardized manner by an experienced neuropsychologist. All participants completed a semi-structured interview and the RCFT task, developed by Meyers and Meyers (1995), in which the participant is asked to copy a complex figure and then reproduce the same figure from memory three minutes later in an immediate recall task. A delayed recall, where the participant had to again reproduce the image, was performed 30 minutes later, followed by a recognition task. During the recognition task, the participant had to circle the designs that were present in the original RCFT, among distractors (Meyers & Meyers, 1995). Participants were awarded a maximum score of 36 for each recall condition, with 0-2 points being awarded for each item within a condition (0 points = element inaccurately drawn, and unrecognizable or not present and/or incorrectly placed; 0.5 points = element inaccurately drawn but recognizable and incorrectly placed; 1 point = element was inaccurately drawn but correctly placed or accurately drawn but incorrectly placed; 2 points = element was accurately drawn and correctly placed). For the recognition condition, a total of 12 points (1 per correct item) was possible. A manual cross-checking of the standards of administration and scoring was used in the correction of the test (Strauss, Sherman, & Spreen, 2006). The Z scores of all components were calculated. No standard scores are available for the copy trial (Meyers & Meyers, 1995), therefore this trial was not included in the analyses.

Patients also completed a cognitive evaluation which included the Vocabulary, Similarities, Block Design and Matrix Reasoning subtests from the second edition of the Wechsler Abbreviated Scale of Intelligence WASI-II (Wechsler, 2011). A full IQ score as well as Performance and Verbal IQ scores were calculated using these four subtests of the WASI-II.

In addition to RCFT performance comparisons to a matched control group, T scores for RCFT and WASI-II tests were computed with the goal of comparing visual memory and intellectual performance to the general population. The block design and matrix subtests were included in the Perceptual Reasoning Index (PRI), and the Vocabulary and Similarity subtests were included in the Verbal Comprehension Index (VCI). T scores were computed by comparing the score obtained by the participants on the WASI-II and the RCFT to healthy population norms. A t score of over 50 is above average and lower than 50 is below average. In general, a t score of above 60 means that the score is in the top one-sixth of the distribution (high average); above 63, the top one-tenth (superior). A t score below 40 indicates low average, and below 37 is borderline (impaired).

Moreover, the digit span task of the Wechsler adult intelligence scale - Fourth Edition (WAIS-IV) was administered to participants. In this task, participants hear a sequence of numerical digits and are asked to recall the sequence correctly. Once the sequence is presented, the participant is asked to either recall the sequence in the order it was presented (forward) or in the reverse order (backward) (Wechsler, 2008). Performance validity in the mTBI group of patients was evaluated by analyzing the Reliable digit span test score (RDS) (Greffensten, Baker, Gola, 1994; Meyers & Volbrecht, 1999). The RDS is a method of exploring the symptom validity of participants. Here, the longest number of digits repeated correctly on both trials of Digit Span (forward and backward) was computed for each patient. A mean score of 7 or less suggests the presence of possible malingering (Schroeder, Twumasi-Ankrah, Baade & Marshall, 2012).

Statistical analysis

Analyses of variance (ANOVA) were used to compare both mTBI groups and the control group on age and years of education. To test the first objective of the present study which is to evaluate the visual memory capacities of mTBI patients and to determine which process(es) may be impaired, one-way analyses of covariance (ANCOVA) were conducted to determine if there was a statistically significant difference between the three groups (i.e., the control, uncomplicated mTBI, and complicated mTBI) on each of the raw scores of the three tasks of the RCFT (i.e., immediate recall, delayed recall and recognition), controlling for chronological age. To test our second objective which is to explore which demographic (age, gender, education), accident-related variables (Type of mTBI and delay of assessment) and intellectual (IQ) variables are associated with any observed impairments, multiple linear regressions with logarithmic transformations were performed on the data set from the patients only. The transformations were used because the results for all the RCFT tasks were found to be non-linear. Adjustments for multiple comparisons were performed, and all statistical tests used an alpha level of 0.01.

Results

Differences of RCFT performance across groups

Table 2 shows the performance scores (mean and SD) obtained on the RCFT for the three groups on the three dependent measures. For both the immediate recall (IR) and delayed recall (DR) conditions, significant group effects were found after controlling for age (IR: $F(2, 134) = 8.421, p < .001$; DR: $F(2, 132) = 6.996, p = .001$). Note here that 2 participants from the mTBI group didn't complete the Delayed recall subtest. Post-hoc analyses revealed no difference between TBI groups, but controls differed from the uncomplicated mTBI group (IR: $p = .001$;

DR: *p*= .002) as well as from the complicated group (IR= *p*= .002; DR= *p*= .010), with the control group performing significantly better (i.e., higher scores) than both mTBI groups. In contrast with the findings for immediate and delayed recall, after controlling for age, no difference across groups was found for the recognition task ($p < .05$).

Table 2. Raw Scores means and standard deviation scores for the RCFT for each group

	Uncomplicated mTBI	Complicated mTBI	Controls
RCFT subtests	M (SD)	M (SD)	M (SD)
Copy	26.69 (3.84)	24.94 (4.20)	29.23 (3.01)
Immediate recall	17.49 (5.28)	16.39 (4.65)	21.45 (4.36)
Delayed recall	17.08 (5.17)	16.42 (4.31)	20.77 (4.70)
Recognition	10.96 (1.15)	10.78 (1.39)	9.73 (1.17)

Performance scores for the entire mTBI sample on RCFT and intellectual IQ tasks are shown in Figure 1, which shows low average (T score below 40) to borderline (T score below 37) performance on the Immediate and Delayed RCFT recall conditions but average (T score around 50) to high average (T score above 60) and homogenous performance across the different IQ tasks.

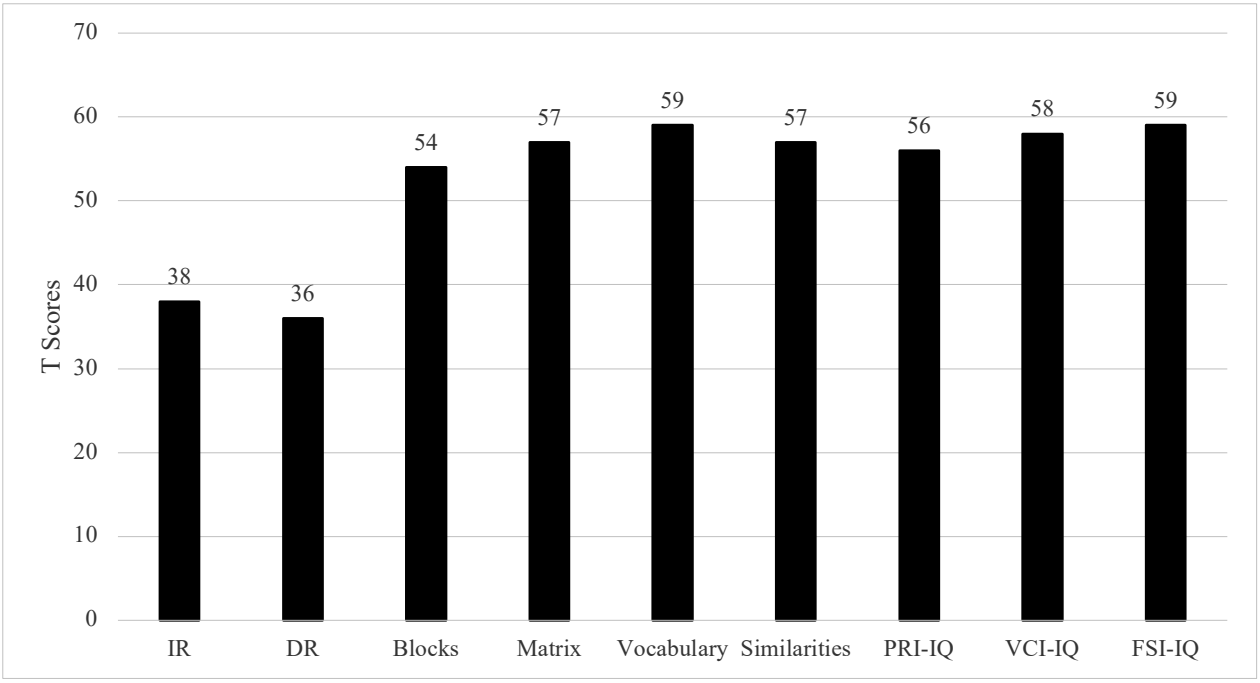

Figure 1. RCFT and IQ test performance (in T scores) of 109 patients with mTBI. IR=Immediate Recall of the RCFT. DR=Delayed Recall of the RCFT. PRI-IQ= Perceptual Reasoning Index of the WASI-II. VCI-IQ= Verbal Comprehension Index of the WASI-II. FSI-IQ= Full Scale Index of the WASI-II.

Associations among demographics, type of mTBI and intellectual (IQ) variables, and RCFT performance

Multiple linear regression analyses were performed on the RCFT scores from the different conditions using the factors age, gender, occupation, education, severity or type of mTBI (uncomplicated vs complicated) and all four subtests of the WASI-III (Blocks, matrix, vocabulary, similarities) as well as with the Perceptual Reasoning Index of the WASI-II (PRI-IQ), Verbal Comprehension Index of the WASI-II (VCI-IQ) and Full Scale Index of the WASI-II (FSI-IQ) and the RCFT conditions.

Table 3 and 4 shows the results of the multiple linear regression analysis. All four subtests of the WASI-II were associated with the immediate recall and delayed conditions of the RCFT. As the block subtest mean score increased (better performance), the mean scores on the

immediate and delayed recall conditions also increased (better performance) (IR: Beta=0.009, p<0.001; DR: Beta=0.009, p<0.000). Performance on the block subtest explained 23.1% of the variance observed in the immediate recall condition of the RCFT and 20.0% of the variance observed in the delayed recall condition. The same pattern was found for the vocabulary subtest (IR: Beta= 0.004, p<0.001, R^2=9.8%; DR: Beta=0.005, p<0.000, R^2=11.5%), the matrix subtest (IR: Beta= 0.005, p<0.01, R^2=6.3%; DR: Beta=0.006, p<0.011, R^2=6.2%) and the similarities subtest (Beta= 0.005, p<0.018, R^2=6.2%; DR: Beta=0.006, p<0.017, R^2=6.5%). Moreover, as performance on the indexes of the WASI-II increased (better performance), performance on the immediate and delayed recall conditions of the RCFT also increased. The verbal comprehension index of the WASI-II explained up to 13.9% of the variance observed in the immediate recall condition of the RCFT (Beta= 0.004, p<0.000) and 15.1% of the variance in the delayed recall condition (Beta= 0.005, p<0.000). The perceptual reasoning index of the WASI-II explained up to 19.6% of the variance observed in the immediate recall condition of the RCFT (Beta= 0.006, p<0.000) and 18.2% of the variance observed in the delayed recall condition (Beta= 0.006, p<0.000). Finally, the percentage of explained variance is 16.4% for the full scale IQ index (Beta= 0.005, p<0.000) for the immediate recall condition and 18.3% for the delayed recall condition (Beta= 0.006, p<0.000). None of the demographics or accident related factors such as age, gender, occupation, education, severity or type of mTBI (uncomplicated vs complicated) were associated with performance on the immediate recall or delayed recall of the RCFT.

Table 3. Multiple linear regression on the immediate recall condition of the Rey Complex Figure Task in 109 patients with mTBI

Variables	*B*	*SE*	*t*	*p*	*R*	R^2
Age	-.002	.001	-1.899	.060	.161	.026
Gender	-.001	.026	-.028	.977	.002	.000
Education	-.001	.005	-.164	.870	.014	.000
Type of mTBI	.001	.029	.048	.962	.005	.000
Blocks	.009	.002	5.392	.000*	.480	.231
Vocabulary	.004	.001	3.349	.001*	.313	.098
Matrix	.005	.002	2.629	.010*	.251	.063
Similarities	.005	.002	2.402	.018*	.248	.062
VCI-IQ	.004	.001	3.740	.000*	.372	.139
PRI-IQ	.006	.001	4.782	.000*	.442	.196
FSI-IQ	.005	.001	4.447	.000*	.405	.164

Note. VCI-IQ= Verbal Comprehension Index of the WASI-II. PRI-IQ= Perceptual Reasoning Index in the WASI-II. FSI-IQ= Full Scale Index in the WASI-II.

