

Atteintes cognitives et cérébrales dans le trouble de l'usage d'alcool et le syndrome de Korsakoff: valeur pronostique, évolution et prise en charge

Angeline Maillard

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Angeline Maillard. Atteintes cognitives et cérébrales dans le trouble de l'usage d'alcool et le syndrome de Korsakoff: valeur pronostique, évolution et prise en charge. Psychologie. Normandie Université, 2020. Français. NNT: 2020NORMC017 . tel-03438101

HAL Id: tel-03438101

<https://tel.archives-ouvertes.fr/tel-03438101>

Submitted on 21 Nov 2021

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THÈSE

Pour obtenir le diplôme de doctorat

Spécialité PSYCHOLOGIE

Préparée au sein de l'Université de Caen Normandie

Atteintes cognitives et cérébrales dans le trouble de l'usage d'alcool et le syndrome de Korsakoff : valeur pronostique, évolution et prise en charge

**Présentée et soutenue par
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**Thèse soutenue publiquement le 20/11/2020
devant le jury composé de**

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Remerciements

En premier lieu, je tiens à remercier les Pr Florence Pasquier et Jean-Louis Nandrino de me faire l'honneur d'être les rapporteurs de ce travail de thèse, ainsi que les Pr Florence Vorspan et Francis Eustache et le Dr Shailendra Segobin pour avoir accepté d'examiner ce travail.

Je remercie également le Pr Francis Eustache et le Dr Béatrice Desgranges de m'avoir accueillie dans leur unité de recherche au cours de ces trois années de thèse.

Mes remerciements suivants s'adressent naturellement à ma directrice de thèse, Anne Lise Pitel. Merci pour ces trois belles années, merci de la confiance que tu m'as accordée. Merci pour tes précieux conseils qui m'ont permis de progresser. Et merci pour ta bonne humeur et ta bienveillance !

Merci à toute l'équipe Alcool, je me suis tout de suite sentie bien avec vous. A mon arrivée j'avais peu de connaissances au sujet des addictions, mais ces années à vos côtés m'ont beaucoup appris. Anne Lise, Monsieur Vabret, Céline, Shail, Nicolas, Alice, Anastasia et Najlaa, un énorme merci !

Pour rester dans le thème, je tiens également à remercier toute l'équipe du service d'addictologie du CHU de Caen. Merci également aux patients et aux sujets sains.

Merci à l'ensemble du staff IRM/TEP, et aux informaticiens de Cyceron.

Je tiens également à remercier tous les doctorants, post-docs et psychologues avec qui j'ai eu le plaisir d'échanger au cours de ces années. Je ne m'aventurerai pas à nommer tout le monde de peur d'oublier des personnes.

Un merci tout particulier à Alice, Anastasia, Clairon, Clémence, Edel, Elizabeth et Gwendoline (c'est par ordre alphabétique Anastasia ne cherche pas à grappiller une place !). Je peux vous remercier pour tant de choses : les soirées, les fous rires, les pauses, les craquages, les tutos Word, pour vos encouragements durant la dernière ligne droite qui finalement était longue, non ? ... mais j'ai surtout envie de vous remercier pour tous les moments partagés autour de déjeuners, goûters, apéros, et diners parce que ça combine deux choses auxquelles j'accorde une grande importance, les amies et la nourriture ! ☺ J'ajoute aussi un merci aux trois p'tits bouts : Eden, Louise et Alice, et merci aux mamans pour toutes les photos envoyées !

Pepette, merci de m'accompagner depuis si longtemps, merci de m'avoir dit, il y a trois ans et demi, « ça coûte rien de postuler tu verras bien ce que ça donne ». Merci d'être là pour moi, tu

sais à quel point tu m'es précieuse ! Merci aussi à Louis, à Basile et à Clémence ! Vous me manquez !

Un énorme merci à ma famille, merci de me soutenir et de croire en moi. Un merci tout particulier à ma Maman, ma Mamie et ma Marraine d'avoir toujours été là pour moi !! Merci aussi à mes frères, mes belles-sœurs et merci à Rafael, Pauline et à bébée Elisa qui est encore bien au chaud ☺

Enfin, merci à mon chéri de m'avoir accompagnée tout au long de cette aventure !! Place au together maintenant ☺

Liste des abréviations

APA : American Psychiatric Association

CFC : Circuit fronto-cérébelleux

CIM : Classification Internationale des Maladies

CP : Circuit de Papez

DSM : Diagnostic and Statistical Manual of Mental Disorders

DTI : Imagerie par tenseur de diffusion

EGW : Encéphalopathie de Gayet-Wernicke

EHPAD : Etablissement d'Hébergement pour Personnes Agées Dépendantes

FAM : Foyer d'Accueil Médicalisé

FDG : ^{18}F -fluorodésoxyglucose

GABA : Acide gamma-aminobutyric

GGT : Gamma-glutamyltransférase

HDJ : Hôpital De Jour

IRM : Imagerie par Résonnance Magnétique

MAS : Maison d'Accueil Médicalisée

MDPH : Maison Départementale des Personnes Handicapées

NMDA : N-methyl-D-aspartate

OMS : Organisation Mondiale de la Santé

SK : Syndrome de Korsakoff

SSR : Soins de Suite et de Réadaptation

TCC : Thérapies Cognitivo-Comportementales

TEP : Tomographie par Emission de Positons

TUAL : Trouble de l'usage d'alcool

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CADRE THEORIQUE

I. ALCOOL, DEPENDANCE ET TROUBLE DE L'USAGE

1. Ethanol

1.1. Molécule et boissons alcoolisées

L'éthanol est une molécule de la famille chimique des alcools dont la formule semi-développée est $\text{CH}_3\text{-CH}_2\text{-OH}$. Cette molécule est naturellement émise lors de la fermentation des sucres, dans un milieu liquide qui est privé de dioxygène. En effet, certains types de levures permettent de métaboliser les sucres, retrouvés dans des fruits mûrs ou diverses plantes sucrières, en éthanol et en dioxyde de carbone. Ce processus permet d'obtenir des boissons alcoolisées.

La proportion d'alcool d'une boisson varie en fonction du mode de production et de la matière première. Le titre alcoolométrique volumique d'une boisson est exprimé en degré « ° » ou fraction volumique « %vol ». Selon les levures utilisées, le processus de fermentation va aboutir à des boissons ayant une concentration maximale d'environ 15%vol d'éthanol, par exemple la bière et certains vins. Pour obtenir des boissons plus concentrées en alcool, comme les spiritueux ou les liqueurs. Il faut passer par des procédés tels que la distillation de boissons fermentées qui permet de séparer un mélange dont les substances ont des températures d'ébullition différentes afin d'obtenir le distillat, ou encore le mutage qui consiste à arrêter artificiellement la fermentation en ajoutant 5 à 10% d'alcool pur, cette opération va permettre de conserver une certaine quantité de sucre dans le vin tout en ayant une boisson à forte teneur en alcool.

L'expression de la consommation d'alcool par un individu peut se faire en « unité d'alcool ». En France, un verre ou une unité standard contient 10 grammes d'alcool pur, c'est en général ce qui est contenu dans les verres servis dans les débits de boissons (les bars, restaurants, etc. ; **Figure 1**). Le nombre d'unités d'alcool contenues dans une bouteille apparaît de plus en plus sur les étiquettes. Cependant, si vous commandez une bière de 33cl titrant à 8%vol et que vous souhaitez savoir combien d'unités d'alcool elle contient, il faut multiplier le degré d'alcool par le volume ($8*0.33$) puis par la densité de l'alcool (0.8), ce qui donne 2.1 unités (21 grammes d'alcool). Il est important de noter que l'unité d'alcool n'est pas équivalente

dans tous les pays. Par exemple, aux Etats-Unis une unité contient 14 grammes d'alcool pur alors qu'au Royaume-Uni elle contient 8 grammes d'alcool pur, ce qui peut compliquer les comparaisons entre les études.



Figure 1 : Unité standard d'alcool (10g d'alcool pur) en fonction du degré et volume.

1.2. Mode d'action

1.2.1. Absorption et élimination

Après absorption, sous forme de boisson, l'alcool va passer par le tractus gastro-intestinal puis être distribué rapidement vers les organes très vascularisés comme le foie, le cœur, les poumons et le cerveau. L'hydrosolubilité de l'alcool va faire qu'il sera distribué dans la totalité de l'eau du corps humain (environ 50 à 60% de la masse). A quantité égale d'alcool consommé, nous ne réagissons pas tous de la même manière. En effet, la distribution de l'alcool est influencée par des facteurs dont la proportion corporelle de liquide dépend. Il existe notamment un effet du genre. Le corps d'une femme étant composé de davantage de tissus adipeux, dans lequel l'alcool se diffuse moins, et de moins de liquide que celui d'un homme, la concentration sanguine d'alcool est plus élevée chez les femmes. Un effet de l'âge est également notable. Les adolescents ont généralement un poids inférieur à celui des adultes ; l'alcool va donc se répartir dans une quantité de liquide inférieur, augmentant sa concentration dans le sang.

L'élimination de l'alcool se fait principalement par le métabolisme oxydatif qui a lieu dans le foie. De manière beaucoup plus limitée, l'alcool est éliminé via les poumons (air expiré), les reins (urines), et la peau (sueur).

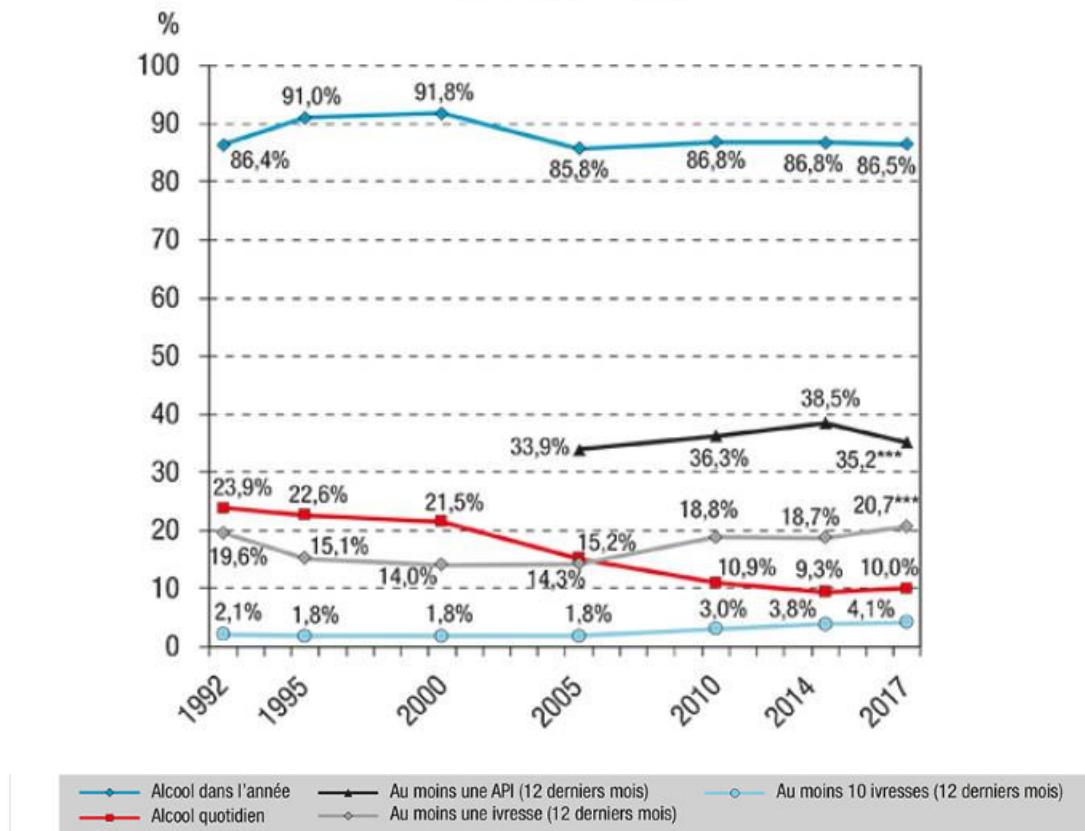
1.2.2. Effet psychotrope

L'éthanol est un psychotrope qui a un effet dépresseur sur le cerveau. Il agit entre autres sur les récepteurs GABA_A du GABA (acide gamma-aminobutyric) et les récepteurs NMDA (N-methyl-D-aspartate) du glutamate (Abrahao *et al.*, 2017). En condition normale, l'activité cérébrale est caractérisée par un équilibre entre les neurotransmissions inhibitrices (système GABAergique) et les neurotransmissions excitatrices (système glutamatergique). L'alcool est un agoniste des neurotransmetteurs GABA, c'est-à-dire qu'il imite leur action, ce qui entraîne une exagération de l'effet inhibiteur. Par ailleurs, en se fixant sur les récepteurs du glutamate, l'éthanol inhibe les neurotransmissions excitatrices, en empêchant la dépolarisation du neurone. Une prise aigüe d'alcool entraîne donc un ralentissement du fonctionnement du système nerveux central. L'effet des consommations chroniques sera, quant à lui, développé par la suite.

2. Epidémiologie

Depuis la mise en place des campagnes de prévention il y a un demi-siècle, la consommation d'alcool baisse régulièrement, passant de 26 litres d'alcool pur par an et par habitant de plus de 15 ans en 1961 à 11.6 litres en 2018. Une évolution des modes de consommation est observée depuis le début des années 2000, avec une diminution des consommations régulières et quotidiennes et une augmentation de la proportion de personnes qui déclarent avoir eu au moins une ivresse au cours de l'année (**Figure 2** ; Richard *et al.*, 2019). En 2017, 86.5% des personnes âgées de 18 à 75 ans ont déclaré avoir consommé de l'alcool au cours des 12 derniers mois.

4a : Parmi les 18-75 ans



* , ** , *** : évolution significative entre 2014 et 2017, aux seuil de 5%, 1% et 0,1%.
 Sources : Baromètres de Santé publique France 1992, 1995, 2000, 2005, 2010, 2014, 2017.
 API : alcoolisation ponctuelle importante.

Figure 2 : Evolution des indicateurs de consommation d'alcool entre 1992 et 2017 en France métropolitaine. *D'après Richard et al., 2019.*

Malgré cette diminution des consommations, la France se situait toujours au 6^{ème} rang des pays les plus consommateurs de l'Union Européenne en 2016 (WHO, 2018). L'alcool reste ainsi la deuxième cause de mortalité évitable (49 000 morts par an) après le tabac (Roerecke and Rehm, 2013). En effet, l'alcool est la cause directe de nombreuses pathologies (e.g., dépendance, syndrome d'alcoolisation fœtale, cirrhose, cancers, encéphalopathies, traumatismes crâniens) et contribue au développement et au maintien d'autres pathologies (e.g., cardio-vasculaires, digestives, pulmonaires, psychiatriques, ou encore le développement d'une démence ; Connor *et al.*, 2016; Schwarzinger *et al.*, 2018; Onaemo *et al.*, 2020; Rehm and Shield, 2020; Thompson *et al.*, 2020). Par ailleurs, les consommations chroniques et excessives d'alcool ont non seulement des conséquences sur l'individu mais également sur les sphères familiale, sociale et professionnelle (Rehm, 2011).

L'Organisation Mondiale de la Santé (OMS) a mis en place des recommandations de consommations à faible risque. Les seuils proposés sont les suivants : pas plus de 3 unités par jour pour les hommes et 2 unités par jour pour les femmes. Il est également recommandé de ne jamais boire plus de 4 unités par occasion et de s'abstenir de toute consommation d'alcool au moins un jour par semaine. Ces recommandations sont reprises et adaptées selon les pays. Actuellement, Santé publique France recommande « maximum 2 verres par jours, et pas tous les jours ». Donc si vous consommez une bière de 33cl à 8%vol, il serait raisonnable de ne plus consommer d'alcool durant le reste de la journée. D'autant plus qu'une étude récente a montré que toute consommation d'alcool entraîne des risques pour la santé et que ces risques augmentent avec la quantité consommée (Griswold *et al.*, 2018). Dès lors que vous consommez de l'alcool, la notion de risque zéro n'existe pas.

3. Evolution des concepts et des critères diagnostiques

3.1. De l'alcoolisme à la dépendance

Benjamin Rush, en 1784, a été le premier à évoquer les conséquences médicales des consommations excessives et chroniques d'alcool en précisant qu'elles entraînent des effets « sur le corps et l'esprit ». Il a également très tôt décrit la notion de perte de contrôle vis-à-vis de l'alcool. Cette notion est également au cœur de la définition que Pierre Fouquet a proposée en décrivant que les patients ont perdu « la liberté de s'abstenir de boire des boissons alcoolisées ». Le terme d'« alcoolisme chronique » a été introduit par Magnus Huss (1849), pour caractériser « les manifestations pathologiques de l'intoxication alcoolique ». En 1960, Elvin M. Jellinek a fait évoluer la définition de l'alcoolisme en y intégrant les concepts de maladie et de dépendance tout en proposant une vision globale et sociale du trouble (Jellinek, 1960).

Les classifications internationales des troubles mentaux sont des supports fondamentaux pour comprendre et diagnostiquer les maladies sur la base de critères précis. Parmi ces classifications, il existe la Classification Internationale des Maladies (CIM) proposée par l'OMS et le manuel diagnostique et statistique des troubles mentaux (DSM ; Diagnostic and Statistical Manual of Mental Disorders) de l'American Psychiatric Association (APA). Dans le

DSM-I, le DSM-II et la CIM-8, les critères diagnostiques de l'alcoolisme étaient réunis avec les troubles de la personnalité et les névroses. Les travaux d'Edwards et Gross en 1976, définissant le syndrome de dépendance à l'alcool et le différenciant de l'usage nocif, ont été déterminants dans l'évolution des critères diagnostiques (Edwards and Gross, 1976). Ainsi, en 1980 dans le DSM-III, une classification bimodale qui différencie abus et dépendance est introduite. La dépendance se distingue alors de l'abus par la présence d'une tolérance au produit et des symptômes de sevrage.

3.2. Conception catégorielle : abus et dépendance

Dans le DSM-IV (American Psychiatric Association, 1994) et la CIM-10 (World Health Organization., 1994), cette distinction entre les critères d'abus et de dépendance est toujours présente, tout en tenant compte des aspects comportementaux, physiologiques et des conséquences de la consommation d'alcool.

Les critères **d'abus** à une substance selon le DSM-IV sont les suivants :

A. Mode d'utilisation inadéquate d'une substance conduisant à une altération du fonctionnement ou à une souffrance cliniquement significative, caractérisée par la présence d'au moins une des manifestations suivantes au cours d'une période de 12 mois :

- (1) Utilisation répétée d'une substance conduisant à l'incapacité de remplir des obligations majeures, au travail, à l'école, ou à la maison
- (2) Utilisation répétée d'une substance dans des situations où cela peut être physiquement dangereux
- (3) Problèmes judiciaires répétés liés à l'utilisation d'une substance
- (4) Utilisation de la substance malgré des problèmes interpersonnels ou sociaux, persistants ou récurrents, causés ou exacerbés par les effets de la substance

B. Les symptômes n'ont jamais atteint, pour cette classe de substance, les critères de la Dépendance à une substance.

Les critères **de dépendance** à une substance selon le DSM-IV sont les suivants :

Mode d'utilisation inadapté d'une substance conduisant à une altération du fonctionnement ou une souffrance, cliniquement significative, caractérisé par la présence de trois (ou plus) des manifestations suivantes, à un moment quelconque d'une période continue de 12 mois :

- (1) Tolérance : besoin de quantités plus fortes pour obtenir l'effet désiré, ou effet diminué en cas d'utilisation continue d'une même quantité
- (2) Sevrage caractérisé par un syndrome de sevrage ou la prise de la même substance pour soulager les symptômes de sevrage
- (3) La substance est souvent prise en quantités plus importantes ou pendant une période plus prolongée que prévu
- (4) Désir persistant, ou efforts infructueux, pour diminuer ou contrôler l'utilisation de la substance
- (5) Beaucoup de temps passé à des activités nécessaires pour obtenir la substance ou à récupérer de ses effets
- (6) Activités sociales, professionnelles ou de loisirs importantes abandonnées à cause de l'utilisation de la substance
- (7) L'utilisation de la substance est poursuivie bien que la personne sache avoir un problème psychologique ou physique persistant ou récurrent susceptible d'avoir été causé ou exacerbé par la substance

Spécifier si :

Avec dépendance physique : présence d'une tolérance ou d'un sevrage (c'est-à-dire item 1 ou 2)

Sans dépendance physique : absence de tolérance ou de sevrage (c'est-à-dire tant de l'item 1 que de l'item 2).

Les critères de dépendance de la CIM-10 diffèrent légèrement de ceux du DSM-IV. En effet, le critère relatif à « la prise de quantités plus importantes » (3) du DSM n'est pas retrouvé dans la CIM. Cependant, l'OMS a intégré dans sa classification la notion de « craving » ou désir puissant et compulsif d'utiliser une substance psychoactive. Alors que cette conception catégorielle a été conservée dans la dernière (11^{ème}) version de la CIM qui devrait entrer en vigueur le 1^{er} janvier 2022, une refonte des critères diagnostiques a été effectuée dans le DSM-5 (American Psychiatric Association, 2013) qui propose de conceptualiser les « troubles liés à l'usage d'une substance » selon un continuum dimensionnel (**Figure 3**).

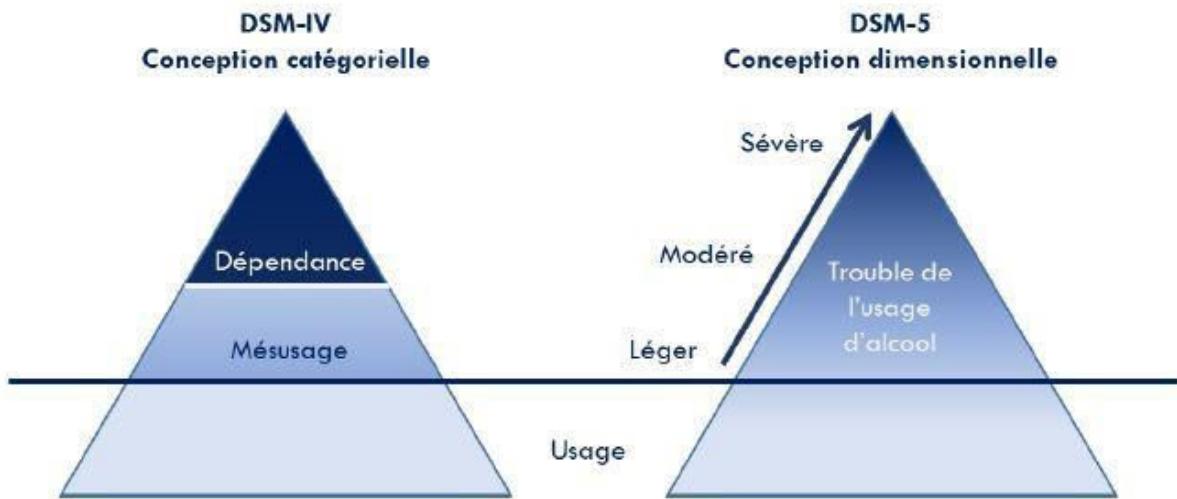


Figure 3 : Evolution d'une approche catégorielle différenciant l'abus de la dépendance (DSM-IV) vers une approche dimensionnelle du Trouble de l'Usage d'Alcool (TUAL ; DSM-5). *Adaptée de Le Berre et al. 2019.*

3.3. Conception dimensionnelle : trouble lié à l'usage d'alcool

Des études épidémiologiques ont mis en évidence que le critère d'abus tel qu'il est décrit dans le DSM-IV a une faible validité et qu'il ne peut pas être considéré comme un stade prodromal de la dépendance étant donné que cette dernière peut survenir sans pour autant que les critères d'abus soient réunis (Hasin *et al.*, 2013). En suivant les recommandations de cette étude, les critères d'abus et de dépendance sont donc regroupés au sein d'un continuum de sévérité dans le DSM-5 (Figure 3). Il est à noter qu'en plus du changement de conception du trouble, il y a également eu des changements au sein des critères diagnostiques. En effet, le critère concernant les « problèmes judiciaires répétés liés à l'utilisation d'une substance », présent dans le DSM-IV, a été abandonné, et le critère de « craving », présent dans la CIM-10, a été ajouté. Ainsi, les « troubles liés à l'usage de substance » regroupent 11 critères qui sont examinés au cours d'une période de 12 mois. Ce trouble s'exprime ainsi selon un continuum de sévérité allant de « léger » si 2 ou 3 critères sont présents, à « modéré » si le patient présente 4 ou 5 critères, à « sévère » lorsque 6 critères ou plus sont présents. Le trouble de l'usage d'alcool (TUAL) est caractérisé par une prévalence de 13.9% de la population mondiale (Grant *et al.*, 2015).

La conception dimensionnelle du DSM-5 permet de rendre compte de la variabilité des tableaux cliniques et ainsi de proposer une prise en charge plus individualisée. Cette notion de continuum n'a pas seulement été appliquée au TUAL mais aussi à la classification de « troubles neurocognitifs » introduite dans le DSM-5. Le DSM-5 reconnaît ainsi l'existence de « troubles neurocognitifs induits par l'usage d'une substance » et notamment l'alcool en lien avec les nombreux travaux montrant l'impact de la consommation chronique et excessive d'alcool sur le cerveau.

Les études qui seront présentées par la suite ont utilisé différents critères diagnostiques en fonction de la période à laquelle elles ont été réalisées. Cependant, pour simplifier mon propos, je vais utiliser le terme TUAL pour toutes les études présentées, qu'elles incluent des patients TUAL sévères, des patients alcoolodépendants, ou des patients « alcooliques ».

4. Complications neurologiques liées à l'alcool

Que ce soit en prise aigüe ou en consommation chronique, l'alcool a des effets sur le corps et sur le système nerveux central. Les consommations chroniques et excessives d'alcool, associées à d'autres facteurs tels que des maladies hépatiques ou une carence nutritionnelle peuvent entraîner des complications neurologiques sévères (Zahr and Pfefferbaum, 2017). Dans le cadre de ce travail de thèse, seules certaines complications neurologiques seront abordées. De ce fait, je développerai dans cette partie uniquement les complications induites par le sevrage d'alcool et l'encéphalopathie de Gayet-Wernicke, tandis que le syndrome de Korsakoff fera l'objet du chapitre III de ce cadre théorique.

4.1. Complications liées au sevrage d'alcool

Comme évoqué précédemment, la consommation aigüe d'alcool déséquilibre temporairement l'homéostasie entre le système GABAergique et le système glutamatergique. Les consommations chroniques d'alcool, quant à elles, induisent une neuro-adaptation via une baisse de l'efficacité des récepteurs au GABA et une augmentation du nombre de récepteurs NMDA, permettant de garantir l'équilibre entre inhibition et excitation. De ce fait, pour obtenir

l'effet recherché par les consommations, les individus doivent augmenter les quantités d'alcool : c'est l'effet de tolérance. L'arrêt brutal des consommations d'alcool entraîne une hyperexcitabilité cérébrale. D'une part, la stimulation du système GABAergique est fortement diminuée ; d'autre part l'alcool ne bloque plus les récepteurs NMDA, toujours plus nombreux qu'en condition normale, le glutamate s'exprime donc de façon exacerbée (**Figure 4**). L'hyperglutamatergie induite par le sevrage provoque alors une entrée massive d'ions calcium dans les neurones, entraînant une mort neuronale (Tsai and Coyle, 1998). Les lobes frontaux qui contiennent de nombreuses voies glutamatergiques, seraient plus susceptibles d'être impactés par la neurotoxicité du sevrage (Kril *et al.*, 1997).

Ces changements neurochimiques se traduisent cliniquement par un syndrome de sevrage caractérisé par des symptômes dysautonomiques (nausée, tachycardie), moteurs (tremblements), d'hyper vigilance (insomnie) et psychiatriques (anxiété, désinhibition). Dans les cas de sevrage sévère, les patients peuvent présenter des complications neurologiques telles que des crises convulsives et un *délirium tremens* (hallucinations, agitation, fièvre...). Ces complications pouvant entraîner la mort, elles nécessitent une prise en charge urgente notamment par l'administration de benzodiazépines qui inhibent le système glutamatergique (Muncie, 2013).

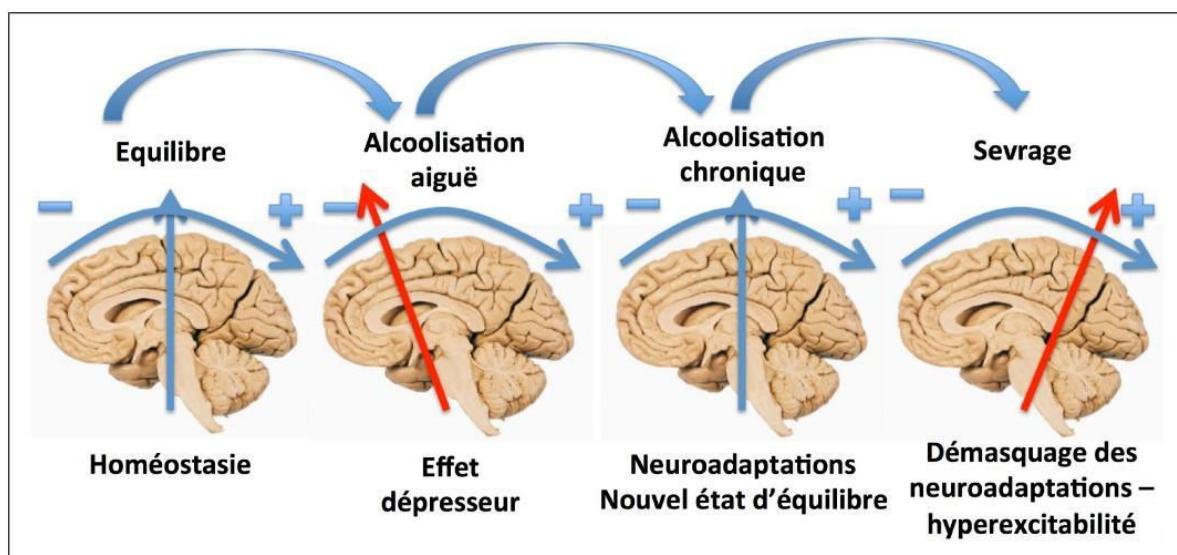


Figure 4 : Neuro-adaptation induite par les consommations chroniques d'alcool et effet de démasquage lors du sevrage. *D'après Naassila, 2018.*

4.2. Encéphalopathie de Gayet-Wernicke

Trente à 80% des patients TUAL présentent une carence en vitamine B1, la thiamine (Thomson *et al.*, 2009). En effet, ces patients ont tendance à négliger leur alimentation et à présenter des dysfonctionnements gastro-intestinaux et hépatiques qui ont pour conséquence de compromettre l'absorption, le stockage et la phosphorylation de la thiamine (Thomson, 2000; Coulbault *et al.*, 2019). Cette déficience thiaminique peut provoquer une encéphalopathie de Gayet-Wernicke (EGW), qui a été initialement caractérisée par une triade de symptômes cliniques : une confusion (désorientation spatio-temporelle), une ataxie (troubles de l'équilibre), et des anomalies oculomotrices (nystagmus, paralysie du mouvement des yeux) (Wernicke, 1881). Cependant, des études post-mortem ont montré que l'EGW est sous-diagnostiquées *in vivo* (Harper, 1983; Harper *et al.*, 1986). Les critères ont ainsi été redéfinis par Caine *et al.* (1997) qui suggèrent que l'EGW est associée à au moins deux des signes suivants :

- Une carence nutritionnelle
- Des anomalies oculomotrices
- Un dysfonctionnement cérébelleux (démarche et posture statique instables)
- Et une altération de l'état mental et/ou des troubles mnésiques.

Le traitement de l'EGW consiste en l'administration de thiamine, de préférence en intraveineuse. Bien qu'il n'y ait pas de directives thérapeutiques universelles, les doses recommandées sont de 200 à 500 mg tds pendant 5 à 7 jours, suivi par une administration orale (Latt and Dore, 2014). Lorsque les patients ne reçoivent pas rapidement une supplémentation appropriée en thiamine, 20% de décès sont observés et parmi ceux qui survivent, 85% développent un syndrome de Korsakoff, une complication neurologique qui fera l'objet du chapitre III de cette introduction.

RESUME

L'alcool est une substance toxique qui va être rapidement distribuée vers les organes très vascularisés du corps humain, dont le cerveau sur lequel il va avoir un effet dépresseur.

Dans la population générale, les quantités d'alcool consommées diminuent depuis un demi-siècle, mais l'alcool reste tout de même la cause de nombreux décès et de diverses pathologies.

Alors que le terme « alcoolique » a longtemps été utilisé pour caractériser les patients ayant des consommations chroniques et excessives d'alcool, la conception de cette pathologie a évolué pour laisser place au « trouble de l'usage d'alcool ».

Associées à divers facteurs, les consommations chroniques et excessives d'alcool peuvent entraîner des complications neurologiques sévères. Mais bien avant ces complications, il existe des atteintes cérébrales et cognitives qui seront exposées dans le chapitre suivant.

II. ATTEINTES CEREBRALES ET COGNITIVE DANS LE TROUBLE DE L'USAGE D'ALCOOL

Au cours des dernières décennies, de nombreux travaux ont montré l'impact des consommations chroniques et excessives d'alcool sur le cerveau et le fonctionnement cognitif, ceci sans pour autant qu'il y ait des complications neurologiques notables.

Au cours de ce chapitre, les altérations cérébrales structurales et métaboliques seront abordées, puis dans un second temps, les déficits neuropsychologiques, principalement les troubles de la mémoire et des fonctions exécutives, seront développés. Par la suite, nous exposerons les effets de l'abstinence sur ces altérations cérébrales et cognitives. Enfin, nous verrons comment les troubles cognitifs se répercutent sur la prise en charge addictologique et quels sont les facteurs qui peuvent déterminer la rechute.

1. Les atteintes cérébrales

1.1. Atteintes structurales

Les atteintes structurales induites par l'alcool ont d'abord été mises en évidence par des études *post-mortem*. Le développement des techniques d'imagerie, avec notamment le CT-scan et l'imagerie par résonnance magnétique (IRM), a ensuite permis d'observer les changements structuraux *in vivo*. L'IRM structurale met en évidence les altérations macrostructurales des volumes de substance grise et de substance blanche. L'IRM, à l'aide de l'imagerie par tenseur de diffusion (DTI), permet également d'étudier l'intégrité des faisceaux de substance blanche (microstructure), et donc de détecter des changements très fins, qui apparaissent avant les modifications macrostructurales (Pfefferbaum *et al.*, 2006). La DTI est une technique qui fournit des informations sur la distribution et la mobilité des molécules d'eau dans le cerveau. La mesure la plus utilisée est l'anisotropie fractionnelle (FA) qui pourrait refléter l'intégrité axonale et de la gaine de myéline (Pfefferbaum *et al.*, 2006). Les données acquises en DTI sont

également utilisées pour des analyses de tractographie qui permettent la reconstruction et l'analyse de la connectivité structurale.

1.1.1. De la substance grise

Nous l'avons déjà évoqué, le cortex frontal est particulièrement vulnérable aux effets de l'alcool (Xiao *et al.*, 2015; Mackey *et al.*, 2019). Une diminution de la densité neuronale dans le cortex frontal a, en effet, été trouvée lors d'études *post-mortem* (Harper and Matsumoto, 2005; Kril and Harper, 2012). Les études IRM ont mis en évidence une réduction de 11% du volume du cortex préfrontal des patients TUAL par rapport à des sujets contrôles (Wobrock *et al.*, 2009). Au sein de cette région, le cortex dorso-latéral serait particulièrement atteint, l'atrophie pouvant aller jusqu'à 20% de son volume (Chanraud *et al.*, 2007; Makris *et al.*, 2008; Le Berre *et al.*, 2013). Des altérations des cortex frontaux ventro-latéral, médian, et orbitofrontal sont également fréquemment rapportées dans le TUAL (Le Berre *et al.*, 2013; Zois *et al.*, 2017, Zou *et al.*, 2018a; Durazzo and Meyerhoff, 2019; Mackey *et al.*, 2019). À durée de dépendance et quantité totale d'alcool consommée équivalentes, le volume du cortex frontal est davantage diminué chez les patients âgés que chez les patients jeunes, suggérant que la vulnérabilité des lobes frontaux augmente avec l'âge (Pfefferbaum *et al.*, 1997).

Les consommations chroniques et excessive d'alcool entraînent également des altérations du cervelet et notamment du vermis (Chanraud *et al.*, 2010a; Le Berre *et al.*, 2013, Ritz *et al.*, 2016b), du gyrus cingulaire (Demirakca *et al.*, 2011; Pitel *et al.*, 2012; Fama *et al.*, 2019; Klaming *et al.*, 2019), de l'insula (Demirakca *et al.*, 2011, Zou *et al.*, 2018a; Fama *et al.*, 2019; Mackey *et al.*, 2019), des gyri précentral, postcentral et supramarginal (Chanraud *et al.*, 2009a), du cortex pariétal (Gazdzinski *et al.*, 2005; Fama *et al.*, 2019), et du cortex temporal incluant le gyrus parahippocampique et l'hippocampe (Gazdzinski *et al.*, 2005; Cardenas *et al.*, 2007; Wilson *et al.*, 2017, Zou *et al.*, 2018a; Fama *et al.*, 2019). De plus, les volumes de nombreuses structures sous-corticales telles que les thalamus (Gazdzinski *et al.*, 2005; Pitel *et al.*, 2012; Segobin *et al.*, 2019), les corps mamillaires (Sullivan *et al.*, 1999; Pitel *et al.*, 2012), les noyaux caudés, et l'amygdale (Le Berre *et al.*, 2013; Charlet *et al.*, 2014) sont diminués chez les patients TUAL par rapport à des sujets contrôles (**Figure 5**).