Table 4. Multiple linear regression on the delayed recall condition of the Rey Complex Figure Task in 109 patients with mTBI

Variables	*B*	*SE*	*t*	*p*	*R*	R^2
Age	-.001	.001	-.551	.583	.054	.003
Gender	.015	.031	.492	.624	.048	.002
Education	.001	.0005	.136	.892	.014	.000
Type of mTBI	.005	.030	.171	.864	.017	.000
Blocks	.009	.002	5.018	.000**	.458	.209
Vocabulary	.005	.001	3.619	.000**	.339	.115
Matrix	.006	.002	2.592	.011*	.250	.062
Similarities	.006	.002	2.436	.017*	.254	.065
VCI-IQ	.005	.001	3.884	.000**	0.388	.151
PRI-IQ	.006	.001	4.531	.000**	.427	.182

FSI-IQ	.006	.001	4.716	.000**	.428	.183

Note. VCI-IQ= Verbal Comprehension Index of the WASI-II. PRI-IQ= Perceptual Reasoning Index in the WASI-II. FSI-IQ= Full Scale Index in the WASI-II. *p<0.05; **p<0.001

Table 5 shows the multiple linear regression analysis with a logarithmic transformation on the recognition condition of the RCFT. No variable was significantly associated with performance on the recognition condition.

Table 5. Multiple linear regression on the recognition condition of the Rey Complex Figure Task in 109 patients with mTBI

Variables	*B*	*SE*	*t*	*p*	*R*	R^2
Age	-.001	.000	-1.781	.078	.174	.030
Gender	.004	.011	.372	.711	.037	.001
Education	-.001	.002	-.630	.530	.064	.004
Type of mTBI	-.009	.010	-.899	.371	.089	.008
Blocks	.001	.001	1.082	.282	.110	.012
Vocabulary	.000	.000	-.514	.608	.051	.003
Matrix	-.001	.001	-.792	.430	.079	.006
Similarities	5.960	.001	.007	.995	.001	.000
VCI-IQ	-2.15	-.005	-.045	.965	.005	.000
PRI-IQ	.000	.000	.226	.821	.024	.001
FSI-IQ	.000	.000	-.221	.826	.022	.000

Note. VCI-IQ= Verbal Comprehension Index of the WASI-II. PRI-IQ= Perceptual Reasoning Index in the WASI-II. FSI-IQ= Full Scale Index in the WASI-II.

Reliable digit span test scores (RDS)

The longest number of digits repeated correctly on both trials of Digit Span (forward and backward) was computed for each mTBI patient. Of a total of 109 mTBI patients, one patient

obtained a score of 5 (1.8%), one patient obtained a score of 6 (1.8%) and 5 patients obtained a score of 7 (4.5%). In sum, a total of 6.48% of the cohort obtained a score of 7 or less.

Discussion

Differences between mTBI groups and controls on the RCFT

The first aim of this study was to compare the performance on the RCFT across mTBI patient groups (uncomplicated and complicated) and healthy control participants. The findings of the present study partially support our hypothesis, that patients with mTBI would demonstrate poorer performance on all RCFT conditions compared to controls. Indeed, we observed significantly lower performances in the mTBI groups than the control group for both the immediate and delayed recall conditions. These group differences cannot be explained by variables such as age and education, given that the level of education didn't differ across the groups and that age was controlled for in the analyses. In contrast with the two recall conditions, no difference across groups was shown for the recognition condition. These findings support the idea that the recall conditions of the RCFT are useful for discriminating between patients with mTBI and healthy controls but aren't sensitive enough to discriminate between uncomplicated and complicated mTBI. Despite the observed differences across groups, the clinical significance of this difference with regards to actual deficits in visual memory recall following a mTBI remained unclear. Thus, in follow-up analyses it was important to explore the T scores of our patient groups. These results highlighted the presence of performances in the low average and borderline range for both recall conditions of the RCFT, which allows us to draw conclusions about the vulnerability of the recall processes in visual memory following a mTBI.

The findings of the present study are consistent with the previous RCFT literature, which also finds impairments in organization skills and visual memory following TBI of any severity

(Ashton et al., 2005; Leininger et al., 1990; Fisher et al., 2000; Ponsford et al., 2011; Schwarzt, Penna, & Novack, 2009). Memory impairments are the most common cognitive complaint following TBI (Capruso & Levin, 1992), and studies that explored visual memory post-TBI have also detected impairments at that level (Brooks, 1976; Meyers & Meyers, 1995). An study done by Ashton et al (2005) is consistent with our finding on recall and recognition processes whereby they found that the recognition performance of the patients was superior to their performance on the delayed recall condition. However, our results on the recognition condition differ from the ones from Gaines and colleagues (2016) who showed a difference in the recognition condition between a mTBI group assessed several months post injury and a control group. The main difference between the previous study and the present study is the mechanism of the accident that caused the mTBI and the longer delay before assessment in the group of veterans tested by Gaines et al. The deployed veterans may have suffered from a blast injury which is different from a road or sport accident, or a fall. However, studies show that the cognitive outcomes from blast-related mTBI are similar to those following civilian forms of mTBI (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2011; Belanger et al., 2009; Bolzenius, Roskos, Salminen, Paul, & Bucholz, 2015). Thus, replicating the present results would be important with several other mTBI population seen at different delays post injury.

Recall versus recognition

In the present study, despite the difference between mTBI patients and healthy controls on the recall conditions of the RCFT, no difference was demonstrated on the recognition condition. In fact, a ceiling effect in performance was found for all groups. We can speculate that in our mTBI group, even in the presence of a normal CT scan, some selective and micro hippocampal

damage may have occurred. In fact, a brain structure of key importance in TBI is the hippocampus. Some studies have suggested that the memory impairments observed after a TBI may be due to excitotoxic and hypoxic insult that affects specifically the hippocampus (Rosenfeld et al., 2012). Moreover, post-acute atrophy of the hippocampus has now been demonstrated in several TBI studies (Bigler et al., 1997). More recently, a study done with mTBI patients has demonstrate altered diffusivity of hippocampal subregions, indicating impaired grey matter microstructural integrity (Leh et al., 2017).

Variables associated with the RCFT conditions

We also aimed to explore the influence of factors such as education and intellectual functioning on visual memory. Factors such as age, gender, education and occupation were not associated with performance on any of the RCFT conditions. These results were unexpected because several previous studies have shown that education level is one of the most commonly reported variables to be significantly related to RCFT performance (Ardila, Rosselli, & Rosas, 1989; Kixmiller, Verfaellie, Mather, & Cermak, 2000; Rosselli & Ardila, 1991). However, the previous studies that have found a relationship between education and RCFT scores included participants that had less than 8 years of education. In the present study, none of the participants had less than 9 years of education and the mean education level was 14 years for each of our groups. It is thus logical to assume that the lack of significant relationship between education and performance on the four RCFT subtests is due to the high level of education of our mTBI patients. Moreover, in the present study we replicated the results obtained by Ashton et al. 2005, who also did not find a relationship between education, injury severity characteristic and the RCFT, but did find a relationship with IQ.

In the present study, we found a significant relationship between the Performance IQ index derived from the WASI-II and both recalls RCFT conditions (immediate recall and delayed recall). This is not surprising as the PIQ index includes the Matrix Reasoning and the Block design tasks, two non-verbal tasks requiring good perceptual organizational abilities and visuo-constructive skills (Block design), which are also involved in the RCFT. Likewise, previous research has shown strong to moderate correlations between performance on various tests measuring these latter functions and RCFT scores (Ashton et al., 2005; Kixmiller et al., 2000; Meyers & Meyers, 1995). Our findings suggest that Performance IQ, measured with perceptual organization and visuo-constructive tasks significantly predict visual memory performance.

We also found associations between the RCFT immediate and delayed recall and Verbal IQ. These results were not expected as no such links have been found in previous studies and are thus novel findings. Indeed, the only known paper that has looked at Verbal IQ did not include it in their hierarchical regression model (Ashton et al., 2005). However, we can speculate about the influence of verbal abilities on RCFT scores involving simultaneously visuo-perceptual abilities, organizational skills and visual memory. We suggest that RCFT tasks involve other cognitive processes, such as working memory (WM). In fact, WM is one of the frequently reported complaints following mTBI (Lundin, de Boussard, Edman, & Borg, 2006; Paniak et al., 2002;). This novel finding should be replicated in future studies.

Uncomplicated versus complicated mTBI

In the present investigation and as hypothesized, no difference was found between the uncomplicated (without intracranial abnormalities) and complicated (with intracranial abnormalities) mTBI groups on RCFT subtests. Even if complicated mTBI patients present

visible and measurable brain abnormalities (positive CT scans), these lesions aren't associated with greater cognitive alterations and deficits. In fact, there is ambiguity in the current literature regarding the differences in cognitive function that can be observed between these two mTBI groups. At first glance, it seems that most studies aiming to compare cognitive abilities between patients with complicated and uncomplicated mTBI at different time points after the mTBI find no differences between the groups. In the present study, the group of complicated mTBI was very small, which may have had an impact on the findings too. In fact, these studies all conclude that there are cognitive alterations in both groups, but no differences between them (de Guise et al., 2010; Hanlon, Demery, Martinovich, & Kelly, 1999; Hofman et al., 2001; Sadowski-Cron et al., 2006).

Study Limitations

The first limitation of the present study results from the study design. Specifically, the quasi-experimental design used here does not establish any causal links between the variables included in this study given that participants were not randomly assigned to groups, due to the fact that mTBI participants formed a group well before the establishment of the research project. But also, patients cannot be randomly assigned given that group membership is dependent on their injury. A second limitation results from the fact that it is impossible to identify and control for all potential extraneous variables, which could have affected our results (e.g., number of past mTBI, socio-economic status, general health condition before the accident). Another possible limitation is related to the composition of the control group (i.e., healthy participants) that was included in order to determine if the cognitive pattern observed in patients was attributable to a general injury or if it was specific to a brain injury. Study including two control groups, one healthy and one with patients with a general injury (e.g., orthopedic injury) is recommended. However, there is a lack of

consensus in the literature regarding this issue, and it is not clear if an injured control group constitutes a better control group than a community sample. Mathias, Dennington, Bowden, & Bigler (2013) conducted a large-scale study, which compared the performance of community controls to that of injured controls. The authors did not find any differences between both these groups, and therefore concluded that injured patients are not necessarily the best control group for mTBI groups (Mathias et al., 2013). Moreover, according to the criteria established by Cohen (1988), a sample of 26 participants per group has sufficient power (80%) to detect large effects (f = .40) and to conduct analyses of variance at a threshold of significance of p. <.05. Therefore, the number of participants in the mild complicated TBI group (n = 19) in the current study does not reach the power target for group comparison analyses, which may limit the generalizability of the results related to the first objective of our study only. Similarly, a larger number of patients would improve the power of prediction obtained in the regression analysis. However, we believe that our low but significant R-squared value (between 6 and 23%) can still offer important insight about how changes in IQ scores are associated with changes in RCFT performance. For example, an R-squared of 25% may be quite good explanatory value, and an R-squared of 10% or even less could have some informational value (Everitt, 2002). In addition, our R-squared are quite comparable with those reported by Ashton and colleagues in a similar study (Ashton, Donders, & Hoffman, 2005).