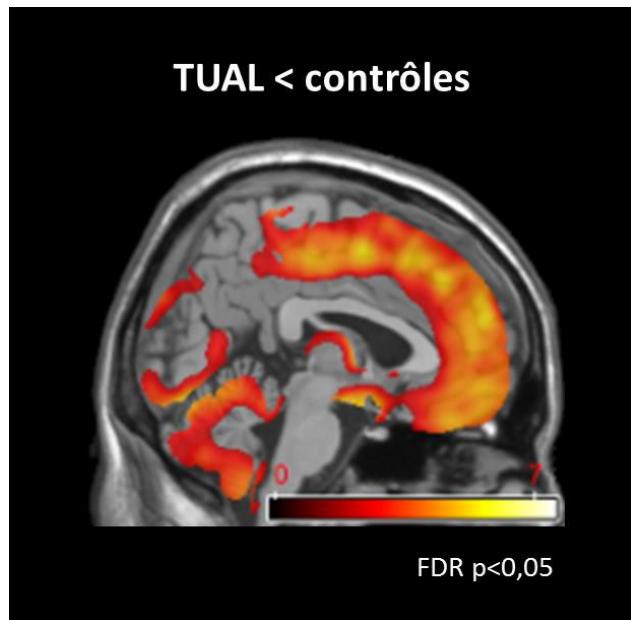


Figure 5 : Profil d’atrophie du volume de substance grise chez des patients TUAL comparés à des sujets contrôles. *Adaptée de Pitel et al., 2012.*

1.1.2. De la substance blanche

Chez les patients TUAL, l’atrophie de la substance blanche est visible dans l’ensemble du cerveau (Pfefferbaum *et al.*, 2001; Demirakca *et al.*, 2011) (Figure 6). Certaines régions semblent particulièrement atteintes, c’est notamment le cas du corps calleux et du pont (Mechtcheriakov *et al.*, 2007; Pitel *et al.*, 2012; Wang *et al.*, 2016). Au-delà de ces atteintes macrostructurales, les études conduites en DTI mettent en évidence des altérations de l’intégrité du corps calleux (Pfefferbaum *et al.*, 2000; Trivedi *et al.*, 2013, Zou *et al.*, 2018b; De Santis *et al.*, 2019), de la capsule interne et externe ainsi que du cingulum (Pfefferbaum *et al.*, 2009; Segobin *et al.*, 2015), de la corona radiata (Segobin *et al.*, 2015, Zou *et al.*, 2018b), du fornix (Pfefferbaum *et al.*, 2009; Trivedi *et al.*, 2013; Segobin *et al.*, 2015, Zou *et al.*, 2018b; De Santis *et al.*, 2019), et des pédoncules cérébelleux (Segobin *et al.*, 2015). Par ailleurs, les atteintes du mésencéphale et du pont sont caractérisées par le fait qu’il y a 18% de fibres en moins chez les patients TUAL que chez les sujets contrôles (Chanraud *et al.*, 2009b).

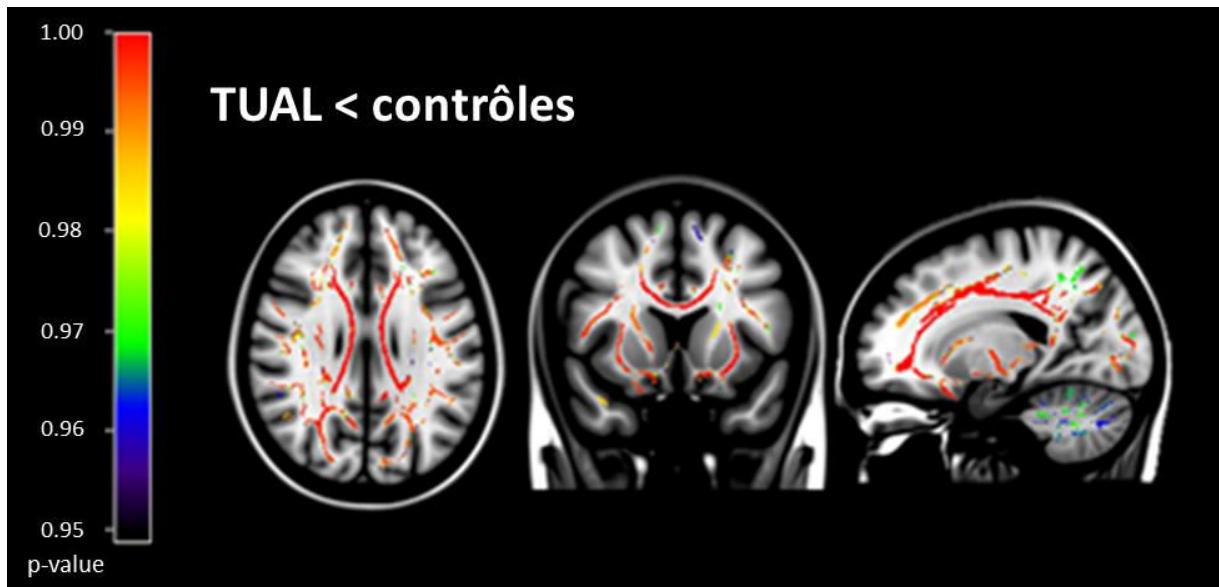


Figure 6 : Atteintes cérébrales de la substance blanche chez des patients TUAL comparés à des sujets contrôles. *Adaptée de Segobin et al., 2015.*

1.2. Atteintes métaboliques

La Tomographie par Emission de Positons (TEP) est une technique d'imagerie moléculaire qui permet d'observer *in vivo* certains processus biologiques et d'étudier le devenir de différentes molécules injectées dans le corps humain. La TEP donne un aperçu des modifications fonctionnelles en fournissant une mesure de l'activité cérébrale. Il existe de nombreux traceurs mais dans le cadre de cette thèse nous nous concentrerons sur la TEP au ^{18}FDG (^{18}F -fluorodéoxyglucose). Ce traceur a une composition chimique proche de celle du glucose, principale source d'énergie du cerveau. La TEP-FDG permet donc d'étudier le métabolisme cérébral du glucose au repos, notamment au niveau des synapses (Jueptner and Weiller, 1995). L'alcool inhibe le transport du glucose au niveau de la barrière hémato-encéphalique, entraînant un dysfonctionnement de cette dernière et une dégénérescence neuronale (Muneer *et al.*, 2011), il est donc important d'étudier les modifications métaboliques dans le TUAL.

Les études, moins nombreuses que celles ayant exploré les altérations structurales chez les patients TUAL, montrent un hypométabolisme cortical global (Volkow *et al.*, 1992, Ritz *et al.*, 2016b; Tomasi *et al.*, 2019) qui serait particulièrement important dans les lobes frontaux et le cortex cingulaire antérieur (Wang *et al.*, 1993; Dao-Castellana *et al.*, 1998; Clergue-Duval *et*

al., 2020). Chez des patients TUAL avec des signes de dégénérescence cérébelleuse (nystagmus, ataxie des membres inférieurs et troubles de la coordination des membres supérieurs), Gilman *et al.* (1990) ont mis en évidence un hypométabolisme frontal et cérébelleux du vermis supérieur. Alors que chez les patients TUAL sans signes de dysfonctionnement cérébelleux, seul l'hypométabolisme frontal a été trouvé. Les auteurs ajoutent que le métabolisme du vermis supérieur est lié à la sévérité des symptômes moteurs.

Une étude menée dans le laboratoire a, quant à elle, montré un hypermétabolisme cérébelleux (lobule VIII) associé à un hypométabolisme des cortex pré-moteur et frontaux chez des patients TUAL sans complications neurologiques (Ritz *et al.*, 2019). Le fait que l'hypermétabolisme soit corrélé aux scores d'ataxie et aux déficits de mémoire de travail indique qu'il reflèterait davantage un phénomène de plasticité cérébral maladaptatif ou inadapté qu'un mécanisme compensatoire.

1.3. Conséquences fonctionnelles des altérations cérébrales

Les altérations structurales et métaboliques décrites dans le TUAL influencent, entre autres, le fonctionnement de deux circuits cérébraux : le circuit fronto-cérébelleux (CFC) et le circuit de Papez (CP).

1.3.1. Le circuit fronto-cérébelleux

Le circuit fronto-cérébelleux (CFC ; **Figure 7A**), identifié initialement chez les primates non-humains (Kelly and Strick, 2003), est constitué de deux boucles parallèles et indépendantes. Dans la première boucle dite motrice, le cervelet antérieur (vermis IV-VI) projette vers le thalamus qui lui-même projette vers le cortex moteur. Ce dernier envoie à son tour des informations au cervelet en passant par le pont (Chanraud *et al.*, 2010b). Cette boucle est impliquée dans le contrôle de la marche et de l'équilibre (Sullivan *et al.*, 2000b, 2006). Au sein de la seconde boucle, dite exécutive, le cervelet (Crus I and II, et lobules VII et VIII) projette vers le cortex préfrontal (aires de Broadmann 9 et 46) en passant par le thalamus. Puis à son tour, le cortex préfrontal projette vers le cervelet en passant par le pont. Cette boucle soutient les fonctions exécutives et la mémoire de travail (Marvel and Desmond, 2010). Les analyses de DTI et de tractographie (Oishi *et al.*, 2011) ont permis de montrer que le cervelet

et le thalamus sont connectés par les pédoncules cérébelleux supérieurs. Le cortex préfrontal reçoit les informations du thalamus grâce à la partie antérieure de la corona radiata, et transfère des informations au pont via les fibres de corticopontines. Enfin, le pont communique avec le cervelet en passant par les pédoncules cérébelleux moyens.

Les altérations structurales du CFC seraient liées aux déficits des fonctions exécutives présentés par les patients TUAL (Sullivan, 2003; Chanraud *et al.*, 2007; Zahr *et al.*, 2017). De plus, l'altération des fibres de substance blanche dans le mésencéphale a également été corrélée avec de faibles performances exécutives (Chanraud *et al.*, 2009b). Les altérations conjointes des structures et des connexions du CFC prédiraient mieux les dysfonctionnements exécutifs que les seules altérations du cortex préfrontal (Sullivan, 2003; Chanraud *et al.*, 2007).

1.3.2. Le circuit de Papez

Le circuit de Papez (CP ; **Figure 7B** ; Papez, 1937), qui a été mis en lien avec les capacités mnésiques et particulièrement de mémoire épisodique (Aggleton and Brown, 1999), implique la formation hippocampique, le thalamus, les corps mamillaires, et le gyrus cingulaire. L'hippocampe est connecté aux corps mamillaires via le fornix. Puis le faisceau mamillothalamique assure le transfert des informations des corps mamillaires vers le thalamus. Le gyrus cingulaire reçoit des informations du thalamus via la capsule interne. Puis le transfert des informations entre le gyrus cingulaire et l'hippocampe se fait par le cingulum.

Chez les patients TUAL, il y a une altération des structures de ce circuit (Sullivan and Pfefferbaum, 2009; Pitel *et al.*, 2012; Segobin *et al.*, 2019) ainsi qu'une déconnexion de ces régions les unes avec les autres (Segobin *et al.*, 2015, 2019). Alors que les études ne montrent pas de relation entre la diminution de volume de substance grise et les performances en mémoire épisodique, il a été mis en évidence que ces capacités cognitives dépendraient davantage de l'intégrité du cingulum et du fornix (Pfefferbaum *et al.*, 2009; Schulte *et al.*, 2010; Trivedi *et al.*, 2013). Les consommations chroniques et excessives détérioreraient ces fibres de substance blanche, conduisant à une interruption de la propagation des informations au sein du CP.

1.3.3. Le thalamus

Le thalamus joue un rôle clé aussi bien dans le CFC que dans le CP. Cependant, les noyaux du thalamus seraient affectés différemment en fonction du circuit et des conséquences

cognitives. En effet, le noyau médiolateral serait principalement impliqué dans le CFC, alors que c'est le noyau antérieur qui serait majoritairement impliqué dans le CP. Dans le cas du CP, les atteintes du fornix entraînent une déconnexion entre le noyau antérieur du thalamus et de l'hippocampe ce qui sous-tendrait les déficits de mémoire épisodique (Segobin *et al.*, 2019).

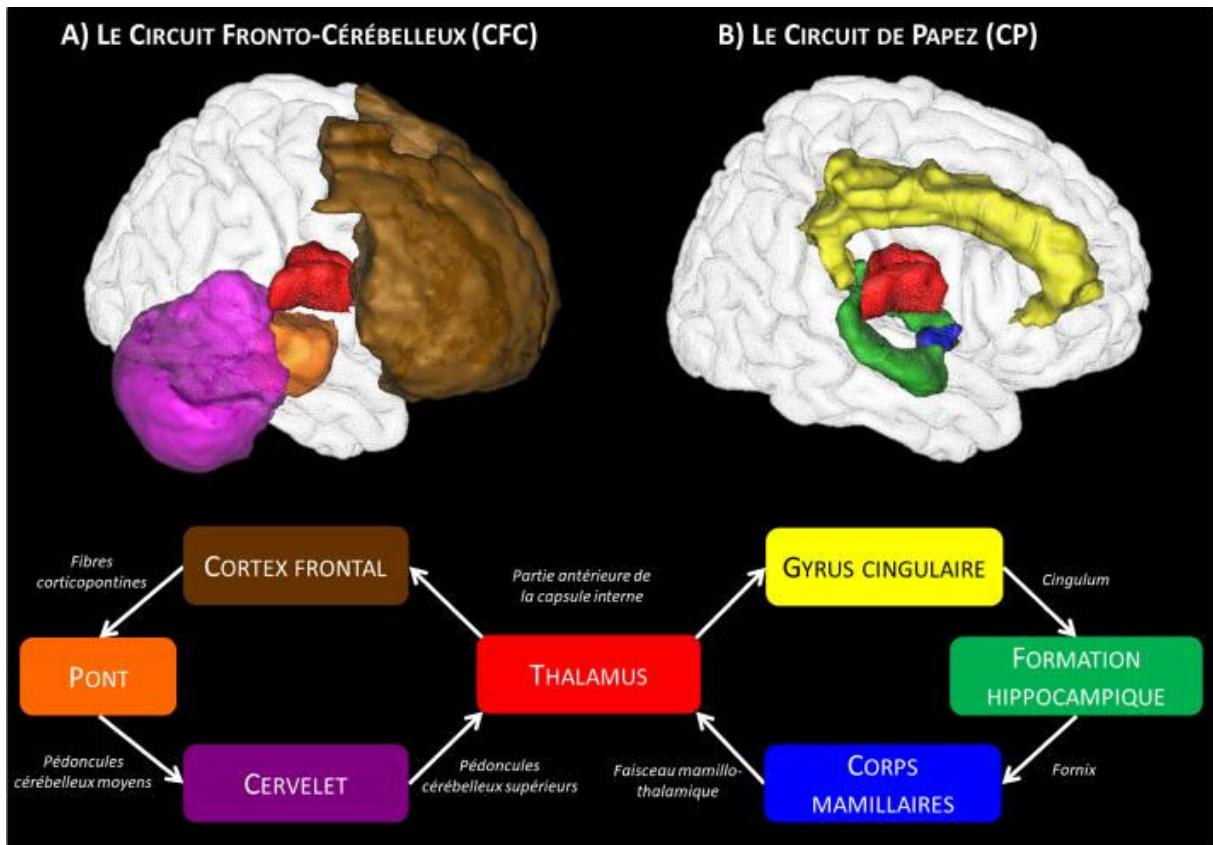


Figure 7 : Illustration des régions et faisceaux de fibres participant à l'organisation du circuit Fronto-Cérébelleux (CFC) et du circuit de Papez (CP). *Adaptée de Pitel *et al.*, 2015.*

2. Les troubles neuropsychologiques

Comme nous venons de le voir, les patients TUAL présentent des altérations cérébrales structurales et fonctionnelles qui impactent leur fonctionnement cognitif. Parmi les patients TUAL, 50 à 80% présentent des altérations motrices et des troubles cognitifs (Vabret *et al.*, 2013; Oscar-Berman *et al.*, 2014). La littérature rapporte notamment des déficits cognitifs dans diverses sphères telles que la mémoire, les fonctions exécutives, les fonctions attentionnelles ainsi que la cognition sociale. La nature et la sévérité des troubles peuvent varier d'un patient à

un autre, résultant en une importante hétérogénéité des profils neuropsychologiques observés chez les patients TUAL.

Les critères de « troubles neurocognitifs » du DSM-5 permettent d'identifier les troubles neurocognitifs « légers à modérés » (mild) et les troubles neurocognitifs sévères (major). La sévérité des troubles est déterminée par le retentissement des déficits neuropsychologiques dans la vie quotidienne (ne plus être capable de payer ses factures par exemple) et le fait que les patients nécessitent d'avoir recours à une assistance. Le DSM-5 reconnaît également que ces troubles peuvent être induits par l'usage d'une substance au-delà de la prise aigue et après la phase de sevrage. Les troubles neurocognitifs consécutifs aux consommations chroniques d'alcool, ou d'autres substances, sont ainsi reconnus en dehors de l'ivresse et en l'absence de complications neurologiques.

2.1. La mémoire épisodique

La mémoire épisodique est généralement décrite comme le système de mémoire en charge de l'encodage, du stockage et de la récupération des événements personnellement vécus qui peuvent être associé à un contexte spatio-temporel précis. La mémoire épisodique permet de se remémorer des événements passés et de se projeter dans le futur. La récupération des souvenirs est associée à un niveau de conscience autonoétique qui est l'impression de revivre les événements vécus et de voyager mentalement dans le temps (Wheeler *et al.*, 1997; Tulving, 2001). La mémoire épisodique est non seulement le système de mémoire le plus sophistiqué mais également le plus sensible aux pathologies, aux traumatismes et à la toxicité.

De nombreuses études ont exploré les capacités de mémoire épisodique des patients TUAL à l'aide de tâche classiques telles que l'apprentissage de listes de mots (Sherer *et al.*, 1992), et d'associations visage-nom (Beatty *et al.*, 1995), ou une tâche de rappel différé d'une figure complexe (Sullivan *et al.*, 1992). Les capacités d'apprentissage sont altérées aussi bien pour les informations verbales que non verbales. Bien que les patients TUAL aient des performances plus faibles que celles des sujets contrôles au test du Rappel Libre Rappel Indicé (RLRI), ils semblent avoir le même taux d'apprentissage au fur et à mesure des essais (Pitel *et al.*, 2007a). Les patients TUAL sont déficitaires à une tâche de reconnaissance après un encodage spontané, mais également à une tâche de rappel libre après un encodage profond. Ces

résultats suggèrent des troubles de l'encodage et de la récupération, alors que les capacités de stockage semblent préservées (Pitel *et al.*, 2007a). De plus, la reconnaissance du contexte spatial et temporel lié à l'encodage des informations est altérée (Salmon *et al.*, 1986, Pitel *et al.*, 2007a). Les patients TUAL présentent également des déficits de mémoire de la source (Schwartz *et al.*, 2002). Enfin, le niveau de conscience associée au souvenir est altéré (Pitel *et al.*, 2007a).

L'altération des capacités de récupération en mémoire épisodique pourrait être liée à des difficultés dans la mise en place de stratégies efficaces lors de l'encodage et de la récupération des informations (Noël *et al.*, 2012). Cependant, seule une faible relation a été établie entre les performances de mémoire épisodique et des fonctions exécutives (Pitel *et al.*, 2007a), ce qui suggère que les troubles de mémoire épisodique ne peuvent pas uniquement être interprétés comme la conséquence d'un dysfonctionnement exécutif.

La composante prospective de la mémoire épisodique, c'est-à-dire la capacité de se rappeler d'effectuer une action qui a été prévue au préalable, est également altérée chez les patients TUAL (Heffernan, 2008).

Enfin, les capacités de mémoire autobiographique des patients TUAL ont également été explorées. Cette mémoire concerne les événements personnellement vécus situés dans le temps et l'espace (composante épisodique), ainsi que les connaissances générales sur soi (composante sémantique) (Conway, 2001). Les patients TUAL rappellent moins de souvenirs spécifiques et plus de souvenirs généraux (D'Argembeau *et al.*, 2006) que les sujets contrôles. Cependant, lorsque les patients rappellent un souvenir spécifique, ils fournissent autant de détails que les sujets contrôles. Ainsi, la quantité de souvenirs épisodiques des patients TUAL est inférieure à celle des sujets contrôles, mais leurs souvenirs semblent qualitativement préservés. De plus, il a été mis en évidence que les patients TUAL sont particulièrement déficitaires lorsqu'il s'agit de rappeler des souvenirs récents, ce qui pourrait refléter l'altération de l'encodage pendant la période de consommation (Nandrino *et al.*, 2016). Concernant les souvenirs remontant à l'enfance, les auteurs montrent également que les patients récemment abstinents relatent moins de souvenirs que des patients abstinents depuis 6 mois et que des sujets contrôles.

L'ensemble de ces données suggèrent une atteinte des différentes composantes de la mémoire épisodique chez les patients TUAL, caractérisée non seulement par des déficits de récupération des informations, mais également par des troubles authentiques de l'encodage des souvenirs.

2.2. Mémoire de travail et fonctions exécutives

La mémoire de travail est un système de mémoire à court-terme qui permet le stockage temporaire et la manipulation d'informations nécessaires pour des tâches cognitives complexes telles que la compréhension du langage, l'apprentissage et le raisonnement. La mémoire de travail est composée de trois systèmes esclaves sous le contrôle de l'administrateur central (Baddeley and Hitch, 1974; Baddeley, 2000). Les systèmes esclaves sont des systèmes de stockage à court-terme comprenant la boucle phonologique qui traite les informations verbales, le calepin visuo-spatial qui est en charge des informations visuospatiales, et le buffer épisodique qui fait le lien entre les informations multimodales. Bien que les patients TUAL présentent une altération du stockage des informations verbales et non verbales (Beatty *et al.*, 1996, Pitel *et al.*, 2007a; Kopera *et al.*, 2012), la composante non-verbale de la mémoire de travail semble plus impactée que la composante verbale (Sullivan *et al.*, 2000b). Un dysfonctionnement du buffer épisodique a également été montré (Pitel *et al.*, 2007a). Enfin, l'administrateur central qui peut être assimilé aux fonctions exécutives est classiquement décrit comme altéré.

Les fonctions exécutives sont des fonctions de haut niveau qui contrôlent et régulent le système cognitif. Elles permettent de diriger nos pensées et actions vers un but, de nous adapter aux changements de notre environnement, et de faire face à des situations nouvelles et non-routinières (Alvarez and Emory, 2006). Ce n'est pas un concept unitaire mais un système multifactoriel comprenant plusieurs composantes, telles que la flexibilité mentale, la planification, la mise à jour, l'organisation, la prise de décisions, la déduction de règles et l'inhibition, qui interagissent les unes avec les autres (Jurado and Rosselli, 2007; Hull *et al.*, 2008).

Un dysfonctionnement exécutif est mis en évidence chez 2/3 des patients TUAL (Ihara *et al.*, 2000, Brion *et al.*, 2017a). Les études montrent que les patients TUAL ont des performances inférieures à celles des sujets contrôles à la partie B du *Trail Making Test*, qui évalue les capacités de flexibilité réactive et de *shifting* (Moriyama *et al.*, 2002; Loeber *et al.*, 2009; Oscar-Berman *et al.*, 2009; Noël *et al.*, 2012). Des épreuves telles que le *Wisconsin Card Sorting Test* mettent également en évidence des perséverations, des difficultés de conceptualisation et d'inhibition des réponses automatiques chez les patients TUAL (Ratti *et al.*, 2002; Chanraud *et al.*, 2007; Salgado *et al.*, 2009). Les patients TUAL présentent également des difficultés d'organisation, de flexibilité mentale spontanée et de génération de stratégies lorsqu'ils sont

évalués avec des tâches de fluences verbales et visuelles (Fama *et al.*, 2004b, Pitel *et al.*, 2007a; Oscar-Berman *et al.*, 2009). Par ailleurs, des déficits d'inhibition verbale et visuelle sont soulignés par des performances déficitaires, respectivement, à l'aide du test de Stroop (Tedstone and Coyle, 2004; Konrad *et al.*, 2012; Schulte *et al.*, 2012), et du *Hayling test* (Noël *et al.*, 2001a, 2012). Une méta-analyse a d'ailleurs indiqué que le *Hayling test* est très sensible aux effets de l'alcool (Stephan *et al.*, 2017). De plus, les patients TUAL ont des performances inférieures à celles des sujets contrôles à une tâche de *n-back*, évaluant les capacités de mise à jour (Pitel *et al.*, 2007a), ainsi que lorsqu'ils sont évalués avec l'épreuve de la *tour de Londres*, reflétant les habiletés de planification (Noël *et al.*, 2001a; Goudriaan *et al.*, 2006). Des déficits de prise de décision ont également été trouvés dans des études utilisant une épreuve de *Gambling* (Goudriaan *et al.*, 2005, Noël *et al.*, 2007a; Brevers *et al.*, 2014, Le Berre *et al.*, 2014b). Ces dysfonctionnements exécutifs ont été mis en évidence également aux moyens de tâches informatisées (Brion *et al.*, 2017a) et de batteries d'évaluation écologique des fonctions exécutives (Ihara *et al.*, 2000; Moriyama *et al.*, 2002).

Malgré les nombreux déficits exécutifs observés dans le TUAL, des études suggèrent que les troubles d'inhibition pourraient être la caractéristique centrale du profil neuropsychologique de ces patients (Kamarajan *et al.*, 2005, Noël *et al.*, 2007b). Cependant, Brion *et al.* (2017) ont montré que les patients TUAL ont des déficits modérés d'inhibition alors que les capacités de *shifting* et de mise à jour sont plus sévèrement atteintes, concluant que les déficits exécutifs liés à l'alcool n'impliquent pas uniquement l'inhibition mais également d'autres composantes.

2.3. Autres fonctions cognitives

2.3.1. Les fonctions attentionnelles

L'attention est définie par Mesulam (1999) comme une attribution préférentielle des ressources limitées vers des événements qui sont devenus pertinents sur le plan comportemental. Trois processus attentionnels sont généralement distingués : 1) l'attention selective qui permet de se focaliser sur ce qui est pertinent et d'inhiber les stimuli distracteurs ; 2) l'attention soutenue qui permet de maintenir un niveau de réponse consistant pendant une longue période de temps ; et 3) l'attention divisée qui permet d'exécuter simultanément deux tâches. Alors que les deux premiers processus semblent préservés chez les patients TUAL,

l'attention divisée est altérée (Tedstone and Coyle, 2004). Si on s'intéresse à la vitesse de traitement, parfois considérée comme reflétant le niveau de base de l'attention, les résultats sont plus hétérogènes. En effet, Noël *et al.* (2001a) rapportent que les patients ont des performances préservées aux partie A du *Trail Making Test*, et du *Hayling test*, et à la planche dénomination de couleur du test de Stroop. Alors que dans une autre étude, les patients ont des performances altérées à la partie A du *Trail Making Test* (Nowakowska-Domagała *et al.*, 2017).

2.3.2. Emotions et cognition sociale

Les consommations chroniques et excessives d'alcool altèrent le traitement des émotions. En effet, les patients TUAL ont tendance à être alexithymique, c'est-à-dire qu'ils ont des difficultés à caractériser et exprimer leur état émotionnel (Uzun *et al.*, 2003; Maurage *et al.*, 2017). La détection et l'interprétation des émotions des autres est également problématique (de Timary *et al.*, 2010) ; il leur serait notamment difficile d'identifier les émotions en s'appuyant sur l'expression faciale (Philippot *et al.*, 1999; Kornreich *et al.*, 2002), la prosodie (Brion *et al.*, 2018), ou la posture corporelle (Maurage *et al.*, 2009). Les patients auraient besoin que les émotions soient exprimées avec plus d'intensité pour pouvoir les identifier (D'Hondt *et al.*, 2015). La comorbidité entre le TUAL et les troubles de l'humeur est bien établie, et lorsque les patients TUAL présentent des symptômes anxieux ou dépressifs, ils sont plus sensibles aux émotions négatives (Schuckit, 2006).

La cognition sociale fait référence à des processus cognitifs tels que le décodage des émotions, la théorie de l'esprit (capacité à se représenter les états mentaux d'autrui) et l'empathie (habileté à comprendre et partager les ressentis d'autrui), qui sont impliqués dans les interactions sociales. Les études qui se sont intéressées à la cognition sociale dans le TUAL montrent que les patients présentent des déficits de théorie de l'esprit (Bosco *et al.*, 2014; Nandrino *et al.*, 2014; Maurage *et al.*, 2015; Onuoha *et al.*, 2016). Des dissociations entre les versants affectif et cognitif de la théorie de l'esprit et de l'empathie ont été mises en évidence (Maurage *et al.*, 2011, 2016). En effet, les patients ne semblent pas avoir de difficultés pour identifier et comprendre les intentions et pensées des autres, alors que leurs capacités à comprendre et ressentir les émotions et sentiments des autres sont altérées. Les déficits de cognition sociale observés chez les patients TUAL peuvent perturber leurs relations interpersonnelles et les conduire vers un cercle vicieux dans lequel leur mécanisme d'adaptation

est de consommer de l'alcool pour surmonter l'isolement social (Kornreich *et al.*, 2002; Maurage *et al.*, 2017; Hoffman *et al.*, 2019).

2.4. Facteurs d'hétérogénéité des troubles neuropsychologiques

Alors qu'environ 20% des patients TUAL ne présentent pas de déficits cognitifs, le profil neuropsychologique des autres patients est particulièrement hétérogène (Ihara *et al.*, 2000; Vabret *et al.*, 2013). En effet, 50 à 75% d'entre eux ont des atteintes des fonctions exécutives qui peuvent être associées ou non à des troubles de la mémoire, alors que d'autres patients présentent une altération cognitive globale. Différents facteurs pouvant contribuer à l'hétérogénéité de ces atteintes ont été identifiés (**Figure 8**).

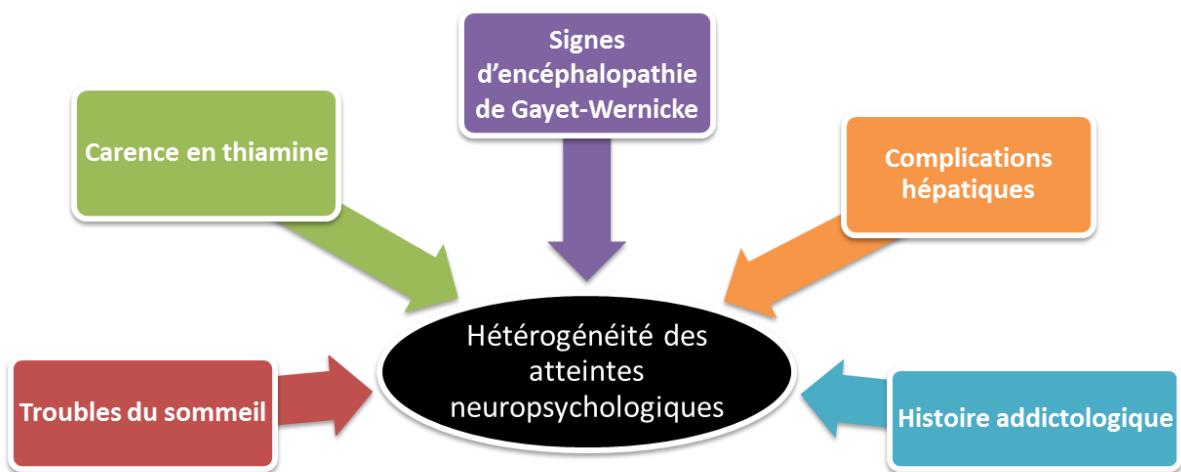


Figure 8 : Facteurs contribuant à l'hétérogénéité des atteintes neuropsychologiques dans le TUAL. *Adaptée de Maillard *et al.*, 2020.*

Des relations ont notamment pu être établies entre les déficits neuropsychologiques et la quantité totale d'alcool consommée au cours de la vie (Ryback, 1971) ou encore l'ancienneté du TUAL (Sullivan *et al.*, 2000b). Par ailleurs, comme nous l'avons déjà décrit (chapitre I partie

4.1.), le sevrage est neurotoxique. Des études ont mis en évidence que le fait d'avoir expérimenté au moins deux sevrages entraînerait des déficits exécutifs plus importants que lorsqu'un seul sevrage a été réalisé (Duka *et al.*, 2003; Loeber *et al.*, 2010). Une relation entre la sévérité du sevrage et les performances des fonctions exécutives a récemment été trouvée dans une étude menée dans le laboratoire (Laniepce *et al.*, 2020).

La présence de signes d'EGW peut expliquer, au moins partiellement, l'hétérogénéité des déficits neuropsychologiques des patients TUAL. En effet, en utilisant les critères de Caine *et al.* (1997) dans un groupe de patients TUAL sans complications neurologiques, Pitel *et al.* ont trouvé un continuum d'atteintes cognitives entre : 1) les patients ne répondant à aucun critère de l'EGW (27%), qui ont des performances équivalentes à celles des sujets contrôles, 2) les patients répondant à un critère (57%), qui présentent des déficits légers à modérés, et 3) les patients répondant à deux critères ou plus (16%), qui ont les déficits les plus sévères dans chacun des domaines cognitifs examinés (Pitel *et al.*, 2011). L'utilisation de ces critères peut également permettre de repérer les patients à risque de développer une EGW et d'adapter la prise en charge de ces derniers.

De plus, le niveau de thiamine dans le sang et dans le sérum a été mis en lien avec les déficits cognitifs (Coulbault *et al.*, 2019). Le niveau de thiamine permet notamment de prédire les performances mnésiques des patients TUAL (Ritz *et al.*, 2016a). Le niveau de gamma-glutamyltransférase (GGT) a été mis en lien avec les performances de flexibilité mentale des patients TUAL (Junghanns *et al.*, 2004). Par ailleurs, les atteintes hépatiques, évaluées par le FibroMètre®, sont également associées à des déficits exécutifs (Ritz *et al.*, 2016a). L'alimentation joue un rôle important dans le fonctionnement cognitif (Scarmeas *et al.*, 2018). Une étude a notamment indiqué que chez des patients TUAL, l'indice de masse corporelle, qui reflète le statut nutritionnel, est associé à des troubles cognitifs (Gautron *et al.*, 2018). Il a également été mis en évidence que l'association d'une déficience thiaminique, d'une dénutrition et d'atteintes hépatiques permettrait de prédire la sévérité des troubles neuropsychologiques (Ritz *et al.*, 2016a).

Enfin, les patients TUAL rapportent fréquemment des troubles du sommeil (Laniepce *et al.*, 2019). Il existe notamment un lien entre le sommeil lent et les fonctions exécutives, plus la proportion de sommeil lent est faible plus les performances exécutives sont altérées (Laniepce *et al.*, 2020). Les consommations chroniques et excessives d'alcool sont également associées à des déficits de la consolidation mnésique qui est dépendante du sommeil (Junghanns *et al.*, 2009).

Ces facteurs jouent un rôle dans l'hétérogénéité des atteintes neuropsychologiques mais vont également influencer la récupération des atteintes cognitives et cérébrales.

3. Réversibilité des atteintes avec l'arrêt de l'alcool

De nombreuses études ont montré que les altérations cérébrales et cognitives, décrites dans le TUAL, sont réversible, au moins en partie, avec l'arrêt des consommations d'alcool (Pitel *et al.*, 2009b; van Eijk *et al.*, 2013; Mulhauser *et al.*, 2018), et ce même en l'absence de stimulation. Pour décrire ce phénomène, Goldman (1990) fait référence à la récupération dépendante du temps ou encore à la récupération spontanée. Pour étudier cette récupération, les études s'appuient sur des plans expérimentaux qui peuvent être transversaux, consistant à comparer plusieurs groupes de patients qui sont à des durées d'abstinence différentes, ou longitudinaux qui permettent d'examiner les changements d'un même groupe de patients au cours du temps.

D'un point de vue méthodologique, la caractérisation de la rechute ou de la réussite du traitement lors du suivi nécessite l'utilisation de critères. Jusqu'à récemment, la prise en charge addictologique post-sevrage avait pour objectif le maintien de l'abstinence totale. Cependant, certains patients pourraient être plus motivés, en tous cas au départ, par une réduction des consommations que par la perspective d'une abstinence stricte (DeMartini *et al.*, 2014). L'objectif thérapeutique serait ainsi non plus l'arrêt total des consommations d'alcool mais la diminution des risques associés aux consommations. En parallèle, l'OMS a défini des niveaux de risques associés aux consommations selon les conséquences qui en découlent : très hauts risques, hauts risques, risques modérés, et faibles risques (**Tableau 1**). L'Agence Européenne du Médicament considère désormais qu'une réduction de deux niveaux des risques associés aux consommations peut être utilisée comme objectif thérapeutique secondaire dans les essais cliniques (European Medicines Agency, 2010). La FDA considère, quant à elle, que l'absence de jours de consommation abusive peut également être un objectif thérapeutique alternatif à l'abstinence stricte (Food and Drug Administration, 2015).

Tableau 1 : Niveaux de risques associés aux consommations d’alcool définis par l’OMS (quantité en grammes par jour)

	Hommes	Femmes
Faibles risques	1 à 40 g	1 à 20 g
Risques modérés	41 à 60 g	21 à 40 g
Hauts risques	61 à 100 g	41 à 60 g
Très hauts risques	101+ g	61+ g

3.1. Récupération cérébrale

Le maintien d’une période d’abstinence à plus ou moins long terme permet d’observer une récupération cérébrale dans de nombreuses études (Pfefferbaum *et al.*, 1995; Johnson-Greene *et al.*, 1997; Agartz *et al.*, 2003; Cardenas *et al.*, 2007; Alhassoon *et al.*, 2012; Segobin *et al.*, 2014). Une longue période d’abstinence (au moins un an) a été associée à une augmentation des valeurs de FA, notamment au sein du corps calleux (Alhassoon *et al.*, 2012; Pfefferbaum *et al.*, 2014), suggérant une restauration de la myéline des axones. Cette amélioration de l’intégrité des fibres de substance blanche a également été montrée au cours du premier mois d’abstinence (Gazdzinski *et al.*, 2010; De Santis *et al.*, 2019), et elle est accompagnée d’une augmentation du volume de substance blanche (Agartz *et al.*, 2003).

Alors que Wobrock *et al.* (2009) indiquent une diminution de 5 à 6% du volume des ventricules latéraux au cours des neuf mois qui suivent le sevrage, le volume de substance grise des lobes frontaux ne semble pas évoluer. Les auteurs suggèrent alors que la récupération est seulement partielle. Cependant, d’autres études explorant la récupération cérébrale après sept mois d’abstinence, ont décrit une augmentation des volumes de substance grise (Durazzo *et al.*, 2015, Zou *et al.*, 2018a), qui atteint même un volume équivalent à celui des sujets contrôles au niveau des lobes frontaux (Durazzo *et al.*, 2015). Une amélioration notable du volume de substance grise est également remarquée dès les premières semaines post-sevrage (20 jours, Pfefferbaum *et al.*, 1995; deux semaines, van Eijk *et al.*, 2013). De façon intéressante, il a été montré que l’amélioration de volume de substance grise n’est pas linéaire (Durazzo *et al.*, 2015, Zou *et al.*, 2018a). En effet, les changements intervenant au cours du premier mois d’abstinence sont plus importants que ceux qui interviennent entre le premier et le septième mois d’abstinence.

Par ailleurs, des études ont mis en évidence qu'après une longue période d'abstinence, le débit sanguin cérébral des lobes frontaux revient à un niveau normal (Gansler *et al.*, 2000), et que le métabolisme de glucose s'améliore partiellement avec notamment une diminution de l'hypométabolisme frontal médial et orbitofrontal chez les patients TUAL abstinents depuis 10 à 32 mois (Johnson-Greene *et al.*, 1997).

Une étude menée dans le laboratoire a évalué la récupération cérébrale, au cours des six mois post-sevrage, en corrélant les quantités totales d'alcool consommées au cours de la période de suivi et les changements de volumes cérébraux régionaux (Segobin *et al.*, 2014). Il a été montré que la quantité des consommations d'alcool était négativement corrélée avec le volume de différentes régions cérébrales (cervelet, striatum, et gyrus cingulaire notamment) : les consommations importantes étaient liées à une faible récupération. De plus, le degré de récupération n'était pas le même selon les régions, suggérant que la dynamique de plasticité neuronale serait dépendante des régions. Enfin, les résultats ont également révélé que des consommations d'alcool très limitées (inférieures à 10g d'alcool pur par jour, une unité) entre l'évaluation post-sevrage et l'évaluation de suivi n'empêchaient pas la récupération cérébrale. Récemment, une autre étude a mis en évidence que huit mois après le sevrage d'alcool, les patients qui ont diminué leurs consommations de deux niveaux selon les critères de l'OMS, présentent des volumes de substance grise équivalents à ceux des patients qui sont restés abstinents au cours de cette période. A l'opposé, les patients qui ont eu des consommations à hauts risques au cours des huit mois ont des volumes thalamiques et frontaux inférieurs à ceux des patients ayant diminué leurs consommations d'alcool et des sujets contrôles (Meyerhoff and Durazzo, 2020). Cardenas *et al.* (2007) ont également mis en évidence que huit mois après le sevrage, la récupération de substance grise du thalamus, du cervelet, du gyrus cingulaire antérieur et de l'insula, entre autres, est plus limitée chez les patients rechuteurs que chez les patients ayant maintenu une abstinence.

3.2. Récupération cognitive

Tout comme pour la récupération cérébrale, les déficits neuropsychologiques observés après le sevrage d'alcool sont réversibles, au moins partiellement.

3.2.1. A court-terme

Les études qui ont exploré les changements cognitifs qui interviennent à court-terme, c'est-à-dire au cours des semaines qui suivent le sevrage, révèlent des résultats contradictoires, surtout concernant les fonctions exécutives. En effet, certaines études révèlent une amélioration des performances exécutives des patients TUAL (Kish *et al.*, 1980; Mann *et al.*, 1999; Manning *et al.*, 2008; Kaur *et al.*, 2020), tandis que d'autres indiquent une persistance du dysfonctionnement exécutif (Loeber *et al.*, 2010; Mulhauser *et al.*, 2018), et notamment des troubles de l'inhibition (Petit *et al.*, 2017). Concernant les performances de mémoire épisodique, une amélioration précoce a été mise en évidence (trois semaines post-sevrage pour Manning *et al.*, 2008 ; 10 jours pour Mulhauser *et al.*, 2018).

3.2.2. A moyen-terme

Certains travaux ont examiné la récupération des patients TUAL à moyen-terme, i.e. après quelques mois d'abstinence. Dans leur méta-analyse, Stavro *et al.* (2013) ne montrent pas d'effet de l'arrêt des consommations durant quelques mois sur les performances cognitives. Les résultats de l'étude longitudinale de Ros-Cucurull *et al.* (2018) sont moins tranchés. En effet, les auteurs rapportent que six mois après le sevrage, les performances cognitives des patients qui sont restés abstinents ne sont pas différentes de celles des patients ayant rechuté. Les analyses ne montrent pas non plus d'amélioration significative des performances au cours de cette période. Cependant, lorsque les auteurs comparent les patients abstinents et les sujets contrôles, ils montrent, malgré tout, que les performances du groupe de patients abstinents tendent à se normaliser. D'autres travaux indiquent qu'il y a une amélioration (Loeber *et al.*, 2010; Ioime *et al.*, 2018), voire même une normalisation (Pitel *et al.*, 2009b) du fonctionnement cognitif après six mois d'abstinence.

3.2.3. A long-terme

Alors que certaines études montrent que, chez les patients TUAL, les déficits de mémoire et des fonctions exécutives persistent à long-terme, i.e. après une période d'abstinence d'au moins un an (Munro *et al.*, 2000; Nowakowska-Domagała *et al.*, 2017), d'autres études indiquent au contraire une récupération, voire même une normalisation, de ces performances cognitives (Rourke and Grant, 1999; Fein *et al.*, 2006; Stavro *et al.*, 2013). Les études

s'accordent sur le fait, qu'après une longue période d'abstinence, les performances de mémoire épisodique des patients TUAL reviennent à un niveau équivalent à celui des sujets contrôles (Reed *et al.*, 1992; Rourke and Grant, 1999; Munro *et al.*, 2000).

3.2.4. Impact de la rechute

Un déclin des performances de flexibilité, entre l'évaluation post-sevrage et la seconde évaluation réalisée six mois après la première, a été mis en évidence chez des patients définis comme rechuteurs car ils avaient consommé au moins une unité d'alcool au cours de la période de suivi (Pitel *et al.*, 2009b). Ce résultat suggère que la reprise des consommations d'alcool entraîne une détérioration encore plus importante des fonctions exécutives. Rourke et Grant (1999) ont également mis en évidence un effet néfaste de la reprise des consommations sur les habiletés motrices.

3.2.5. Facteurs influençant la récupération

Le fait que les résultats soient contradictoires d'une étude à l'autre peut s'expliquer par l'influence que certains facteurs ont sur la récupération. Parmi ces facteurs, il y a notamment le nombre de sevrages expérimentés par les patients (Loeber *et al.*, 2010). Par exemple, les patients qui ont fait moins de deux épisodes de sevrage d'alcool améliorent davantage leurs performances de flexibilité et de *shifting* à l'arrêt des consommations que ceux qui ont fait plus de sevrages. Etant donné que les patients non-fumeurs semblent mieux récupérer que les patients fumeurs, il est également important de prendre en compte le statut tabagique (Durazzo *et al.*, 2015). L'âge que les patients ont lorsqu'ils arrêtent de consommer de l'alcool peut également expliquer l'hétérogénéité des résultats (Rourke and Grant, 1999; Munro *et al.*, 2000; Ros-Cucurull *et al.*, 2018). Un ralentissement de la dynamique de récupération, pouvant être lié à une diminution de la plasticité cérébrale, a été décrit chez les patients TUAL âgés. La récupération peut également être influencée par une utilisation simultanée de benzodiazépines (Manning *et al.*, 2008; Petit *et al.*, 2017). Enfin, du fait de l'hétérogénéité des profils cognitifs chez les patients TUAL, les études transversales (e.g. Nowakowska-Domagała *et al.*, 2017) fournissent des résultats moins fiables que les études longitudinales (e.g. Ioime *et al.*, 2018).

La récupération semble dépendre de la durée d'abstinence mais également des fonctions cognitives étudiées. En effet, la récupération cognitive pourrait se faire en fonction de la

dynamique de récupération des différentes régions cérébrales. Cependant, les études ayant exploré conjointement la récupération cognitive et cérébrale sont rares. Brandt *et al.* (1983) évoquent le fait que la récupération cognitive est en lien avec une récupération anatomique et fonctionnelle de différents substrats cérébraux. L'augmentation de volume cérébral a été mise en lien avec des modifications métaboliques et une augmentation des capacités attentionnelles (Bartsch *et al.*, 2007), ainsi qu'avec une amélioration de la vitesse de traitement des informations (Durazzo *et al.*, 2015).

4. Retentissement des troubles cognitifs sur la prise en charge addictologique

Les troubles neuropsychologiques observés chez les patients TUAL récemment sevrés peuvent empêcher les patients de bénéficier pleinement des prises en charge généralement proposées à la suite du sevrage (McCrady and Smith, 1986; Fein *et al.*, 1990; Tapert *et al.*, 2004). Au cours de cette partie, nous explorerons comment les déficits cognitifs peuvent impacter la prise en charge addictologique usuelle, ce qui nous amènera à proposer une alternative.

4.1. La motivation à changer de comportement

Les troubles neuropsychologiques précédemment décrits peuvent ralentir le processus motivationnel qui est nécessaire pour abandonner un comportement de consommations excessives d'alcool. Or, un haut niveau de motivation est crucial pour que les patients s'engagent dans une prise en charge addictologique (DiClemente *et al.*, 1999). L'entretien motivationnel est une technique thérapeutique qui peut dans un premier temps aider à évaluer quelles sont les dispositions du patient à changer de comportement. Cette technique peut également permettre d'engager un patient ambivalent ou résistant dans un processus de changement. L'entretien motivationnel favorise le développement de motivations internes pour changer les habitudes de consommation (Miller and Rollnick, 1991). D'après le modèle transthéorique de Prochaska et DiClemente (1982), les changements de comportement

impliquent une évolution de la motivation en cinq étapes (pré-contemplation, contemplation, décision, action, maintien) auxquelles s'ajoutent un stade additionnel de rechute dans lequel le patient entre si les efforts qu'il a fait jusque-là échouent.

Le processus de motivation à abandonner les comportements inadaptés en faveur d'un style de vie plus sain nécessite que le patient soit conscient que ses consommations d'alcool sont problématiques, qu'il résolve son ambivalence, qu'il décide d'arrêter de consommer, et qu'il mette en place des stratégies pour agir différemment. Les troubles de mémoire épisodique, les dysfonctionnements exécutifs, et les déficits de prise de décision ont été mis en lien avec les stades motivationnels (Blume *et al.*, 2005; Le Berre *et al.*, 2012, 2013). En effet, un faible niveau motivationnel (pré-contemplation et contemplation) a été mis en lien avec de faibles performances de mémoire épisodique et de fonctions exécutives ainsi qu'avec une réduction du volume de substance grise au niveau du cervelet, des lobes frontaux et du gyrus fusiforme. En revanche, les patients qui n'ont pas d'altérations cérébrales et de déficits cognitifs seraient à un stade motivationnel plus avancé. Ces résultats suggèrent que les patients qui présentent des déficits cognitifs sont moins en mesure de se remémorer les conséquences négatives liées aux consommations d'alcool et qu'ils ne sont pas à même de réaliser une balance décisionnelle pour engager le changement. Un ensemble de capacités cognitives complémentaires est donc nécessaire pour prendre conscience et résoudre l'ambivalence liée au TUAL. Du fait des déficits cognitifs et de leur faible motivation au changement, certains patients ne seraient ainsi pas en mesure de poursuivre une prise en charge addictologique standard incluant de la psychoéducation ou des thérapies cognitivo-comportementales (Le Berre *et al.*, 2012).

4.2. Nouveaux apprentissages complexes

Lorsqu'un patient a fini son sevrage d'alcool, il se voit proposer de poursuivre sa prise en charge aux moyens d'outils thérapeutiques divers. Actuellement, les services d'addictologie proposent principalement des thérapies cognitivo-comportementales (TCC) basées sur des modèles de prévention de la rechute, ainsi que des ateliers de psychoéducation.

L'objectif des TCC est que le patient apprenne à reconnaître les principales situations à risque de rechute et à les déjouer en appliquant des schémas de réponses comportementales adaptées. En effet, la rechute est conçue comme le produit final de l'accumulation d'une série

d'événements, de décisions et de schémas de pensées automatiques (Lukasiewicz and Frénoy-Peres, 2006). Les patients doivent donc identifier et contrôler les épisodes de *craving* ou d'envie d'alcool (circonstances, intensité, etc.) et anticiper et gérer les situations à risque (émotionnelles, relationnelles, environnementales). Les interventions visent aussi à augmenter le sentiment d'efficacité personnelle et la confiance en soi du patient, ce qui va réduire le risque de rechute ultérieur.

Par ailleurs, la psychoéducation consiste à fournir, aux patients, des informations et connaissances concernant les addictions. L'hypothèse générale est que les patients qui savent, comprennent, et apprennent ce qu'est l'alcool, comment il agit sur le corps et le cerveau, et quelles sont les conséquences des consommations excessives, sont plus motivés à changer leurs comportements et leurs habitudes et sont plus actifs durant la prise en charge.

Les TCC cherchent donc à modifier des comportements routiniers et la psychoéducation à apprendre de nouvelles connaissances générales. Ces thérapies requièrent donc l'apprentissage et la mise en œuvre de nouvelles compétences, procédures, et habitudes sans l'alcool. Cependant, en lien avec leurs troubles de mémoire épisodique et des fonctions exécutives, les patients TUAL présentent des difficultés pour l'apprentissage de nouveaux concepts sémantiques et de nouvelles procédures cognitives (Pitel *et al.*, 2007b). Les patients peuvent acquérir ces compétences mais plus lentement que des sujets contrôles, ce qui suggère que les nouveaux apprentissages complexes réalisés précocement après le sevrage nécessitent davantage de répétitions.

4.3. Proposition d'aménagement de la prise en charge

Pour bénéficier pleinement des prises en charge addictologique, les capacités cognitives de haut niveau sont essentielles. Chez des patients TUAL présentant des troubles neuropsychologiques, il n'est pas pertinent de proposer de telles thérapies immédiatement après le sevrage. Une prise en charge adaptée au profil cognitif des patients est à privilégier. En effet, comme nous l'avons décrit dans la section 3.2. de ce chapitre, l'arrêt des consommations d'alcool permet une récupération cognitive. Le fait de repousser de quelques semaines le début de la prise en charge addictologique en proposant aux patients un séjour en soins de suite et de réadaptation (SSR) pourrait permettre cette récupération cognitive. En effet, durant ce séjour

les patients seraient à l'abri des consommations d'alcool, auraient des repas complets et réguliers, et bénéficieraient d'une prise en charge pluridisciplinaire. La récupération induite par ce séjour leur permettrait, par la suite, de mieux s'emparer des différentes notions abordées durant les ateliers de psychoéducation et de TCC (**Figure 9**).

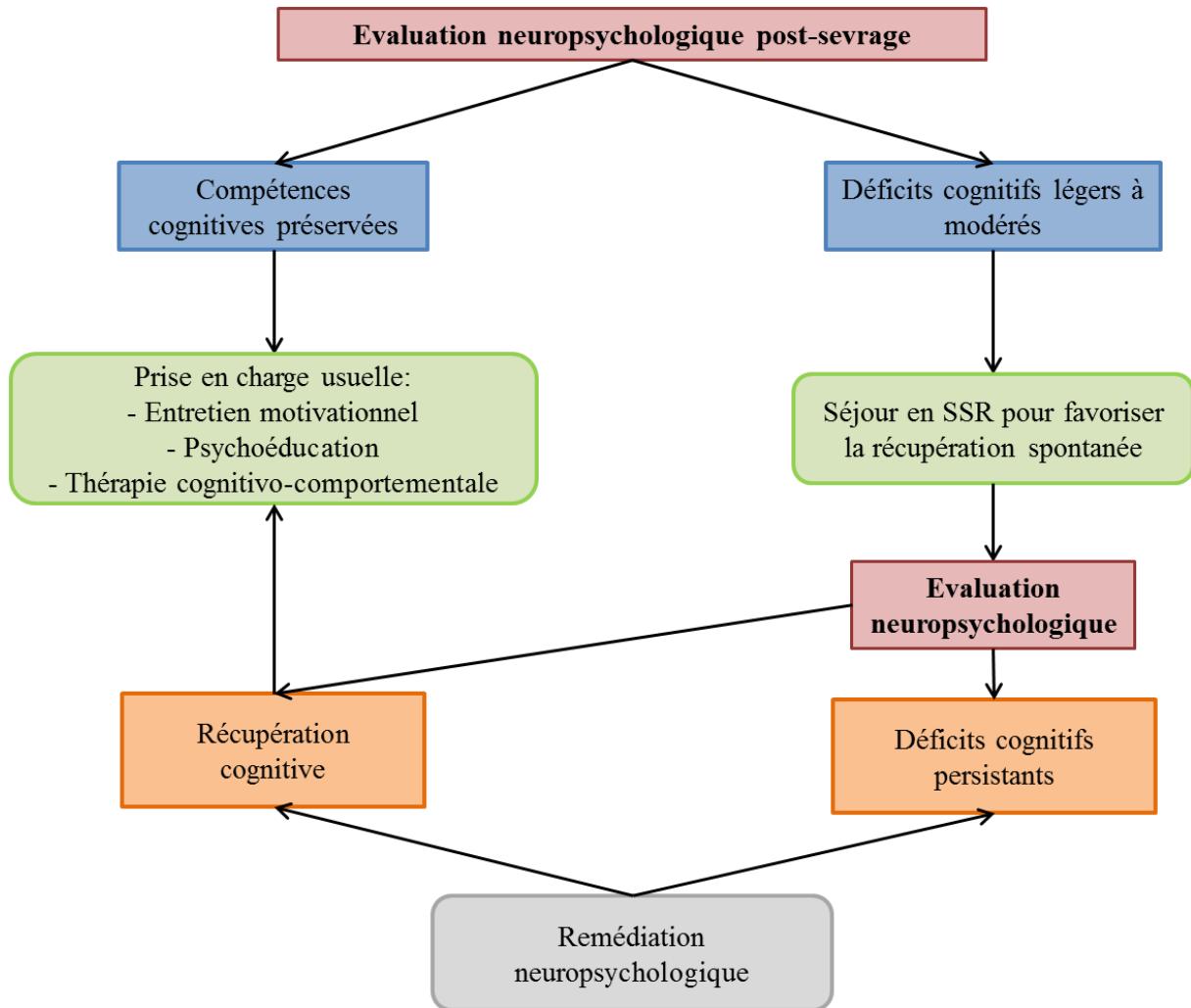


Figure 9 : Comment adapter la prise en charge addictologique en tenant compte des capacités cognitives des patients TUAL.

5. Facteurs de vulnérabilité à la rechute

Le TUAL est une pathologie chronique caractérisée par un fort taux de rechute. La rechute fait partie intégrante du processus de soin et il faut pouvoir préparer les patients à gérer cela. De nombreuses études ont examiné les facteurs qui peuvent influencer la capacité à maintenir

ou non le contrat thérapeutique (abstinence ou réduction des consommations). Une récente revue de littérature a identifié un ensemble de facteurs biologiques et psychologiques (Sliedrecht *et al.*, 2019).

5.1. Facteurs Biologiques

5.1.1. Altérations cérébrales

L'altération de certaines régions cérébrales a été associée à la rechute. Les lobes frontaux sont particulièrement impliqués, les études rapportent notamment une atrophie plus marquée au niveau du cortex orbitofrontal, du cortex préfrontal dorsolatéral, et du cortex cingulaire antérieur chez les futurs rechuteurs que chez les patients qui resteront abstinents (Cardenas *et al.*, 2011; Durazzo *et al.*, 2011; Beck *et al.*, 2012; Durazzo and Meyerhoff, 2017; Zois *et al.*, 2017; Wang *et al.*, 2018). Une diminution du débit sanguin cérébral (Noël *et al.*, 2002) ainsi qu'une hypoactivation (Sebold *et al.*, 2017) du cortex préfrontal médian ont également été trouvées chez des groupes de patients TUAL ayant rechuté respectivement deux mois et neuf mois après l'arrêt des consommations. Les volumes pariétaux (Rando *et al.*, 2011), insulaires (Wu *et al.*, 2018; Durazzo and Meyerhoff, 2019), amygdaliens (Wräse *et al.*, 2008; Cardenas *et al.*, 2011; Wu *et al.*, 2018), hippocampiques (Cardenas *et al.*, 2011; Wu *et al.*, 2018) et thalamiques (Segobin *et al.*, 2014; Wang *et al.*, 2018) ont également été mis en lien avec le risque de rechute. Récemment, une étude a mis en évidence que les patients TUAL pour lesquels l'atrophie frontale et insulaire persiste après un mois d'abstinence sont ceux qui répondent le moins favorablement aux interventions psychosociales et pharmacologiques (Durazzo and Meyerhoff, 2019).

5.1.2. Troubles du sommeil

Les études ayant exploré les liens entre les troubles du sommeil et la rechute ont montré qu'après le sevrage, un sommeil perçu comme étant de mauvaise qualité augmenterait le risque de rechuter précocement (Conroy *et al.*, 2006; Brower *et al.*, 2011; Smith *et al.*, 2014). Des mesures objectives de sommeil ont permis de confirmer ce résultat. En effet, une longue latence

d'endormissement (Brower *et al.*, 1998; Drummond *et al.*, 1998) et de nombreux réveils nocturnes (Conroy *et al.*, 2006) contribueraient à la reprise des consommations. Un lien entre la rechute et la proportion de sommeil lent au cours de la nuit a également été retrouvé (Gillin, 1994; Clark *et al.*, 1998; Drummond *et al.*, 1998). Alors qu'il a été proposé que l'alcool est initialement utilisé comme automédication pour pallier aux troubles du sommeil (He *et al.*, 2019), le fait que les patients aient une histoire d'automédication des insomnies ne semble pas influencer le résultat de la prise en charge (Brower *et al.*, 2001).

5.1.3. Hormones et biomarqueurs

Bien qu'ils ne soient pas fréquemment étudiés, les niveaux hormonaux et de certains biomarqueurs spécifiques à l'alcool semblent être de bons indices pour déterminer le risque de rechute. Il a, par exemple, été montré que les situations stressantes pour les patients TUAL sont associées à une diminution du niveau de cortisol salivaire et à une rechute plus rapide (Junghanns *et al.*, 2003; Higley *et al.*, 2011). Par ailleurs, un marquage positif d'éthylglucuronide urinaire, un métabolite de l'alcool, après le sevrage après le sevrage (Barrio *et al.*, 2017), ainsi qu'une valeur élevée de GGT au moment de l'hospitalisation (Aguiar *et al.*, 2012) sont également associés à un taux de rechute élevé.

5.2. Facteurs Psychologiques

5.2.1. Troubles neuropsychologiques

Alors que cliniquement, il semble désormais assez évident qu'un patient qui présente des troubles neuropsychologiques a davantage de risques de rechuter, les résultats des études ne sont pas tous consitants. En effet, certaines études rapportent que des déficits de mémoire de travail (Noël *et al.*, 2002), une réponse inhibitrice altérée (Noël *et al.*, 2002; Camchong *et al.*, 2013; Czapla *et al.*, 2016) et des troubles attentionnels (Allsop *et al.*, 2000; Garland *et al.*, 2012) observés à l'issue du sevrage peuvent être des facteurs de rechute. En revanche, d'autres travaux ne montrent pas de différence entre les performances cognitives post-sevrage des patients qui par la suite ont rechuté et celles de ceux qui ont maintenu une abstinence au cours de la période de suivi (Moriyama *et al.*, 2002; Pitel *et al.*, 2009b; Manning *et al.*, 2016).

5.2.2. Prise de Décision, Impulsivité et Craving

Le TUAL est parfois considéré comme un déséquilibre entre trois systèmes en interaction. Le système réflexif, sous-tendu par le cortex préfrontal, anticipe les conséquences d'une décision et exerce un contrôle inhibiteur. Le système impulsif est associé au striatum et à l'amygdale, il est impliqué dans l'évaluation affective des stimulations ce qui conduit à des comportements impulsifs. Ces systèmes seraient régulés par l'insula qui traduit les signaux intéroceptifs en ressentis conscients, comme le *craving* (Noël *et al.*, 2013). Face à de l'alcool, la prise de décision va donc dépendre de l'équilibre entre ces systèmes.

Les patients TUAL présentent un biais attentionnel pour les stimuli liés à l'alcool. Ainsi, leur attention est captée, dans l'environnement, par les informations de type publicité pour de l'alcool à un arrêt de bus, une bouteille d'alcool dans une poubelle, ou encore une tête de gondole du rayon alcool au supermarché. Les ressources attentionnelles vont être automatiquement accaparées par ces indices, favorisant l'apparition d'un *craving* (Wiers *et al.*, 2013). Or, un score de *craving* post-sevrage élevé est associé à un risque important de rechuter trois mois et 12 mois après le sevrage (Stohs *et al.*, 2019). Une autre étude a également mis en évidence que le score de *craving* était plus élevé chez des patients TUAL ayant rechuté au cours d'une période de 24 mois que chez des patients ayant maintenu une abstinence au cours de cette période (Weinland *et al.*, 2019).

Quand les patients TUAL sont confrontés à des indices liés à l'alcool ils ont tendance à agir de façon impulsive en favorisant la récompense immédiate d'une consommation et en ignorant les conséquences négatives à long terme de leur choix. Dans les conduites addictives le système impulsif serait hyper activé et le système réflexif hypo activé ce qui favoriserait des comportements de consommations, sur-appris et automatiques, augmentant ainsi le risque de rechutes (Noël *et al.*, 2013). Les patients continuent de boire, en dépit des conséquences néfastes sur leurs relations sociales, leur travail, leur santé et leurs finances, ceci est en lien avec des troubles de la prise de décision (Noël *et al.*, 2007b; Loeber *et al.*, 2009, Le Berre *et al.*, 2014b). On parle alors de « myopie » pour le futur (Le Berre *et al.*, 2014b). Ces troubles de prise de décision sont également en jeu dans les ré-alcoolisations et dans le phénomène de rechute. Une étude a en effet mis en évidence que des déficits de prise de décisions, au moment de l'entrée dans une communauté thérapeutique, sont associés à un abandon prématûre de la prise en charge sans que les patients aient atteint leurs objectifs thérapeutiques, alors que l'impulsivité est liée à un taux de rechute élevé (Barreno *et al.*, 2019).

5.2.3. Emotions et relations interpersonnelles

Plus de 40% des rechutes après le sevrage d'alcool sont liées à des difficultés émotionnelles (Zywiak *et al.*, 2003). Dans leur étude, Rupp *et al.* (2017) ont indiqué que les patients ayant rechuté au cours de la période de suivi de trois mois sont ceux qui présentaient initialement les plus faibles performances de reconnaissance des émotions. Ces déficits de traitement des émotions ont été mis en lien avec des difficultés dans les relations interpersonnelles (Kornreich *et al.*, 2002; Hoffman *et al.*, 2019).

Les patients TUAL présentant des déficits cognitifs interprètent mal leurs propres états émotionnels ainsi que les émotions et intentions des autres, ce qui peut potentiellement résulter en des comportements et des interactions sociales inadaptés (Maurage *et al.*, 2011). Une étude utilisant une tâche informatisée de *cyberball*¹ a mis en évidence que les patients TUAL présentent un sentiment d'exclusion sociale supérieur à celui des sujets contrôles (Maurage *et al.*, 2012). De manière intéressante, les auteurs ont montré que lorsque les patients sont à nouveau inclus socialement, le sentiment d'exclusion persiste, suggérant des ruminations négatives (Zadro *et al.*, 2006). Ces déficits sociaux et émotionnels contribuent au cercle vicieux du TUAL. En effet, les consommations d'alcool sont fréquemment utilisées comme stratégie d'adaptation pour surmonter les difficultés interpersonnelles, et notamment pour faire face à l'isolement social. A son tour, l'augmentation des consommations d'alcool pourrait aggraver les déficits des habiletés sociales et émotionnelles. De ce fait, les déficits de cognition sociale peuvent être considérés comme un facteur de vulnérabilité à la rechute des patients TUAL. En revanche, certaines études ont mis en avant un effet « protecteur » de la qualité du soutien social, d'un contexte social positif, ou encore du fait d'avoir eu un enfant pour les femmes (Sliedrecht *et al.*, 2019 pour revue).

5.2.4. Comorbidités psychiatriques et addictologiques

Les troubles de l'usage de substance sont fréquemment associés à des comorbidités psychiatriques (Aguiar *et al.*, 2012). Ces comorbidités, que ce soit la dépression (Curran *et al.*, 2000; Driessens *et al.*, 2001), les troubles anxieux (Driessens *et al.*, 2001; Schellekens *et al.*,

¹ Le *cyberball* est un jeu virtuel de lancer de balle qui est utilisé pour étudier l'ostracisme, et les sentiments de rejet et d'exclusion sociale. Au cours de ce jeu, le participant est amené à croire qu'il joue avec deux autres personnes. La tâche comprend des phases d'inclusion pendant lesquelles les deux partenaires jouent avec le participant et des phases d'exclusion au cours desquelles ils se lancent la balle uniquement l'un à l'autre.

2015), ou encore les troubles de la personnalité (Lopez-Quintero *et al.*, 2011; Chiappetta *et al.*, 2014) sont souvent mises en cause dans la reprise des consommations d'alcool. De même, les patients qui présentent des troubles de l'usage d'autres substances associés au TUAL, y compris du tabac, sont plus susceptibles de rechuter que des patients qui n'ont qu'un TUAL (Lopez-Quintero *et al.*, 2011; Copeland *et al.*, 2012; Chiappetta *et al.*, 2014; Durazzo and Meyerhoff, 2017).

RESUME

Les consommations chroniques et excessives d'alcool entraînent des altérations cérébrales structurales et métaboliques qui conduisent au dysfonctionnement de deux circuits cérébraux : le circuit de Papez et le circuit fronto-cérébelleux. L'altération de ces circuits va entraîner des dysfonctionnements cognitifs et notamment des fonctions exécutives et de la mémoire épisodique.

Le maintien d'une abstinence va permettre la réversibilité de ces atteintes cérébrales et cognitives.

Cependant, ces troubles cognitifs observés post-sevrage vont empêcher les patients de bénéficier pleinement de la prise en charge addictologique usuelle (psychoéducation, thérapies cognitivo-comportementales). Il semble donc important pour ces patients de retarder le début de la prise en charge afin de permettre une récupération cognitive qui devrait favoriser le maintien de contrat thérapeutique.

La présence d'altérations cérébrales et cognitives, associée à d'autres facteurs psychologiques et biologiques augmente le risque de rechute de ces patients. Il est donc primordial de les considérer dans la mise en place des prises en soins addictologiques.

III. ATTEINTES CEREBRALES ET COGNITIVES DANS LE SYNDROME DE KORSAKOFF

Une théorie postule que l'alcool affecte le cerveau et la cognition selon un continuum de sévérité allant de léger à modéré chez les patients TUAL, jusqu'à des déficits et altérations cérébrales sévères dans le SK (Ryback, 1971; Parsons, 1998). Les comparaisons entre les patients TUAL avec et sans SK permettent de mieux comprendre les spécificités cognitives et cérébrales du SK et les mécanismes physiopathologiques qui sous-tendent ces spécificités.

1. Description clinique

Le syndrome de Korsakoff (SK) est une complication neurologique qui est principalement observée à la suite d'une encéphalopathie de Gayet-Wernicke. Cependant, le développement du SK peut également être insidieux (Cutting, 1978). C'est lors d'une conférence à Paris en 1889 que Serguei Korsakoff a décrit le cas d'un malade de 37 ans, présentant des consommations d'alcool chroniques et excessives, et dont les amis avaient noté l'apparition de troubles de la mémoire et de la marche (Korsakoff, 1889). Une aggravation des troubles de mémoire avec le temps a été décrite, le patient présentait alors un oubli à mesure ayant des répercussions importantes dans la vie quotidienne. Initialement appelée « névrite multiple » par Korsakoff, cette pathologie prendra le nom de syndrome de Korsakoff en 1897. Par ailleurs, Korsakoff a mentionné que l'apparition des troubles mnésiques était précédée d'un syndrome confusionnel et d'une agitation, parfois associés à une ataxie et des troubles oculomoteurs. Il décrivait alors, sans y faire référence, les symptômes de l'EGW décrits quelques années auparavant (voir Chapitre I partie 4.2.).

La prévalence du SK serait de 1 à 2% dans la population générale et de 12 à 14% chez les patients TUAL (Harper *et al.*, 1998). Ce taux de prévalence serait d'autant plus élevé dans les milieux défavorisés et chez les personnes âgées de 50 à 60 ans (MacRae and Cox, 2003).

Le SK se caractérise par une amnésie antérograde massive et une amnésie rétrograde d'amplitude variable. Ce syndrome amnésique s'accompagne d'une anosognosie, de

confabulations et de fausses reconnaissances (Arts *et al.*, 2017). Alors que ces derniers symptômes sont plutôt retrouvés au début de la maladie, le syndrome amnésique est considéré comme irréversible. Le DSM-5 y fait référence en tant que « trouble neurocognitif majeur induit par l'alcool, de type amnésie-confabulatoire» (American Psychiatric Association, 2013).

Ainsi dans la suite de ce chapitre, nous ferons une synthèse de la littérature afin de décrire les altérations cérébrales et cognitives dans le SK, puis nous évoquerons les quelques études qui se sont intéressées à l'évolution cognitive et cérébrale de ces patients avec le temps, pour enfin faire le point sur la prise en charge clinique des patients SK actuellement, en France.

2. Les atteintes cérébrales

2.1. Atteintes structurales

2.1.1. De la substance grise

Les premières études ayant permis d'observer les altérations cérébrales dans le SK ont été réalisées post-mortem. Bien que les auteurs de ces études ne s'accordent pas tous sur les lésions qui sont cruciales au développement du SK, des altérations des corps mamillaires, ainsi que des noyaux dorso-médians et antérieurs des thalamis ont fréquemment été mises en cause (Kril and Harper, 2012 pour revue). Des études *in vivo* utilisant des techniques de CT-scan ont également montré des atteintes diencéphaliques avec notamment une diminution de la densité de substance grise au niveau des thalamis (Shimamura *et al.*, 1988) et une dilatation du troisième ventricule cérébral, ainsi que des atteintes corticales caractérisées par un élargissement de la fissure inter hémisphérique (Shimamura *et al.*, 1988; Jacobson and Lishman, 1990). Ces résultats ont été confirmés par des travaux en IRM qui décrivent également une atrophie corticale (**Figure 10**). En effet, une diminution des volumes de substance grise au niveau des thalamis (Visser *et al.*, 1999; Colchester, 2001, Pitel *et al.*, 2009a, 2012, Le Berre *et al.*, 2014a), des corps mamillaires (Sullivan *et al.*, 1999; Visser *et al.*, 1999; Krabbendam *et al.*, 2000, Pitel *et al.*, 2009a, 2012), de l'hippocampe (Visser *et al.*, 1999; Sullivan and Marsh, 2003; Sullivan and Pfefferbaum, 2009), de l'amygdale (Le Berre *et al.*, 2014a), de l'insula (Pitel *et al.*, 2012), des aires motrices supplémentaires, des cortex frontaux et cingulaires (Pitel *et al.*, 2009a, 2012),

et du cervelet (Sullivan *et al.*, 2000a, Le Berre *et al.*, 2014a) a été observée chez les patients SK par rapport à des sujets contrôles.

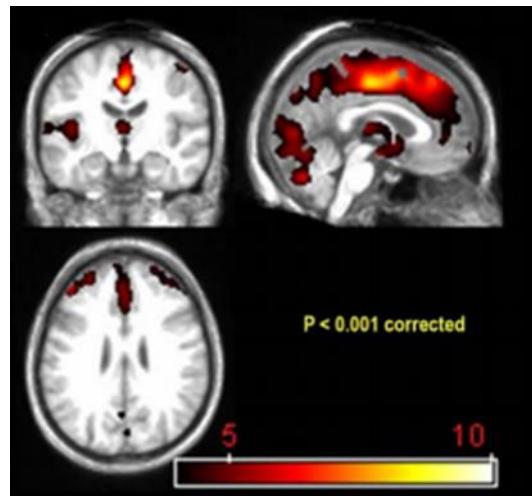


Figure 10 : Atteintes cérébrales structurale de la substance grise chez des patients SK comparés à des sujets contrôles. *Adaptée de Pitel *et al.*, 2009a.*

De plus, des travaux ont mis en évidence que les altérations de l'insula (Pitel *et al.*, 2012), de l'hippocampe (Visser *et al.*, 1999; Sullivan and Pfefferbaum, 2009), des corps mamillaires (Visser *et al.*, 1999; Sullivan and Pfefferbaum, 2009; Pitel *et al.*, 2012), et du thalamus (Visser *et al.*, 1999; Sullivan and Pfefferbaum, 2009; Pitel *et al.*, 2012; Segobin *et al.*, 2019) sont plus importantes chez les patients SK que chez les patients TUAL sans complications neurologiques.

Alors que Sullivan et Marsh (2003) mettent en lien de faibles volumes hippocampiques avec un indice d'amnésie élevé chez des patients SK, une autre étude ne retrouve, quant à elle, pas d'altération de l'hippocampe dans un groupe de 11 patients SK (Colchester, 2001). En revanche, une étude post-mortem (Harding, 2000) et une étude menée dans notre laboratoire (Segobin *et al.*, 2019) s'accordent sur le fait que les atteintes des noyaux antérieurs des thalamus seraient spécifiques aux patients SK car non présentes chez les patients TUAL, et de ce fait joueraient un rôle majeur dans la sévérité de l'amnésie.

2.1.2. De la substance blanche

Quelques études ayant examiné la macrostructure de la substance blanche dans le SK rapportent une diminution du volume notamment au niveau du corps calleux, du fornix, du cingulum, des pédoncules cérébelleux et du pont (Pitel *et al.*, 2009a, 2012; Sullivan and

Pfefferbaum, 2009) comparativement à des sujets contrôles (**Figure 11**). Des travaux en DTI ont également permis de mettre en évidence des altérations de la microstructure de ces structures (Nahum *et al.*, 2015; Segobin *et al.*, 2015, 2019) mais également de révéler une atteinte de l'intégrité de la corona radiata, et de la capsule interne (Segobin *et al.*, 2015).

Comparativement à des patients TUAL sans complications neurologiques, les altérations du pont, du corps calleux, et de la partie antérieure de la corona radiata sont plus importantes chez les patients SK (Sullivan and Pfefferbaum, 2009; Pitel *et al.*, 2012; Segobin *et al.*, 2015).

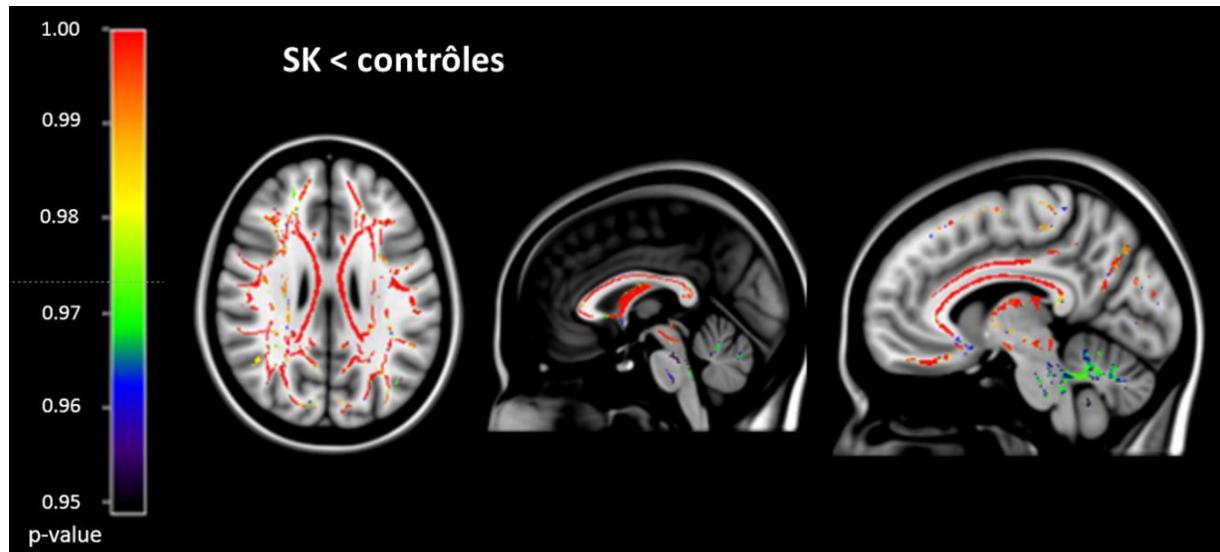


Figure 11 : Atteintes cérébrales de la substance blanche chez des patients SK comparés à des sujets contrôles. *Adaptée de Segobin *et al.*, 2015.*

2.2. Atteintes métaboliques

Un large profil d'atteintes métaboliques a également été trouvé dans le SK (**Figure 12**). Les études réalisées en TEP mettent en évidence que les patients SK présentent un hypométabolisme des lobes frontaux et des aires motrices (Paller *et al.*, 1997; Aupée *et al.*, 2001; Fellgiebel *et al.*, 2003; Reed *et al.*, 2003, Pitel *et al.*, 2009a), du gyrus cingulaire (Fazio *et al.*, 1992; Joyce *et al.*, 1994; Paller *et al.*, 1997; Reed *et al.*, 2003, Pitel *et al.*, 2009a), des hippocampes (Fazio *et al.*, 1992; Reed *et al.*, 2003, Pitel *et al.*, 2009a), des corps mamillaires (Pitel *et al.*, 2009a), et des thalamus (Fazio *et al.*, 1992; Aupée *et al.*, 2001; Reed *et al.*, 2003,

Pitel *et al.*, 2009a), ainsi qu'un hypermétabolisme du cervelet (Martin *et al.*, 1992; Fellgiebel *et al.*, 2004).