We also believe that the imaging technique employed to detect cerebral damage (i.e., CT scan) is not very sensitive in a mTBI population and we strongly recommend other more sensitive techniques, such as anatomical imaging technique (MRI) or diffuse tensor imaging (DTI). To better understand the relationship between involvement of the cerebral regions and the RCFT following a mTBI, studies using more sensitive imaging techniques, such as anatomical MRI or DTI, should

be pursued. Finally, and importantly, it may be suggested that lower performance in the mTBI group is the result of a lack of motivation or suboptimal effort in this group. We explored this possibility as an alternate explanation for group differences. The present study did not assess symptom validity with objective and specific measure of motivation, such as the Test of Memory Malingering (TOMM) (Tombaugh, 1996). Assessment of motivation is not systematically done in all neuropsychological evaluations in Quebec, Canada. Rather, universal and accessible health care is provided to the mTBI population. All mTBI patients are covered or insured and receive compensation if they are involved in a vehicle or work-related accident. They all receive necessary services corresponding to their needs, such as tests, medical and neuropsychological exams, and rehabilitation interventions. In our cohort of mTBI patients, no patients were involved in litigation. However, we considered the possible confound of poor effort using the RDS test score (Greffensten, Baker, Gola, 1994) and found that a total of 6.4% of our mTBI cohort may have shown poor motivation to perform the RCFT, which is a very low percentage not representative of the entire cohort. In a study done with mTBI patients, RDS score was found to be a valid way to measure validity performance. They found that a cutoff score of less than or equal to 7 accurately classified 75% of individuals in the incomplete effort group and 69% of patients with TBI. Moreover, the authors found that applying this cutoff score to a non-litigating mTBI group yielded a 77% correct classification rate (Axelrod, Fichtenberg, Millis &Wertheimer, 2006).

Conclusions

In contrast with the recognition processes involved in visual memory, recall processes seem to be more vulnerable following mTBI, and both verbal and performance IQ seem to be related to visual memory performance. The RCFT is a useful measure of visual memory deficits

in mTBI patients and we believe that it would be valuable in clinical settings with mTBI patients. Early detection of post-TBI cognitive impairment would enable clinicians to respond early with appropriate interventions. However, future studies are needed to better understand the factors affecting RCFT scores in mTBI patients.

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Declaration of Interest

The authors report no conflicts of interest.

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ARTICLE 2: IMPROVING THE ASSESSMENT OF TRIGEMINAL SENSITIVITY: A PILOT STUDY

Benoit Jobin[1,2], Cécilia Tremblay[3], Fanny Lecuyer Giguere[2,4], Jason Steffener[5], Johannes Frasnelli[2,3]

1. Department of Psychology, Université du Québec à Trois-Rivières, 3351 boul des Forges, Trois-Rivières, Québec, G9A 5H7, Canada.
2. Research center, Sacré-Cœur Hospital of Montreal, 5400 boul Gouin Ouest, Montreal, Québec, H4J 1C5, Canada.
3. Department of Anatomy Université du Québec à Trois-Rivières, 3351 boul des Forges, Trois-Rivières, Québec, G9A 5H7, Canada.
4. Department of Psychology, University of Montréal, 90 av Vincent-D'indy, Montreal, Quebec, H3C 3J7, Canada.
5. Faculty of Health Sciences, University of Ottawa, 125 University, Ottawa, Ontario, K1N 6N5, Canada.

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Abstract

The trigeminal system is a chemosensory system, next to smell and taste, allowing intranasal sensations such as freshness, spiciness, etc. The lateralization task is used to measure trigeminal sensitivity and consists in identifying the nostril stimulated by an odorous substance in a two-alternative forced-choice procedure. However, when performed in the standard method, this task takes almost 25 to 30 minutes to administer and only gives access to few information. The aim of this pilot study was to compare two alternative methods of administering the lateralization task with the standard method in a group of 53 participants (41.6 years; 32 women). Specifically, we compared (1) the standard method of 40 constant stimuli with a duration of 500ms, (2) a short version of 20 variable stimuli ranging from 200ms to 600ms (Different Duration method - DD) and (3) an automatic adaptive staircase method where the test adjusts the duration of stimulation according to the participant's responses (Adaptive Duration method - AD). Based on the number of correct answers and the thresholds obtained with the automatic staircase method, the average scores for the two alternative methods correlate with the score at the standard method. In addition, both alternative methods are able to discriminate between participants with a high sensitivity and those with a lower sensitivity. Finally, the DD method is significantly shorter in terms of administration time than the other two methods. This pilot study presents two novel methods to evaluate trigeminal sensitivity which each have a specific superiority over the established technique. The DD method cuts testing time in half whereas the AD method provides threshold estimates for individual nostrils.

Keywords: Chemosensory perception, Measurement, Localization, Trigeminal system, Olfactometer.

Introduction

The trigeminal system is a chemical sense, next to smell and taste, that allows the perception of chemical information through stimulation of chemoreceptors located on the trigeminal nerve (Cranial Nerve V) (Tucker, 1971; Doty, 1975). It allows the perception of sensations such as freshness, warmth, burning and pungency from odorous stimuli (Doty et al., 1978; Laska et al., 1997; Frasnelli et al., 2011a). The olfactory and trigeminal systems are closely linked. Indeed, almost all odorants lead to the activation of both systems, at least in higher concentrations (Doty et al., 1978). The trigeminal system has received particular attention recently, as it allows for the distinction between olfactory dysfunction due to Parkinson's disease and other forms of olfactory dysfunction (Tremblay et al., 2017, 2019), which may be used for early detection of Parkinson's disease.

Typically, the trigeminal system is behaviorally assessed using the trigeminal lateralization task (Kobal et al., 1989; Berg et al., 1998; Hummel et al., 2003). This task is based on the fact that for humans the localization of an odorant, i.e. the identification of the stimulated nostril following monorhinal stimulation, is only possible if the stimulus activates the trigeminal system (Kobal et al., 1989). In other words, we cannot localize pure olfactory stimuli. The lateralization task consists in presenting a trigeminal stimulus of a given concentration and duration to one nostril while odorless air is presented to the other nostril. Participants are then instructed to identify the stimulated nostril (forced choice). Since for a single trial the success rate is 50%, typically 40 randomized and counterbalanced repetitions are carried out (Hummel et al., 2003; Wysocki et al., 2003; Frasnelli et al., 2006; Tremblay et al., 2017). Trigeminal sensitivity is then estimated by the number of correct identifications. This technique is widely used in olfactory studies and provides a reliable behavioral assessment of the trigeminal sensitivity (Berg et al., 1998; Kobal et al.,

1989; Roscher et al., 1996). It allows to discriminate individuals with reduced trigeminal sensitivity associated to olfactory dysfunction and controls (Hummel et al., 2003).

The test has the advantage of being easy to administer, as odorants can be presented in polypropylene squeeze bottles or rigid glass bottles (Wysocki et al., 2003; Tremblay and Frasnelli, 2018; Frasnelli and Hummel, 2005 ; Hummel et al., 2003; Frasnelli et al., 2006; Frasnelli et al., 2011). However, it has some important limitations. First, since an inter-stimulus interval (ISI) of 35-40s has to be respected in order to avoid habituation (Hummel & Kobal, 1999), test duration is in the range of 30 minutes. This poses a problem for participants' vigilance and renders the test not well applicable in a clinical context. Second, the approach does not allow for the estimation of a perception threshold, as the same stimulus is presented throughout the test. Rather, the method has a poor resolution as it scores range between 20 if the participant takes a guess at each trial and 40 if the participant has a perfect performance. Third, this method does not allow for an estimation of sensitivity for each nostril separately. Therefore, there is a need for an improved test with shorter duration and/or scores of higher data quality.

One approach to improve the test is to use stimuli of different concentrations (Wysocki et al., 1997). Since the trigeminal system acts as a mass detector rather than a concentration detector (Cometto-Muñiz and Cain, 1984; Cometto-MuñIz, 1998) and since it is technically easier to vary the duration of the stimulus than its concentration, another approach has been introduced (Naka et al., 2014). Here, trigeminal stimuli are varied in terms of duration rather than concentration. Indeed, increasing the duration of a given stimulus yields stronger (perceived) intensity which is indistinguishable from the same stimulus in a higher concentration but a shorter duration (Frasnelli et al., 2003). With the advent of low priced olfactometers (Lundström et al., 2010) –

devices for the automated, computer-controlled delivery of odorous stimuli – and even portable devices (Hummel et al., 2016), this approach provides a shortcut to present stimuli with different intensities potentially allowing for the measure of perception thresholds.

We therefore set out to investigate the potential of two alternative lateralization methods to evaluate trigeminal sensitivity: (1) the Different Duration (DD) method with a total of 20 stimulations of different durations, and (2) the Adaptive Duration (AD) method that consist of an adaptive staircase adjusting the stimulus duration according to the participant's response. We assessed their validity by comparing them to the standard procedure with a single stimulus duration.

We hypothesized that (1) scores obtained with DD and AD correlated with those of the standard method; (2) DD and AD allow for the discrimination of participants with a higher trigeminal sensitivity from participants with a lower trigeminal sensitivity as determined by the standard method and (3) DD and AD have shorter test durations than the standard method.

Material and methods

The study was conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects and approved by the local Ethics Committee of the Sacré-Coeur Hospital (SCH) in Montréal (CIUSSS-NIM #2017-1321). After a detailed explanation of the study, all participants gave their written consent prior to inclusion.

Participants

A total of 58 individuals were recruited through ads posted at SCH and online. We excluded participants with (1) a diagnosis of neurological disease or any psychiatric disorder, (2) nasal congestion, nasal polyps, septum deviation, or sinusitis, (3) a history of traumatic brain injury, (4) seasonal allergies, (5) substance abuse including tobacco. Participants were instructed not to eat or drink (other than water) one hour prior to testing. We also excluded participants with olfactory dysfunction as assessed by the identification test of the Sniffin' Sticks test (Hummel et al., 1997). Specifically, we only included participants with scores corresponding to normosmia (18-40 years of age: score >11/16; 41-60 years of age: score >10/16; >61 years of age: score>9/16 ; Oleszkiewicz et al., 2019). In total 53 participants (mean age: 41.6, standard deviation: 20.9; range 19-83) years (32 women) were thus included in the study.

Trigeminal evaluation

For all tests, stimuli were presented by an olfactometer to the participants. We used an eight-channel computer-controlled (PsychoPy 2.7.3; Python (Peirce, 2007)) air compressor (Lundström et al., 2010), in which the presentation of odorants is possible when the compressed air is odorized by passing through containers (glass bottles; 60 mL) filled with odorants. The stimuli were delivered through an air pulse, flow rate of 2.5 L/min. We used eucalyptol (Novotaste, Dollard-Des-Ormeaux, QC; 5mL, 5% in propylene glycol) as stimulus with known trigeminal impact (Frasnelli et al., 2017). One tube was inserted in each nostril, these tubes were both linked to channels connected to one bottle containing 5 ml of eucalyptol and one empty bottle for neutral air. By doing so, for each stimulation, one nostril received eucalyptol, while the other nostril received odorless air. The participant had to identify the nostril stimulated with eucalyptol.

The stimuli were presented with an ISI of 35s between each stimulation to avoid any effects of habituation/sensitization to the odorant.

All participants were submitted to three lateralization tasks, in a pseudo-randomized order.

1. Standard method. Participants received a total of 40 stimulations, 20 in each nostril (pseudo-randomized, counterbalanced). All the stimuli had a duration of 500ms. The number of correct localizations was counted to obtain an individual score out of 40. A higher value indicates a higher trigeminal sensitivity.

2. Different Duration method. In this method, participants received four stimuli (two on each nostril; pseudo-randomized, counterbalanced) of five different durations (200ms, 300ms, 400ms, 500ms, and 600ms), resulting in a total of 20 trials. The number of correct localizations was counted to obtain an individual score out of 20. Further, we counted the number of correct trials per duration (0 to 4).