Les patients SK présentent un métabolisme de glucose inférieur à celui des patients TUAL au niveau des lobes frontaux, du gyrus cingulaire et des lobes pariétaux (Paller *et al.*, 1997).

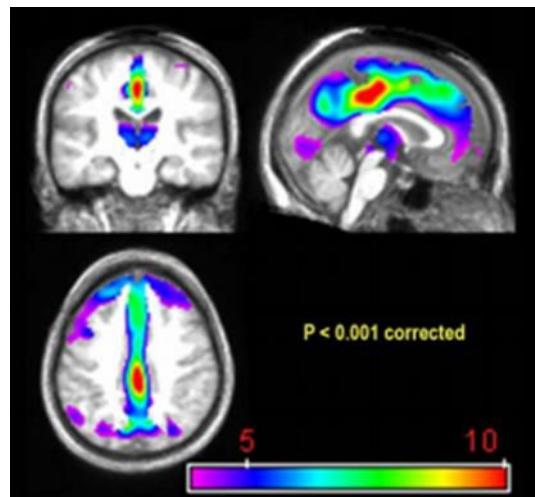


Figure 12 : Atteintes cérébrales du métabolisme de glucose chez des patients SK comparés à des sujets contrôles. *Adaptée de Pitel et al., 2009a.*

Tout comme dans le TUAL, les structures cérébrales altérées sont impliquées dans le CP et le CFC. Les altérations et dysfonctionnements de ces circuits sous-tendent également des déficits cognitifs que nous allons décrire dans la partie suivante. Dans un premier temps, nous évoquerons les troubles de mémoire épisodique qui résultent principalement des altérations du CP, et pourraient notamment s'expliquer par une déconnexion des thalamus avec les hippocampes via les altérations du fornix (Nahum *et al.*, 2015; Segobin *et al.*, 2019). Dans un second temps, nous aborderons les troubles de la mémoire de travail et des fonctions exécutives qui sont le reflet des altérations du CFC (Oscar-Berman, 2012 pour revue).

3. Les troubles neuropsychologiques

3.1. La mémoire épisodique

Bien que diverses sphères cognitives soient altérées dans le SK, c'est le déficit disproportionné de la mémoire qui définit cette pathologie (Kopelman *et al.*, 2009; Arts *et al.*, 2017). En effet, les patients présentent, au premier plan, une amnésie antérograde, également appelée oubli à mesure. Depuis 130 ans, les différentes publications ont cherché à mieux comprendre ce déficit massif de mémoire épisodique. Ainsi, une étude menée dans le laboratoire a montré que la spécificité du SK réside dans la sévérité des atteintes épisodiques et dans le déficit disproportionné des capacités d'encodage en mémoire épisodique (Pitel *et al.*, 2008). L'utilisation de stratégies trop superficielles lors de l'encodage ne permettrait pas de récupérer les informations lors d'une tâche de reconnaissance (Butters and Cermak, 1980). Des déficits de récupération des informations en mémoire épisodique ont également été mis en évidence car malgré la mise en place d'un encodage renforcé, les performances de rappel libre et indicé des patients SK sont déficitaires (d'Ydewalle and Van Damme, 2007; Pitel *et al.*, 2008). Ces déficits de mémoire épisodique ne diffèrent pas selon le sexe (El Haj *et al.*, 2020). Le versant prospectif de la mémoire épisodique est également déficitaire dans le SK (Altgassen *et al.*, 2016; Lloyd *et al.*, 2020), ce qui impacte l'autonomie dans la vie quotidienne.

Par ailleurs, les études ont également rapporté que les patients SK encodent moins efficacement le contexte spatio-temporel des événements que les sujets contrôles (Kopelman *et al.*, 1997; Postma *et al.*, 2006; Pitel *et al.*, 2008; Kessels and Kopelman, 2012). Ils présenteraient notamment plus de difficultés à reconnaître le contexte temporel que le contexte spatial des événements (Downes *et al.*, 2002; Pitel *et al.*, 2008) et pour intégrer les diverses informations contextuelles les unes avec les autres (El Haj *et al.*, 2016). De plus, les patients SK ont tendance à sous-estimer le temps qui s'est écoulé au cours d'une activité (El Haj *et al.*, 2017). La confusion liée au contexte temporel entraînerait un déficit de mémoire de la source (Brion *et al.*, 2017b).

Par ailleurs, à l'aide du paradigme R/K/G (Gardiner *et al.*, 1998), qui permet d'étudier le niveau de conscience associé à un souvenir, il a été mis en évidence que les patients SK ont une altération de la conscience autonoétique (d'Ydewalle and Van Damme, 2007; Pitel *et al.*, 2008). Les patients éprouvent ainsi plus de difficultés à faire le voyage mental dans le temps afin de

se remémorer des souvenirs autobiographiques (El Haj and Nandrino, 2017). Une amnésie rétrograde d'amplitude variable a, en effet, été décrite dans cette pathologie. Cette amnésie suivrait le gradient temporel de Ribot, les souvenirs anciens des patients étant relativement préservés comparativement aux événements des années précédant le développement du SK (Fama *et al.*, 2004a). Cette amnésie rétrograde affecte aussi bien les connaissances sémantiques que les connaissances autobiographiques (Kopelman, 1995). Ces déficits de mémoire autobiographique ont récemment été mis en lien avec les performances d'imagerie mentale (visuelle et spatiale) (Robin *et al.*, 2020).

3.2. Mémoire de travail et fonctions exécutives

Au second plan du tableau neuropsychologique des patients SK, se trouvent les déficits de la mémoire de travail (Joyce and Robbins, 1991; Pitel *et al.*, 2008) et des fonctions exécutives (Brokate *et al.*, 2003; Van Oort and Kessels, 2009; Moerman-Van Den Brink *et al.*, 2019).

Il a été mis en évidence que lorsqu'ils sont évalués avec une tâche de fluence verbale, les patients Korsakoff présentent des difficultés d'organisation et pour générer des stratégies (Pitel *et al.*, 2008), ce qui impacterait notamment les performances de mémoire de travail (Joyce and Robbins, 1991). En effet, Joyce et Robbins ont remarqué que lorsqu'ils corrigent les performances à une tâche de mémoire de travail spatiale par le score de stratégie, alors les performances se normalisent. De plus, des déficits de mise à jour des informations sont retrouvés lorsque les patients sont évalués avec une tâche de *n-back* (Brokate *et al.*, 2003; Pitel *et al.*, 2008) ou avec une tâche informatisée (Moerman-Van Den Brink *et al.*, 2019). De la même manière, des déficits de flexibilité mentale ont été montrés à l'aide de différentes tâches standardisées telles que le Trail Making Test et les fluences verbales (Joyce and Robbins, 1991; Brokate *et al.*, 2003; Oscar-Berman *et al.*, 2004; Pitel *et al.*, 2008) tout comme avec une tâche informatisée (Moerman-Van Den Brink *et al.*, 2019). Les capacités de planification sont également altérées dans le SK (Joyce and Robbins, 1991; Van Oort and Kessels, 2009). Enfin, concernant l'inhibition, plusieurs études montrent des performances déficitaires au score d'interférence du test de Stroop (Pitel *et al.*, 2008; El Haj and Nandrino, 2018), alors qu'une évaluation informatisée révèle que les patients Korsakoff sont aussi précis que les sujets contrôles à une tâche « antisaccade » (Moerman-Van Den Brink *et al.*, 2019). Par ailleurs, les auteurs de cette dernière étude montrent que même si les temps de réponse à la tâche « stop

signal » sont allongés chez les patients Korsakoff, les deux groupes ne sont pas significativement différents l'un de l'autre.

Les divergences observées peuvent s'expliquer par des aspects méthodologiques liés au type de tâche utilisé, par un effet du genre sur les performances d'inhibition (El Haj *et al.*, 2020), mais également par une hétérogénéité entre les patients SK. En effet, même si des études utilisant une batterie d'évaluation écologique (Behavioural Assessment of the Dysexecutive Syndrome) ont également retrouvé des déficits exécutifs chez une grande partie des patients SK (Van Oort and Kessels, 2009; Maharasingam *et al.*, 2013), il est important de noter que 20% des patients ont des performances préservées à tous les subtests de cette batterie. 80% des patients sont décrits comme étant déficitaires à au moins un subtest, ce qui indique une grande variété des profils exécutifs dans le SK (Van Oort and Kessels, 2009).

4. Évolution des atteintes cognitives et cérébrales

Les résultats évoqués jusqu'ici montrent l'intérêt que les chercheurs portent à la description sémiologique du SK. Les travaux ont ainsi permis de caractériser les atteintes spécifiquement observées dans cette pathologie et donc de mieux comprendre les mécanismes qui induisent l'amnésie a priori irréversible du SK. Cependant, très peu d'études ont examiné les changements cognitifs et cérébraux qui pourraient intervenir au cours des mois et années qui suivent le diagnostic de cette pathologie. Pourtant, les patients SK qui bénéficient d'une prise en charge en milieu institutionnel restent, pour la plupart, abstinents. Or nous avons vu dans le chapitre II partie 3. qu'une réversibilité des atteintes cérébrales et cognitives est observée chez les patients TUAL abstinents, voire même chez les patients TUAL qui consomment des quantités d'alcool très limitées. La littérature ne comprend que quatre études longitudinales de patients SK, parmi lesquelles une seule étude de groupe (Fujiwara *et al.*, 2008) et trois études de cas (Noël *et al.*, 2001b; Fellgiebel *et al.*, 2003, 2004).

Concernant les modifications cognitives, l'étude de Fujiwara *et al.* a évalué les changements qui interviennent au cours d'une période de deux ans, chez un groupe de 20 patients ayant eu un diagnostic de SK environ huit ans auparavant (Fujiwara *et al.*, 2008). Les résultats de cette étude montrent une amélioration significative des capacités de vitesse de traitement, de flexibilité et de mémoire visuelle entre les deux évaluations

neuropsychologiques. Cependant, les performances de mémoire visuelle, tout comme celles de mémoire verbale, restent sévèrement déficitaires même 10 ans après le début de la pathologie, sans pour autant qu'un déclin cognitif global ne soit observé. Les performances attentionnelles et exécutives restent également, pour la plupart, plus faibles que celles du groupe de sujets contrôles. Une étude de cas a, quant à elle, décrit l'évolution des performances cognitives d'un patient au cours des neuf premiers mois qui ont suivi le développement du SK (Noël *et al.*, 2001b). Les résultats des trois évaluations neuropsychologiques présentées dans cette publication mettent également en évidence une persistance des troubles de mémoire épisodique verbale et visuelle, accompagnée d'une normalisation de certaines performances exécutives, notamment de mémoire de travail, de flexibilité et de déduction de règles.

Concernant les modifications cérébrales, l'équipe de Fellgiebel *et al.* a publié deux études de cas permettant de rendre compte de l'évolution clinique et du métabolisme du glucose cérébral au cours des premiers mois suivant le diagnostic de SK. Ils ont montré que la désorientation temporelle, les performances mnésiques et l'hypométabolisme thalamique persistent avec le temps, alors que les confabulations disparaissent rapidement, et que la désorientation spatiale, les autres fonctions cognitives et l'hypométabolisme cortical s'améliorent au fur et à mesure des mois (Fellgiebel *et al.*, 2003). Les auteurs montrent également que l'hypermétabolisme cérébelleux observé initialement disparaît conjointement à l'amélioration de l'ataxie (Fellgiebel *et al.*, 2004).

5. Prise en charge clinique du SK

Le tableau clinique du SK se caractérise donc par des déficits cognitifs fréquemment accompagnés par des troubles moteurs, une désorientation spatio-temporelle, une anosognosie, des confabulations et des fausses reconnaissances, ainsi que des modifications du comportement, des troubles affectifs et du traitement des émotions (Arts *et al.*, 2017 pour revue). Les troubles n'évoluent pas tous de la même manière avec le temps, et les répercussions qu'ils vont avoir sur la vie des patients au quotidien et sur leur entourage sont majeurs. En accord avec les critères diagnostiques de troubles neurocognitifs sévères du DSM-5 (American Psychiatric Association, 2013), les patients SK ne peuvent que rarement vivre de manière totalement autonome car leurs déficits neuropsychologiques empêchent l'indépendance dans les activités de la vie quotidienne.

Dès lors que le diagnostic de SK est établi, la question du devenir de ces patients se pose rapidement. En effet, l'organisation du système de santé actuel privilégie des hospitalisations courtes qui ne sont pas adaptées à ces patients. Une évaluation pluridisciplinaire de ces patients doit être réalisée afin de les orienter au mieux. Un retour à domicile est envisageable uniquement si un aidant est présent afin de garantir la sécurité du patient et veiller au maintien de l'abstinence. Cette option est souvent compromise par le fait que les patients sont socialement isolés ou que personne dans l'entourage ne peut assurer ce rôle d'aidant. Dans un premier temps, un séjour en SSR, si possible spécialisés en addictologie, peut permettre une prise en charge adaptée tout en préparant un projet institutionnel pour la suite. Cependant, il existe très peu de structures spécialisées pour accueillir des patients SK.

Actuellement, en France, ces patients peuvent être accueillis dans des EHPAD (Etablissements d'Hébergement pour Personnes Agées Dépendantes) avec une demande de dérogation d'âge si les patients ont moins de 60 ans. D'une part cette dérogation est de plus en plus difficile à obtenir, d'autre part ce type d'environnement n'est pas idéal pour les patients SK. Ils sont aussi parfois reçus dans des foyers et maisons d'accueil médicalisés (FAM et MAS) comme l'unité Serge Korsakoff dans la MAS de l'Hôpital Nord 92, à Villeneuve la Garenne, qui peut accueillir 15 patients atteints du SK. Les familles d'accueil peuvent aussi être une solution, même si elles ont en général peu d'expérience avec les problématiques de ces patients. Il existe également des initiatives locales, notamment dans le Nord, comme une résidence d'accueil créée par l'association Baptiste pour l'entraide et la jeunesse, à Capinghem, et la maison Vauban, à Roubaix. Ces deux structures proposent des hébergements individuels avec des espaces collectifs et une présence sur place 24 heures sur 24.

Dans tous les cas, les démarches sont longues et nécessitent souvent une demande d'orientation par la MDPH (Maison Départementale des Personnes Handicapées) qui prend elle-même plusieurs mois pour aboutir. De plus, il y a très peu de places dans les structures spécialisées et par conséquent, les patients sont souvent accueillis dans des structures non adaptées. Il est donc important de bien décrire le devenir cognitif et cérébral des patients SK afin de développer des systèmes de prise en charge et de rééducation qui permettront d'atteindre un niveau maximal d'autonomie et de privilégier la qualité de vie de ces patients.

RESUME

Le syndrome de Korsakoff (SK) est une complication neurologique caractérisée par une amnésie antérograde massive et une amnésie rétrograde d'amplitude variable. Le tableau clinique s'accompagne également d'une anosognosie, de confabulations et de fausses reconnaissances.

Chez les patients SK, des altérations cérébrales structurales de la substance grise et de la substance blanche, ainsi que du métabolisme de glucose sont retrouvées dans des régions corticales du circuit de Papez et du circuit fronto-cérébelleux.

Ces altérations cérébrales entraînent des déficits cognitifs, et notamment des troubles sévères de la mémoire épisodique, ainsi que des dysfonctionnements exécutifs plus ou moins importants.

Les quelques études ayant examiné l'évolution des patients SK avec le temps rapportent une amélioration du tableau clinique malgré une persistance de l'amnésie antérograde.

Du fait des troubles neuropsychologiques sévères, les patients SK ne peuvent pas vivre de manière autonome, or la prise en charge de ces patients pose actuellement problème car les structures adaptées à ce syndrome sont extrêmement rares.

*PARTIE
EXPERIMENTALE*

1. Problématique générale et objectifs

Les consommations chroniques et excessives d'alcool sont associées à des altérations cérébrales et à des déficits cognitifs sous-tendus par le dysfonctionnement de deux circuits cérébraux : le CP et le CFC. Ces atteintes cognitives et cérébrales empêchent les patients TUAL de bénéficier pleinement des prises en charge addictologiques usuelles et augmentent le risque de rechute. Les études mettent en évidence une réversibilité de ces atteintes avec l'abstinence. En revanche, les patients SK présentent une amnésie antérograde sévère considérée comme irréversible même si l'évolution cognitive et cérébrale de ces patients est peu documentée.

Ainsi, au travers de trois études originales, l'objectif de ce travail de thèse est d'examiner la valeur pronostique, l'évolution ainsi que la prise en charge des atteintes cognitives et cérébrales dans le TUAL et le SK.

- 1) La première étude vise à déterminer, aux moyens d'une approche multimodale, quels sont les facteurs qui permettent de distinguer les patients qui rechuteront dans l'année suivant le sevrage de ceux qui maintiendront des consommations à faible risque.
- 2) La seconde étude examine l'effet d'un séjour de trois semaines en SSR sur le fonctionnement cognitif de patients TUAL qui présentent des troubles neuropsychologiques post-sevrage. De manière plus exploratoire, nous comparerons également l'effet de deux types de prise en charge sur la récupération cognitive.
- 3) Enfin, la troisième étude a pour but d'analyser l'évolution cognitive et cérébrale chez des patients SK.

2. Etude 1 : Déterminants de la rechute des patients TUAL (article en préparation)

Le TUAL est une pathologie chronique hautement récidivante. En effet, au cours de l'année qui suit le sevrage d'alcool, 60 à 80% des patients rechutent (Moos and Moos, 2006). Les altérations cérébrales et cognitives observées post-sevrage, ainsi que les comorbidités psychiatriques et addictologiques comptent parmi les facteurs qui contribuent à la survenue de la rechute (Sliedrecht *et al.*, 2019 pour revue).

Alors que l'abstinence totale a longtemps était considérée comme le seul objectif thérapeutique acceptable, depuis quelques années les organisations de santé estiment qu'une réduction des consommations peut être envisagée (European Medicines Agency, 2010; Food and Drug Administration, 2015). De plus, il a été mis en évidence qu'après le sevrage, des consommations très limitées n'empêchent pas la récupération cérébrale (Segobin *et al.*, 2014). Et contrairement aux patients ayant eu des consommations élevées au cours d'une période de huit mois, les patients ayant fortement diminué leurs consommations ont, au moment du suivi, des volumes frontaux et thalamiques équivalents à ceux des patients qui sont restés abstinents (Meyerhoff and Durazzo, 2020). Ainsi, l'objectif de cette étude était de déterminer si, à l'issue du sevrage, il est possible de distinguer des facteurs pronostiques du statut addictologique six mois et un an après l'arrêt des consommations.

Cinquante-quatre patients TUAL récemment sevrés et 36 sujets contrôles ont été inclus dans cette étude. Ils ont bénéficié d'une évaluation clinique, neuropsychologique, et d'imagerie cérébrale incluant des examens d'IRM et de TEP-FDG (T1). Les données concernant le statut des consommations d'alcool ont été recueillies six mois (T2) et un an (T3) après l'évaluation T1. Ainsi, à T2 et à T3, les patients ont été classés en deux groupes selon le statut des consommations :

- Consommateurs à faible risque : consommations inférieures ou égales à 14 unités/semaine pour les hommes et 7 unités/semaines pour les femmes.
- Rechuteurs : consommations supérieures à 14 unités/semaine pour les hommes et 7 unités/semaines pour les femmes, ou notion de perte du contrôle des consommations.

Les résultats montrent que les patients rechuteurs à T2 avaient, à l'issue du sevrage, un score d'alexithymie significativement plus élevé que les sujets contrôles. Par ailleurs, les patients rechuteurs à T3 présentaient après le sevrage un usage de nicotine plus important, ainsi que des performances de mémoire épisodique et de mémoire de travail plus faibles que les sujets contrôles. Concernant ces variables, il n'y a pas de différence significative entre les performances des consommateurs à faible risque et celles des sujets contrôles.

Comparativement aux sujets contrôles, les deux sous-groupes de patients présentaient, à l'issue du sevrage, des altérations cérébrales. Cependant, l'atrophie du mésencéphale est uniquement retrouvée chez les patients ayant rechuté à T2. Par ailleurs, seul le groupe de patients rechuteurs à T3 présentait, au moment du sevrage, une atteinte des cortex cingulaire antérieur et préfrontal ventromédian, ainsi que des amygdales. Les résultats de cette étude montrent également un hypermétabolisme cérébelleux et hippocampique chez les patients rechuteurs à T2, associé à un hypermétabolisme du gyrus cingulaire antérieur chez les patients rechuteurs à T3. L'hypométabolisme frontal et pariétal est présent aussi bien chez les rechuteurs que chez les consommateurs à faible risque.

Nos résultats suggèrent qu'une alexithymie observée post-sevrage serait en faveur d'une rechute dans les six mois, potentiellement en lien avec des altérations du système limbique. Par ailleurs, les atteintes du mésencéphale, des amygdales et des lobes frontaux indiquent qu'un dysfonctionnement du circuit de la récompense serait un facteur de mauvais pronostic. Les altérations des cortex cingulaire antérieur et préfrontal ventromédian retrouvées chez les rechuteurs, en association avec l'atrophie hippocampique, suggèrent également l'implication de troubles de la prise de décision dans la rechute. En effet, nos résultats semblent évoquer un déséquilibre entre le système impulsif et limbique hypermétabolique et le système réflexif qui est hypométabolique. Enfin, en accord avec la littérature, le phénomène de rechute semble également être associé à la consommation de nicotine.

PROGNOSIS FACTORS OF LOW-RISK DRINKING AND RELAPSE IN ALCOHOL USE
DISORDER: A MULTIMODAL ANALYSIS

Article en préparation

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ABSTRACT

Aims: The objective of the present study was to specify the determinants of low-risk drinking and relapse at different time points.

Methods: Fifty-four AUD patients and 36 healthy controls (HC) underwent clinical, neuropsychological and neuroimaging investigations including MRI and ¹⁸FDG-PET early in abstinence (T1). Data about alcohol status was collected six months (T2) and one year (T3) after detoxification. Patients were classified, at both T2 and T3, as “low-risk drinkers” (LR) or “relapsers” (R).

Results: Regarding clinical data, only R differed from HC on the TAS 20 score, based on the T2 alcohol status, and on the Fagerstrom, based on the T3 alcohol status. Concerning neuropsychological data, only R differed from HC on episodic and working memory performance, based on the T3 alcohol status. Regarding structural abnormalities, only R had midbrain damage at T2. Moreover, based on the T3 alcohol status, some brain structures such as the amygdala, ventromedial prefrontal cortex and anterior cingulate gyrus were damage only in R. Finally, R exhibited a hypermetabolism in the cerebellum and hippocampi at T2, combined to a hypermetabolism in the anterior cingulate gyrus at T3, whereas R and LR both had a frontal hypometabolism, based on the T2 as well as T3 alcohol status.

Conclusion: The present study highlighted that early in abstinence, several measures could have a prognosis value regarding the six-month and one-year treatment outcomes in terms of low-risk drinking and relapse. Alexithymia seems to be a determinant of an early relapse, and nicotine use might be regarded as a potential determinant of a one-year relapse. Structural brain damage early in abstinence may also be related to relapse. There may be involvement contribution of the reward circuit to the six-month relapse, and brain structures sustaining impulsivity and decision-making may be determinant of a one-year relapse. Moreover, the cerebellar hypermetabolism, reflecting a phenomenon of maladaptive plasticity may be a

determinant of the relapse. Finally, an imbalance between a hypermetabolism of the limbic system and a hypometabolism of the frontal executive system may also predict a one-year relapse.

1. INTRODUCTION

Alcohol Use Disorder (AUD) is a highly prevalent public health problem with considerable individual and societal costs. It is defined by the National Institute on Alcohol Abuse and Alcoholism as a chronic brain disease, characterized by a high rate of relapse (1,2). Several psychological and biological factors seem to increase the risk of relapse. Among the psychological factors, alcohol craving (3,4), impulsivity (5,6), altered emotion processing and interpersonal relationships (7,8), smoking status (9), comorbid psychiatric disorders (10,11) and other substance use disorders (12) have frequently been related to alcohol relapse. Regarding the impact of neurocognitive disorders, results are less consistent. Some studies indicated that memory and executive deficits do not seem to be associated with a higher risk of relapse (13–15), whereas others showed that processing speed, working memory and inhibition performance early in abstinence may distinguish future relapsers from abstainers (16–18). Among biological factors, sleep disorders (19,20), brain alterations (9,16,21–23), and specific biomarkers of alcohol use such as urine ethylglucoronide and gamma glutamyl transferase (24) may be reliable relapse predictors. Studies failed to find associations between family history and risk of relapse (25). Few investigations used an integrative approach of relapse prediction by considering these clinical, neuropsychological as well as structural and functional brain variables all together.

Because the attrition rate is high in longitudinal studies of AUD and relapse frequently occurs within 6 months after detoxification (26,27), studies usually examine predictors of an early relapse (14,16,19,23,28,29). Studies including a later follow-up examination are scarce (2,11). Yet, relapse can be regarded as a dynamic process influenced by different determinants

according to the follow-up delay. Further studies investigating determinants of early as well as later relapse are thus required.

Until recently, total abstinence from alcohol was considered as the only acceptable treatment target. However, new medications targeting a reduction of alcohol consumption reached the market and resulted in a paradigm shift. Recent findings also highlighted that very limited alcohol consumption during the follow-up period does not hamper brain recovery (21). It has also been shown that a reduction of alcohol use is associated with a meaningful decrease of alcohol-related consequences and improvements in mental health (30). Even though abstinence remains the safest treatment option, reduction of alcohol consumption is thus now considered as a relevant alternative. In this perspective, the World Health Organization (WHO) has defined four drinking risk levels (very high, high, medium, and low). The European Medicines Agency (EMA) considers that a two-level reduction in the WHO drinking risk levels can be used as a secondary endpoint for clinical trials (31). According to these guidelines, Meyerhoff and Durazzo showed that eight months after their discharge, gray matter (GM) volumes of AUD patients who had reduced alcohol consumption by two-levels were comparable to those of abstainers (32). On contrary, AUD patients with high-risk alcohol consumption had significantly lower thalamic and frontal volumes than abstainers and low-risk drinkers.

Considering these new AUD treatment outcomes, the objective of the present study was to specify the determinants of low-risk drinking and relapse at different time points. We conducted a multimodal analysis by exploring several clinical, neuropsychological and neuroimaging measures in early detoxified AUD patients. Two follow-up examinations were conducted six months and one year after the discharge in order to specify, at each time point, the risk level associated with alcohol drinking.

2. METHOD

2.1. Participants

Fifty-four AUD patients and 36 healthy controls (HC) were included in this study approved by the local ethics committee of Caen University Hospital (CPP Nord-Ouest III, no. IDRCB: 2011-A00495-36). To be included, participants had to have French as their native language, to be between 18 and 70 year old, and to have at least 8 years of schooling. None of them had a history of neurological, endocrinial, or infectious diseases, and comorbid psychiatric disorder. Participants did not fulfill the criteria for substance use disorder (other than alcohol for AUD patients) except tobacco. Participants gave their informed written consent to the study prior to their inclusion. The study was carried out in line with the declaration of Helsinki (1964).

AUD patients were recruited by clinicians while they were receiving withdrawal treatment as inpatients at Caen University Hospital. They met both criteria for alcohol dependence (DSM-IV-TR)(33) and criteria for AUD (DSM-5)(34). HC were recruited to match the demographics (age, sex, and education) of the AUD patients. They were interviewed with the Alcohol Use Disorder Identification Test (AUDIT)(35) to ensure that they did not meet the criteria for alcohol abuse (AUDIT < 7 for men and < 6 for women). None of the controls had a score at the Beck Depression Inventory (BDI) superior to 29 (36). Demographical and clinical data are presented in Table 1.

2.2. Study Design

A baseline clinical, neuropsychological and neuroimaging assessment was conducted 11.04 ± 4.34 days after the last alcohol drink (T1). Assessments were administered after the detoxification program, i.e. when patients did not present physical symptoms of alcohol

withdrawal anymore, using the Cushman score (37). They were free from benzodiazepines for 3.84 ± 3.28 days at inclusion.

Data about alcohol status was collected at six months (T2) and one year (T3) after discharge. According to the “Dietary guidelines for Americans 2015-2020”, patients were classified, at both T2 and T3, as “low-risk drinkers” (LR) when they had consumed no more than 14 drinks/week for men and 7 drinks/week for women, and “relapsers” (R) when their alcohol consumption exceeded these thresholds or when they had lost the control of their consumption during the follow-up period. According to the time point of the follow-up (T2 or T3) and the alcohol status, patients were classified as LR^{T2} or R^{T2} , and LR^{T3} or R^{T3} (Figure 1).

2.3. Clinical evaluation at baseline (T1)

All participants completed standardized questionnaires that evaluated alcohol consumption (AUDIT), depression (BDI), anxiety symptoms (State-Trait Anxiety Inventory; STAI)(38), nicotine dependence (Fagerstrom)(39), impulsivity (Barratt Impulsiveness Scale; BIS 11)(40) and alexithymia (Toronto Alexithymia Scale; TAS 20)(41). The highest Cushman score (37), the number of previous alcohol detoxifications, the amount of alcohol consumed the month preceding the withdrawal (number of units of 10g of pure ethanol per day), and the duration of heavy drinking (years) were recorded by clinicians.

2.4. Neuropsychological examination at baseline (T1)

Verbal episodic memory. The delayed free recall of a French version of the Free and Cued Selective Reminding Test (FCSRT) (42) was used.

Visual episodic memory. The 30-minute delayed recall of the Rey-Osterrieth Complex Figure (ROCF) (43) was used.

Working memory. The backward digit span of the WAIS-III (44) was used.

Flexibility. The number of perseverative errors of the Modified Card Sorting Test (MCST)(45) was used.

Inhibition. The interference score of the Stroop test (46), corresponding to the difference between the time needed to complete the interference condition (Word-Color condition) and the time needed for the denomination condition (Color condition), was used.

Attention. The overall performance index of the d2 test (47) was used.

Visuoconstruction. The copy score of the ROCF was used.

2.5. Brain Imaging examination at baseline (T1)

While the entire sample (N=36) of HC underwent the neuroimaging investigations, MRI was conducted in only 47 AUD patients, and FDG-PET in 37 AUD patients (out of the 54 AUD patients in total).

2.5.1. MRI volumetric Data

For each participant, a high-resolution T1-weighted anatomical image was acquired on a Philips Achieva 3T scanner (Philips Healthcare, Amsterdam, Netherlands) using a 3D fast-field echo sequence (sagittal; repetition time = 20ms; echo time = 4.6ms; flip angle = 10°; 180 slices; slice thickness, 1mm; field of view, 256x256mm²; matrix, 256x256).

Volumetric data sets were preprocessed using the SPM12 toolbox (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>, Statistical Parametric Mapping software; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Briefly, T1-weighted images were spatially normalized into the Montreal Neurological Institute (MNI) space (voxel size = 1.5mm³; matrix = 121x145x121) and segmented into gray matter, white

matter, and cerebrospinal fluid. The normalized gray matter and white matter images were modulated by the Jacobian determinants to preserve brain volume. The segmented images and normalization parameters estimated from this VBM protocol were used for the preprocessing of the PET data. The resulting images were smoothed by a Gaussian kernel of 8mm full-width-at-half-maximum (FWHM).

2.5.2. PET Data

PET scan of each participant was acquired using a Discovery RX VCT 64 PET-CT scanner (GE Healthcare, Chicago, IL, USA) with a resolution of $3.76 \times 3.76 \times 4.9 \text{ mm}^3$ and axial field of view of 157mm. Subjects had fasted for at least six hours before scanning and had been asked not to smoke on the day of the PET examination. To minimize anxiety, the PET procedure was explained in details beforehand. The head was positioned on a head-rest relative to the canthomeatal line and gently restrained with straps. FDG uptake was measured in the resting condition, with eyes closed, in a quiet and dark environment. Subjects were told to avoid focusing on any specific mental process during scanning. A catheter was inserted into a vein of the arm to inject the radiotracer. About 3 to 5 mci of FDG was injected as a bolus at time 0, and a 10-minute data acquisition period started 50 minutes post-injection that was preceded by the acquisition of a low-dose CT transmission scan (140kV, 10mA). Forty-seven planes were acquired with septa out (3D listmode data acquisition), and the image was reconstructed with ordinary Poisson-ordered-subtest expectation maximization algorithm (OP-OSEM; 21 subtests, 2 iterations) using a voxel size of $1.95 \times 1.95 \times 3.2 \text{ mm}^3$. During data acquisition, head motion was continuously monitored with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn on the forehead. Under the current clinical setup, and in the absence of a motion detection and quantification device, movements could not be corrected for at sinogram level. Only one 10-minute frame was acquired, and manufacturer's software and

limitations did not allow further splitting of the listmode data for potential frame-by-frame realignment.

The PET data were first corrected for cerebrospinal fluid and white matter partial volume effects (PVEs) in gray matter, using the voxel-by-voxel “modified Müller-Gartner” method(48). Using SPM12, the PVE-corrected PET data set was then co-registered (rigid-body coregistration) onto their respective native MRIs and normalized into the MNI space by reapplying the normalization parameters estimated from the VBM protocol described above (final voxel size = 2mm³ and matrix = 79x95x79).

To account for inter-individual variations in PET measurements, semiquantitative normalization was performed by scaling the PET images using a concatenation of the cerebellar lobules III, IX and X as a reference region(49). Finally, the resulting images were smoothed with a Gaussian kernel 10mm FWHM.

2.5.3. Masking of MRI and PET data

The gray matter mask was obtained by averaging the unmodulated gray matter images from the HC group in MNI space, and thresholding the resultant mean image at 0.5. The resulting GM mask was applied to both the GM and PET data sets.

The same principle was used for creating a white matter mask.

2.6. Statistical analyses

Demographical, clinical and neuropsychological data.

Given the sample sizes and the fact that several variables were not normally distributed (according to Shapiro-Wilk’s tests), non-parametric tests were used.

First, we compared the entire group of AUD patients to HC by means of Mann-Whitney's tests on the data collected at T1.

Then, group effects (R vs. LR vs. HC) were analyzed using Kruskal-Wallis ANOVAs. When significant, *post-hoc* pairwise comparisons were performed to compare R vs. LR, R vs. HC, and LR vs. HC, using Dwass-Steel-Critchlow-Fligner tests (DSCF). These analyses have been achieved using alcohol status both at T2 and T3.

Given the number of comparisons carried out, we used Bonferroni's corrections. We thus used $p < 0.003$ for the analysis of the 14 demographical and clinical variables and $p < 0.007$ for the 7 neuropsychological variables. For DSCF, the statistical threshold was set to $p < 0.05$.

Brain imaging data.

Analyses were performed in SPM 12 using minimum cluster size of $k=60$ for MRI data and $k=25$ for PET data, both corresponding to a cluster size of approximately 200 mm^3 .

First, voxel-based two-sample t-tests were conducted to compare GM and WM volumes, as well as metabolism between the entire group of AUD patients and HC on the T1 data.

Then, voxel-based two-sample t-tests were conducted to compare GM and WM volumes, as well as metabolism between R vs. LR, R vs HC, and LR vs HC. For each comparison, the two contrasts were systematically analyzed. These analyses have been achieved using alcohol status both at T2 and T3.

For all neuroimaging comparisons, age was used as a covariate, and for volumetric comparisons, total intracranial volume was also included in the analysis.

Analyses were first conducted using an uncorrected $p < 0.001$ threshold. Then a more stringent threshold corrected for multiple comparisons (Family-Wise Error (FWE), $P < 0.05$) was applied.

Significant clusters of gray matter volumes and metabolism were labeled using the Harvard-Oxford cortical and subcortical structural, and the probabilistic cerebellar atlases implemented in FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>). White matter clusters were labelled using the MRI Atlas of Human White Matter (50).

3. RESULTS

3.1. Comparisons between AUD patients and HC at T1

AUD patients differed significantly from HC on the BDI ($U = 249, p < 0.001$), STAI B ($U = 363, p < 0.001$), TAS 20 ($U = 522, p = 0.001$), Fagerstrom ($U = 360, p < 0.001$), and AUDIT ($U = 0, p < 0.001$) scores (Table 1). Compared to HC, AUD patients were impaired on verbal episodic memory ($U = 508, p < 0.001$), working memory ($U = 487, p < 0.001$), inhibition ($U = 611, p = 0.006$), and attention ($U = 529, p < 0.001$) (Table 2).

Neuroimaging data are presented in Figure S1.

3.2. Alcohol status at follow-up

At T2 (6 months): Among the 54 patients who completed the baseline assessment, alcohol status was obtained for 42 patients, including 28 who self-reported their alcohol consumption by phone and 15 for whom information was collected in available medical records. Among these 42 patients, 15 were classified as LR^{T2} , and 27 as R^{T2} , based on their alcohol consumption during the 6-month follow-up. Thirty six of these 42 patients underwent the MRI examination (12 LR^{T2} and 24 R^{T2}). Thirty one of those 36 also had the FDG-PET examination (11 LR^{T2} and 20 R^{T2}) at T1.

At T3 (one year): Among the 42 patients of T2, alcohol status was also obtained at T3 for 41 patients (20 self-reported their alcohol consumption during a clinical interview, and data

were collected in available medical records for the other 21). Alcohol status was obtained, based on available medical records, for one more patient for whom no information regarding alcohol status was available at T2. Among these 42 patients, 9 were classified as LR^{T3} , and 33 as R^{T3} according to their alcohol consumption during the one-year follow-up. Thirty six of the 42 patients underwent the MRI examination (7 LR^{T3} and 29 R^{T3}). Thirty one of those 36 also had the FDG-PET examination (6 LR^{T3} and 25 R^{T3}) at T1.

3.3. Comparisons between HC, LR^{T2} , and R^{T2} data at T1

3.3.1. Demographical and clinical data

A group effect was found for the BDI, STAI B, Fagerstrom, AUDIT, and TAS 20 scores (all $p < .001$). Between-groups comparisons showed statistical differences between R^{T2} and HC, and LR^{T2} and HC, but not between LR^{T2} and R^{T2} on the BDI, STAI B, Fagerstrom, and AUDIT. On the TAS 20, a statistical difference was found only between R^{T2} and HC (Table 1).

3.3.2. Neuropsychological data

A group effect was found for the verbal episodic memory, working memory ($p = 0.003$ in both cases), and attention ($p = 0.004$). For episodic memory and working memory, between-group comparisons revealed statistical differences between R^{T2} and HC, and LR^{T2} and HC. For attention, between-groups comparisons revealed statistical difference only between LR^{T2} and HC (Table 2).

3.3.3. Neuroimaging data

Results are presented in Figure 2.

Gray matter.

Compared to LR^{T2} , R^{T2} had lower GM volume in the right lingual gyrus ($p < 0.001$ uncorrected). There were no significant results using an FWE correction ($p < 0.05$). No significant result was found for the opposite contrast.

Compared to HC, R^{T2} had widespread GM alteration ($p < 0.001$ uncorrected). Using a more stringent threshold, R^{T2} had GM shrinkage in large brain clusters including parts of the frontal, parietal, temporal (including medial temporal lobes namely hippocampi and parahippocampal gyri), occipital, insular, supplementary motor, cingulate cortices as well as in the cerebellum, and in subcortical structures such as thalami, hypothalami (including mammillary bodies), amygdala, and caudate nuclei (FWE, $p < 0.05$). The opposite contrast did not reveal any significant difference.

Compared to HC, LR^{T2} showed smaller volume of GM bilaterally in the frontal, cingulate (anterior and middle), temporal (including medial temporal lobes namely hippocampus and parahippocampal gyri), parietal, occipital, insular, and supplementary motor cortices, as well as in the caudate nuclei, thalami, and hypothalami (including mammillary bodies), and in the left amygdala, lobule 6 and crus I of the cerebellum ($p < 0.001$ uncorrected). We found no significant results using FWE correction ($p < 0.05$). The opposite contrast did not reveal any significant difference.

White matter.

Compared to LR^{T2} , R^{T2} had lower WM volume in the right cingulum, body and splenium of the corpus callosum, and posterior corona radiata ($p < 0.001$ uncorrected). There were no significant results using an FWE correction ($p < 0.05$). The opposite contrast did not reveal any significant difference.

Compared to HC, R^{T2} had widespread WM volume reduction ($p < 0.001$ uncorrected). When a more stringent threshold was applied, R^{T2} had WM shrinkage in large clusters including parts of the midbrain, fornix, corpus callosum, corona radiata, thalamic radiation, superior fronto-occipital fasciculus, superior longitudinal fasciculus, internal capsule, right cerebral

peduncle, left cingulum and in the WM of the middle frontal gyrus (FWE, $p < 0.05$). The opposite contrast did not reveal any significant difference.

LR^{T2} showed smaller volume than HC in the WM of the frontal gyri, corpus callosum, corona radiata, posterior thalamic radiation, superior fronto-occipital fasciculus, retrolenticular part of the internal capsule, superior longitudinal fasciculus, in the left cingulum, and anterior limb of internal capsule ($p < 0.001$, uncorrected). No results were significant after FWE correction ($p < 0.05$). No significant result was found for the opposite contrast.

Metabolism.

At T1, there was no significant difference between R^{T2} and LR^{T2} regarding the regional glucose metabolism ($p < 0.001$ uncorrected).

Compared to HC, R^{T2} had **hypometabolism** bilaterally in the medial, middle, and superior frontal gyri, as well as in the left paracingulate gyrus, and in the right inferior parietal lobule ($p < 0.001$ uncorrected). The opposite contrast revealed that R^{T2} had bilateral **hypermetabolism** in lobules V-IX, Crus I and II of the cerebellum, as well as in the temporal gyrus (including parahippocampal gyrus and hippocampi), right precentral gyrus, and in the left postcentral gyrus ($p < 0.001$ uncorrected). There were no significant results using an FWE correction ($p < 0.05$).

Compared to HC, LR^{T2} had **hypometabolism** in the bilateral inferior parietal lobule, and in the superior and middle frontal gyri ($p < 0.001$ uncorrected). The opposite contrast showed that LR^{T2} had **hypermetabolism** in the left middle temporal gyrus only ($p < 0.001$ uncorrected). We found no significant results using FWE correction ($p < 0.05$).

3.4. Comparisons of HC, LR^{T3}, and R^{T3} data at T1

3.4.1. Demographical and clinical data

A group effect was found for the BDI, STAI B, AUDIT, Fagerstrom, and TAS 20 scores (all $p < 0.001$). Between-group differences were found between LR^{T2} and HC, and between R^{T2} and HC, but not between LR^{T2} and R^{T2} on the BDI, STAI B and AUDIT. On the Fagerstrom and TAS 20, statistical differences were observed between R^{T3} and HC only (Table 1).

3.4.2. Neuropsychological data

A group effect was found for the verbal episodic memory and working memory ($p = 0.003$ in both cases). Between-group comparisons revealed statistical difference only between R^{T2} and HC (Table 2).

3.4.3. Neuroimaging data

Results are presented in Figure 3

Gray matter.

At T1, there was no group difference in GM volume between R^{T3} and LR^{T3} ($p < 0.001$ uncorrected).

The comparison between R^{T3} and HC revealed a similar pattern of results to that observed for the comparison between R^{T2} and HC.

LR^{T3} showed smaller GM volume than HC bilaterally in the insula, hippocampi, thalamus, middle frontal, precuneus, lingual, parahippocampi, and Heschl gyri, as well as in the right postcentral, precentral, inferior and superior frontal gyri ($p < 0.001$ uncorrected). The analysis did not reveal any significant difference after FWE correction ($p < 0.05$). The opposite contrast did not reveal any significant difference.

White matter.

R^{T3} had lower WM volume than LR^{T3} in the right posterior corona radiata, as well as in the body and splenium of corpus callosum, and in the WM of the cingulate gyrus ($p < 0.001$ uncorrected). Using FWE correction ($p < 0.05$), the analysis did not reveal any significant difference. The opposite contrast did not reveal any significant difference.

Comparisons between R^{T3} and HC revealed a similar pattern of results to that observed for the comparison between R^{T2} and HC.

LR^{T3} showed smaller volume than HC in the WM of the frontal gyri, genu and body of the corpus callosum, anterior corona radiata, right posterior thalamic radiation, left anterior limb of internal capsule, posterior corona radiata, and superior fronto-occipital fasciculus ($p < 0.001$ uncorrected). We found no significant results after FWE correction ($p < 0.05$). The opposite contrast did not reveal any significant difference.

Metabolism.

At T1, there was no significant difference of metabolism between R^{T3} and LR^{T3} ($p < 0.001$ uncorrected).

Compared to HC, R^{T3} had **hypometabolism** bilaterally in the medial, middle and superior frontal gyri, in the paracingulate gyri, and in the right inferior parietal lobule ($p < 0.001$ uncorrected). The opposite contrast revealed that R^{T3} had bilateral **hypermetabolism** in the lobules V-IX, Crus I and II of the cerebellum, as well as in the anterior cingulate and temporal gyri (including parahippocampal gyrus and hippocampi), in the right precentral and left postcentral gyri ($p < 0.001$ uncorrected). There were no significant results using an FWE correction ($p < 0.05$).

Compared to HC, LR^{T3} had **hypometabolism** in the right middle frontal gyrus ($p < 0.001$ uncorrected). The opposite contrast showed that LR^{T3} had **hypermetabolism** in the left middle

temporal gyrus ($p < 0.001$ uncorrected). No results were significant after FWE correction ($p < 0.05$).

4. DISCUSSION

The objective of the present study was to specify the determinants of low-risk drinking and relapse at different time points. For this purpose, clinical, neuropsychological and neuroimaging data, collected in early detoxified AUD patients, were compared according to the alcohol status of AUD patients six months and one year after the baseline assessment. Our findings indicate that future relapsers and low-risk drinkers had different profiles of results for several clinical and neuropsychological variables when examined early in abstinence and compared to healthy controls. Some volumetric differences appeared when relapsers were directly compared to low-risk drinkers. And the difference regarding the profiles of volumetric and metabolic alterations were even more pronounced when the groups of AUD patients were analyzed relative to healthy controls.

Results of the present study revealed that only patients classified as relapsers six months as well as one year after the discharge presented alexithymia as revealed by their TAS 20 score which was significantly higher than in controls. These results suggest that patients who had difficulties in identifying and describing their emotions are more susceptible to relapse within the first 6 months following the detoxification, which is consistent with previous studies reporting that negative affect and emotion processing deficits increase the risk of an early relapse (5,7,51).

No other clinical or demographical variables seemed to differentiate, early in abstinence, relapsers and low-risk drinkers six months after the detoxification. On the opposite, based on the alcohol status at one year, results showed that only relapsers had, at baseline, significantly

higher nicotine use than controls. Nicotine use, which has previously been related to relapse (9,52), seems to be potential clinical determinants of a one-year relapse.

Compared to controls, the entire group of AUD patients exhibited impaired neuropsychological performance in accordance with the literature (53). These cognitive deficits have previously been linked with the motivation to change drinking behavior (54,55). For example, memory impairments and executive dysfunctions would hamper patients to remember the negative consequences of alcohol use and to inhibit automatic drinking behaviors. Hence, patients with the worst cognitive performance would be more likely to relapse (56). Regarding classification at six months both groups of AUD patients had working memory deficits, whereas at one year, only relapsers differed from controls. These results suggest that patients who exhibited low working memory performance at baseline are at risk to relapse six to twelve months after the detoxification. Contrary to a previous investigation (13), results of the present study showed that verbal episodic memory impairments might be a determinant of relapse since only relapsers exhibited deficits early in abstinence, based on the one-year alcohol status. Results did not show that flexibility or inhibition might influence the relapse. Previous results are inconsistent (13–18) regarding the prognosis value of executive deficits. Such discrepancy may be related to the different neuropsychological tasks used in most of the studies that may not be sensitive enough to processes underlying relapse. In effect, studies that found a link between impaired response inhibition and a high rate of relapse used a go/no-go task (17,18) or the Hayling test (16). A recent investigation, using a go/no-go task as well as the Stroop test, as in the present study, confirmed that the first one was associated with relapse whereas the second one was unrelated to treatment outcomes (6). Other executive functions, such as decision-making, may also be better determinants of premature treatment dropout and relapse (6).

The direct comparison between relapsers and low-risk drinkers showed some differences regarding GM and WM volume. And the difference regarding the profiles of

shrinkage was even more pronounced when the subgroups of AUD patients were compared to controls. AUD patients who relapsed within the first year following detoxification presented widespread GM and WM shrinkage. Results also showed reduction in GM and WM volume in AUD patients classified as low-risk drinkers based on the six months follow-up. However, results concerned smaller brain clusters than those found in relapsers versus controls. The profile of macrostructural brain abnormalities observed early after detoxification was even more limited in patients who had maintained low-risk drinking within the first year after discharge, suggesting that patients who relapsed between the sixth month and the first year following the discharge were more damaged than patients who maintain low-risk drinking within this period. In relapsers and low-risk drinkers, results showed reduced volume in frontal and cingulate cortices (9,22,23,57,58), in insula (59,60), as well as in hippocampi (22,59) and thalamci (21,23), such regions have been linked to relapse. Because these regions are cortical nodes of the executive control, salience and limbic networks, and that baseline abnormalities were less pronounced in low-risk drinkers than in relapsers, this suggests that low-risk drinkers were more able to control their alcohol use to maintain drinking at a low-risk level. In addition, some regions such as the amygdala, the ventromedial prefrontal cortex and anterior cingulate gyrus were damage in low-risk drinkers only based on the six months follow-up. This result suggest that patients with alteration in these regions relapsed between the six months and one year follow-up, probably because of impulsive behaviors (61), decision-making impairments (62), and emotion processing deficits (5,7,51). Finally, the present study found shrinkage of the midbrain only in future relapsers, associated with smaller amygdala and prefrontal cortex volumes. This finding suggests the involvement of the reward circuit in early relapse (1).

To our knowledge, no study had considered glucose metabolism as a potential determinant of relapse. Compared to controls, AUD patients presented a frontal and parietal hypometabolism at baseline. In future relapsers at 6 months, the hypometabolism was

associated to a hypermetabolism in the cerebellum, hippocampi and parahippocampal gyrus. This pattern was accompanied by a hypermetabolism in the anterior cingulate gyrus based on the one year follow-up. The cerebellar hypermetabolism observed in our study has previously been considered as a maladaptive plasticity phenomenon (63). The fact that this result was found only in future relapsers reinforce this idea, and suggests that this specific brain alteration may be a possible determinant of relapse. In addition, hypermetabolism of the hippocampus and anterior cingulate gyrus, which are both involved in the limbic circuit (64), might reflect an overactivation of emotional states difficult to control because of frontal hypometabolism. This overactivation of limbic/emotional system associated to an underactivation of the frontal/executive system would result in relapse (65). Future studies are needed to confirm whether this profile of hypermetabolism can be considered as a determinant of relapse, and to explore whether sustained abstinence allows glucose metabolism to normalize.

Limitations of the present study include the small sample sizes, notably in the low-risk drinking groups, because of attrition, the absence of a group of abstainers, and the lack of clear information about the amount of alcohol use within the follow-up.

To conclude, the present study highlighted that early in abstinence, several measures could have a prognosis value regarding the six-month and one-year treatment outcomes in terms of low-risk drinking and relapse. Alexithymia seems to be a determinant of a relapse within the six months following the detoxification, and nicotine use might be regarded as a potential determinant of a one-year relapse. Structural brain damage appear also link to relapse. There is notably an involvement of the reward circuit in a six-months relapse, and brain structures sustaining impulsivity and decision-making seems to be determinant of a one-year relapse. Moreover, an imbalance between the limbic and frontal executive system may also predict a one-year relapse. Hypermetabolism in the cerebellum, anterior cingulate gyrus, and hippocampi could be relevant biomarkers to identify future relapsers.

Fundings

This study was funded by Fondation pour la Recherche Medicale (FMR, ING20140129160), ANR-Retour post-doctorant 2010, Conseil Regional Basse Normandie, and MILDECA.

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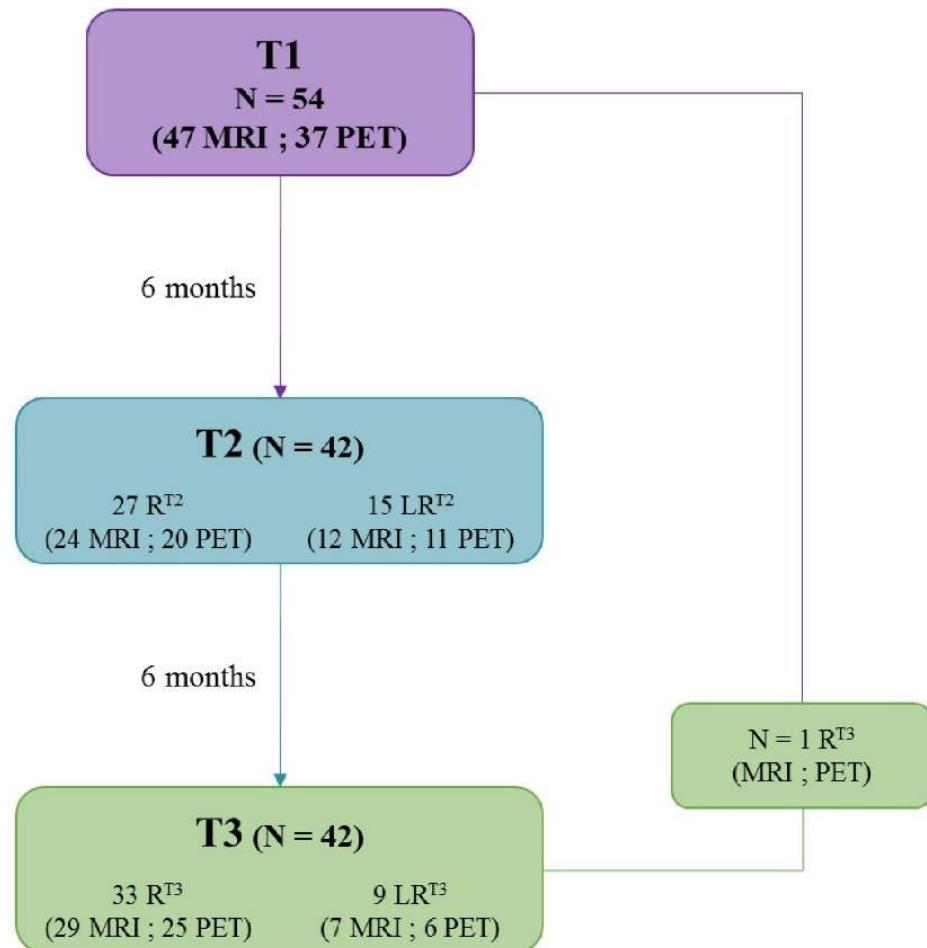
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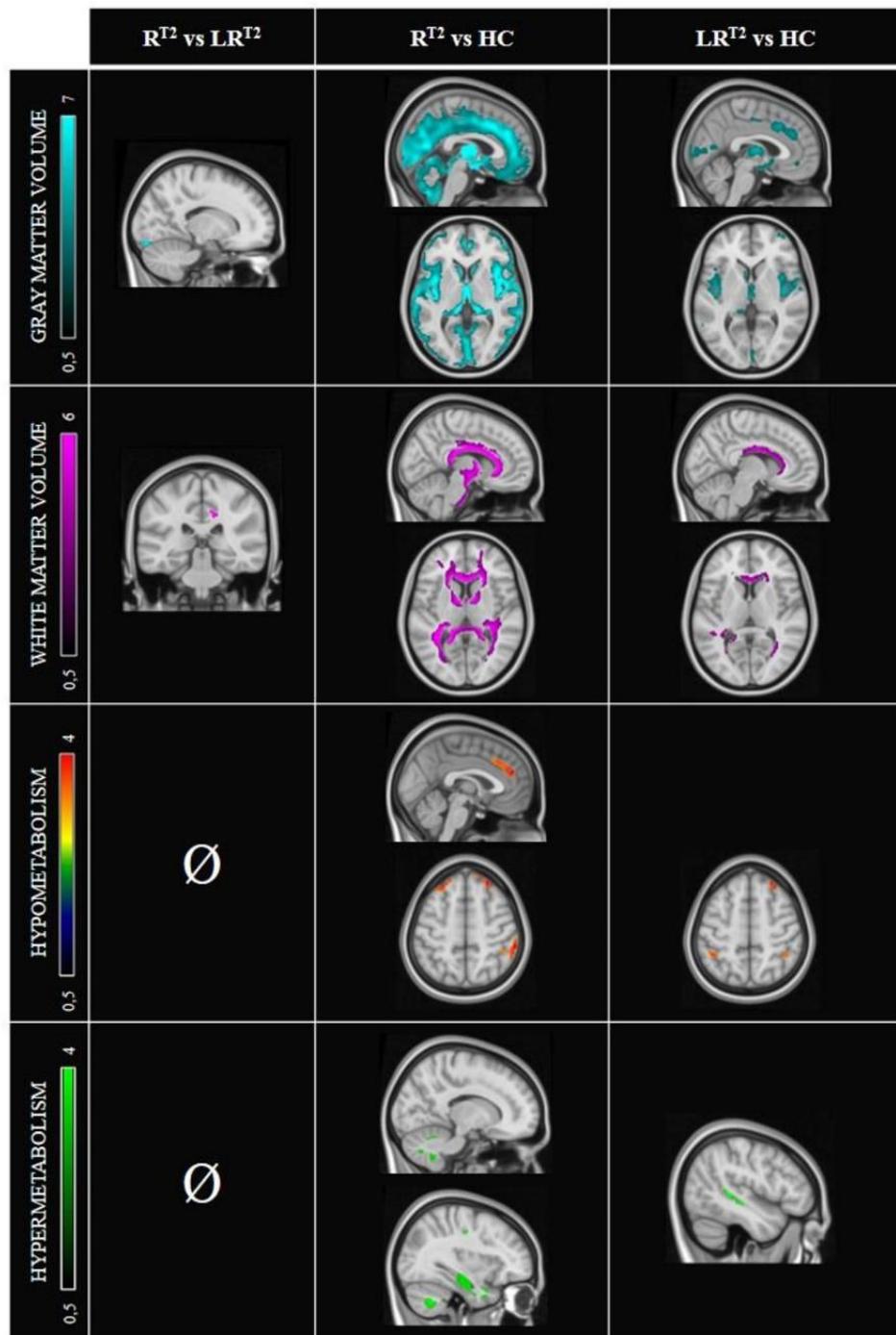
FIGURES

Figure 1: Study design and sample size at each time point and for each measure



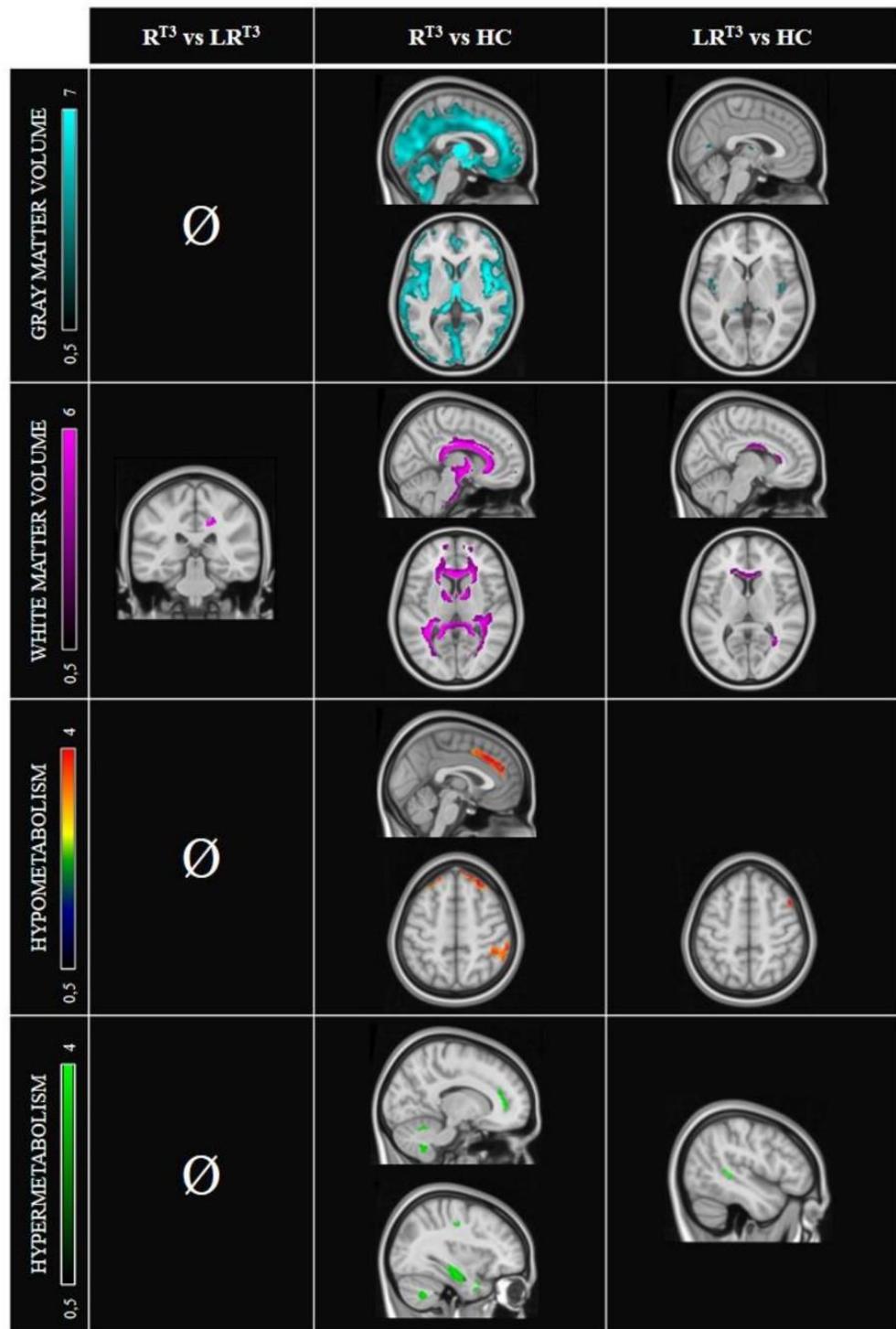
LR = Low-risk drinkers; R = Relapsers; T1 = early in abstinence.

Figure 2: Structural and metabolic abnormalities in relapsers (R) and low-risk drinkers (LR) compared with healthy controls (HC) based on alcohol status at 6 months (T2)



Results are presented using a threshold of $p < 0.001$, uncorrected for multiple comparisons ($k=60$ for MRI data and $k=25$ for PET data). \emptyset : no significant results. Color bars represent T-values. Abbreviations: HC = Healthy controls; LR = Low-risk drinkers; R = Relapsers.

Figure 3: Structural and metabolic abnormalities in relapsers (R) and low-risk drinkers (LR) compared with healthy controls (HC) based on alcohol status at one year (T3)



See legend Figure 2.

TABLES

Table 1. Demographical and clinical data in each group and between-group comparisons

Variable	Participants		6-month status (T2)				One-year status (T3)			
	HC N = 36	AUD N = 54	R ^{T2} N = 27	LR ^{T2} N = 15	Statistics ^a (df=2)	Pairwise comparisons ^b	R ^{T3} N = 33	LR ^{T3} N = 9	Statistics ^a (df=2)	Pairwise comparisons ^b
Age	45 [39-47.8]	46 [38.8-54]	41 [37-54]	48 [39-54]	2.87 p=0.238		41 [37.5-52.5]	53 [47-61.5]	6.44 p=0.04	
Education (years of schooling)	12 [11-12]	11 [10-14]	11 [10-12]	12 [10-14]	0.91 p=0.635		11 [10-14]	12 [10-14.5]	1.42 p=0.491	
Sex ratio (M/F)	30/6	45/9	21/6	13/2	p=0.744		27/6	7/2	p=0.926	
BDI	3 [0-5]	12 * [5.8-17.3]	10 [5-18]	11 [2-17]	27.73 p<.001	1) p=0.757 2) p < .001 3) p = 0.002	10 [5-17.5]	11 [3-15.5]	27.73 p<.001	1) p=0.829 2) p < .001 3) p=0.011
STAI A	25.5 [22-29]	30 [24-35.8]	29 [23-37]	29.5 1MD	4.53 p=0.104		28 [23.5-35.5]	30 [22.5-34.5]	4.33 p=0.115	
STAI B	33.5 [28.3-38.8]	44 * [36-56]	46 1MD	48.5 [34-56]	19.86 p<.001	1) p=0.990 2) p < .001 3) p = 0.002	45 [34-57.5]	52 [37-52]	20.50 p<.001	1) p=0.997 2) p < .001 3) p=0.006
BIS 11	66 [56-71]	71.5 [61.3-79]	72 1MD	69.5 [61-79]	4.82 p=0.09		71 [60.5-79.5]	71 [54.5-77]	4.43 p=0.109	
TAS 20	45 [40-52]	55 * [49-63]	60 1MD	50.5 3MD	17.04 p<.001	1) p=0.09 2) p < .001 3) p=0.797	59 1MD	52 [34-60.5]	14.00 p<.001	1) p=0.146 2) p < .001 3) p=0.894
Fagerstrom	0 [0-0]	4 * [2-6]	4 1MD	2.5 [2-6]	22.44 p<.001	1) p=0.756 2) p < .001 3) p = 0.005	4 [2-6.5]	0 [0-5]	26.83 p<.001	1) p=0.130 2) p < .001 3) p=0.254
AUDIT	3 [1-4]	29 * [25.8-32.3]	29 [25-32]	29 [23-31]	57.76 p<.001	1) p=0.838 2) p < .001 3) p < .001	29 [25.5-32]	29 [18-30]	58.83 p<.001	1) p=0.341 2) p < .001 3) p < .001
Duration of dependence	N/A	9.5 [5-18.8] 2MD	8 [5-16]	15 [4-21]	N/A	1) p=0.193	9 [5-18]	15 [7-24]	N/A	1) p=0.231
Number of previous detoxifications	N/A	1 [1-2] 1MD	1 [1-2]	1 [0-1]	N/A	1) p=0.350	1 [1-2]	1 [0.5-1.5]	N/A	1) p=0.729
Cushman score	N/A	5 [3.5-6.5] 1MD	5 [3-7]	4 [3-6]	N/A	1) p=0.661	5 [3-6.5]	4 [3.5-4.5]	N/A	1) p=0.290
Alcohol consumption (units/day)	N/A	19.85 [13.4-25]	17 [13-25.5]	20 [12-25]	N/A	1) p=1.000	19 [13.8-25.3]	20 [8.5-24.5]	N/A	1) p=0.519

Median [1st – 3rd quartiles] are reported

^a: Kruskal-Wallis ANOVA; significant results at p < 0.007 are in bold

^b: Dwass-Steel-Critchlow-Fligner pairwise comparisons 1) Comparisons between R and LR; 2) Comparisons between R and HC; 3) Comparisons between LR and HC; significant results at p < 0.05 are in bold

*: Significant difference at p < 0.007 between AUD and HC, using Mann-Whitney's tests

Note: AUDIT = Alcohol Use Disorder Identification Test; BDI = Beck Depression Inventory; BIS = Barratt Impulsiveness Scale; STAI = State-Trait Anxiety Scale; TAS = Toronto Alexithymia Scale; AUD = Alcohol Use Disorder; HC = Healthy controls; LR = Low-risk drinkers; R = Relapsers.

Table 2. Neuropsychological performance (raw data) in each group and between-group comparisons

Variable	Participants		6-month status (T2)				One-year status (T3)			
	HC N = 36	AUD N = 54	R ^{T2} N = 27	LR ^{T2} N = 15	Statistics ^a (df=2)	Pairwise comparisons ^b	R ^{T3} N = 33	LR ^{T3} N = 9	Statistics ^a (df=2)	Pairwise comparisons ^b
FCSRT: delayed recall	13 [12-14]	11 * [9-13]	11 [10-13]	12 [7-13]	11.33 p=0.003	1) p = 0.995 2) p = 0.008 3) p = 0.035	11 [10-13]	12 [7-13]	11.37 p=0.003	1) p = 0.774 2) p = 0.007 3) p = 0.056
ROCF: delayed recall	17 [11.5- 22.9]	19.25 [16-25.8]	17 [8-22.5]	19.5 [13.1- 24.1]	3.94 p=0.139		17 [11.5- 23.3]	20 [11.8- 24.8]	2.78 p=0.249	
Backward digit span	5 [4.3-6]	4 * [3-5]	4 [3-5]	4 [3-5]	11.94 p=0.003	1) p = 0.924 2) p = 0.011 3) p = 0.014	4 [3-5]	4 [3-5.5]	11.50 p=0.003	1) p = 0.997 2) p = 0.005 3) p = 0.077
MCST: perseverative errors	1 [0-1]	1 [0-4]	1 [0-4]	2 [0.8-4]	5.03 p=0.081		1 [0-3]	2 [0-8.5]	3.53 p=0.171	
Stroop: interference score (sec.)	47 [33-59.5]	58 * [46-83]	50 [37-66.5]	63 [51-84]	7.80 p=0.02		50 [37.3-65]	65 [53-87.5]	8.44 p=0.015	
D2: overall performance index	416 [378-450]	343 * [275-411]	378 [284-433]	341 [256-393]	11.10 p=0.004	1) p = 0.532 2) p = 0.058 3) p = 0.006	378 [281-427]	316 [250-396]	9.52 p=0.009	
ROCF: copy score	36 [34-36]	35 [33-36]	35 [33-36]	35.5 [34-36]	3.05 p=0.217		35 [33-36]	36 [34.5-36]	3.87 p=0.145	

Median [1st – 3rd quartiles] are reported

^a: Kruskal-Wallis ANOVA; significant results at p < 0.007 are in bold

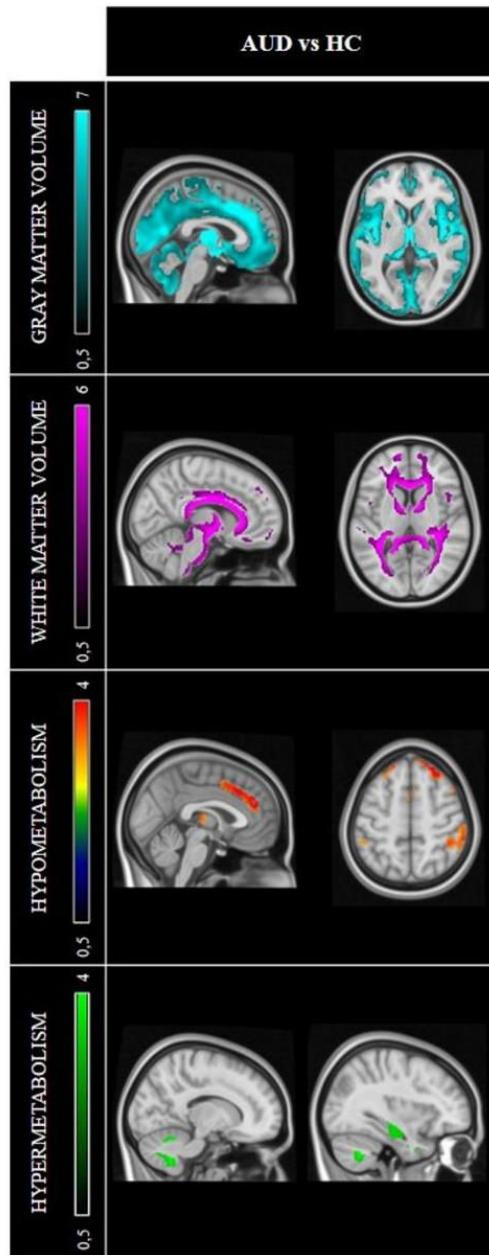
^b: Dwass-Steel-Critchlow-Fligner pairwise comparisons 1) Comparisons between R and LR; 2) Comparisons between R and HC; 3) Comparisons between LR and HC; significant results at p < 0.05 are in bold

*: Significant difference at p < 0.007 between AUD and HC, using Mann-Whitney's tests

Note: FCSRT = Free and Cued Selective Reminding Test; MCST = Modified Card Sorting Test; ROCF = Rey-Osterrieth complex figure; AUD = Alcohol Use Disorder; HC = Healthy controls; LR = Low-risk drinkers; R = Relapsers.

SUPPLEMENTARY

S1: Patterns of structural and metabolic abnormalities in AUD patients compared to HC



Results are presented using a threshold of $p < 0.001$, uncorrected for multiple comparisons ($k=60$ for MRI data and $k=25$ for PET data). Color bars represent T-values. Abbreviations: AUD = Alcohol Use Disorder; HC = Healthy controls.

3. Etude 2 : Récupération cognitive dans le TUAL (*article publié dans Addictive Behaviors*)

Les résultats de la première étude de cette thèse ont mis en évidence que de nombreux réseaux fonctionnels, sous-tendant divers processus cognitifs, sont impliqués dans le phénomène de rechute. D'un point de vue cognitif, la littérature indique que le contrôle inhibiteur et la mémoire de travail sont associés à la reprise des consommations (Noël *et al.*, 2002; Camchong *et al.*, 2013). En effet, les troubles neuropsychologiques présents à l'issue du sevrage empêchent les patients de bénéficier pleinement de la prise en charge psychosociale et augmentent le risque de rechuter (McCrady and Smith, 1986). Il faudrait donc attendre une amélioration du fonctionnement cognitif avant de proposer une prise en charge cognitivement coûteuse.

En effet, des travaux ont mis en évidence une récupération neuropsychologique avec l'abstinence. Ainsi, une amélioration, voire même une normalisation de la mémoire épisodique, est observée rapidement après l'arrêt des consommations d'alcool (Manning *et al.*, 2016; Mulhauser *et al.*, 2018). Les résultats sont moins constants concernant les fonctions exécutives (Nowakowska-Domagała *et al.*, 2017; Petit *et al.*, 2017), notamment en lien avec la prise de benzodiazépines, l'âge du patient à l'arrêt de l'alcool ou encore le *design* expérimental de l'étude (transversal ou longitudinal).

Dans la continuité de ces études, nous avons donc examiné si retarder la prise en charge addictologique de quelques semaines permettrait une amélioration du fonctionnement cognitif. Plus précisément, nous avons évalué la récupération cognitive à très court terme, en s'affranchissant des biais méthodologiques des études précédentes. Nous avons également cherché à déterminer si la prise en charge délivrée au cours des premières semaines d'abstinence avait une influence sur le fonctionnement cognitif.

Depuis une dizaine d'années, un partenariat entre le CHU de Caen et le SSR Korian de Ifs permet de proposer aux patients qui présentent des troubles neuropsychologiques post-sevrage, un séjour de trois semaines en SSR, afin de favoriser la restauration physique et cognitive. Dans le cadre de cette étude rétrospective, les données cliniques et neuropsychologiques de 84 patients TUAL ont été recueillies. Le SSR propose aux patients une prise en charge pluridisciplinaire incluant des séances de kinésithérapie, d'ergothérapie et un

suivi diététique. L'accès à des ateliers de stimulation cognitive est plus limité, du fait de la présence d'un seul neuropsychologue au SSR. Le groupe de patients TUAL a, *a posteriori*, été divisé en deux groupes en fonction de la nature et de l'intensité de la prise en charge, avec comme critère principal de classification le fait d'avoir ou non bénéficié d'ateliers de stimulation cognitive. Il s'avère que les patients ayant bénéficié d'une prise en charge neuropsychologique ont également eu une prise en charge plus intense. Les groupes ont ainsi été nommés « Intensif » versus « Occasionnel ». Les patients ont tous bénéficié d'un bilan neuropsychologique, évaluant la mémoire épisodique, la mémoire de travail, la flexibilité, l'inhibition, et la vitesse de traitement, avant et à l'issue du séjour en SSR.

Dans le groupe entier de patients, les résultats de cette étude mettent en évidence une amélioration significative de toutes les performances cognitives évaluées. De plus, la proportion de patients qui normalisent leurs performances est significative pour toutes les composantes cognitives à l'exception de la vitesse de traitement. Dans le groupe « Intensif », une amélioration significative des cinq composantes cognitives évaluées est observée. De plus, une proportion significative de patients normalisent leurs performances de mémoire épisodique, de mémoire de travail et de flexibilité. Dans le groupe « Occasionnel », l'amélioration significative concerne uniquement la mémoire épisodique, la vitesse de traitement et les capacités d'inhibition. La proportion de patients qui normalisent leurs performances n'est significative pour aucune des composantes cognitives évaluées.

Nos résultats confirment la réversibilité des atteintes cognitives avec l'abstinence et mettent même en évidence une normalisation des performances dès les premières semaines d'abstinence. Ces résultats suggèrent que retarder la prise en charge addictologique usuelle permettrait une récupération cognitive et donc aux patients ayant des troubles neuropsychologiques post-sevrage d'en bénéficier pleinement. Nos résultats montrent également qu'une prise en charge de faible intensité permet une amélioration cognitive au cours des premières semaines d'abstinence mais qu'une prise en charge plus intense, incluant de la stimulation cognitive, permet une amélioration globale et une normalisation de certaines composantes cognitives.