3. Adaptive Duration method. In this method, the same procedure was used simultaneously for both nostrils in a randomly interleaved manner. We followed a staircase procedure; each staircase (left and right nostril) started with a first stimulation of 500ms. Stimulus duration was either reduced or increased according to the participant's response: after two consecutive correct trials, stimulus duration was reduced by 200ms. After incorrect localization, however, stimulus duration was increased by 200ms. The minimal stimulus duration was 100ms. After four reversals points (increase or decrease in stimulation duration) for each staircase separately, the test ended. For each side, the average of the 4 reversal durations was used as an estimate of the detection threshold with higher values indicating lower trigeminal sensitivity. We therefore

obtained a threshold for the left and one for the right nostril (See Figure 1). Such adaptive techniques have accuracies in the range of 70% (Leek, 2001).

Procedure

Participants were stimulated passively (Frasnelli et al. 2008), i.e., air was blown into their nostrils. After installation of the tubing, participants were instructed to look at a computer screen. During the experiment a white cross was presented in the middle of the screen. Shortly before stimulation, the cross turned red for a duration of 1500ms during which the participants were instructed to exhale. Then the cross turned blue, and the participants were instructed to hold their breath, and the stimulus was delivered. After stimulus presentation, participants identified the stimulated nostril by pressing the left or right arrow on a keyboard. Then the cross turned white again to indicate the ISI during which participants could breathe normally. This automated procedure was the same for all three methods.

Analyses

Statistical analysis was performed using SPSS software (23.0; IBM Inc., Chicago IL). First, we performed Spearman's rank correlations to verify whether total score and sub-scores of two alternative methods correlate with scores at the standard method. Second, we formed two groups (high sensitivity, low sensitivity) based on the median score at the standard method. To test the validity of DD, we computed a repeated-measures (rm) ANOVA (all ANOVAs with Greenhousse-Geisser correction) with group (2 levels: high sensitivity, low sensitivity) as between subject factor and stimulation duration (5 levels: 200ms, 300ms, 400ms, 500ms, and 600ms) as within subject variable. Then, we performed t-tests between groups for each stimulation duration scores. To test the validity of the AD, we computed a rm ANOVA with group (2 levels: high sensitivity, low sensitivity) as between subject factor and side (2 levels: left

nostril, right nostril) as within subject variable. Next, we performed receiver operating characteristics (ROC) curves to compare air under the curves (AUC) which represent the efficiency to discriminate between high and low sensitivity groups of DD and AD methods. Third, we compared test durations. Given that the standard method (23.3 minutes test duration) and the DD (11.7 minutes test duration) have constant durations and the duration of the AD method differed based on the number of trials performed to reach four reversal points, we only performed a one-sample t tests to compare the AD's time duration with the standard method's duration. We set α at 0.05 and used a Bonferroni-Holm correction for multiple comparisons.

Results

Mean scores at each method are described in Table 1.

Correlations

Scores obtained in both new tests were significantly correlated to those of the standard method: DD (total score: $r = 0.76$, $p < 0.001$; 200ms: $r = 0.51$, $p < 0.001$; 300ms: $r = 0.60$, $p < 0.001$, 400ms: $r = 0.54$, $p < 0.001$, 500ms: $r = 0.43$, $p < 0.001$, 600ms: $r = 0.51$, $p < 0.001$) and AD (left nostril: $r = -0.48$, $p < 0.001$; right nostril $r = -0.61$, $p < 0.001$) (See Figure 2).

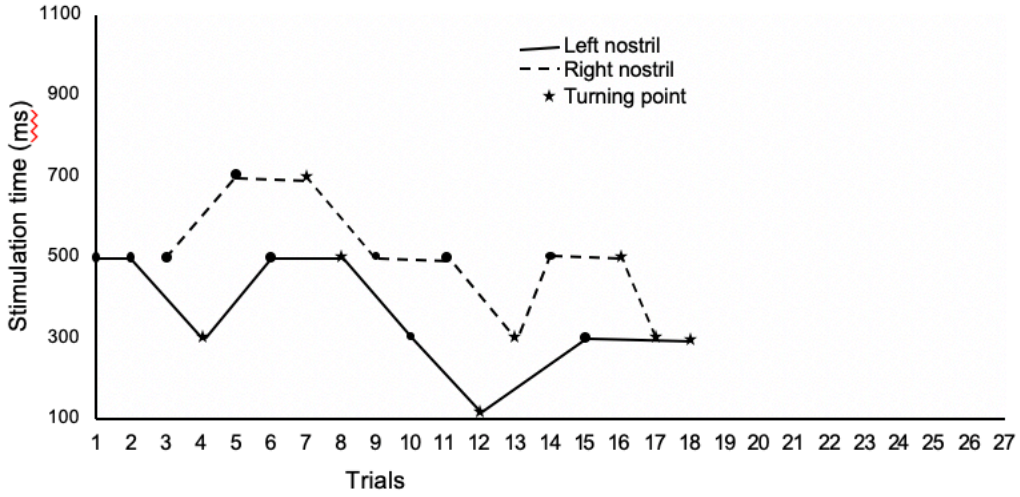

Fig 1. An example of scoring for the AD method.

Discrimination between high and low sensitivity

For the DD, the ANOVA revealed a significant main effect of group [$F(1, 46) = 40.14$, $p < 0.001$, $R2 = 0.47$] and duration [$F(3.28, 150.63) = 6.32$; $p < 0.001$, $R2 = 0.12$]. Post-hoc t-tests revealed a significant difference between the high sensitivity group and the low sensitivity group for each stimulation duration (200ms: $t(46) = -4.39$, $p < 0.001$; 300ms: $t(37.11) = -4.40$, $p < .001$; 400ms: $t(30.05) = -3.82$, $p < 0.001$; 500ms: $t(31.36) = -2.53$, $p = .01$; 600ms: $t(31.78) = -3.55$, $p = 0.001$). Further, independently of the group, post-hoc test showed that the average score at 200ms stimulation duration was significantly lower than the average score at durations of 500ms and 600ms. No other differences were found for other stimulus durations (see Figure 3a). For the mean AD thresholds, ANOVA revealed a significant main effect of group [$F(1, 46) = 13.83$, $p < 0.001$, $R2 = 0.23$]. There was no effect of side [$F(1, 46) = 0.45$, $p = 0.83$].

Table 1. Mean scores of participants at individual methods

Standard method	Mean	SD
Total score (out of 40)	31.83	7.03
Different duration method	Mean	SD
score at 200ms (out of 4)	2.83	1.09
score at 300ms (out of 4)	3.25	0.99
score at 400ms (out of 4)	3.20	1.04
score at 500ms (out of 4)	3.47	0.75
score at 600ms (out of 4)	3.50	0.70
Total score (out of 20)	16.30	3.30
Alternative duration method	Mean	SD
Left nostril threshold (ms)	579	635
Right nostril threshold (ms)	530	640

Post-hoc t-tests revealed a significant difference between the high sensitivity group and low sensitivity group for each nostril (left nostril: $t(27.80) = 2.30$, $p = 0.03$; right nostril: $t(26.50) = 2.79$, $p = .01$ (see Figure 3b).

For the discrimination between high and low sensitivity groups, AUC for DD's total score was 0.91. At each duration, AUC was 0.80 at 200ms, 0.82 at 300ms, 0.75 at 400ms, 0.66 at 500ms and 0.73 at 600s. At the AD method, AUC was 0.69 for the left nostril threshold and 0.77 for the right nostril threshold. (See Figure 4)

Test duration

The total testing time for the DD was fixed at 11.7 min and the total testing time for standard method was fixed at 23.3 min. Mean duration for AD (31.0 min) was significantly longer than the duration time for the standard method ($t(52) = -8.76$, $p < 0.001$). In the AD, the average number of trials was 42.3 (36.0).

Discussion

In this pilot study, we assessed two alternative methods to measure trigeminal sensitivity based on a lateralization task and compared them to a standard method to evaluate trigeminal sensitivity. We show that scores obtained with both novel methods correlate with scores obtained with the standard method. Additionally, they allow to distinguish between individuals with high or low sensitivity underlining the validity of the two novel methods. Furthermore, each method has a specific superiority over the standard method, as one procedure cuts testing time in half, whereas the other provides threshold estimates for individual nostrils.

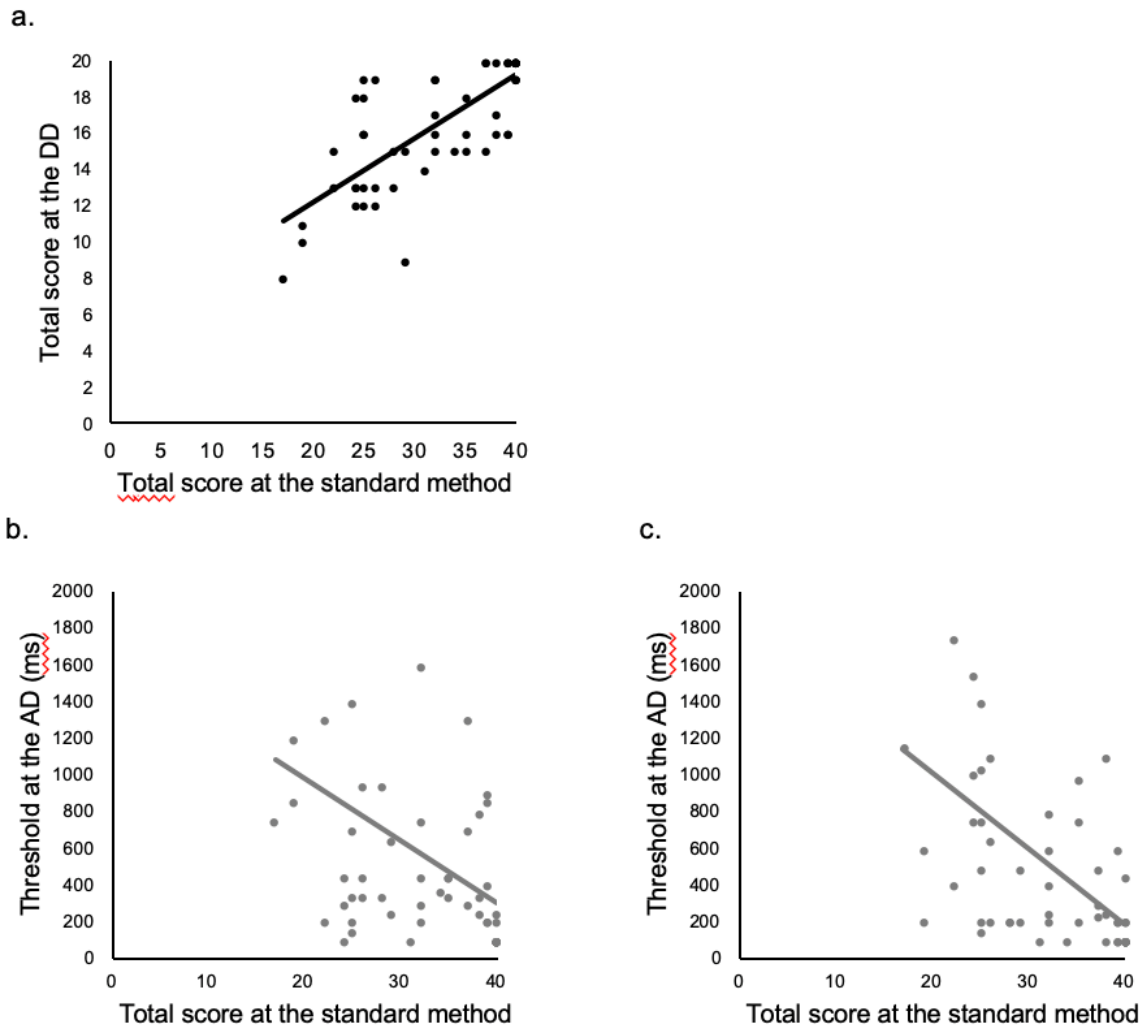

Figure 2: a: Correlation between average total score at the standard method and average total score at the Different Duration method. **b:** Correlation between average total score at the standard method and the left nostril threshold obtained at the Adaptive Duration method. **c:** Correlation between average total score at the standard method and the right nostril threshold obtained at the Adaptive Duration method.