Short-term neuropsychological recovery in alcohol use disorder: A retrospective clinical study



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HIGHLIGHTS

- Three weeks of sobriety allow a significant neuropsychological improvement.
- Neuropsychological performance can return to normal after 3 weeks of abstinence.
- An intensive care program including cognitive training favor an overall recovery.

ARTICLE INFO

ABSTRACT

Keywords:

Alcohol use disorder
Neuropsychology
Cognitive recovery
Training

Background: Neuropsychological impairments found in recently detoxified patients with alcohol use disorder (AUD) can limit the benefit of psychosocial treatments and increase the risk of relapse. These neuropsychological deficits are reversible with abstinence. The aim of this retrospective clinical study was to investigate whether a short-term stay as inpatients in a convalescent home enables neuropsychological deficits observed in recently detoxified AUD patients to recover and even performance to return to normal.

Methods: Neuropsychological data were collected in 84 AUD patients. Five neuropsychological components were assessed before and after a three-week stay in a convalescent home offering multidisciplinary support. Baseline and follow-up performance were compared in the entire group of patients and in subgroups defined by the nature and intensity of the therapy (OCCASIONAL: occasional occupational and physical therapy; INTENSIVE: intensive occupational and physical therapy and neuropsychological training).

Results: In the entire group of patients, neuropsychological performance significantly improved between baseline and follow-up for all 5 components and even returned to a normal level for 4 of them. The ratio of patients with impaired performance was significantly lower at follow-up than baseline examination for 3 components in the INTENSIVE group only.

Conclusion: Recently detoxified AUD patients with cognitive deficits benefit from a short-term stay in an environment ensuring sobriety and healthy nutrition. Cognitive recovery may be enhanced by intensive care including neuropsychological training. Alcohol programs could be postponed in patients with cognitive deficits in order to offer psychosocial treatment when patients are cognitively able to benefit from it.

1. Introduction

It is well-known that alcohol use disorder (AUD), characterized by chronic and excessive alcohol consumption, is associated with brain damage and cognitive deficits (Epstein, Pisani, & Fawcett, 1977; Fama et al., 2019; Oscar-Berman, Shagrin, Evert, & Epstein, 1997; Parsons,

1977; Pitel et al., 2011). Indeed, executive functions and episodic memory abilities were repeatedly reported as impaired in recently detoxified AUD patients (Le Berre, Fama, & Sullivan, 2017; Oscar-Berman, Valmas, Sawyer, Ruiz, Luhar, & Gravitz, 2014 for a review). Dysfunctions of these cognitive components can alter motivation to change behavior, decision-making abilities and new complex learning (Blume,

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Schmaling, & Marlatt, 2005; Le Berre et al., 2012), which are crucial processes involved in the motivation to abandon excessive drinking behavior and to engage in alcohol treatment (DiClemente, Bellino, & Neavins, 1999). Altered decision-making abilities would hamper patients to modify alcohol habits in order to maintain abstinence. For these reasons, it seems clinically evident that efficient cognitive abilities are crucial when sobriety or reduction of alcohol consumption is considered. All together, neuropsychological impairments observed early in abstinence may thus limit the benefit of psychosocial treatment and increase the risk of relapse. As found in other psychopathological states such as schizophrenia (Harvey, Green, Keefe, & Velligan, 2004) and depression (Culpepper, Lam, & McIntyre, 2017), cognitive deficits limit the benefit of psychosocial treatments and notably of cognitive behavioral therapies (CBT). In AUD patients, psychoeducation, CBT or motivational interview, which are routinely proposed during the first weeks of sobriety, may thus not be clinically appropriate for AUD patients with impaired neuropsychological abilities (Fein, Bachman, Fisher, & Davenport, 1990; McCrady & Smith, 1986; Tapert, Ozyurt, Myers, & Brown, 2004).

It is now clear that cognitive deficits observed early after detoxification can be partially or totally reversible with drinking cessation even in the absence of any stimulation. Several studies indicated improvements of cognitive abilities in long-term abstinent AUD patients (more than one year) and even a return to a normal level of performance (Fein, Torres, Price, & Di Sclafani, 2006; Reed, Grant, & Rourke, 1992; Stavro, Pelletier, & Potvin, 2013). However, Munro, Saxton, and Butters (2000) highlighted that memory deficits and certain executive dysfunctions were still present after a two-year period of abstinence. Similarly, Nowakowska-Domagala, Jabłkowska-Górecka, Mokros, Koprowicz, and Pietras (2017) showed that executive deficits persist in AUD patients who have been abstinent for one year. Regarding medium-term abstinence (several months), some studies showed that six months without alcohol consumption allow neuropsychological functions to recover (Ioime et al., 2018; Loeber et al., 2010). Pitel et al. (2009) even highlighted that patients abstinent for six months perform on par with controls regarding memory and executive functions. On the opposite, other studies only found partial or nonsignificant improvement during the first year of abstinence (Ros-Cucurull et al., 2018; Stavro et al., 2013). With regard to the effects of short-term abstinence (several weeks), results are also inconsistent. Some studies reported that one month of sobriety is sufficient to recover from alcohol-related cognitive deficits (Kish, Hagen, Woody, & Harvey, 1980; Mann, Günther, Stetter, & Ackermann, 1999) while other investigations showed that neuropsychological impairments can still be observed after the first weeks of sobriety (Mulhauser, Weinstock, Ruppert, & Benware, 2018; Stavro et al., 2013). Manning et al. (2008) and Petit et al. (2017) both found that working memory recovers after three weeks of abstinence while executive dysfunction persists.

The discrepancies in these results may be related to different factors modulating the neuropsychological recovery. Indeed, the number of previous detoxifications could influence the recovery of flexibility abilities (Loeber et al., 2010). It is also important to take account of the smoking status of AUD patients as non-smoker AUD patients seem to better recover than smoker patients (Durazzo, Mon, Gazdzinski, Yeh, & Meyerhoff, 2015). The age of drinking cessation can also explain the heterogeneity in the findings (Munro et al., 2000; Ros-Cucurull et al., 2018). A slowdown in the dynamics of cognitive recovery, which may be related to decreased brain plasticity, has been described in older AUD patients. Cognitive recovery may also be affected by the concurrent use of benzodiazepines (Manning et al., 2008; Petit et al., 2017). Further studies including AUD patients without psychotropic drugs are thus required. In addition, because of the heterogeneity in the cognitive profile of AUD patients, the use of cross-sectional design comparing patients with different lengths of abstinence (e.g. Nowakowska-Domagala et al., 2017) yields less reliable results than longitudinal studies that investigate the same group of patients over the

course of abstinence (e.g. Ioime et al., 2018). Finally, several studies suggest that neuropsychological recovery can be influenced by cognitive training. After three months of cognitive training, AUD patients had higher memory and learning abilities than after three months of working therapy (Bell, Vissicchio, & Weinstein, 2016). In the same vein, Rupp, Kemmler, Kurz, Hinterhuber, and Fleischhacker (2012) showed that 12 sessions of cognitive stimulation during six weeks favor cognitive improvement in certain executive functions and memory components compared to conventional treatments. All together, these results are encouraging since they suggest that psychosocial treatments could be postponed in AUD patients with neuropsychological deficits in order to offer psychoeducation, CBT or motivational interview when patients are cognitively able to benefit from them (McCrady & Smith, 1986, for review).

The main purpose of this retrospective clinical study was thus to investigate, in recently detoxified benzodiazepine-free AUD patients, whether a short-term stay as inpatients in a convalescent home enables neuropsychological deficits to recover and even performance to return to normal. In a more exploratory perspective, an additional objective was to examine, in a clinical setting, the effect of intensive and multidisciplinary care including neuropsychological training compared to occasional physical and/or occupational therapy. Finally, the present study also explored the relations between recovery on the one hand and demographic and clinical data on the other hand.

2. Material and methods

2.1. Patients

For this retrospective study, data were collected for 84 AUD inpatients (71 men and 13 women) through clinical practice in Caen University Hospital and the convalescent home Korian Côte Normande at Ifs from 2011 to 2018. The inclusion criteria were the presence of the DSM IV criteria for alcohol dependence (American Psychiatric Association, 1994) or DSM 5 criteria for AUD (American Psychiatric Association, 2013). Patients were included when they had performed a neuropsychological assessment (in the Addiction department of Caen University Hospital) both before and after a short-term stay in a convalescent home (Korian Côte Normande at Ifs). Alcohol history is presented in Table 1. Because they reflect the reality of the population in addiction departments in France, patients who presented comorbidities were included when clinicians hypothesized that these comorbidities would not hinder them to benefit from the therapies proposed in the convalescent home. Nine patients presented psychiatric comorbidities (4 bipolar, 4 anxiety syndrome, and 1 major depression) and 15 patients had previous neurological history including head injuries, stroke, and glioma. However, patients with intelligence quotient below 70 as well as patients with suspicion of neurodegenerative disorders, Korsakoff's syndrome or fetal alcohol spectrum disorder were excluded. Fifty-nine patients were smokers and 10 had consumed other substances before alcohol detoxification (benzodiazepines, cannabis, buprenorphine). All patients were free from psychotropic medication during the follow-up period, except for those who already had a stable mood regulator treatment (5 out of the 9 patients with psychiatric comorbidities).

2.2. Study design

The overall design of the study is illustrated in Fig. 1. Patients followed a symptom-triggered detoxification protocol at Caen University Hospital consisting of monitoring patients and providing long-acting benzodiazepines only when symptoms of alcohol withdrawal developed. Symptoms were identified with a validated assessment tool, the Cushman score (Cushman, Forbes, Lemer, & Stewart, 1985). A baseline neuropsychological assessment was administered to AUD inpatients at least 48 h after the detoxification program (ie no physical symptoms of

Table 1

Demographic, clinical and disease-related characteristics of the INTENSIVE and OCCASIONAL groups.

Variables	ENTIRE GROUP (N = 84) (M ± SD or N)	INTENSIVE GROUP (N = 54) (M ± SD or N)	OCCASIONAL GROUP (N = 30) (M ± SD or N)
<u>Demographic variables</u>			
Men/Women ratio	71/13	46/8	25/5
Age (years)	53,38 ± 8,57	53,04 ± 8,72	54,00 ± 8,40
Education (years)	11,31 ± 2,10	11,50 ± 2,11	10,97 ± 2,08
<u>Clinical variables</u>			
Number of days in the convalescent home	23,29 ± 7,21	22,61 ± 6,68	24,50 ± 8,05
Number of days between assessments	33,17 ± 11,90	33,50 ± 12,38	32,57 ± 11,17
Overall number of therapy sessions	11,83 ± 8,63	15,07 ± 6,01	6,00 ± 9,62 ***
Number of neuropsychological training sessions	3,23 ± 2,97	5,02 ± 2,16	–
Number of physical therapy sessions	7,54 ± 5,93	9,57 ± 4,84	3,87 ± 6,02 ***
Number of occupational therapy sessions	4,30 ± 3,78	5,50 ± 3,23	2,13 ± 3,79 ***
<u>Disease-related factors</u>			
Daily alcohol consumption (units ^a)	17,76 ± 10,35 (5MD)	18,02 ± 11,05 (1MD)	17,23 ± 8,92 (4MD)
AUD duration (years)	21,73 ± 11,66 (9MD)	21,85 ± 11,18 (6MD)	21,52 ± 12,68 (3MD)
Smokers	59 (2MD)	37 (1MD)	22 (1MD)
Polysubstance users	10 (1MD)	6 (1MD)	4
Psychiatric comorbidity	9 (1MD)	7 (1MD)	2
Neurological history	15 (1MD)	12 (1MD)	3

N: sample size; M: mean; SD: standard deviation; MD: missing data

^a: an alcohol unit = 10 g of pure ethanol

***p < 0,001, Mann-Whitney's tests used to compare demographic and clinical characteristics between the INTENSIVE and OCCASIONAL groups

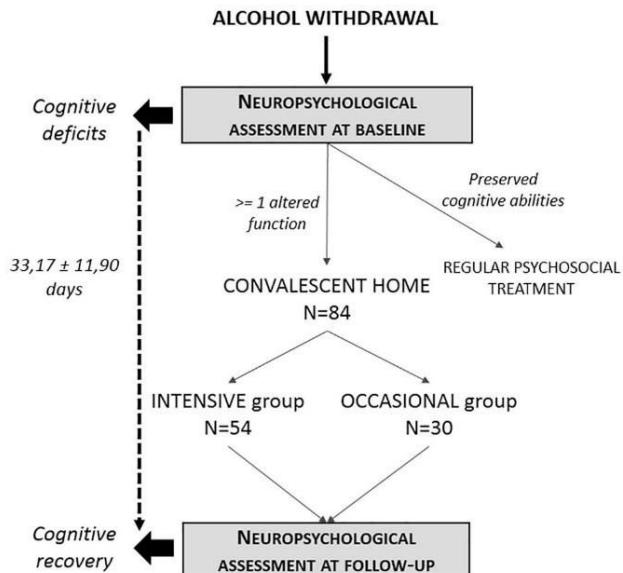


Fig. 1. Study design. After alcohol withdrawal, AUD patients performed a first neuropsychological assessment. When they had preserved cognitive abilities, patients attended the regular psychosocial treatment, whereas when at least one neuropsychological component was impaired, they were offered to stay in a convalescent home. The entire group of patients was *a posteriori* subdivided in two groups (INTENSIVE versus OCCASIONAL) depending on the therapy they could benefit from. One month after the first neuropsychological assessment, patients underwent a follow-up assessment. In order to study the cognitive recovery, we compared baseline and follow-up neuropsychological assessments in the entire group and in each group separately.

alcohol withdrawal and no benzodiazepine when they were assessed). The neuropsychological status was examined through five neuropsychological components: episodic memory, working memory, flexibility, inhibition and processing speed. When at least one neuropsychological component was impaired, patients were offered to stay in the convalescent home Korian Côte Normande for three weeks during which all patients remained abstinent. The first objective of this stay is to favor time-dependent physical and cognitive recovery. This convalescent home also offers multidisciplinary care. Physical therapy,

occupational therapy, and dietary advice can systematically be offered to patients whereas access to neuropsychological training is limited to the scarce availability of the only neuropsychologist of the convalescent home. The neuropsychological training sessions consist of exercises that stimulate cognitive functions such as inhibition, flexibility, attention, and working memory. Physical therapy, occupational therapy, dietary advice and neuropsychological training were offered to the patients who were free to participate or not. Since the beginning of the collaboration between the addiction department and the convalescent home, the nature and frequency of each type of treatment were documented for each patient.

To meet our secondary objectives, patients were *a posteriori* subdivided in two groups depending on the nature and the intensity of the therapy they could benefit from. The main criterion we used to split the group was the possibility to attend neuropsychological training sessions or not. When we compared patients who had benefited from neuropsychological training sessions (N = 54) with those who could not attend neuropsychological training (N = 30), we found that the first group had on the overall benefited from more occupational/physical therapy sessions (15,07 ± 6,01) than the second one (6,00 ± 9,62). Thus, the two groups differed not only on the nature of the treatment (neuropsychological and occupational/physical therapy vs occupational/physical therapy only) but also on the frequency of the training sessions. The two groups were consequently named INTENSIVE (N = 54) and OCCASIONAL (N = 30) to emphasize that given our clinical retrospective study design, the present study cannot disentangle the effect of the nature versus frequency of the sessions. After a short-term stay, all the patients underwent a follow-up neuropsychological assessment at Caen University Hospital.

2.3. Neuropsychological assessment

Because data were collected retrospectively through clinical practice, neuropsychological examinations sometimes included different tests classically used to assess the same cognitive component. For the same reason, the sample size can vary depending on the cognitive task (Fig. 3).

- *Baseline examination*

Episodic Memory. A French version of the Free and Cued Selective

Reminding Test (FCSRT, Grober & Buschke, 1987; Van der Linden et al., 2004) or a French version of the California Verbal Learning Test (CVLT, Delis, Kramer, Kaplan, & Ober, 1987; Nolin, 1999) were used. For the FCSRT, performance on the 3 free recalls of learning trials was used. For the CVLT, performance on the 5 free recalls of learning trials was used.

Executive Functions. Inhibition was assessed by means of the Stroop test (Stroop, 1935). The time (in seconds) needed to complete the interference condition (Word-Color condition) minus the time needed for the denomination condition (Color condition) was calculated. Flexibility was assessed by means of the Modified Card Sorting Test (MCST, Cianchetti, Corona, Foscol, Scalas, & Sannio-Fancello, 2005). The number of perseverative errors was recorded.

Working Memory. Verbal working memory was assessed by means of the digit span task (forward and backward, WAIS-III; Wechsler, 1997). The final score corresponded to the number of correctly reported sequences. The standardized score was used.

Processing speed. Time needed to complete the denomination task (Color condition) of the Stroop test (Stroop, 1935) was recorded.

• Follow-Up examination

Episodic memory was assessed using a parallel version of the FCSRT (Van der Linden et al., 2004) to avoid a potential test-retest effect, which is particularly problematic for memory assessment. The other functions were assessed using the same tasks as those administered during the baseline session since no parallel forms are available for these tests, and executive tasks are less affected by test-retest effect (Bachoud-Levi et al., 2001).

2.4. Statistical analyses

All neuropsychological measures were first transformed into z-scores which were obtained using the mean and standard deviation of the standardized norms for each neuropsychological test and each patient adjusted for age, gender, and level of education when available. Regarding episodic memory, an average of the z-score for the free recall trials was computed for each patient. Thus all cognitive variables were on the same scale with 0 as the mean and 1 as the standard deviation of the reference population. When necessary, the direction of the z-score was reversed so that all the z-scores had the same direction: the higher the z-score, the better the performance.

Given that the sample size varied depending on the cognitive components studied and the fact that some data were not normally distributed (according to Shapiro Wilk tests), we chose to conduct non-parametric tests for all analyses.

First, in order to determine whether a short-term stay as inpatients in a convalescent home enables neuropsychological recovery, we compared cognitive performance between baseline and follow-up examinations by means of Wilcoxon's tests in the entire group of patients. We also investigated whether the cognitive changes between baseline and follow-up were clinically meaningful. To this end, both at baseline and follow-up examinations and for each patient, the neuropsychological performance was classified as impaired or preserved according to a binary z-score approach. The individual performance was considered as impaired when a z-score was strictly below -1.65 standard deviations from the mean. The proportion of patients with preserved and impaired performance was then compared between baseline and follow-up using Yates corrected Chi-square tests.

Second, we explored whether an intensive and multidisciplinary therapy including a neuropsychological training would result in better recovery than occasional physical and/or occupational therapy. To this end, we first compared the INTENSIVE and OCCASIONAL groups on demographic and clinical variables, as well as on the neuropsychological performance both at baseline and follow-up using Mann-Whitney's tests or Yates corrected Chi-square tests. We then used Wilcoxon's tests to examine neuropsychological changes between baseline and follow-

up in each group, and Yates corrected Chi-square tests to compare the proportion of patients with preserved and impaired performance between baseline and follow-up examinations in each group.

Last, we gauged the cognitive recovery by computing a ratio (follow-up performance - baseline performance divided by the baseline performance for each patient). Spearman's correlations were conducted to examine the relationships between this score of cognitive recovery on the one hand and the number of days in the convalescent home, the number of therapy sessions, and demographic as well as disease-related variables on the other hand.

We performed statistical analyses with the complete sample of patients as well as 1) without patients who presented neurological comorbidities, 2) without patients who presented psychiatric comorbidities, and 3) without these two samples.

3. Results

3.1. Comparison between neuropsychological performance at baseline and Follow-up in the entire group

In the entire group of patients, flexibility, inhibition, and processing speed were impaired (z-scores < -1.65) at baseline, whereas episodic memory and working memory components were relatively preserved (z-scores > -1.65). Wilcoxon's comparisons (Fig. 2) revealed significant differences between baseline and follow-up examinations: cognitive performance was better at follow-up than baseline for all components (episodic memory [$T = 394, p < 0.001$]; working memory [$T = 172, p < 0.001$]; flexibility [$T = 120, p < 0.001$]; inhibition [$T = 84, p < 0.001$]; and speed processing [$T = 96, p < 0.001$]). These results were unchanged when patients with comorbidities were removed from the sample. Episodic memory and working memory were still preserved at follow-up. Inhibition and processing speed abilities were also preserved on this second assessment (z-scores > -1.65). Yet, the flexibility component remained impaired (z-score < -1.65), whereas when analyses were performed without patients who presented comorbidities, flexibility performance always returned to a normal level.

Chi-square tests showed that the proportion of patients with preserved or impaired performance in the entire group was significantly different between baseline and follow-up assessments for episodic memory ($\chi^2 = 9.31, p < 0.01$), working memory ($\chi^2 = 8.94, p < 0.01$), flexibility ($\chi^2 = 14.94, p < 0.001$), and inhibition ($\chi^2 = 5.11, p = 0.02$), indicating that there were fewer patients with impaired performance at follow-up than baseline (Fig. 3).

3.2. Comparisons between demographic and clinical variables in the INTENSIVE and OCCASIONAL groups

The statistical analyses did not reveal any significant difference in terms of demographic, clinical, or disease-related variables between the patients of the INTENSIVE and OCCASIONAL groups at baseline (Table 1). However, patients in the INTENSIVE group benefited from more therapy sessions than patients in the OCCASIONAL group ($U = 341, p < 0.001$). More precisely, the number of physical therapy sessions was significantly higher in the INTENSIVE group than in the OCCASIONAL group ($U = 357, p < 0.001$) as well as for the number of occupational therapy sessions ($U = 349, p < 0.001$). Only patients in the INTENSIVE group benefited from neuropsychological training sessions (5.50 ± 3.23).

3.3. Comparisons between neuropsychological performance in the INTENSIVE and OCCASIONAL groups at baseline

Analyses did not reveal any significant difference between the INTENSIVE and OCCASIONAL groups at baseline, except for the flexibility component (Fig. 4): patients in the INTENSIVE group had lower

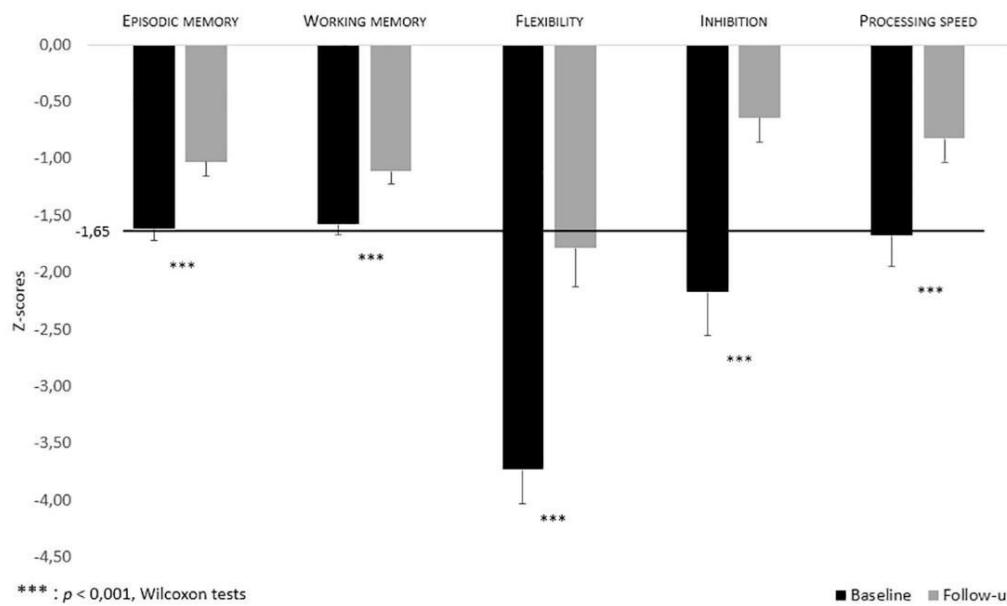


Fig. 2. Neuropsychological performance at Baseline and Follow-up. ***: significant difference between baseline and follow-up performance, with a p-value strictly below 0.001 at Wilcoxon test. The black line represents the threshold for considering performance as impaired (z-score < -1.65) or preserved (z-score > -1.65).

flexibility performance than patients in the OCCASIONAL group ($U = 129.5, p = 0.04$). When comorbid patients were excluded, the difference was no more significant. However, regarding the proportion of patients with impaired performance, no between-group difference was found at baseline (Fig. 3).

3.4. Comparisons between neuropsychological performance at baseline and Follow-up in each group

In the INTENSIVE group, analyses revealed a significant improvement between baseline and follow-up performance for all five components (episodic memory [$T = 149.5, p < 0.001$]; working memory [$T = 40.5, p < 0.001$]; flexibility [$T = 43, p < 0.001$]; inhibition [$T = 46, p < 0.001$]; and processing speed [$T = 50.5, p < 0.001$]).

In the OCCASIONAL group, analyses revealed a significant improvement between baseline and follow-up performance for episodic memory ($T = 58, p < 0.01$); inhibition ($T = 6, p < 0.01$) and processing speed ($T = 10, p = 0.01$) only (Fig. 4).

Regarding the comparisons of the proportion of patients with impaired and preserved performance between baseline and follow-up, Chi-square tests showed more patients with preserved performance at follow-up than at baseline only in the INTENSIVE group (Fig. 3) for episodic memory ($\chi^2 = 5.52, p = 0.02$), working memory ($\chi^2 = 6.45, p = 0.01$), and flexibility ($\chi^2 = 17.08, p < 0.001$).

There were no major changes when patients with comorbidities were removed from the samples, as for the two next parts.

3.5. Comparisons between neuropsychological performance in the INTENSIVE and OCCASIONAL groups at Follow-up

No differences were found between the two groups regarding neuropsychological performance at follow-up (Fig. 4).

3.6. Relationships between neuropsychological changes and clinical variables

There was no significant relationship between cognitive changes on the one hand and demographic, clinical, or disease-related variables (all p values > 0.05).

4. Discussion

The present investigation aimed at determining whether a short-term stay (three weeks) as inpatients in a convalescent home enables neuropsychological deficits observed early in abstinence to recover and even performance to return to normal. In accordance with previous studies (Oscar-Berman et al., 2014; Pitel et al., 2007), baseline results collected early in abstinence indicated that AUD patients exhibited a slowdown in the processing speed, low memory performance and executive dysfunction including altered flexibility and inhibition abilities. Comparisons between baseline and follow-up examinations confirm that cognitive performance significantly improves during the first weeks of sobriety (Kish et al., 1980; Mann et al., 1999). Contrary to Petit et al. (2017) who described persistent executive impairments after 3 weeks of abstinence, we found recovery of inhibition abilities within the same time period.

For four cognitive components (episodic memory, working memory, inhibition, and processing speed), performance returned to a normal level (z-scores > -1.65) at follow-up. Improvement of flexibility was not sufficient to observe a normalization of the performance at follow-up (zscore < -1.65) because baseline results were very severely impaired. Regarding the proportion of patients with preserved and impaired performance, there were fewer patients with impaired episodic and working memory as well as executive performance at follow-up than at baseline. The absence of clinically meaningful changes regarding the ratio of patients with impaired and preserved processing speed performance may be related to the low proportion of impaired patients at baseline. Both when considered the average performance of the group or the individual results, our data suggest that neuropsychological abilities can return to normal not only after several years (Rosenbloom, Pfefferbaum, & Sullivan, 2004; Rourke & Grant, 1999) or several months of abstinence (Pitel et al., 2009) but also after several weeks without alcohol consumption.

Psychosocial treatments are usually proposed early in abstinence, right at the time when alcohol-related neuropsychological deficits are the most severe. Thus, the timing of most psychosocial treatments may not be appropriate for patients with cognitive impairments (McCrady & Smith, 1986). Our results suggest that the neuropsychological recovery observed after just a few weeks of sobriety could enable AUD patients to

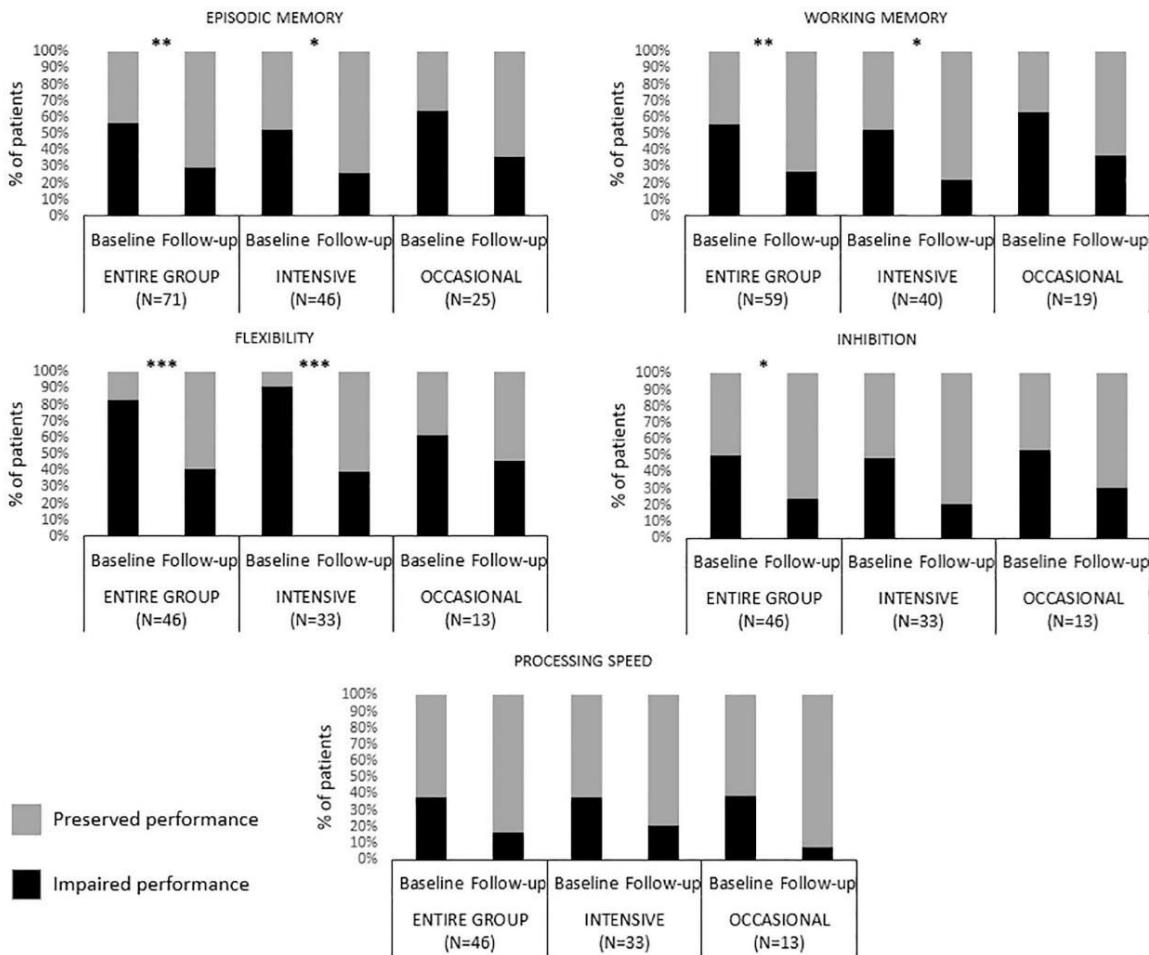


Fig. 3. Ratio of patients with preserved and impaired neuropsychological performance at Baseline and Follow-up in the ENTIRE group, as well as in the INTENSIVE and OCCASIONAL groups. The performance of each patient was classified as impaired or preserved according to a binary z-score approach (Cut-off z-score: -1.65). *, **, *** represent significant differences in the proportion of patients with impaired and preserved performance between baseline and follow-up, with p-values respectively below 0.05, 0.01, and 0.001 at Chi-square tests. The proportion of patients with impaired performance differed significantly between the two groups neither at baseline nor at follow-up examinations.

be cognitively able to effectively benefit from motivational interview, psychoeducation and CBT. After short-term abstinence, efficient inhibition abilities would make patients more able to control alcohol craving but the use of novel adaptative strategies in risky situations (Giancola & Moss, 1998) may still be difficult because of residual flexibility deficits. Such persistent flexibility impairments could reflect premorbid cognitive alterations that would make patients particularly vulnerable to develop AUD (Mulhauser et al., 2018). Interestingly, when patients with psychiatric and/or neurological comorbidities were excluded from the analyses, flexibility performance returned to a normal level at follow-up. This result suggests that cognitive impairments related to psychiatric and/or neurological diseases may slow down the course of recovery (Bourne et al., 2013; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Whiting, Deane, Simpson, McLeod, & Ciarrochi, 2017).

While drinking cessation is the main factor that influences cognitive recovery, other variables have been suggested to modulate its dynamics and extent. The present study does not confirm the role of age (Munro et al., 2000; Ros-Cucurull et al., 2018) and smoking status (Durazzo et al., 2015), and does not indicate a relationship between alcohol-related variables and cognitive recovery. Diet may also support neuropsychological recovery through regular and healthy meals provided in the convalescent home. Biological comorbidities including

malnutrition (Ritz et al., 2016) and altered thiamine metabolism (Coulbault et al., 2019) are associated with neuropsychological impairments. As all patients included in the present study were well-fed and benefited from nutritional monitoring during convalescence, the effect of this variable could not be examined.

Another factor has been described to influence cognitive recovery. The concept of experience-dependent recovery suggests that neuropsychological skills may indeed be enhanced by the practice of cognitive tasks (Goldman, 1990). In an exploratory perspective, the present study enabled us to investigate the effect of intensive and multidisciplinary care on cognitive recovery. Between baseline and follow-up, the INTENSIVE group significantly improved all five cognitive components, whereas the OCCASIONAL group only improved episodic memory, inhibition, and processing speed performance. For flexibility, the difference in the recovery of the two groups may be related to a larger margin of improvement observed in the INTENSIVE group. Indeed, at baseline, the INTENSIVE group performed lower than the OCCASIONAL group only on the flexibility task. However, this difference may be driven by the presence of patients with psychiatric and neurological comorbidities as there was no more significant difference at baseline when these patients were excluded from the analyses. Our results also show that in the OCCASIONAL group, the proportion of patients with preserved performance did not increase from baseline to

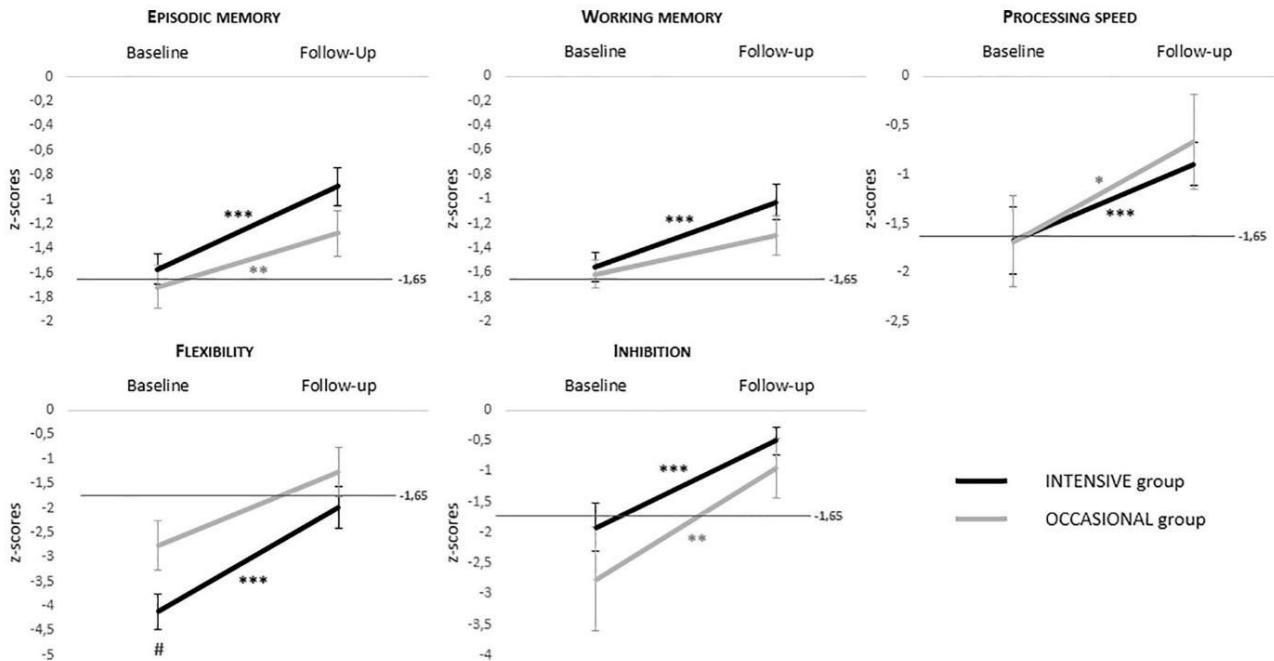


Fig. 4. Neuropsychological performance at Baseline and Follow-up in the INTENSIVE and OCCASIONAL groups. Means and standard errors. # represents a significant difference between the performance of the two groups at baseline, with a $p < 0.05$ at the Mann-Whitney test. *, **, *** represent significant differences between baseline and follow-up performance within each group, with p -values respectively below 0.05, 0.01, and 0.001 at Wilcoxon tests. The dark gray lines represent the threshold for considering performance as impaired (z -score < -1.65) or preserved (z -score > -1.65).

follow-up. On the opposite, in the INTENSIVE group, there were significantly more patients with preserved episodic memory, working memory and flexibility performance at follow-up than at baseline. To sum up, even a short-term mild intensity program based on occasional physical and occupational therapy allows cognitive improvement during the first weeks of sobriety (Kish et al., 1980; Mann et al., 1999). But a more intensive program including cognitive training seems to favor an overall neuropsychological recovery and even a normalization of some cognitive components. The present results are in agreement with those of Bell et al. (2016) and Rupp et al. (2012), who showed that cognitive training programs (respectively three months and six weeks) allow a better cognitive recovery than usual treatment.

It is worthwhile keeping in mind that the present investigation is a retrospective clinical study, which does not permit to determine whether cognitive recovery is modulated by the nature and/or the intensity of the program. Another limitation of this study relates to the tasks used for the cognitive assessment. Performance was analyzed with neuropsychological tasks classically used in routine practice. Other experimental tasks, not frequently used in clinical settings, would be more sensitive to alcohol effects (Stephan et al., 2017). It would thus be interesting to complete the neuropsychological assessment using decision-making tasks, social cognition tasks, and more ecological tests, which would probably better reflect daily life difficulties. Ideally, the use of parallel versions of the tasks, when available, should also be used, not only for memory assessment, to avoid test-retest effects. Moreover, given the retrospective nature of this research, the experimental design (exact modalities of treatment, randomization of the different treatment options and use of blind experimenters) is not as well controlled as it would be with a randomized controlled trial (RCT). Further RCT are thus required to set up solid programs favoring cognitive recovery and specifying whether the nature or intensity of the care matters. For a better differentiation between time-dependent or treatment-dependent recovery, future studies need to include non-treated comparison groups. In a more sophisticated prospective study with three experimental groups, a passive control group with no

treatment could be proposed to measure spontaneous recovery only related to sobriety. The clinical setting in which this study was conducted offering systematically occasional physical and occupational therapy, the OCCASIONAL group was considered as an active control group. From a clinical perspective, psychosocial treatments involving efficient cognitive abilities should be postponed in order to propose programs including physical, cognitive and nutritional support that seem to favor cognitive recovery of AUD patients with neuropsychological deficits. While the present study was conducted in AUD inpatients, day center programs could be a relevant alternative so that patients can face their daily life without alcohol. Finally, it would also be interesting to examine whether the recovery observed after short-term sobriety allows AUD patients to engage more actively and efficiently in psychosocial treatment ultimately decreasing the rate of relapse.

To conclude, early detoxified AUD patients who are cognitively impaired could be transferred to an environment in which they would be well-fed, alcohol would be prohibited, and a multidisciplinary treatment would be offered. The cognitive improvement observed during a short-term stay in such environment would enable patients to effectively benefit from psychosocial programs to eventually reduce alcohol relapse.

CRediT authorship contribution statement

Angéline Maillard: Formal analysis, Writing - original draft. **Hélène Poussier:** Investigation. **Céline Boudehent:** Investigation, Writing - review & editing. **Coralie Lannuzel:** Investigation. **Angel Vicente:** Investigation. **François Vabret:** Conceptualization, Writing - review & editing. **Nicolas Cabe:** Writing - review & editing. **Anne-Lise Pitel:** Conceptualization, Writing - review & editing, Supervision.

Acknowledgments

The authors are grateful to Alice Laniepce and Claire André for their

helpful comments on the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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4. Etude 3 : Evolution cognitive et cérébrale dans le SK (article soumis)

Alors que les résultats de la deuxième étude de cette thèse ont confirmé la réversibilité précoce des troubles cognitifs chez les patients TUAL, la récupération cognitive et cérébrale dans le SK n'a été que très peu étudiée. En effet, deux études de cas ont permis de montrer, dès les premières semaines qui suivent le diagnostic, une normalisation du métabolisme de glucose dans toutes les régions cérébrales sauf au niveau des thalamus (Fellgiebel *et al.*, 2003, 2004). Par ailleurs, une étude de groupe a montré que les performances cognitives de 20 patients SK abstinents depuis huit ans ne semblent pas se dégrader au cours d'une période de deux ans (Fujiwara *et al.*, 2008). Les auteurs indiquent également que seule une légère amélioration des capacités de flexibilité, de vitesse de traitement et de mémoire visuelle est observée chez ces patients, tout en ajoutant que les performances restent malgré tout altérées. Afin de pouvoir adapter la prise en charge des patients SK, des études sont nécessaires pour clarifier l'évolution des atteintes cognitives et cérébrales.

L'objectif de cette étude était donc d'évaluer les changements cognitifs et cérébraux dans le SK. Nos hypothèses étaient que : 1) Contrairement à ce qui est observé dans les maladies neurodégénératives, nous ne devrions pas observer de déclin cognitif ou de détérioration cérébrale ; 2) L'évolution des altérations dépendantes du CP et du CFC devrait être différente. Ainsi, les déficits de mémoire épisodique, sous-tendus par une atrophie et un hypométabolisme du CP, devraient persister au cours du temps alors que les fonctions exécutives pourraient potentiellement s'améliorer en fonction de l'évolution du CFC.

Deux groupes de huit patients SK recrutés au CHU de Caen (SK^C) et à la Maison Vauban de Roubaix (SK^R) ont bénéficié d'une évaluation neuropsychologique et en neuroimagerie, incluant des examens d'IRM et de TEP-FDG. Le premier groupe a été évalué environ deux mois après le diagnostic (SK^C-T1) et réévalué un an après l'inclusion (SK^C-T2). Les patientes du second groupe ont été évaluées environ 10 ans après le diagnostic de SK. Des comparaisons longitudinales ont été réalisées entre les données de SK^C-T1 et de SK^C-T2, et des comparaisons transversales entre les données de SK^C-T1 et de SK^R. Les performances neuropsychologiques ont également été interprétées d'un point de vue clinique en les classant comme altérées ou

préservées selon les données normatives des tests. De plus, les profils d'altérations cérébrales ont été décrits en comparant les différents groupes de patients à un groupe de 44 sujets contrôles.

Les comparaisons entre les groupes de patients SK ne montrent pas de déclin cognitif ni de détérioration cérébrale au cours du temps. Les résultats n'ont pas non plus mis en évidence d'amélioration importante ; seule une récupération modeste du volume et du métabolisme de quelques régions du CFC est observée. Il est intéressant de noter que les patients du groupe SK^C-T1 présentent des déficits sévères de la mémoire épisodique ainsi que des déficits d'inhibition, de vitesse de traitement et d'accès à des informations sémantiques. Ils présentent également un profil étendu d'atrophie et d'hypométabolisme, ainsi qu'un hypermétabolisme cérébelleux. La mémoire épisodique reste sévèrement altérée aussi bien dans le groupe SK^C-T2 que dans le groupe SK^R. Contrairement à ce qui est observé dans le groupe de SK^C à T1 et T2, le groupe SK^R a des capacités d'inhibition préservées. Par ailleurs, le profil d'atrophie est similaire, mais moins étendu dans le groupe SK^C-T2, et encore plus limité dans le groupe SK^R. Cependant, les thalami, l'hypothalamus et le fornix restent sévèrement atrophiés. De plus, l'hypométabolisme est encore très important dans les groupes SK^C-T2 et la SK^R et persiste notamment dans les thalami et l'hypothalamus. Le métabolisme cérébelleux diminue avec le temps et semble même se normaliser chez les patients SK^R.

Nos résultats montrent que dans le syndrome de Korsakoff, les altérations structurales et métaboliques du CP persistent au cours du temps, en accord avec la nature irréversible de l'amnésie. Il n'y a pas de récupération comme observée dans le TUAL, ni de signes de déclin progressif comme dans les maladies neurodégénératives. Seule une récupération partielle des atteintes liées au CFC peut être observée.

IS THERE COGNITIVE AND BRAIN CHANGES OVER TIME IN KORSAKOFF'S SYNDROME?

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Paper: 4497

Abstract: 249

Title: 71

References: 50

Tables: 2

Figures: 2

[120] MRI; [122] PET; [201] Memory; [206] Executive function; [258] Alcohol

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Study funding: Supported by Fondation pour la Recherche Médicale (FMR, ING20140129160), ANR-Retour post-doctorant 2010, Conseil Régional Basse Normandie, and MILDECA.

The recruitment of the healthy controls was supported by Institut National de la Santé et de la Recherche Médicale (Inserm), Fondation Plan Alzheimer (Alzheimer Plan 2008-2012), Programme Hospitalier de Recherche Clinique (PHRCN 2011-A01493-38 and PHRCN 2012 12-006-0347), Agence Nationale de la Recherche (LONGVIE 2007), Région Basse-Normandie, Association France Alzheimer et maladies apparentées, Fondation Vaincre Alzheimer.

Competing interests: All authors declare no conflict of interest in any form or kind in relation to this study and its publication.

Glossary: AUD = Alcohol Use Disorder; DTI = diffusion tensor imaging; FCC = frontocerebellar circuit; FDG = ¹⁸F-2-fluoro-deoxy-glucose; FWHM = full width at half maximum; KS = Korsakoff's syndrome; PC = Papez circuit; PVEs = partial volume effects

ABSTRACT

Objective: To investigate, in Korsakoff patients (KS), cognitive and brain changes over months and up to 10 years after the diagnosis.

Methods: Two groups of eight KS patients underwent neuropsychological and neuroimaging investigations including structural MRI and ¹⁸F-FDG-PET. The KS^C group was examined early after the KS diagnosis (KS^C-T1) and one year later (KS^C-T2). The KS^R group was evaluated 10 years after the diagnosis. Longitudinal comparisons in KS^C explored short-term changes while cross-sectional comparisons between KS^C-T1 and KS^R informed about long-term changes.

Results: No cognitive nor brain deterioration occurred over time in KS patients. There was no clear improvement either, with only modest recovery in the frontocerebellar circuit. Compared to the norms, KS^C-T1 had severe episodic memory impairments and some executive dysfunctions. They also presented widespread atrophy and hypometabolism, as well as cerebellar hypermetabolism compared to 44 healthy matched controls. Episodic memory remained significantly impaired in KS^C-T2 and KS^R. Contrary to KS^C at T1 and T2, KS^R had preserved inhibition abilities. Atrophy was similar but less extended in KS^C-T2, and even more limited in KS^R. At all times, the thalamus, hypothalamus, and fornix remained severely atrophied. Hypometabolism was still widespread in KS^C-T2 and KS^R affecting notably the diencephalon. Cerebellar metabolism decreased over time and normalized in KS^R.

Conclusion: In KS, structural and metabolic alterations of the Papez circuit persisted over time, in accordance with the irreversible nature of amnesia. There was neither significant recovery as observed in patients with alcohol use disorder nor progressive decline as in neurodegenerative diseases.

1. INTRODUCTION

Korsakoff's syndrome (KS) is an alcohol-induced major neurocognitive disorder, whose main feature is a severe anterograde amnesia supposed to persist even at a chronic stage. Two brain circuits, namely the Papez circuit (PC)¹, sub-serving episodic memory, and the frontocerebellar circuit (FCC)², subtending notably working memory and executive functions, are known to be affected in terms of brain shrinkage, altered glucose metabolism and structural connectivity, leading to associated neuropsychological dysfunctions³⁻⁶.

While recovery in patients with Alcohol Use Disorder (AUD) without KS is well-documented, longitudinal studies in KS patients are very rare, with one group study showing 20 KS patients improving on flexibility, processing speed and visual memory in a 2-year follow-up, 8 years after initial diagnosis⁷. Regarding neuroimaging, findings are limited to case reports showing normalization of hypometabolism in frontal, occipital and cingulate regions but persistent amnesia and confabulations⁸. In the absence of robust group comparisons, clinical settings have to rely on anecdotal, and hence disparate, evidence regarding the extent and nature of recovery in KS.

The objective of the present study was to investigate cognitive and brain changes over months and even years after the diagnosis of KS. We hypothesized that, 1) contrary to neurodegenerative diseases, no further cognitive decline, nor brain deterioration would be observed; 2) the dynamics in alterations to the PC and FCC would be different: episodic memory impairments, sub-served by an atrophied and hypometabolic PC, would persist over time, whereas executive dysfunction could potentially improve following possible recovery of the FCC.

2. MATERIALS AND METHODS

2.1. Participants, standard protocol approvals, registrations, and patient consents

Two groups of eight KS patients were included according to the criteria of the DSM-5⁹ for alcohol-induced major neurocognitive disorder, amnestic-confabulatory type and persistent. KS patients were recruited as inpatients at Caen University Hospital (France; **KS^C**; $n = 8$; six men) and in a nursing home (Maison Vauban, Roubaix, France; **KS^R**; $n = 8$; all women) as part of the ALCOBRAIN study approved by the local ethics committee (CPP Nord-Ouest III, no. IDRCB: 2011-A00495-36). All patients had a history of heavy drinking (longer than 20 years), but it was difficult to obtain accurate information about their alcohol intake because of their amnesia. The background information came mainly from family members and medical records. The two groups of KS patients were matched for age and education ($P = 0.71$ and $P = 0.67$, respectively) but not for sex repartition ($P = 0.01$). Age, education (years of schooling), sex repartition, as well as depression (BDI)¹⁰, anxiety scores (State-Trait Anxiety Inventory, STAI)¹¹ and nicotine dependence level (Fagerstrom's score)¹² are reported in Table 1.

KS^C patients were included and examined over the first months following the diagnosis of KS (64.5 ± 38.09 days after drinking cessation) and underwent a follow-up examination one year after the first one. Thereafter, these longitudinal evaluations will be distinguished as **KS^C-T1** and **KS^C-T2**. During the follow-up period, most of the **KS^C** patients stayed as inpatients, lived in foster family or foster care. However, one patient went back home, and family members reported alcohol use (six units of 10 grams of pure ethanol per day) during the first eight months of the follow-up period. **KS^R** patients were included several years after the diagnosis of KS (10 years on average). Since they were living in a nursing home, they all had been abstinent for several years.

Forty four healthy controls (**HC**; 21 men, 23 women) from the “Imagerie Multimodale de la Maladie d’Alzheimer à un stade Précoce” (IMAP) cohort in Caen, approved by a regional

ethics committee (CPP Nord-Ouest III; nb. NCT01638949), were recruited in the present study.

They matched for age, education, and sex ratio with the KS^C group ($P = 0.40$, $P = 0.12$ and $P = 0.16$, respectively). They matched for age and education with the KS^R group ($P = 0.29$ and $P = 0.11$, respectively) but not for sex ratio since all KS^R were women (Table 1).

To be included, all participants had to have French as their native language. No participant had a co-morbid psychiatric disorder, a history of serious chronic pathology (diabetes, hepatitis, HIV, endocrinial disorder, as revealed by participants' blood tests), or neurological problems (traumatic head injury causing loss of consciousness for >30 min, epilepsy, stroke, etc.) that might have affected cognitive function and that might hinder cognitive and brain recovery. Participants did not fulfill the DSM-5 criteria for substance use disorder (other than alcohol for some KS patients) over the last 3 months (except tobacco).

All the participants gave their informed written consent to the study before examinations. For KS patients, informed consent was also collected from guardians and caregivers. The study was carried out in line with the declaration of Helsinki (1964).

Table 1 about here.

2.2. Study Design

A detailed neuropsychological assessment was administered only to KS patients. All participants (KS patients and HC) underwent neuroimaging investigations including MRI and FDG-PET examinations. This study combined longitudinal (KS^C -T1 versus KS^C -T2) comparisons exploring short-term (one year) cognitive and brain changes, and cross-sectional (KS^C -T1 versus KS^R) comparisons informing about long-term (about 10 years) changes.

2.3. Neuropsychological examination

Verbal episodic memory. A French version of the Free and Cued Selective Reminding Test (FCSRT)¹³, and a French version of the California Verbal Learning Test (CVLT)¹⁴ were

used for KS^C-T1. KS^C-T2 solely performed a parallel version of the FCSRT while only the CVLT was carried out for the KS^R. For each test, two scores were selected: 1) the last free recall of learning trials (the third for the FCSRT; the fifth for the CVLT), and 2) the delayed free recall.

Visual long-term memory. The 30-minutes delayed recall of the Rey-Osterrieth Complex Figure¹⁵ was used for all patients.

Working memory. The digit span task (forward and backward, WAIS-III)¹⁶ was used for all patients. The raw score, corresponding to the sum of correctly reported sequences, was then transformed in standardized score.

Inhibition. The Stroop test's interference score¹⁷ was used for all patients. The difference between time needed to complete the interference condition (Word-Color condition) and the time needed for the denomination condition (Color condition) was calculated.

Flexibility. For all patients, flexibility was assessed by the letter and category fluency tasks¹⁸. The two tasks involve switching capacities, however, the letter fluency task also requires abilities to generate strategies, whereas the category fluency task rather requires access to semantic information.

Processing speed. Time needed to complete the denomination task (Color condition) of the Stroop test was recorded in all patients.

2.4. Brain Imaging Data Acquisition and Preprocessing

2.4.1. MRI volumetric Data

For each participant, a high-resolution T1-weighted anatomical image was acquired on a Philips Achieva 3T scanner (Philips Healthcare, Amsterdam, Netherlands) using a 3D fast-field echo sequence (sagittal; repetition time = 20ms; echo time = 4.6ms; flip angle = 10°; 180 slices; slice thickness, 1mm; field of view, 256x256mm²; matrix, 256x256).

Volumetric data sets were preprocessed using the SPM12 toolbox (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>, Statistical Parametric Mapping software; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Briefly, T1-weighted images were spatially normalized into the Montreal Neurological Institute (MNI) space (voxel size = 1.5mm³; matrix = 121x145x121) and segmented into gray matter, white matter, and cerebrospinal fluid. The normalized gray matter and white matter images were modulated by the Jacobian determinants to preserve brain volume. The segmented images and normalization parameters estimated from this VBM protocol were used for the preprocessing of the PET data. The resulting images were smoothed by a Gaussian kernel of 8mm full-width-at-half-maximum (FWHM).

The gray matter mask was obtained by averaging the unmodulated gray matter images from the HC group in MNI space, and thresholding the resultant mean image at 0.5. The same principle was used for creating a white matter mask.

2.4.2. PET Data

PET scan of each participant was acquired using a Discovery RX VCT 64 PET-CT scanner (GE Healthcare, Chicago, IL, USA) with a resolution of 3.76x3.76x4.9mm³ and axial field of view of 157mm. Subjects had fasted for at least six hours before scanning and had been asked not to smoke on the day of the examination. To minimize anxiety, the PET procedure was explained in details beforehand. The head was positioned on a head-rest relative to the canthomeatal line and gently restrained with straps. FDG uptake was measured in resting condition, eyes-closed, in a quiet and dark environment. Subjects were told to avoid focusing on any specific mental process during scanning. A catheter was inserted into a vein of the arm to inject the radiotracer. About 3 to 5 mci of FDG was injected as a bolus at time 0, and a 10-minute data acquisition period started 50 minutes post-injection that was preceded by the acquisition of a low-dose CT transmission scan (140kV, 10mA). Forty-seven planes were

acquired with septa out (3D listmode data acquisition), and the image was reconstructed with ordinary Poisson-ordered-subtest expectation maximization algorithm (OP-OSEM; 21 subtests, 2 iterations) using a voxel size of $1.95 \times 1.95 \times 3.2 \text{ mm}^3$. During data acquisition, head motion was continuously monitored with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn on the forehead. Under the current clinical setup, and in the absence of a motion detection and quantification device, movements could not be corrected for at sinogram level. Only one 10-minute frame was acquired, and manufacturer's software and limitations did not allow further splitting of the listmode data for potential frame-by-frame realignment.

The PET data were first corrected for cerebrospinal fluid and white matter partial volume effects (PVEs) in gray matter, using the voxel-by-voxel "modified Müller-Gartner" method¹⁹. Using SPM12, the PVE-corrected PET data set was then co-registered onto their respective native MRIs and normalized into the MNI space by reapplying the normalization parameters estimated from the VBM protocol described above (final voxel size = 2 mm^3 and matrix = $79 \times 95 \times 79$).

To account for inter-individual variations in PET measurements, semiquantitative normalization was performed by scaling the PET images using a concatenation of the cerebellar lobules III, IX and X as a reference region²⁰. Finally, the resulting images were smoothed with a Gaussian kernel 10mm FWHM.

2.5. Statistical analyses

Neuropsychological data. All neuropsychological measures were brought to the same scale by transforming them into z-scores using the mean and standard deviation of the standardized norms.

Neuropsychological changes. Given the sample sizes and the fact that some data were not normally distributed (Shapiro-Wilk's tests), two-tailed non-parametric tests were conducted for all neuropsychological analyses. To investigate the short-term changes, we compared cognitive performance between KS^C-T1 and KS^C-T2 by means of Wilcoxon's tests. The long-term changes were studied by means of Mann-Whitney's tests to compare KS^C-T1 and KS^R. We applied Bonferroni's corrections to account for multiple comparisons (8 comparisons, significant *P*-value<0.006).

Neuropsychological performance. Performance was considered as impaired when a z-score was strictly below -1.65 standard deviations from the mean.

Brain imaging data. Analyses of brain imaging data were performed in SPM 12 using corrections for multiple comparisons (Family-Wise Error (FWE), *P*<0.05). When no result was significant at *P*<0.05 FWE, a more lenient threshold of *P*<0.001 uncorrected for multiple comparisons was used. We chose a minimum cluster size of *k*=60 for MRI data and *k*=25 for PET data, both corresponding to a cluster size of approximately 200mm³. In order to examine improvement as well as decline over time, and atrophy/hypometabolism as well as hypertrophy/hypermetabolism compared to controls, the two contrasts were systematically analyzed. For all volumetric comparisons, total intracranial volume was used as a covariate. Significant clusters of gray matter and metabolism were labeled using the Harvard-Oxford cortical and subcortical structural, and the probabilistic cerebellar atlases implemented in FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>). White matter clusters were labelled using the MRI Atlas of Human White Matter²¹.

Brain changes. Short-term changes (gray and white matter structure, and metabolism) were analyzed using voxel-based paired *t*-tests to compare KS^C-T1 and KS^C-T2. Long-term changes were examined using voxel-based two-sample *t*-tests to compare KS^C-T1 and KS^R.

Brain structure and metabolism. Voxel-based two-sample *t*-tests were conducted to describe brain structure (gray and white matter) and metabolism in each sample of KS patients (KS^C-T1 and KS^C-T2, and KS^R) relative to HC.

2.6. Data availability

All data and materials used within this study will be made available, upon reasonable request, to research groups wishing to reproduce/confirm our results.

3. RESULTS

3.1. Neuropsychological changes

3.1.1. Short-term changes: longitudinal comparisons (KS^C-T1 versus KS^C-T2)

After Bonferroni's corrections, there was no significant difference between KS^C-T1 and KS^C-T2 (Table 2).

3.1.2. Long-term changes: cross-sectional comparisons (KS^C-T1 versus KS^R)

There was no significant difference between KS^C-T1 and KS^R on the neuropsychological tasks after Bonferroni's corrections (Table 2).

3.2. Neuropsychological performance

Regarding the KS^C group, at T1 as well as T2, all neuropsychological scores were impaired, i.e. z-scores strictly below -1.65 standard deviation, except performance on the digit span and letter fluency tasks.

In the KS^R group, all neuropsychological scores were impaired, except performance on the interference score, digit span and letter fluency tasks (Table 2).

Table 2 about here.

3.3. Brain changes

No brain changes were significant at $p<0.05$ (FWE). For the sake of completeness, results that were significant at $p<0.001$, uncorrected for multiple comparisons, are presented in Figure 1.

3.3.1. Short-term changes: longitudinal comparisons (KS^C -T1 versus KS^C -T2)

Gray matter. Comparisons revealed higher gray matter volume at T2 than T1 in small clusters including parts of the bilateral angular gyrus, lateral occipital cortex and precuneus, and in the left supramarginal and fusiform gyri, parietal lobule, and temporal pole.

White matter. Comparisons indicated that at T2, patients had higher white matter volumes than at T1 in small clusters including parts of the splenium and body of the corpus callosum, right cingulum, and in the left corticospinal tract, pontine crossing tract, middle cerebellar peduncle, cerebral peduncle, and superior longitudinal fasciculus.

Metabolism. Comparisons showed higher metabolism at T2 than at T1 in small clusters including parts of the right thalamus and precuneus, in the left lateral occipital cortex, angular gyrus, and parietal lobule.

The opposite contrast [$T1>T2$] did not reveal any significant differences regarding brain volume or metabolism.

3.3.2. Long-term changes: cross-sectional comparisons (KS^C -T1 and KS^R)

Gray matter. Small clusters including parts of the left angular gyrus, supramarginal gyrus, cerebellar Crus I and lobule VI, right occipital pole, precuneus, posterior cingulate gyrus, and bilateral fusiform gyrus had higher gray matter volume in KS^R than in KS^C -T1. The opposite contrast did not reveal any significant differences.

White matter. No significant differences were found between KS^C-T1 and KS^R regarding white matter volumes.

Metabolism. KS^R had higher metabolism than KS^C-T1 in small clusters including parts of the left lateral occipital cortex, supramarginal gyrus, angular gyrus, frontal pole, as well as in the right fusiform gyrus, and inferior temporal gyrus. KS^R presented lower metabolism than KS^C-T1 in the lobules VI, VIIIa, and VIIIb of the cerebellum.

Figure 1 about here.

3.4. Brain structure and metabolism

Results are considered as significant at $p < 0.05$ (FWE) and presented in Figure 2.

3.4.1. Gray matter volume

Compared to HC, KS^C-T1 had gray matter shrinkage in large brain clusters including parts of the frontal, parietal, temporal (including medial temporal lobes namely hippocampus and parahippocampal gyri), occipital, insular, motor, and cingulate cortices as well as in subcortical structures such as thalami, hypothalami (including mammillary bodies), amygdala, caudate nuclei, and in the cerebellum.

Compared to HC, KS^C-T2 presented gray matter shrinkage in the same clusters as KS^C-T1, but with smaller sizes than at T1.

Compared to HC, KS^R had lower gray matter volume notably in the bilateral precentral, superior frontal gyrus, and paracingulate cortices, hippocampi and parahippocampal gyri, thalami, hypothalami (including mammillary bodies), amygdala and left insular cortex.

The opposite contrasts did not reveal any significant differences.

3.4.2. White matter volume

Compared to HC, KS^C-T1 patients had lower white matter volumes in the fornix, corpus callosum, corona radiata, thalamic radiation, superior fronto-occipital fasciculus, internal capsule, and left cerebral peduncle, as well as in the white matter of the middle frontal gyrus.

The same pattern of white matter atrophy was observed in KS^C-T2 patients compared with HC, except that the cerebral peduncle volume did not differ from that of the HC group anymore.

The pattern of white matter atrophy of KS^R patients compared to HC was less extended. Comparisons revealed differences in the fornix, superior fronto-occipital fasciculus, thalamic radiation, internal capsule, and corona radiata.

The opposite contrasts did not reveal any significant differences.

3.4.3. Metabolism

Hypometabolism [KS<HC]. Compared to HC, KS^C-T1 had widespread hypometabolism including notably lower metabolism in frontal, parietal, temporal (including hippocampi and parahippocampal gyri), cingulate, insular and occipital cortices, as well as subcortical structures such as thalami, hypothalami, amygdala, and the right caudate and accumbens nuclei. There was also hypometabolism in the lobules IV, V, VI and Crus I of the cerebellum.

Compared to HC, KS^C had a similar profile of hypometabolism at T1 and T2. However, at T2, the metabolism of caudate nucleus and hypothalami was not altered anymore.

Compared to HC, KS^R had the same profile of hypometabolism than KS^C with smaller clusters size. However, contrary to what we observed in KS^C metabolism in amygdala, hippocampi, and cerebellum was preserved.

Hypermetabolism [KS>HC]. Compared to HC, KS^C-T1 had bilateral hypermetabolism in lobules VIIb, VIIIa, and VIIIb of the cerebellum.

The comparison between KS^C-T2 and HC revealed the same pattern of hypermetabolism than at T1, except for the left lobule VIIIb, which was not hypermetabolic anymore.

The comparison between KS^C and HC did not reveal any significant hypermetabolism.

Figure 2 about here.

4. DISCUSSION

The goal of the present study was to investigate, in KS patients, cognitive and brain changes over months and even years after the diagnosis. Regarding damage to the PC and FCC, and associated neuropsychological deficits, our hypotheses were threefold: we expected that 1) there would not be any cognitive decline or brain deterioration over time, 2) episodic memory impairments, sub-served by an atrophied and hypometabolic PC, would persist over time, and 3) executive abilities would improve following possible brain recovery of the FCC. Our results show an absence of cognitive decline or brain deterioration and reveal that despite some structural improvement of certain regional brain volumes over time and a return to normal of the cerebellar hypermetabolism, cognitive performance, especially episodic memory, does not improve in KS patients, even 10 years after the diagnosis.

Papez's circuit

As reported in previous studies, the group of KS^C patients examined several weeks after the diagnosis exhibited severe episodic memory deficits²²⁻²⁴. As hypothesized, one year after the diagnosis and even 10 years later, there was no significant improvement of episodic memory, and neither decline. Performance remained severely impaired over time. These results are in line with a longitudinal study that highlighted that episodic memory did not improve over a two-year period, and was still impaired after 10 years of abstinence in a group of 20 KS

patients⁷. A case-study had also reported the persistence of severe memory impairments in a KS patient after nine months of abstinence²⁵.

These memory deficits are sustained by brain alterations in the PC. In the present study, structural abnormalities found in KS patients early after the diagnosis are consistent with previous studies reporting gray matter shrinkage in thalamci, hippocampi, hypothalamci, and cingulate cortex^{3,26-29}, as well as white matter damage in the fornix, cingulum, and internal capsule^{5,29,30}. Metabolic abnormalities were observed in the same regions as for gray matter shrinkage as previously reported^{3,4,8,31,32}. Those findings thus confirm structural and metabolic alterations to the nodes and tracts of the PC in KS. Using a reliable statistical threshold, longitudinal and cross-sectional comparisons did not highlight ostensible differences between the groups of KS patients. When a more lenient statistical threshold was used, modest improvements in volumes of the right cingulum and cingulate gyrus as well as increased glucose metabolism in the right thalamus were found. The thalamus consists of several nuclear groups including the anterior nuclear group connected to the PC and the dorsomedial group connected to the FCC. As the thalamus is thus shared between the PC and the FCC, and that the spatial resolution of PET data is low, it is not possible to conclude whether the observed recovery of glucose metabolism occurs in the FCC or the PC. Compared to controls, the nodes and tracts of the PC remained significantly altered in the three groups of KS patients. The novelty of the present study is in the finding that the PC remains atrophied and hypometabolic even after 10 years of abstinence. In a case report, Fellgiebel *et al.*, also found persistent hypometabolism in the thalamus of a KS patient abstinent for nine months⁸. In contrast, in AUD patients, brain alterations and associated episodic memory deficits are usually described as recovering during the first weeks of abstinence³³⁻³⁵. These findings reinforce the idea that the persistent anterograde amnesia and alterations to the PC that characterize KS result more from thiamine

deficiency or altered thiamine metabolism than from the neurotoxicity of chronic alcohol consumption *per se*⁶.

Frontocerebellar circuit

As expected, patients recently diagnosed with KS were impaired on inhibition, processing speed and abilities to access to semantic information^{23,36,37}. Contrary to previous studies^{23,38}, we found preserved working memory performance and abilities to generate strategies, even within the first weeks after the diagnosis. Processing speed and access to semantic information remained altered even 10 years after the diagnosis, whereas inhibition abilities returned to normal. A normalization of executive functions had previously been found in a KS patient after nine months of abstinence²⁵.

The heterogeneity in the executive recovery thus differs according to the function examined and might be explained by the dissociation observed between some structural recovery and persistent hypometabolism within the FCC. Executive dysfunctions observed in KS patients examined several weeks after the diagnosis can be explained by the shrinkage of the nodes and tracts of the FCC. In effect, structural abnormalities in frontal and motor cortices, thalami, cerebellum, corona radiata, and pons observed early after the diagnosis have also been reported in previous studies^{26,29,30,39,40}. The present investigation highlights, for the first time in KS patients, changes in gray matter nodes and white matter connection of the FCC over time. Although thalami were still atrophied after 10 years of sobriety, results of longitudinal and cross-sectional comparisons showed that there was some volume recovery in other brain regions of the FCC such as in the cerebellum, pontine crossing tract, and middle cerebellar peduncle. Moreover, when KS patients were compared with controls, only a small part of the frontal cortex and corona radiata were still significantly atrophied 10 years after the diagnosis. These structural modifications could underlie the normalization of inhibition abilities. Such shrinkage

of the FCC, also found in AUD patients⁴¹, seems to reflect the neurotoxicity of excessive and chronic alcohol consumption, inducing a behavioral disinhibition, which seems to improve and return to normal with sustained abstinence⁴²⁻⁴⁴.

Early after the diagnosis of KS, the pattern of metabolic abnormalities in the FCC was consistent with previous studies, indicating a widespread hypometabolism affecting the same regions as for gray matter shrinkage^{3,4,31,45}. However, contrary to structural abnormalities, and except for the modest improvement observed in the right thalamus during the first year following the diagnosis, this hypometabolism persisted, and could explain why certain cognitive functions, including processing speed and abilities to access to semantic information, remained impaired. This finding is in line with a longitudinal study reporting that 10 to 32 months after drinking cessation, only a partial recovery of glucose metabolism was observed in AUD patients⁴⁶. However, these results differ from those of Fellgiebel *et al.*,⁴⁷ who showed that frontal, occipital and cingulate glucose hypometabolism of two KS patients tended to normalize during the first months of abstinence. Interestingly, the observed persistent hypometabolic pattern versus receding pattern of atrophy shows that hypometabolism may not be a direct consequence of the atrophy but a genuine functional deficit.

The cerebellar hypermetabolism observed in the present investigation has also been reported in previous studies conducted in KS^{47,48}. This hypermetabolism has also been found in AUD patients and was considered as a maladaptive plasticity phenomenon⁴⁹ since higher glucose uptake in the cerebellum correlated with lower motor and executive abilities. The hypothesis of maladaptive plasticity is reinforced by the return to a normal level of metabolism observed here in the cerebellum over time, in agreement with a previous study⁴⁷.

Despite some structural changes in the FCC, KS patients remained severely amnesic with persistent alterations of the PC. In accordance with criteria for major neurocognitive disorder from the DSM-5⁹, KS patients are unlikely to be able to live in a completely autonomous way.

That does not mean that no other alternatives are possible for those patients, especially as no decline was observed. Indeed, with an appropriate rehabilitation program and the establishment of everyday routines with adapted supports or using techniques such as errorless learning, KS patients might be autonomous and independent in certain daily life activities⁵⁰.

Methodological considerations

The sample size and the combination of longitudinal and cross-sectional approaches represent the main limits of the present study. However, to our knowledge, only four studies have examined KS patients over time. And among them, only one group study reported neuropsychological changes over a two-year period, and two case reports examined brain glucose metabolism over the first months that followed the diagnosis of KS. Longitudinal investigations of KS patients are indeed extremely rare since it is very difficult to recruit and follow these patients over long periods of time. The present study is thus the first investigation exploring cognitive and brain changes in a group of KS patients and including multimodal imaging and a long-term evaluation. The longitudinal investigation conducted one year after the diagnosis is completed by the cross-sectional investigation including patients with a 10-year diagnosis of KS. Overall, 16 patients have been included in the present study, which is considerable given the rarity of the disease and the extent of the experimental measures. This design enabled the comparison of two groups of KS patients and thus highlight the consistency of brain shrinkage and altered metabolism.

Another limit of the present study is the significant difference in the sex ratio between the two groups of patients. However, the brain structural comparisons have been corrected for the total intracranial volume, and regarding glucose metabolism, the main results did not change when gender was included as a covariate in the analyses.

Finally, alcohol consumption reported for one patient of the KS^C group during the follow-up period could have influenced our results. However, when this patient was removed from analyses, patterns of results remained unchanged, hence the initial sample was retained.

To conclude, regarding the FCC circuit, findings indicate normalization of inhibition abilities and cerebellar metabolism, as well as some structural recovery notably in the cerebellum, pontine and cerebellar peduncle. However, widespread regional hypometabolism and certain executive deficits persist, suggesting persistent FCC dysfunction even after 10 years of drinking cessation. The present study highlights that KS is characterized by definitive shrinkage and hypometabolism of the PC in accordance with a permanent anterograde amnesia. This meticulous collection of cognitive and brain data in different cohorts of KS patients proves, for the first time, the irreversible nature of amnesia in KS. There is neither recovery as observed in patients with AUD, nor decline as in neurodegenerative diseases.

Acknowledgments

The authors would like to thank Hélène Beaunieux, Ludivine Ritz, Coralie Lannuzel, Fausto Viader, Vincent de La Sayette, and the staff members of the nursing home Maison Vauban of Roubaix for their contribution to the recruitment of patients and their comments.

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TABLES

Table 1. Demographical and clinical description of the participants

Variable	HC (n = 44)	KS ^C * (n = 8)	KS ^R (n = 8)	Group differences
Age (years)	53.18 ± 8.19 [40-67]	55.38 ± 7.50 [44-67]	56.25 ± 4.56 [51-63]	HC = KS ^C = KS ^R
Education (years of schooling)	11.57 ± 2.08 [7-15]	10.13 ± 3.27 [6-15]	10.25 ± 1.75 [8-12]	HC = KS ^C = KS ^R
Sex ^a (M/F)	21/23	6/2	0/8	HC = KS ^C HC ≠ KS ^R ($p = 0.01$) KS ^C ≠ KS ^R ($p = 0.011$)
BDI	N/A	10.50 ± 6.65 [0-29]	7.88 ± 6.51 [0-19]	KS ^C = KS ^R
STAI A	N/A	38.88 ± 14.93 [23-66]	29.57 ± 11.69 [20-51]	KS ^C = KS ^R
STAI B	N/A	41.25 ± 11.21 [24-56]	38.00 ± 10.58 [26-57]	KS ^C = KS ^R
Fagerstrom	N/A	3.75 ± 3.41 [0-10]	1.38 ± 1.30 [0-3]	KS ^C = KS ^R

Mean ± standard deviation and range [minimum-maximum] are reported.

Mann-Whitney's tests for independent samples.

^a: Chi-squared tests (P-values are shown when P < 0.05).

*: Data collected at T1

Note: BDI = Beck Depression Inventory; F = female; HC = Healthy controls; KS^C = Patients with Korsakoff's syndrome recruited at Caen University Hospital; KS^R = Patients with Korsakoff's syndrome recruited in a nursing home at Roubaix; M = male; N/A = not available; STAI = State-Trait Anxiety Inventory for adults (A for 'state-anxiety' and B for 'trait-anxiety').

Table 2. Neuropsychological performance (z-scores) in each group and between-group comparisons

	KS ^C -T1	KS ^C -T2	KS ^R	Short-term comparisons ^a	Long-term comparisons ^b
FCSRT: third free recall	-4.73 ± 0.90	-4.54 ± 0.43	N/A	<i>p</i> = 0.553	N/A
FCSRT: delayed recall	-5.30 ± 0.53	-5.18 ± 0.66	N/A	<i>p</i> = 0.835	N/A
CVLT: fifth recall	-3.84 ± 0.78	N/A	-2.82 ± 0.92	N/A	<i>p</i> = 0.031
CVLT: delayed recall	-3.92 ± 0.58	N/A	-3.91 ± 0.63	N/A	<i>p</i> = 0.874
ROCF delayed recall	-2.29 ± 0.52	-1.89 ± 0.56	-1.74 ± 0.70	<i>p</i> = 0.035	<i>p</i> = 0.056
Digit span task	-1.13 ± 1.08	-1.21 ± 1.15	-0.96 ± 0.92	<i>p</i> = 1.000	<i>p</i> = 0.523
Letter fluency	-1.11 ± 1.18	-1.43 ± 1.05	-0.92 ± 0.95	<i>p</i> = 0.219	<i>p</i> = 0.772
Category fluency	-1.87 ± 0.76	-2.28 ± 0.64	-1.74 ± 0.86	<i>p</i> = 0.578	<i>p</i> = 0.354
Stroop: interference score	-3.64 ± 4.07	-2.40 ± 3.05	-0.41 ± 1.59	<i>p</i> = 0.148	<i>p</i> = 0.01
Stroop: processing speed	-2.96 ± 4.22	-2.18 ± 2.06	-1.93 ± 2.13	<i>p</i> = 0.844	<i>p</i> = 0.793

Mean ± standard deviations are reported.