We developed the DD using a reduced number of stimulations to reduce the total testing time and we included different stimulation durations to also get information on trigeminal threshold. Our results show that the total score and each sub-score correlate with scores obtained at the standard method to assess trigeminal sensitivity and that DD's total score is excellent (AUC = 0.91) to discriminate between sensitive and less sensitive participants. This test is also shorter than the standard method, indicating that it is possible to measure trigeminal sensitivity with a test that lasts half the time of the standard research method.

This study is not the first to use 20 stimulations instead of 40 for a lateralization task (e.g. Croy et al., 2014; Naka et al., 2014; Oleszkiewicz et al., 2018) but it is one of the first, to our knowledge, to compare it to the standard method of 40 constant stimuli. Naka et al. (2014) compared a novel device to assess trigeminal sensitivity, using three different concentration of CO2, with a lateralization task of 20 constant stimulations. The results obtained with this new device partially correlated with the lateralization task, only with the two highest CO2 concentrations. Another interesting shorter lateralization task of 26 stimulations is included in the battery developed by Huart (2019). Although this device has good test-retest reliability, it has the same weakness as earlier tests as stimuli of the same strength are presented repeatedly. In the present study, the DD total score and score at each duration correlate with the standard method suggesting that they measure the same underlying variable.

Compared to the different methods discussed, the DD could provide even or more information on trigeminal sensitivity in a shorter assessment time. Specifically, in addition to a global score, it provides a score for each stimulation duration. In theory, the total score at each duration could be used to fit a dose response curve (Lotsch et al., 2004), from which a threshold duration could be obtained. However, this was not possible with the current data set since participants had scores significantly above chance even for the shortest duration. Moreover, there is probably a lack of difference in durations intervals and ceiling effects, at least for the 300ms to 600ms durations in the high trigeminal sensitivity group. Future studies aiming at using this approach should include both shorter stimulus durations and use log-spacing intervals since the nose is an imperfect mass integrator (Wise et al. 2004, 2005, 2006, 2007, 2009). That being said, this DD method is promising, and future studies should further develop this method.

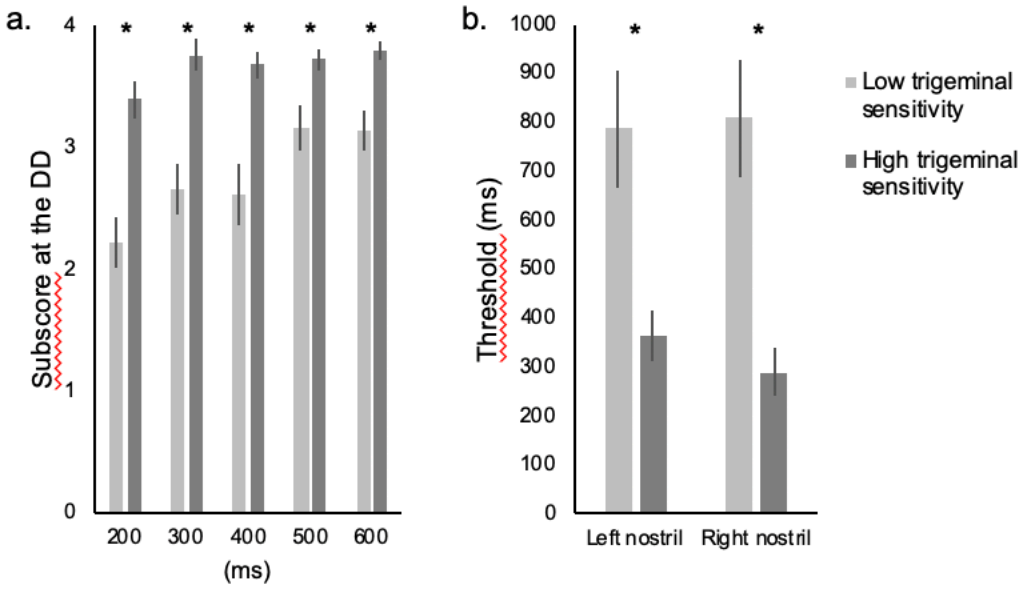

Figure 3: a: Average scores obtained at each duration stimulation for the Different Duration method from the lower trigeminal sensitivity group and the higher trigeminal sensitivity group. Error bars signify the standard error. Asterisks indicate significative differences between scores of the lower trigeminal sensitivity group and the higher trigeminal sensitivity group. **b**: Average thresholds obtained at the Adaptive Duration method from the lower trigeminal sensitivity group and the higher trigeminal sensitivity group. Error bars signify the standard error. Asterisks

indicate significative differences between average thresholds of the lower trigeminal sensitivity group and the higher trigeminal sensitivity group. * = $p < 0.05$

The second method we developed, AD, allowed us to assess a duration threshold for both nostrils individually. Again, this technique yields scores that correlated with the standard method and allowed for an acceptable (AUC ~ 0.7) distinction of high vs low sensitivity. Although this technique takes more time to carry out, it has the advantage of providing an independent measurement for each nostril, which can be very useful in experimental contexts. Both a maximum-likelihood curve-fitting technique (Watson, 2017) or Bayesian methods (Höchenberger and Ohla, 2019) could also reduce the duration of the staircase procedure.

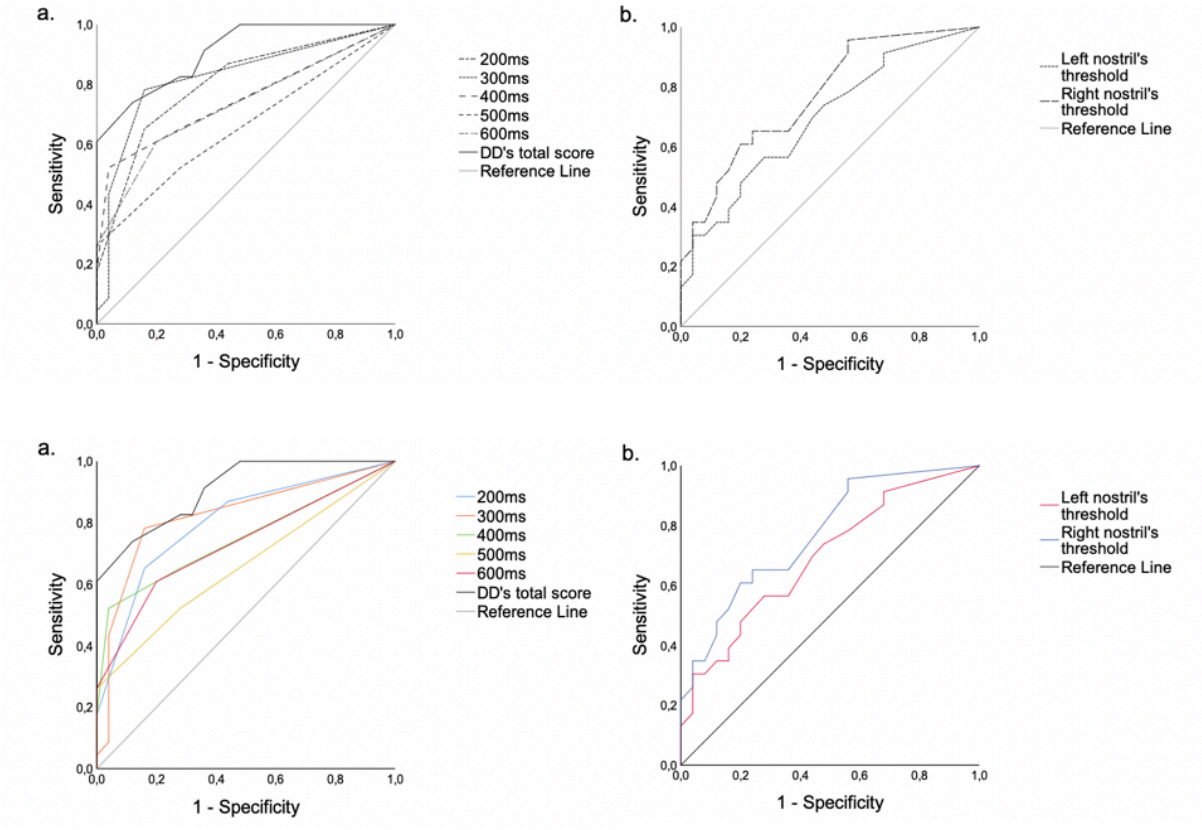

Figure 4: Receiver Operating Characteristics (ROC) curves for the Different Duration method scores **(a)** and thresholds of each nostril at the Adaptive Duration method **(b)** to discriminate between lower trigeminal sensitivity group and the higher trigeminal sensitivity group.

A limitation of our study is that we did not assess test-retest reliability. In the literature, lateralization tasks have a good test-retest reliability in the range of r = 0.41 to 0.69 (e.g. Frasnelli and Hummel, 2005; Naka et al., 2014; Huart et al., 2019). Here, we validated DD and AD methods based on convergent validity with a standard lateralization task which was on the same device and with the same stimulus (eucalyptol). As we mentioned previously, each score obtained at the DD/AD methods correlates with the standard method. Nevertheless, future studies should include assessments of test-retest reliability.

This study provides a promising avenue to develop new methods of assessing intranasal trigeminal sensitivity. Including our results and results of future studies, portable devices similar to the one presented by Hummel et al. (2016) could be developed and be used in a clinical context.

In conclusion, here we present two novel methods to evaluate trigeminal sensitivity which each have a specific superiority over the established technique. The DD method cuts testing time in half and potentially allows for the determination of duration thresholds. The AD method takes more time to be carried out but has the advantage to provide duration threshold for individual nostrils.

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Conflict of interest

The authors declare no conflict of interest.

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ARTICLE 3: VISUAL EPISODIC MEMORY ALTERATIONS AND HIPPOCAMPAL ATROPHY IN ACUTE MILD TRAUMATIC BRAIN INJURY

Fortier-Lebel, Olivier.[1,2], Jobin, Benoît.[1,2,3], Lécuyer-Giguère, Fanny.[2,4], Gaubert, Malo[2,5], Jean-François Giguère[2], Jean-François Gagnon[2,3,6], Boller, Benjamin.[1,3], Frasnelli, Johannes.[2,3,7]

[1] Department of Psychology, Université du Québec à Trois-Rivières, Qc, Canada.

[2] Research Centre of the Hôpital du Sacré-Cœur de Montréal, Qc, Canada.

[3] Research Centre of the Institut universitaire de gériatrie de Montréal, Qc, Canada.

[4] Department of Psychology, Université de Montréal, 90 avenue Vincent d'Indy, Montréal, Québec, H3C 3J7, Canada

[5] Department of Child and Adolescent Psychiatry, Psychosomatic, and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany.

[6] Department of Psychology, Université du Québec à Montréal, Qc, Canada.

[7] Department of Anatomy, Université du Québec à Trois-Rivières, Qc, Canada.

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Abstract

Episodic memory deficit is a symptom frequently observed after a mild traumatic brain injury (mTBI). However, few studies have investigated the impact of a single and acute mTBI on episodic memory and structural cerebral changes. To do so, we conducted two experiments. In the first, we evaluated verbal episodic memory by using a word recall test, in 52 patients (mean age 33.1 (12.2) years) 2-4 weeks after a first mTBI, compared to 54 healthy controls (31.3 (9.2) years) and followed both groups up for six months. In the second, we measured hippocampal volume in a subset of 40 participants (20 mTBI patients, 20 controls) from Experiment 1 using magnetic resonance imaging (T1-weighted images) and correlated memory performance scores to hippocampal volume.

Experiment 1 showed significantly reduced verbal episodic memory within the first month after a mTBI and a tendency for a reduction 6 months later, more pronounced for men. In Experiment 2, patients with mTBI exhibited a generally reduced hippocampal volume; however, we did not observe any linear correlation between hippocampal volume and memory scores.

These results suggest that one single mTBI is associated with both episodic memory alteration and reduced volume of the hippocampus in the acute phase. Future studies are needed to elucidate the link between both measures.

Keywords: Mild Traumatic Brain Injury, MRI, Hippocampus, Volumetry, Memory, HVLT

Introduction

Traumatic Brain Injuries (TBI) impact cognition as well as other aspect of daily life and are associated with high costs for both the patient and the society as a whole (Oberholzer & Muri, 2019). In Western societies such as the US, they have an annual incidence of approximately 500/ 100,000 individuals (Maas et al., 2012). Approximately 80 % of TBI are classified as mild TBI (mTBI) (Capizzi, Woo, & Verduzco-Gutierrez, 2020). Although the term "mild" implies a less severe head trauma, even mTBI can have an important impact on the patients' health. In fact, 10-15% of the victims of mTBI continue to suffer persistent symptoms for months or years, leading to employment, economic and social issues (Iverson, 2005; Nguyen et al., 2016). One of the most frequent symptoms is the impairment of episodic memory, i.e., the ability to recall and mentally reexperience specific episodes from one's personal past (Rabinowitz & Levin, 2014; Tulving, 2002,). In fact, deficits in patients with mTBI were found in many tasks that assess episodic memory such as immediate recall, delayed recall and recognition (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Konrad et al., 2011). However, most of the studies on the topic are conducted on special populations such as veterans or athletes with particular characteristics. Indeed, participants may have suffered multiple mTBI and studies are typically carried out years after the trauma. These factors make it hard to discern the impact of a single mTBI on episodic memory. Nevertheless, a recent study on the general population observed poorer verbal episodic memory scores 1 month and 12 months after a single mTBI. However, participants from the mTBI group were significantly older than controls (Tayim, Flashman, Wright, Roth, & McAllister, 2016) limiting the interpretation, given the known effect of age on episodic memory performance (Park et al., 2002). Therefore, age and similar epidemiological variables have to be well matched to help drawing conclusions.

When looking at sex differences on verbal episodic memory tasks after an mTBI, studies on athletes have shown better performance for women than men in both acute and chronic phase. (Cottle, Hall, Patel, Barnes, & Ketcham, 2017; Covassin, Elbin, Kontos, & Larson, 2010; Covassin et al., 2006; Davis-Hayes et al., 2017). Indeed, women tend to outperform men on those particular tasks even if they generally exhibit more post-concussion symptoms and worse general prognostics after a TBI (Farace & Alves, 2000). However, no studies have yet investigated if these sex differences are present after a single mTBI in the general population.

The hippocampus in the mesial temporal lobe is a brain structure that is central to episodic memory. Indeed, this region is mostly known for its implication in the memory of past events (Bartsch, 2012; Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). Moreover, impairment of the hippocampus, typically associated with atrophy, is linked to episodic memory deficits, such as those reported in Alzheimer's disease (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Moodley & Chan, 2014). One study using automated segmentation and T1-weighted images on a general population, focussed on neuroanatomical changes in the hippocampus after mTBI several years or even decades after the trauma and found bilateral atrophy of the hippocampus (Monti et al., 2013). The impact of a single mTBI on the hippocampus in the acute phase and a possible association between episodic memory and hippocampus volume are however still unknown.

To elucidate the points raised in the previous paragraphs, we designed Experiment 1 in which we evaluated verbal episodic memory 2 to 4 weeks after a mTBI and at a follow up period of six months after the trauma. We hypothesized (1a) verbal episodic memory to be impaired in a group of patients with mTBI compared to controls within first weeks after the trauma; (1b) the

impairment to remain present six months after the trauma. Further, we designed Experiment 2 in which we measured MRI-derived hippocampal volume in a subgroup of participants from Experiment 1. We hypothesized (2a) patients with mTBI to exhibit a volumetric reduction of hippocampus compared to controls; and (2b) hippocampal volume to be correlated to memory performance in mTBI. We also included sex as a between factor in our analysis to verify the hypothesis of a larger episodic memory impairment for men.

EXPERIMENT 1

Material and methods

Both experiments were conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects and approved by the local Ethics Committee of the Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal – Hôpital du Sacré-Coeur de Montréal (CIUSS-NÎM – HSCM) (#2014-1016) and by the Comité mixte d'éthique de la recherche of the Regroupement Neuroimagerie Québec. After a detailed explanation of the study, all participants gave their written consent prior to inclusion.

Participants

We recruited a total of 53 patients (29 men) with mTBI between 2 and 4 weeks after the trauma. Patients were referred and diagnosed by a medical team at the emergency room of CIUSS-NÎM – HSCM using the following criteria: head trauma with (1) confusion, disorientation, and/or loss of consciousness for 30 min or less, (2) posttraumatic amnesia for less than 24h, and (3) Glasgow Coma Scale (GCS) between 13 and 15, observed within the first 30 min after the trauma or upon presentation at the emergency room. One of the 53 patients with mTBI did not complete all tests and had to be excluded, resulting in the inclusion a total of 52 patients with mTBI. We compared

their results to those of 54 (27 men) healthy controls recruited through ads posted at the hospital and online. We collected information such as age, gender, manual dominance and years of education for all participants. Patients and controls were matched with regards to sex, age, and education (See Table 1). Certain data from these participants have been presented in another publication (Lecuyer Giguere et al., 2020).

For both groups, we applied the following exclusion criteria: (1) past history of TBI independent of severity, (2) history of psychiatric or neurological disorders, (3) excessive use of recreational drugs (cannabis: >1 consumption/day; alcohol: >3 consumptions/day; Canadian Center on Substance Use and Addiction 2012), (4) intoxication during the testing, and (5) use of any medication known to interfere with cognitive abilities (antidepressants, benzodiazepines, and hypnotics).

Procedure

First, we carried out semi-structured phone interviews to verify the presence of inclusion and exclusion criteria in participants from both groups. Then, participants were invited to the laboratory within 2 to 4 weeks after the trauma where they provided free and informed consent. Next, we carried out the baseline memory assessment.

Six months after this first evaluation, all participants were invited to the follow-up examination, where we carried out a second memory evaluation using the same procedure as baseline. From the total of 106 participants at baseline, 70 (66%) accepted to return to the laboratory for the follow-up (31 patients and 39 controls).

Memory Assessment

Memory assessment: We used the Hopkins Verbal Learning Test - Revised (HVLT-R) to measure different component of verbal episodic learning and memory; this tool is especially useful in repeated measurements of memory (Benedict, Schretlen, Groninger, & Brandt, 1998). The test begins with a learning phase of three trials to recall a list of 12 words. At each trial, we asked the participant to recall as many words as possible (immediate recall 1, 2, 3). The 3 sub-scores were then summed up to an overall score (total immediate recall). After a 25 minutes interval filled with unrelated tasks (which did not contain any memory, reading, or verbal fluency aspect), we asked the participant again to recall the words on the list (delayed recall). Following that fourth trial, we read another list of 24 words (12 target words and 12 nontarget words, 6 semantically related to the targets, 6 unrelated to the targets) to the participant. Next, we asked them to identify which words were on the original list (recognition). With this task, we were able to evaluate (1) learning (total immediate recall), (2) long-term memory (delayed recall) and (3) recognition.

Analysis

We used SPSS (23.0; IBM Inc., Chicago IL) for the statistical analysis. First, we compared HVLT recall scores between groups at baseline by computing a Multivariate Analysis of Variance (MANOVA) with group (2 levels: mTBI, controls) and sex (2 levels: women, men) as between subject factor, task (2 levels: total immediate recall, delayed recall) as within subject factor, and age as covariate (all MANOVAs and ANOVAs are Greenhouse-Geisser corrected). For post hoc analyses of the effects on the two memory tasks, we carried out separate univariate ANOVAs with group (2 levels: mTBI, controls) and sex (2 levels: women, men) as between subject factor and age as covariate. We next calculated a MANOVA with group (2 levels: mTBI,

controls) and sex (2 levels: women, men) as between subject factor and subtask (3 levels: trial 1, trial 2, trial 3 of immediate recall) as within subject factor and age as covariate.

We further computed a univariate ANOVA for the recognition score, with group (2 levels: mTBI, controls) and sex (2 levels: women, men) as between subject factor and age as covariate. We repeated these analyses for the scores obtained at follow-up. We set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons.

Results

Baseline

For baseline data, the MANOVA revealed a significant interaction between group and task ($F(1, 101) = 4.196$; $p = 0.043$; $R2 = 0.040$) and significant main effects of group ($F(1,101) = 4.462$; $p = 0.037$; $R2 = 0.042$) and task ($F(1, 101) = 286.832$; $p < 0.001$; $R2 = 0.740$), indicating lower memory ability in patients. We did not observe any other significant main effect of sex or age or any other interaction. Post hoc ANOVAs revealed a significant group effect for total immediate recall ($F(1, 101) = 4.890$; $p = 0.029$; $R2 = 0.046$; n.s. after correction) but failed to reach significance for delayed recall ($F(1, 101) = 2.371$; $p = 0.127$; $R2 = 0.23$) (See Table 1 and Figure 1). When looking at Trial 1, 2 and 3 scores separately from total immediate recall between each group, only difference at Trial 3 remains significant after correction ($F(1, 101) = 7.175$; $p = 0.009$; $R2 = 0.066$; see Table 1). For the recognition score, no significant difference was found ($F(1, 101) = 2.463$; $p = 0.120$; $R2 = 0.24$).

Follow up

We observed no significant difference regarding sex and age between the participants who returned for follow-up and participants who did not, with the exception of years of educations that were significantly different between participants who returned (15.0 (2.7) years) and participants who did not (16.3 (2.9) years; t=2.19, p=0.03).

The MANOVA revealed a significant interaction between sex, task and group ($F(1, 65) = 5.36$; $p = 0.024$; $R2 = 0.076$), a significant main effect of sex ($F(1,65) = 7.134$; $p = 0.010$ $R2 = 0.099$) and task ($F(1, 65) = 188.187$; $p < 0.001$; $R2 = 0.743$). Importantly, the main effect of group failed to reach significance ($F(1,65) = 3.232$; $p = 0.077$; $R2 = 0.047$), as did the interaction between group and task ($F(1, 65) = 2.067$; $p = 0.155$; $R2 = 0.031$). We did not observe any other significant main effect or interaction.

We then computed post hoc MANOVA for both groups individually with sex as between subject variable and task as within subject variable. In the mTBI group, we observed a significant interaction between task and sex ($F(1, 28) = 8.347$; $p = 0.007$ $R2 = 0.230$), but not in the control group ($F(1, 36) = 0.15$; $p = 0.902$ $R2 = 0.000$). When looking at comparisons of different memory recall tasks between sex in mTBI, total immediate recall was significantly lower in men (21.60 (5.26) points) than women (26.81 (4.1) points; $F(1,28) = 8.917$; $p = 0.006$; $R2 = 0.242$). When looking at the individuals trials for immediate recall scores in men only, scores were significantly lower in mTBI patients than controls (recall 1: $F(1, 14) = 11.04$; $p = 0.005$ $R2 = 0.441$; recall 2: $F(1, 14) = 14.47$; $p = 0.002$; $R2 = 0.508$; recall 3: $F(1, 14) = 12.36$; $p = 0.003$; $R2 = 0.469$) (See Figure 2).

We did not observe any difference between groups for delayed recall scores ($F(1,28) = 1.373$; $p = 0.251$; $R2 = 0.047$). Similarly, for recognition, we did not observe any main effect of groups ($F(1, 65) = 0.495$; $p = 0.484$; $R2 = 0.008$) or any other interactions.

EXPERIMENT 2

Material and methods

Participants

A subgroup of 20 mTBI patients and 20 controls from Experiment 1 underwent MRI. They were the first 20 participants of each group who accepted to take part to the MRI segment of the study.

Methods

Magnetic resonance imaging: MRI data acquisition: We acquired MRI scans from 40 participants at the Unité de Neuroimagerie Fonctionnelle of the Institut universitaire de gériatrie de Montréal (unf-montreal.ca). Specifically, we obtained high-resolution T1-weighted images using magnetization-prepared rapid acquisition with gradient-echo (MP-RAGE) on a 3-tesla Siemens TrioTIM scanner (Siemens, Erlangen, Germany), with a 12-channel head matrix coil. The parameters of acquisition were the following: repetition time 2.3s, echo time 2.91ms, inversion 900ms, 9-degree flip angle, 176 slices, 256 x 256 mm field of view, 256 x 256 matrix resolution (voxel size: 1 x 1 x 1 mm^3), and 240 Hz/Px bandwidth. We used the Tissue Volumes Utility tool in SPM12 to calculate total intracranial volume (TIV) for each participant.

Hippocampal data: Global volumes (in mm3) for hippocampi were calculated using the FIRST tool available in FSL 5.0.9 (Oxford Centre for Functional MRI of the Brain, Oxford, UK) by

counting the number of voxels inside the boundaries for each structure obtained using optimal parameters (Patenaude & al., 2011). All volumes were finally adjusted for head size by multiplying all values by a scaling factor generated from SIENAX (Smith et al., 2002), another tool included in FSL.

Procedure

Within one week after inclusion into the study, participants were invited to the imaging center. Here, we carried out scanning, which lasted approximately 30 minutes.

Analysis

Memory assessment: to confirm the similarity of this sample to the overall group, we repeated the same statistical analyses as in Experiment 1.

Hippocampal volume at baseline: In order to compare hippocampal volume between groups at baseline, we performed a MANOVA with group (2 levels: mTBI patients, controls) and sex (2 levels: women, men) as between subject factor and side (2 levels: left, right) as within subject factor as well as age and TIV as covariates (all MANOVAs and ANOVAs were Greenhouse-Geisser corrected). For post hoc analyses of the effects of both hippocampi, we carried out separate univariate ANOVAs with group (2 levels: mTBI, controls) and sex (2 levels: women, men) as between subject factor as well as age and TIV as covariate.

Next, to verify relation between memory scores and hippocampal volume, we performed Spearman's ranks correlations (recognition scores were not normally distributed), between baseline and follow-up HVLT subtests (immediate recall, delayed recall and recognition) and left

and right hippocampi for each group separately. Again, we set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons.

Results

Memory assessment

The MANOVA revealed a significant interaction between group and task ($F(1, 35) = 5.288$; $p = 0.028$; $R2 = 0.131$) and significant main effects of group ($F(1,35) = 6.406$; $p = 0.016$; $R2 = 0.155$) and task ($F(1, 35) = 145.822$; $p < 0.001$; $R2 = 0.806$) in the baseline scores. We did not observe any other significant main effect of sex or age or any other interaction.

Post hoc ANOVA revealed a significant difference in the total immediate recall scores ($F(1, 35) = 6.859$; $p = 0.013$; $R2 = 0.164$) and in the delayed recall ($F(1, 35) = 4.421$; $p=0.043$; $R2 = 0.112$ (n.s. after correction). When looking at the individual Trial 1, 2 and 3 of the immediate recall task, only difference at trial 3 remained significant after correction ($F(1, 35) = 8.782$; $p = 0.005$; $R2 = 0.201$). For the recognition score, the MANOVA revealed no significant interaction or main effect of group or sex (see Table 2).

Hippocampal volume

The MANOVA revealed a main effect of group ($F(1, 34) = 4.705$; $p = 0.037$; $R2 = 0.122$) and sex ($F(1, 34) = 5.260$; $p = 0.28$; $R2 = 0.134$), where women had a bigger hippocampus volume, but no interaction between side and group ($F(1, 34) = 2.254$; $p = 0.143$; $R2 = 0.62$) and no main effect of side ($F(1, 34) = 0.276$; $p = 0.603$; $R2 = 0.008$). We decided to carry out post hoc ANOVAs in an exploratory approach to compare each hippocampus between groups. They revealed a significant group difference for the right hippocampus volumes ($F(1, 34) = 6.977$; p

=0.012; R2 = 0.170) but not for the left hippocampus volumes (F(1, 34) = 1.127; p =0.296; R2 = 0.000; see Figure 3).

Correlation between memory scores and hippocampal volume

We did not observe any significant linear correlations between hippocampal volumes and HVLT scores in any groups (Immediate recall and left (r = 0.242; p = 0,133), right hippocampus volume (r = 0.175; p = 0,279; See figure 4); Delayed recall and left (r = 0.185; p = 0,252), right hippocampus volume (r = 0.184; p = 0,256); Recognition and left (r = 0.136; p = 0,402), right hippocampus volume (r = 0.062; p = 0,704).

Discussion

This study aimed at evaluating verbal episodic memory within acute and long-term phase after a single mTBI. To our knowledge, this study was also the first to investigate the hippocampus volume in the acute phase of a single mTBI and to explore its link with episodic memory. This supports the notion that verbal episodic memory is altered within the first month after the trauma but may return to subnormal-to-normal levels at follow up, with men possibly more affected than women at follow up. On a neuroanatomical level, hippocampal volume was smaller in mTBI patients compared to controls in the acute mTBI phase although it was not correlated with memory scores.

We evaluated verbal episodic memory in both experiments and observed that immediate recall and delayed recall – in Experiment 2 only – were impaired in the acute phase in patients suffering from mTBI. This is in line with the notion that delayed recall impairment is common after a mTBI and that this specific deficit is not only observable in concussed athletes (Broadway et al.,

2019; Karr, Areshenkoff, & Garcia-Barrera, 2014). Thus, our results suggests that episodic memory is altered in the acute phase of a mTBI. Indeed, in both of our experiment episodic memory was altered and this is in line with other reports not limited to mTBI (Brooks, 1975). In contrast, recognition seems to be relatively conserved after a single mTBI, which suggests a significant role of TBI severity on this particular memory feature (Arenth, Russell, Scanlon, Kessler, & Ricker, 2012; Roncadin, Guger, Archibald, Barnes, & Dennis, 2004).

We further observed a smaller hippocampal volume in mTBI patients. This is somehow in line with earlier reports, which reported mTBI patients to show smaller hippocampal volumes in the chronic phase years after a mTBI (Monti et al., 2013; Zagorchev et al., 2016). We show that reduced hippocampal volume can already be observed in the acute phase. It is important to note that Zagorchev and al. (2016) did not find any differences in hippocampal volumes in the subacute phase (i.e. 2 months after the mTBI). It is unclear what drives these volume differences; potential candidates being gray matter volume, white matter volume or both (Zhou et al., 2013).

Different hypotheses can be put forward why hippocampal reduction was observable within the acute phase of the present study, but only in the chronic phase of the earlier reports. First, patients' characteristics may be different between studies. In other words, although they were all diagnosed with a first mTBI, patients in the present study may be more heavily affected than those from the earlier report. Unfortunately, Zagorchev et al. did not assess memory performance which would have allowed to test this hypothesis. Second, different hitherto unknown overlapping pathomechanisms may lead to volume reduction in the acute phase, volume normalization in the subacute phase and subsequent volume reduction in the chronic phase following a mTBI. Recent studies suggest non-hemoglobin-bound (non-heme) iron as a potential

candidate causing chronic volume reduction (Daugherty, Haacke, & Raz, 2015; Daugherty & Raz, 2016; Nisenbaum, Novikov, & Lui, 2014). Excessive iron levels in the brain lead to oxidative stress causing cellular dysfunction and death resulting in structural atrophy, as well as encouragement of tau phosphorylation and the formation of neurofibrillary tangles (Jomova & Valko, 2011; Nisenbaum et al., 2014). Hence, non-heme iron is augmented in neurodegenerative diseases and also observed in the hippocampus (Batista-Nascimento, Pimentel, Menezes, & Rodrigues-Pousada, 2012; Bouras et al., 1997; Lu, Cao, Wei, Li, & Li, 2015). Interestingly, chronic mTBI is associated with increased levels of non-heme iron in subcortical brain tissue, although the hippocampus was not investigated (Raz et al., 2011). It is however unclear if these mechanisms can explain hippocampal volume reduction within weeks after a mTBI. Future studies are needed to understand the underlying mechanisms leading to volume changes.

Our study supports the notion that verbal episodic memory scores and hippocampal volume are not linearly associated. Previous studies conducted on athletes in the chronic phase of a mTBI and using similar MRI techniques (T1 MPRAGE) showed inconsistent results: some studies reported a significant correlation between episodic memory scores and hippocampal volume in mTBI (Misquitta et al., 2018; Tremblay et al., 2013) while others did not (Terry & Miller, 2018; Wojtowicz et al., 2018). Nevertheless, one must be careful when comparing athletes with non-athletes, as the former consist of a particular population because of (1) the risk of multiple mTBI, (2) whole body impact and (3) the urge to reinstate the competition and thus potential downplay of symptoms (McCrea et al., 2003; Peskind, Brody, Cernak, McKee, & Ruff, 2013). Future studies are needed to understand the link between hippocampal volume and memory scores.
It is possible that the observed memory decline is related by other underlying cognitive functions and thus brain regions. One potential region is the frontal lobe, which plays a major role in

attention, and which is particularly vulnerable after a head injury (McDonald, Flashman, & Saykin, 2002; Stuss, 2006). Another possible explanation could be the higher depression scores obtained for the mTBI group (Beck Depression Inventory (BDI-II)) as described in the same cohort (Lecuyer Giguere et al., 2020). Depression is known for its negative effects on episodic memory performance after an mTBI (Terry, Brassil, Iverson, Panenka, & Silverberg, 2019). However, no correlations and interaction were found in our sample between these two variables and the hippocampal volume.

We further observed a sex difference for the immediate recall scores at follow-up in patients, where only men, but not women, had poorer scores than controls. However, no sex differences were found at baseline (acute phase) in our sample. Indeed, when specifically investigating memory impairment as a post-concussion symptom, many studies conducted with athletes observed a bigger vulnerably for men on episodic memory and suggest the possibility of a different pattern of impairment for men and women after a head injury (Davis-Hayes et al., 2017; Frommer et al., 2011; Wasserman, Kerr, Zuckerman, & Covassin, 2016). This vulnerability for episodic memory after a mTBI could be partially explained by a general better performance for women in healthy population (Herlitz, Nilsson, & Backman, 1997; Kimura & Clarke, 2002). Nevertheless, we did not find any sex differences at baseline, which differs from the current literature (Cottle et al., 2017; Covassin et al., 2010; Covassin et al., 2006). Here, it is important to stress the fact that we only included participants with a single mTBI differentiating our study from previous one. Without any data on the memory performance before the injury and a small sample, further studies are needed to better understand the difference in memory recovery between men and women after a single mTBI.

Our study has some limitations; the most important ones being that we did not carry out MRI in the whole sample and that MRI was not repeated at follow up. Also, only 66 % of participants at baseline have returned for the follow-up which might contribute to the divergence in memory scores between baseline and follow-up. Finally, the second experiment was carried out on a relatively small sample with 40 participants. Therefore, the results of the current study should be interpreted cautiously.

In conclusion, after a single mTBI, verbal episodic memory is altered in patients compared to healthy controls within the first month post-trauma along with a better recovery for women 6 months later. On a neuroanatomical level, this memory alteration is accompanied by an atrophy of the bilateral hippocampus, a memory-related structure. Futures studies should invest the possible role of MRI measurement in post-trauma acute phase as a marker of chronic symptoms after even a mTBI.

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Conflict of interest

The authors declare no conflict of interest.

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Figures

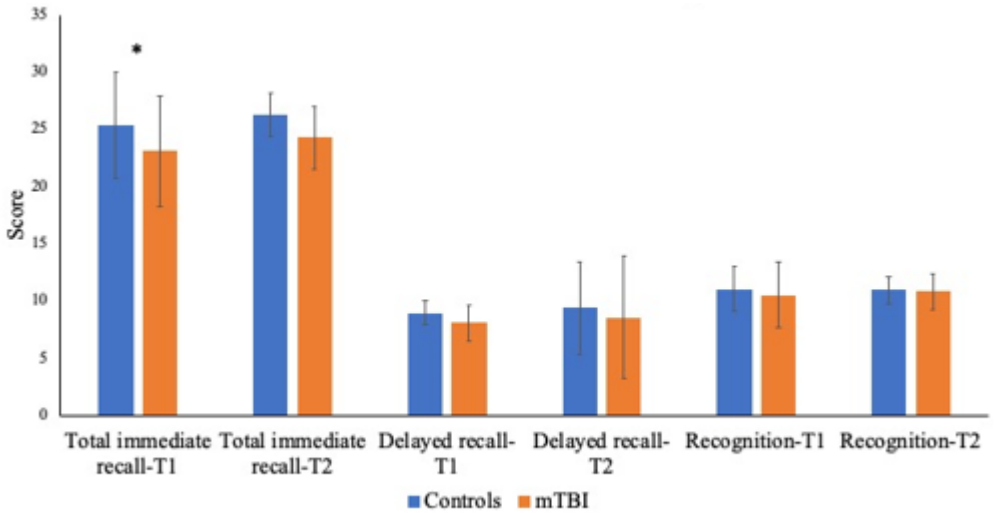

Figure 1. HVLT scores comparison between controls and mTBI patients at both baseline and follow-up. (** $p < .05$; ** $p < .01$, uncorrected.)*

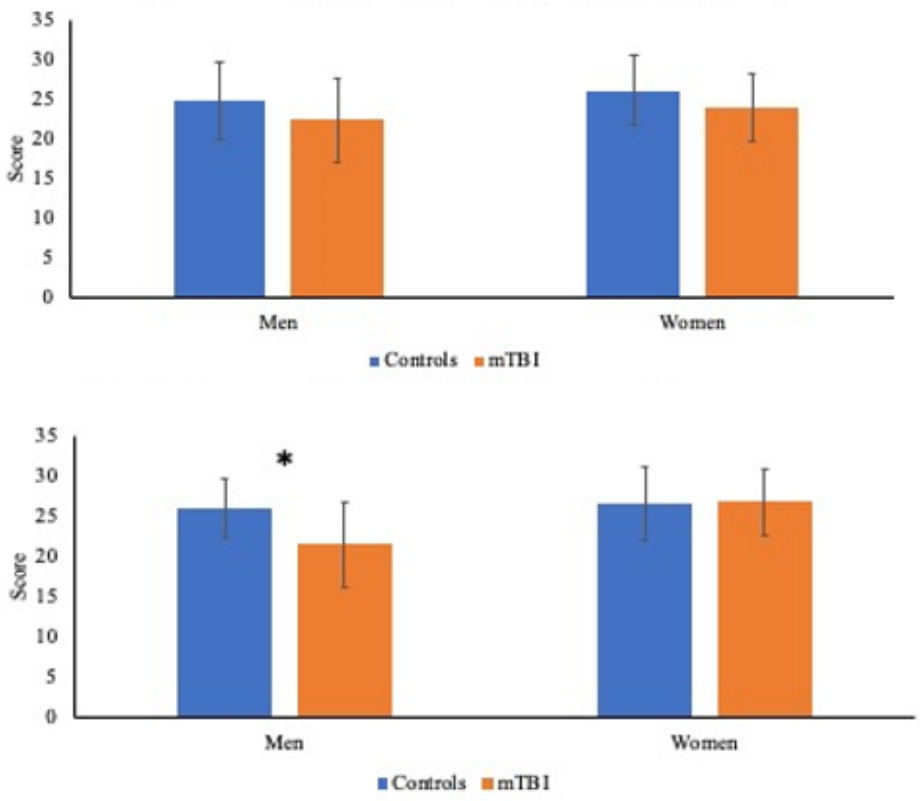

Figure 2. HVLT immediate total score comparison between men and women at both baseline and follow-up. (** p < .05; ** p < .01, uncorrected.)*

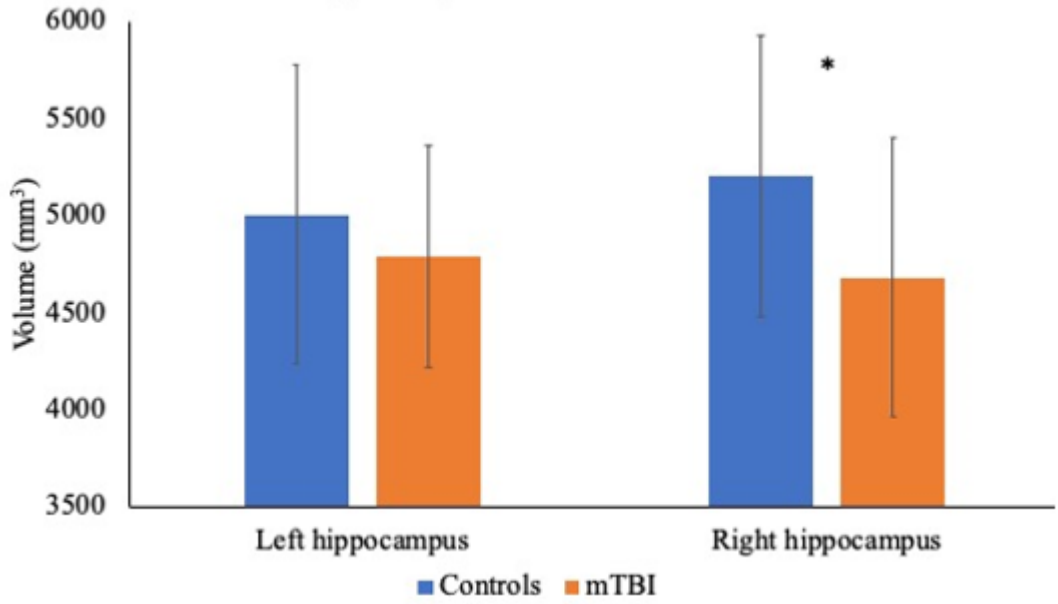

Figure 3. Hippocampal volumes comparison between controls and mTBI patients scanned 2-4 weeks post-trauma. (** p < .05; ** p < .01, uncorrected.)*

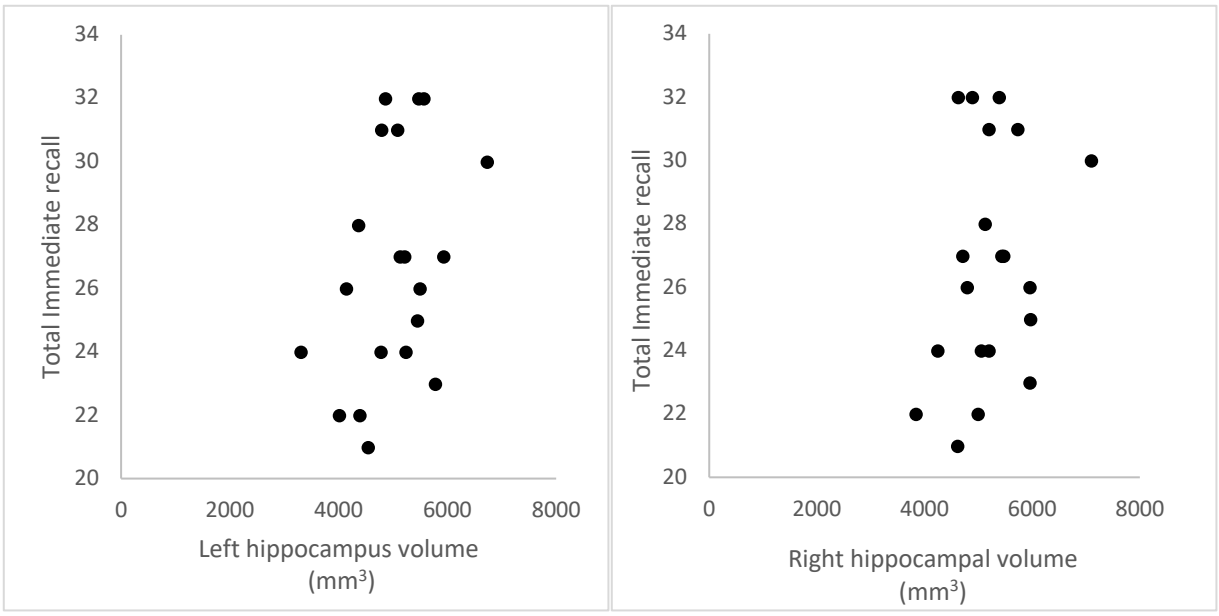

Figure 4. Correlation between HVLT immediate total score and hippocampal volumes.

Tables

Table 1: Experiment 1: *Statistics of patients with mild TBI and controls at baseline and follow-up (SD: standard deviation; HVLT: Hopkins Verbal Learning Test; a Chi-square test; b Controlled for age and sex; * p < .05; ** p < .01, uncorrected)*

Baseline	Controls	Mild TBI	*p*
n	54	52	
Age in years (SD)	31.30 (9.19)	33.12 (12.22)	.387
Women, n (%)	27 (50%)	23 (44.2%)	.552[a]
Years of Education (SD)	15.58 (2.49)	15.25 (3.15)	.547
HVTL trial 1 (SD)	6.18 (1.86)	5.75 (1.84)	.326[b]
HVTL trial 2 (SD)	9.00 (1.90)	8.08 (1.95)	**.029**[b*]
HVTL trial 3 (SD)	10.20 (1.57)	9.27 (1.72)	**.009**[b**]
Total immediate recall (SD)	25.39 (4.68)	23.10 (4.88)	**.029**[b*]
Delayed recall (SD)	8.96 (1.91)	8.13 (2.72)	.127[b]
Recognition (SD)	11.09 (1.05)	10.54 (1.58)	.120[b]
Follow-up	Controls	Mild TBI	*P*
n	39	31	
Age in years (SD)	31.64 (9.72)	34.77 (13.66)	.267
Women, n (%)	17 (44%)	16 (51%)	.504[a]
Years of Education (SD)	15.08 (2.44)	14.90 (3.03)	.791
HVTL trial 1 (SD)	6.72 (1.49)	5.87 (2.00)	**.043**[b*]
HVTL trial 2 (SD)	9.15 (1.79)	8.71 (1.94)	.316[b]
HVTL trial 3 (SD)	10.43 (1.21)	9.71 (2.02)	.081[b]
Total immediate recall (SD)	26.30 (4.03)	24.29 (5.32)	.072[b]
Delayed recall (SD)	9.44 (1.94)	8.61 (2.89)	.203[b]
Recognition (SD)	10.97 (1.16)	10.86 (1.55)	.484

Table 2: Experiment 2: *Statistics of patients with mild TBI and controls at baseline (MRI subgroups) (SD = standard deviation; HVLT: Hopkins Verbal Learning Test; a Chi-square test; b Controlled for age and sex; * p < .05; ** p < .01, uncorrected).*

Baseline	Controls	Mild TBI	*P*
N	20	20	
Age in years (SD)	30.50 (10.36)	31.20 (10.70)	.835
Women, n (%)	8 (40)	10 (50)	.525[a]
Years of Education (SD)	16.15 (2.62)	15.45 (2.09)	.356[b]
HVTL trial 1 (SD)	6.75 (1.55)	5.75 (1.68)	.079[b]
HVTL trial 2 (SD)	9.45 (1.50)	8.10 (2.00)	**.032**[b*]
HVTL trial 3 (SD)	10.50 (1.19)	9.00 (1.86)	**.005**[b**]
Total immediate recall (SD)	26.70 (3.63)	22.85 (5.04)	**.013**[b*]

Delayed recall (SD)	9.30 (1.66)	7.55 (3.20)	**.043**[b*]
Recognition (SD)	11.20 (0.89)	10.30 (1.95)	.794[b]