^a: Wilcoxon's tests (none of the p-values are significant after Bonferroni's corrections): KS^C-T1 vs KS^C-T2

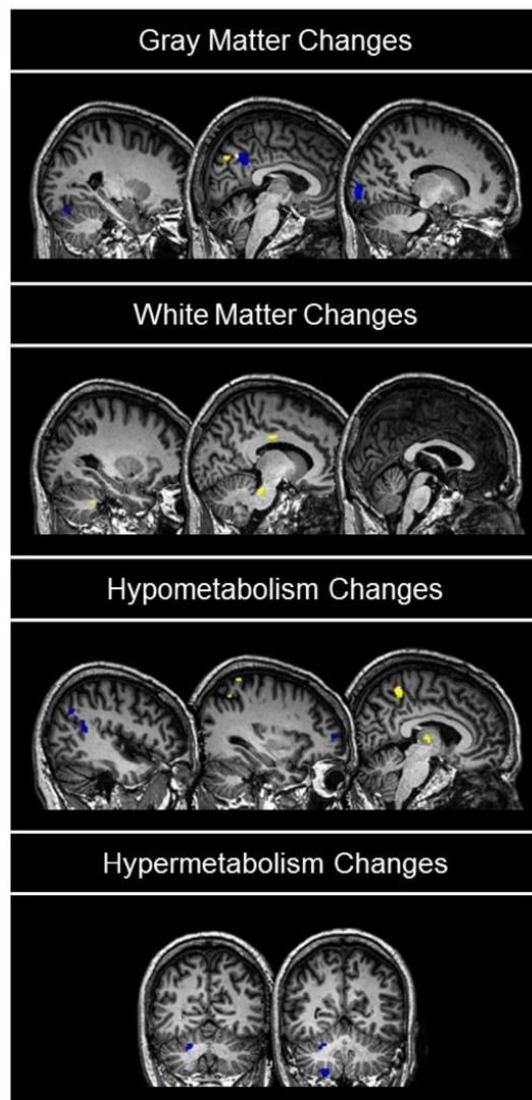
^b: Mann-Whitney's tests (none of the p-values are significant after Bonferroni's corrections) : KS^C-T1 vs KS^R

Bold and italic: impaired performance (z-score < -1.65)

Note: CVLT = California Verbal Learning Test; FCSRT = Free and Cued Selective Reminding Test; KS^C = Patients with Korsakoff's syndrome recruited at Caen University Hospital; KS^R = Patients with Korsakoff's syndrome recruited in a nursing home at Roubaix; N/A = not available; ROCF = Rey-Osterrieth complex figure.

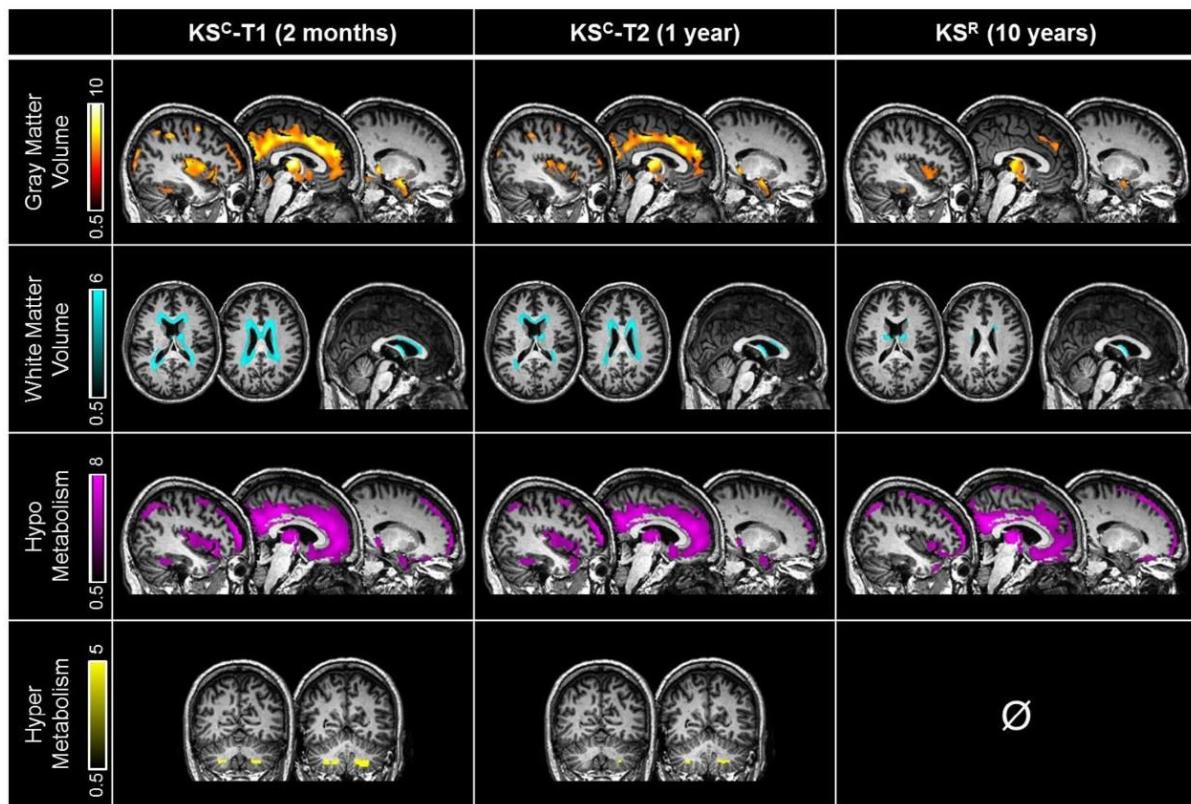
FIGURES

FIGURE 1. DIRECT COMPARISONS AMONG PATIENT GROUPS: ALTERATIONS TO THE PAPEZ AND THE FRONTOCEREBELLAR CIRCUITS.



Results are presented using a threshold of $P < 0.001$, uncorrected for multiple comparisons ($k=60$ for MRI data and $k=25$ for PET data), since there were no significant changes for $P < 0.05$ corrected for Family-Wise Error. Yellow clusters illustrate longitudinal comparisons and show short-term changes (within one year) observed in Korsakoff patients recruited at Caen University Hospital. Blue clusters illustrate cross-sectional comparisons and show long-term changes (within 10 years) observed between Korsakoff patients recruited at Caen University Hospital and examined early after the diagnosis, and Korsakoff patients recruited in a nursing home at Roubaix and examined about 10 years after the diagnosis.

FIGURE 2. SHORT-TERM AND LONG-TERM PATTERNS OF STRUCTURAL AND METABOLIC ABNORMALITIES IN KORSAKOFF PATIENTS.



Results are presented using a threshold of $P < 0.05$ corrected for multiple comparisons (Family-Wise Error; $k=60$ for MRI data and $k=25$ for PET data). All patient groups are compared to controls. KS^C: Patients with Korsakoff's syndrome recruited at Caen University Hospital; T1: early after the diagnosis (about 2 months); T2: about 10 years after the diagnosis; KS^R: Patients with Korsakoff's syndrome recruited in a nursing home at Roubaix. \emptyset : no significant results. Color bars represent T-values.

DISCUSSION GÉNÉRALE

1. Synthèse des résultats

L'objectif général de cette thèse était d'étudier la valeur pronostique, l'évolution, ainsi que la prise en charge des atteintes cognitives et cérébrales dans le TUAL et le SK. Les résultats des trois études menées au cours de cette thèse sont synthétisés dans la **Figure 13**.

En résumé, nos travaux ont tout d'abord permis de montrer que la rechute est un processus dynamique et multi-déterminé impliquant des facteurs neurobiologiques et cliniques (**étude 1**). Par ailleurs, la réversibilité des atteintes cognitives chez des patients TUAL récemment sevrés a été confirmée (**étude 2**). Nous avons également mis en évidence qu'une prise en charge intensive et pluridisciplinaire, incluant des ateliers de stimulation cognitive, induit une récupération plus globale qu'une prise en charge ne comprenant que des séances de kinésithérapie et d'ergothérapie et de manière plus occasionnelle. Enfin, nos résultats ont révélé que chez des patients SK, les atteintes cognitives et cérébrales liées au CP persistent avec le temps alors que celles liées au CFC sont partiellement réversibles (**étude 3**).

Les résultats de ce travail de thèse seront discutés autour de trois axes. Les deux premiers permettront de revenir sur 1) la temporalité et 2) la spécificité de la récupération des atteintes cognitives et cérébrales chez les patients TUAL et SK. La troisième partie aura pour objectif de développer comment la prise en charge des patients TUAL et SK peut être adaptée en tenant compte de la récupération et des déterminants de la rechute.

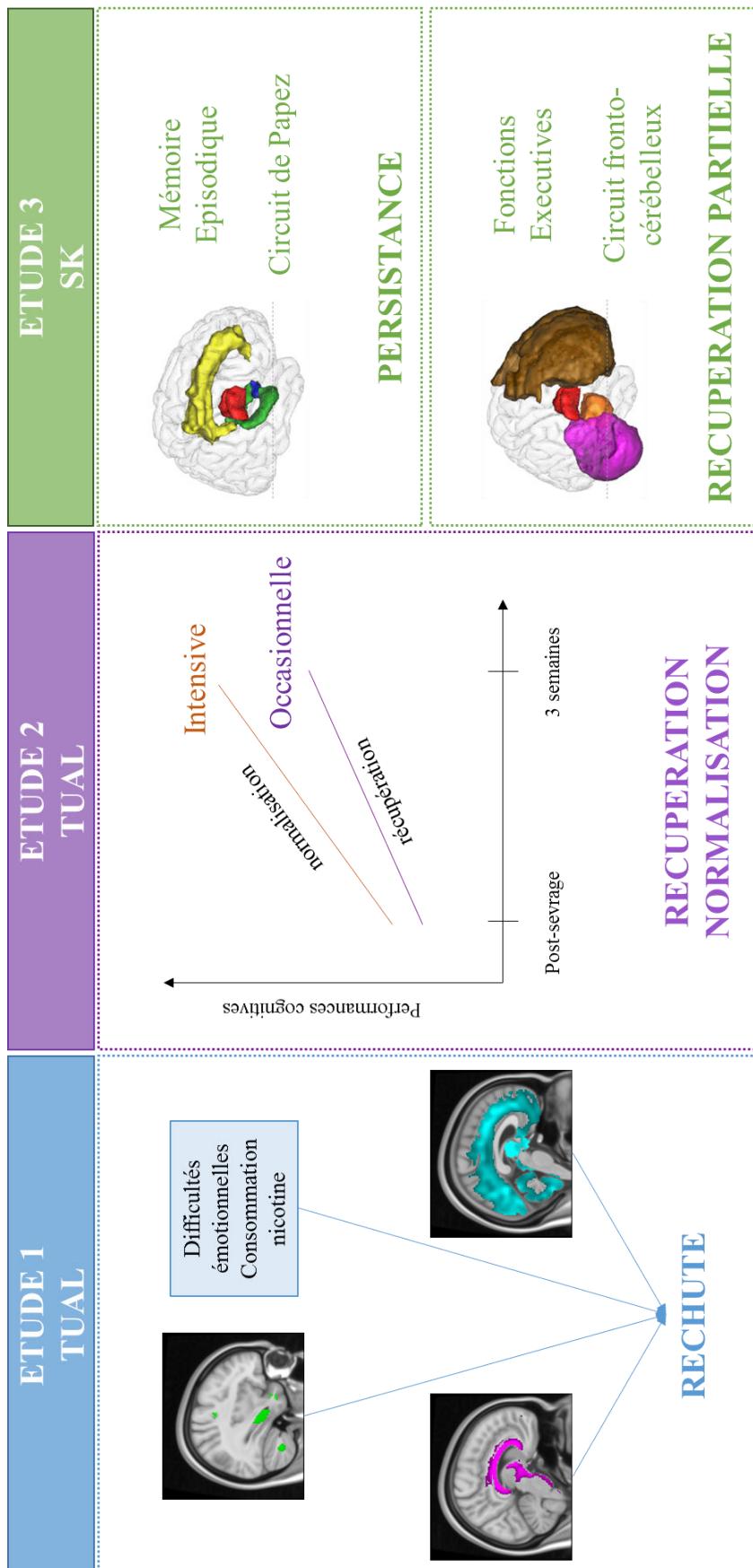


Figure 13 : Synthèse des principaux résultats de ce travail de thèse.

L'étude 1 représente les facteurs qui déterminent la rechute des patients au cours de l'année qui suit le sevrage. L'étude 2 montre l'influence d'une prise en charge de trois semaines en SSR sur la récupération cognitive des patients TUAL. L'étude 3 met en évidence la persistance des déficits sévères de mémoire épisodique et des altérations du circuit de Papez dans le SK, ainsi que la récupération partielle des fonctions exécutives et du circuit fronto-cérébelleux.

2. Temporalité de la récupération

Comme abordé dans le cadre théorique de cette thèse (Chapitre II partie 3), les études s'intéressant à la récupération cognitive et cérébrale utilisent des durées de suivi variables (allant de deux semaines à plusieurs années) après l'arrêt des consommations.

2.1. Dans le trouble de l'usage d'alcool

Les résultats de cette thèse montrent une amélioration significative, et même une normalisation, des performances cognitives dans un groupe de 84 patients TUAL ayant observé une période d'abstinence de trois semaines après le sevrage d'alcool (étude 2). Ces résultats sont en accord avec les précédentes études qui ont également mis en évidence une récupération cognitive à court-terme (Kish *et al.*, 1980; Manning *et al.*, 2008; Kaur *et al.*, 2020), à moyen terme (Pitel *et al.*, 2009b; Loeber *et al.*, 2010; Ioime *et al.*, 2018), et à long terme (Reed *et al.*, 1992; Rourke and Grant, 1999; Fein *et al.*, 2006) dans le TUAL. Nous pouvons faire l'hypothèse que l'amélioration des performances neuropsychologiques que nous observons résulte de la diminution des atteintes cérébrales, également mise en évidence dès les premières semaines suivant l'arrêt des consommations d'alcool. En effet, l'amélioration de l'intégrité des fibres de substance blanche (Gazdzinski *et al.*, 2010; De Santis *et al.*, 2019) associée à la récupération de volume de substance grise (Pfefferbaum *et al.*, 1995; van Eijk *et al.*, 2013) suggère une amélioration de l'efficacité du fonctionnement des réseaux cérébraux qui sous-tendent le fonctionnement cognitif.

Dans le TUAL, l'augmentation du volume de substance grise de certaines régions corticales et la récupération cognitive semblent être plus importantes durant le premier mois d'abstinence qu'au cours des mois suivants (Kish *et al.*, 1980; Durazzo *et al.*, 2015, Zou *et al.*, 2018a). Le volume total de substance blanche (Durazzo *et al.*, 2015) et le volume de certaines structures cérébrales (Zou *et al.*, 2018a) augmentent quant à eux moins rapidement mais de façon linéaire avec le temps. Ces résultats pourraient expliquer le fait que certaines études rapportent une amélioration cognitive seulement après une longue période d'abstinence (Reed *et al.*, 1992; Munro *et al.*, 2000). En effet, la récupération cognitive dépendrait de la dynamique de récupération des régions cérébrales les sous-tendant. Il est d'autant plus intéressant de noter

que les études de Reed *et al.* (1992) et de Munro *et al.* (2000) sont des approches transversales dans lesquelles aucun groupe ne permet d'examiner la récupération précoce. Il est de ce fait également possible de penser que les résultats des études qui évaluent la récupération à moyen-terme pourraient davantage refléter le pic de récupération à court terme, associé à une récupération plus lente par la suite, plutôt qu'une récupération régulière au cours de cette période. La dynamique de récupération est importante dans la prise en charge des patients. De ce fait, davantage d'études longitudinales et multimodales sont nécessaires afin de clarifier la dynamique de récupération cérébrale et cognitive dans le TUAL. D'un point de vue plus clinique, ces données permettraient la mise en place de stratégies favorisant cette récupération.

2.2. Dans le syndrome de Korsakoff

Contrairement à la récupération observée dans le TUAL, les résultats de ce travail de thèse ne mettent pas en évidence d'évolution cognitive au cours de la première année qui suit le diagnostic de SK (étude 3). Une étude de cas a montré une récupération partielle de certains déficits cognitifs, environ six mois après le diagnostic (Noël *et al.*, 2001b). Cette récupération pourrait refléter le passage de la phase aigüe de l'EGW vers la phase chronique du SK. En effet, les composantes cognitives qui montrent des signes d'évolution dans l'étude de cas de Noël *et al.* (2001b) correspondent aux composantes cognitives qui sont préservées dans notre étude.

Nos travaux montrent également que les altérations cérébrales structurales régressent très légèrement au cours de la première année même si, comparativement à des sujets contrôles, les patients SK présentent encore une atrophie importante. Nos résultats mettent également en évidence une persistance des atteintes métaboliques. Bien qu'à notre connaissance, l'évolution des atteintes structurales dans le SK n'ait fait l'objet d'aucune autre étude, l'équipe de Fellgiebel a publié deux études de cas indiquant que le métabolisme de glucose cérébral s'améliorait dès les premières semaines post-diagnostic (Fellgiebel *et al.*, 2003, 2004). Cette différence observée entre nos résultats et ces études de cas pourrait notamment refléter la variabilité des altérations cérébrales (Pitel *et al.*, 2009a) et cognitives (Van Oort and Kessels, 2009) chez les patients SK. Parmi les deux patients présentés par Fellgiebel, l'homme de 40 ans semblent récupérer davantage que la femme de 58 ans (Fellgiebel *et al.*, 2004). La récupération pourrait donc également être influencée par l'âge et le sexe des patients.

L'étude de l'évolution des performances cognitives à très long terme, c'est à dire une dizaine d'années après le diagnostic de SK, n'a permis de mettre en évidence qu'une récupération très partielle du fonctionnement cognitif. Ces résultats sont cohérents avec une précédente étude qui a seulement observé une légère amélioration de certaines composantes cognitives au cours d'une période de deux ans dans un groupe de 20 patients SK abstinents depuis huit ans lors de la première évaluation (Fujiwara *et al.*, 2008). Cette évolution cognitive pourrait être sous-tendue par le fait qu'après une très longue période d'abstinence, l'atrophie de substance grise et de substance blanche est bien moins importante que ce qui est observé au début de la pathologie. Par ailleurs, la persistance de certains troubles cognitifs peut s'expliquer par la durabilité de l'hypométabolisme et de certaines atteintes structurales.

Alors qu'une récente étude épidémiologique a établi un lien entre le TUAL et un risque élevé de démence, notamment l'apparition d'une démence précoce (Schwarzinger *et al.*, 2018), nos résultats ne montrent pas, comme c'est le cas dans les démences, de déclin des performances cognitives ou de détérioration des altérations cérébrales après une longue période d'abstinence. Ces résultats confirment le caractère non dégénératif du syndrome de Korsakoff.

Les résultats de l'étude 3 de cette thèse sont à interpréter avec précaution notamment du fait des faibles effectifs de patients Korsakoff. Cependant, au regard de la littérature existante, nous menons, pour la première fois, une étude de groupe associant un *design* de comparaisons transversales et longitudinales. Cependant, les comparaisons transversales, qui nous ont permis de confirmer certains résultats sur plusieurs cohortes et d'étudier l'évolution à très long terme, ne sont pas les analyses qui fournissent les résultats les plus fiables en termes d'évolution.

Pour résumer, nos travaux, appuyés par ceux d'autres équipes, montrent qu'il y a une différence dans la temporalité de la récupération entre les patients TUAL et les patients SK. En effet, une récupération importante et précoce est observée chez les patients TUAL (étude 2) alors que les patients SK ne montrent des signes d'amélioration cognitive limitée que six mois après le développement de la pathologie, voire même après plusieurs années (étude 3). D'un point de vue clinique, cette différence dans la dynamique de récupération est un facteur qui pourrait aider à établir le diagnostic de SK. La persistance de l'amnésie et de certaines atteintes cérébrales après quelques semaines d'abstinence est d'autant plus importante à prendre en compte, en l'absence des signes pathognomoniques du SK (fausses reconnaissances, anosognosie, confabulations).

3. Spécificité de la récupération

Nos résultats mettent en évidence une récupération des différentes composantes cognitives dans le TUAL, ce dès les premières semaines d'abstinence (étude 2). En revanche, dans le SK, la récupération semble dépendre de la composante cognitive et des réseaux cérébraux étudiés (étude 3).

3.1. Mémoire épisodique et circuit de Papez (CP)

Les résultats de ce travail de thèse ainsi que ceux d'autres études s'accordent sur le fait que les déficits de mémoire retrouvés chez les patients TUAL sont réversibles dès les premières semaines après l'arrêt des consommations d'alcool (Manning *et al.*, 2008; Mulhauser *et al.*, 2018; étude 2). Nous montrons également que les performances de mémoire épisodique de ces patients se normalisent rapidement. En revanche, dans le SK, aucune amélioration des performances mnésiques n'a été révélée au cours de la première année suivant le développement de la pathologie (Noël *et al.*, 2001; voir les analyses longitudinales de l'étude 3). Même plusieurs années après le diagnostic, les déficits de mémoire épisodique restent sévères (Fujiwara *et al.*, 2008; voir les analyses transversales de l'étude 3).

Cette différence de récupération est également visible au niveau des régions du CP. En effet, les études réalisées chez les patients TUAL montrent que la récupération de volume au niveau du gyrus cingulaire (van Eijk *et al.*, 2013; Durazzo and Meyerhoff, 2019) et de l'hippocampe (Gazdzinski *et al.*, 2008) est visible après quelques semaines d'abstinence et continue d'augmenter de façon linéaire au cours des mois qui suivent (Zou *et al.*, 2018a). Des travaux révèlent également une augmentation de volume au niveau du thalamus après quelques mois d'abstinence (Cardenas *et al.*, 2007; Durazzo *et al.*, 2015). Les résultats de la troisième étude de cette thèse montrent qu'au contraire, chez les patients SK, les altérations structurales et métaboliques des régions du CP persistent avec le temps.

Comme déjà mentionné, cette dissociation entre la récupération précoce de ces capacités chez les patients TUAL et l'absence d'amélioration des performances de mémoire épisodique chez les patients SK peut ainsi servir de support pour établir le diagnostic de SK.

3.2. Fonctions exécutives et circuit fronto-cérébelleux (CFC)

Les résultats de la seconde étude de ce travail de thèse indiquent une amélioration des fonctions exécutives, avec notamment une normalisation des performances de mémoire de travail et d'inhibition chez les patients TUAL. La diminution des troubles dysexécutifs a également été montrée à moyen-terme (Pitel *et al.*, 2009b; Ioime *et al.*, 2018) et à long-terme (Rourke and Grant, 1999; Fein *et al.*, 2006). Cependant, certaines études indiquent que ces déficits persistent même après plus d'un an d'abstinence (Munro *et al.*, 2000; Nowakowska-Domagała *et al.*, 2017). Ces résultats peuvent refléter le manque de fiabilité des études transversales, ainsi qu'un effet du ralentissement de la dynamique de récupération qui a été décrit chez les patients TUAL âgés.

Chez les patients SK, les analyses longitudinales et transversales de l'étude 3 ne montrent pas d'amélioration des performances exécutives. Toutefois, il est intéressant de noter que les deux groupes de patients SK qui ont été évalués dans notre étude présentent des capacités de mémoire de travail et de génération de stratégies préservées. Une étude de cas rapportent également qu'après neuf mois d'abstinence, un patient SK présente des performances équivalentes à celles des sujets contrôles à des tâches évaluant la mémoire de travail et la flexibilité (Noël *et al.*, 2001b). Nos résultats mettent également en évidence que, contrairement aux patients évalués au cours de l'année qui a suivi le diagnostic, le groupe de patientes abstinences depuis environ 10 ans présente des capacités d'inhibition qui se situent dans la norme (étude 3). Ce résultat est en accord avec l'étude de Fujiwara *et al.* (2008) dans laquelle les patients SK avaient également des capacités d'inhibition préservées, et ce lors des deux évaluations (huit et 10 ans après le diagnostic). La limite de notre étude et de celle de Fujiwara *et al.* est que nous ne pouvons pas déterminer si ces performances reflètent un bon niveau d'inhibition pré morbide ou si c'est un effet de la récupération en lien avec l'arrêt des consommations d'alcool. Il semblerait qu'un effet lié à la tâche utilisée puisse également expliquer ce résultat. En effet, Noël *et al.* (2001b) indiquent qu'il n'y a jamais de différence entre les performances du patient au score d'interférence du *Stroop* par rapport aux sujets contrôles alors que les performances du patient au *Hayling test* révèlent des déficits du contrôle inhibiteur qui persistent au cours des neuf mois de suivi. Dans notre étude, et celle de Fujiwara *et al.*, les capacités d'inhibition ont été évaluées avec le test de *Stroop*. Or, une méta-analyse a montré que le *Stroop* ne semble pas assez sensible pour évaluer les effets de l'alcool alors qu'au contraire, le *Hayling test* fait partie des tâches les plus sensibles pour évaluer les effets de

l’alcool sur les capacités d’inhibition (Stephan *et al.*, 2017). Nos résultats pourraient donc refléter plusieurs facteurs tels que la sensibilité des tests neuropsychologiques, l’hétérogénéité des déficits exécutifs des patients (Van Oort and Kessels, 2009), ou encore un effet de la récupération liée à l’arrêt des consommations d’alcool.

Que ce soit dans le TUAL ou dans le SK, la récupération des fonctions exécutives ne semble pas homogène. Les différences de résultats entre les études pourraient refléter une différence dans la dynamique de récupération des fonctions exécutives et de leurs substrats cérébraux.

Dans le TUAL, une étude rapporte que le volume des lobes frontaux n’a pas évolué après neuf mois d’abstinence (Wobrock *et al.*, 2009). D’autres études, en revanche, montrent une augmentation de volume au niveau du cortex frontal, du cervelet, du thalamus, et du tronc cérébral (incluant le pont) (Cardenas *et al.*, 2007; Segobin *et al.*, 2014; Durazzo *et al.*, 2015; Durazzo and Meyerhoff, 2019). Comme évoqué dans la partie 2.1. de cette discussion, la récupération ne serait pas linéaire. En effet, il y aurait une augmentation importante du volume du cortex frontal au cours du premier mois d’abstinence, qui continuerait au cours des mois suivants, mais plus lentement (Zou *et al.*, 2018a). Une amélioration de l’hypométabolisme frontal a également été trouvée chez des patients TUAL après une longue période d’abstinence (Johnson-Greene *et al.*, 1997). La récupération ne semble pas uniquement dépendre du temps mais également de la région cérébrale, avec notamment une réversibilité rapide des altérations des lobes frontaux.

Chez les patients SK, nos résultats montrent que l’atrophie des régions du CFC diminue avec le temps pour être finalement très limitée après 10 ans d’abstinence. De plus, l’hypermétabolisme cérébelleux se normalise, en accord avec Fellgiebel *et al.* (2004). Toutefois, l’hypométabolisme frontal et thalamique persiste, même après 10 ans d’abstinence, contrairement à la normalisation de l’hypermétabolisme cérébelleux et de l’hypométabolisme frontal qu’avaient observé Fellgiebel *et al.* (2003, 2004).

Pour résumer, nos résultats et ceux des précédentes études mettent en évidence que les patients SK présentent des atteintes persistantes du CP et de la mémoire épisodique malgré le maintien d’une abstinence prolongée, alors que chez les patients TUAL, ces altérations se normalisent rapidement après l’arrêt des consommations d’alcool. Concernant les fonctions exécutives et le CFC, bien que les résultats soient hétérogènes, une récupération est trouvée

aussi bien dans le SK que dans le TUAL. Ainsi, une double spécificité de la récupération se dessine (**Figure 14**). D'une part, une spécificité de la population clinique. Les deux populations de patients ont eu des consommations chroniques et excessives d'alcool, alors que la carence sévère en thiamine est normalement spécifique aux patients SK. D'autre part, il y a une spécificité du circuit fonctionnel concerné. L'amnésie antérograde persistante et les altérations du CP observées dans le SK sont la conséquence de la déficience en thiamine. Alors que les altérations du CFC et les déficits des fonctions exécutives résulteraient davantage de la neurotoxicité de l'alcool (Charness, 2011; Oscar-Berman, 2012), ou d'autres conditions associées au TUAL telles que les atteintes hépatiques (Ritz *et al.*, 2016a) ou encore la sévérité du syndrome de sevrage (Laniepce *et al.*, 2020).

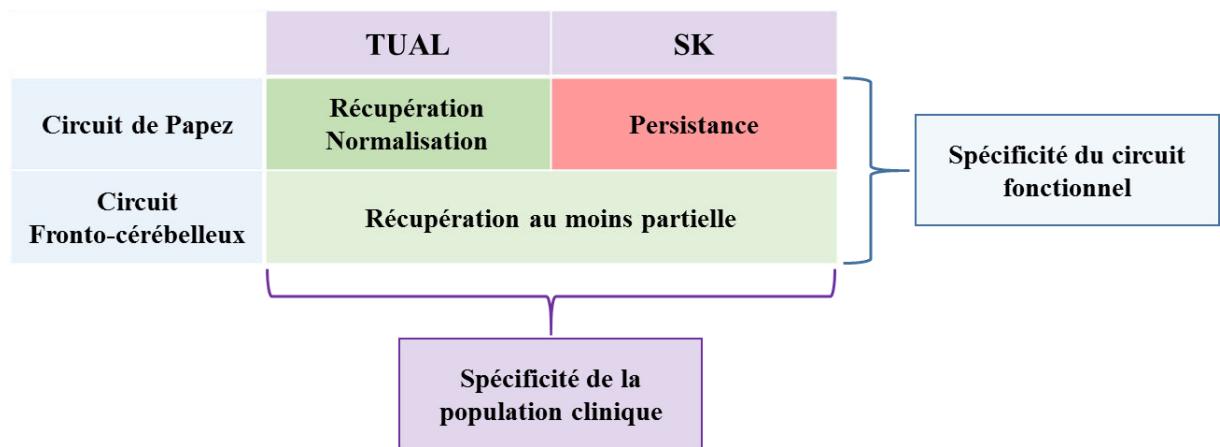


Figure 14 : Double spécificité de la récupération cérébrale et cognitive

4. La récupération au centre de la prise en charge des troubles cognitifs liés à l'alcool

Comme nous l'avons développé tout au long de cette thèse, les consommations chroniques et excessives d'alcool peuvent entraîner des altérations cérébrales et cognitives qui limitent l'efficacité des prises en charge addictologiques usuelles et augmentent le risque de rechute. Les patients TUAL sont bloqués dans un cercle vicieux au sein duquel les troubles cognitifs et altérations cérébrales augmentent le risque de rechuter, alors que la rechute elle-même contribue aux déficits cognitifs (**Figure 15**). Les résultats de la première étude de cette

thèse ont mis en évidence que parmi les patients pour lesquels nous avons pu avoir des informations concernant le statut addictologique, 64% avaient rechuté au moment du suivi à six mois. Cette proportion atteint même 79% lorsqu'on s'intéresse au devenir addictologique un an après le sevrage. Ces résultats sont tout à fait en accord avec ceux d'une précédente étude qui a montré que dans l'année qui suit le sevrage, seuls 20 à 40% des patients arrivent à maintenir l'abstinence ou une consommation contrôlée (Moos and Moos, 2006). La proportion élevée de patients qui rechutent au cours de la première année qui suit le sevrage d'alcool renforce l'idée que la prise en charge addictologique actuelle n'est pas suffisamment efficace, tout particulièrement pour les patients présentant des troubles cognitifs à l'issue du sevrage.

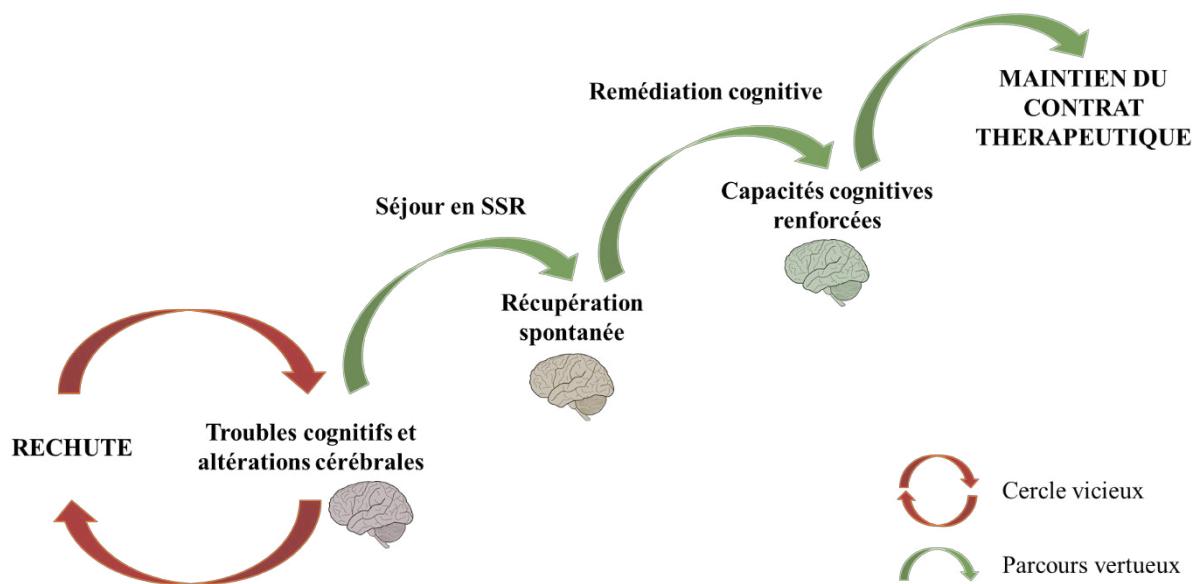


Figure 15 : Comment adapter le parcours de soins des patients TUAL pour favoriser le maintien du contrat thérapeutique.

La rechute étant un phénomène multi-déterminé, il est important que les structures de soins proposent une offre de soins variés afin de personnaliser la prise en charge en tenant compte notamment du profil neuropsychologique des patients. Les objectifs et méthodes thérapeutiques doivent également être adaptés entre les patients TUAL et les patients SK. Un prérequis semble toutefois important pour ces deux populations de patients : la modification des habitudes de vie et notamment l'arrêt, ou au moins la réduction drastique, des consommations d'alcool.

4.1. Prise en charge des TUAL

L'optimisation de la prise en charge des patients TUAL passe avant tout par la réalisation d'un dépistage systématique afin de repérer, à l'issue du sevrage et en dehors des effets des benzodiazépines, les patients qui ne sont pas cognitivement aptes à poursuivre la prise en charge addictologique usuelle, et pour lesquels un ajustement du programme de soins serait bénéfique. Selon les résultats de ce dépistage, un bilan neuropsychologique complet permettra de mettre en place un projet de soin individualisé, prenant en compte les déficits mais également les capacités cognitives préservées.

4.1.1. La restauration physique, psychologique et cognitive

Ainsi, l'allongement de la durée d'hospitalisation des patients ou le transfert vers un SSR est une première option qui a plusieurs avantages pour les patients présentant des troubles cognitifs. Durant cette période, les patients sont à l'abri des consommations d'alcool, ce qui favorise nettement la récupération. Ils sont également bien nourris et bénéficient d'un suivi diététique, ce qui va également jouer un rôle bénéfique sur le fonctionnement cognitif. En effet, la carence nutritionnelle est un des signes de l'EGW (Caine *et al.*, 1997) qui peut être associé à des déficits cognitifs légers à modérés (Pitel *et al.*, 2011). La dénutrition a également été associée à un profil de déficits neuropsychologiques plus sévères (Ritz *et al.*, 2016a). De plus, la dénutrition impacte le bien-être physique et psychologique, ce qui retentit sur le maintien du contrat thérapeutique (Jeynes and Gibson, 2017). Un bon équilibre alimentaire permet donc une amélioration de l'état de santé général des patients TUAL. Par ailleurs, cette période en SSR peut également permettre une récupération des déficits cognitifs secondaires à la prise de benzodiazépines au cours du sevrage par exemple (Curran, 1991). Elle permet donc à la fois une restauration physique, psychologique et cognitive.

4.1.2. La stimulation et/ou remédiation cognitive

Les profils cognitifs des patients étant hétérogènes, tout comme la dynamique de récupération, il est important de personnaliser le projet de soin en fonction de l'évolution des troubles. Cette personnalisation passe notamment par l'utilisation de techniques de prise en charge différentes.

Dans la deuxième étude de cette thèse, nous avons cherché à déterminer, de manière rétrospective et exploratoire, si des ateliers de stimulation cognitive, au cours du séjour en SSR, pouvaient favoriser la récupération cognitive au cours des premières semaines d'abstinence. Nos résultats montrent que les patients ayant bénéficié d'une prise en charge pluridisciplinaire intensive, incluant des ateliers de stimulation cognitive, améliorent leurs performances dans toutes les composantes cognitives étudiées. En revanche, les patients qui ont eu une prise en charge moins intense, comprenant uniquement des séances ponctuelles de kinésithérapie et d'ergothérapie, n'améliorent que certaines composantes cognitives. Il est donc possible de suggérer qu'il y a un effet ajouté de la stimulation cognitive sur la récupération comme proposé par Goldman (1990) avec l'expression « *experience-dependent recovery* ». Cependant, ces résultats sont à interpréter avec précaution. En effet, cette étude a été menée rétrospectivement et des variables importantes n'ont pas pu être contrôlées. La principale limite de cette étude réside en notre incapacité à déterminer si la récupération est modulée par la nature ou par l'intensité de la prise en charge.

C'est dans cette perspective qu'au début de ma thèse, j'ai participé à la mise en place d'un protocole hospitalier de recherche clinique « Alcostim » qui visait à mesurer, chez des patients TUAL présentant des troubles neuropsychologiques post-sevrage, l'effet d'un programme de trois mois de remédiation cognitive sur la consommation d'alcool et l'évolution des performances neuropsychologiques, ceci comparativement à une prise en charge usuelle en Hôpital De Jour (HDJ) addictologique. Ce protocole consistait en un essai randomisé en simple aveugle dans lequel les patients des deux groupes participaient à des ateliers d'HDJ deux fois par semaine. Au cours des premiers mois d'inclusion, nous avons été confrontés à de nombreux arrêts prématurés de la prise en charge et ce, dans les deux groupes. En effet, il semble qu'une prise en charge en HDJ initiée immédiatement après le sevrage ne soit pas adaptée à des patients qui présentent des troubles cognitifs trop importants. La confrontation à l'environnement naturel, trop rapide, augmenterait le risque de rechuter. En l'état, ce protocole a donc été interrompu et des modifications substantielles ont été réalisées afin de combiner cet essai randomisé avec les avantages du séjour en SSR. Ainsi, les prochains patients inclus dans Alcostim bénéficieront d'un séjour en SSR de six semaines au cours duquel ils participeront à l'une ou l'autre des prises en charge, de manière intensive. Cette prise en charge devrait permettre de « booster » la récupération cognitive, avec potentiellement un effet ajouté pour les patients qui auront bénéficié de la remédiation cognitive. L'objectif est de pouvoir par la suite proposer des soins psychosociaux cognitivement coûteux à des patients qui seraient aptes à les

recevoir. En effet, à l’issue de ce séjour, les patients seront réévalués et, en fonction de leur profil neuropsychologique, la suite du parcours de soins sera à nouveau adaptée. S’ils n’ont plus de troubles cognitifs, ils se verront proposer une prise en charge psychosociale. De la remédiation cognitive en HDJ sera proposée s’ils présentent des troubles cognitifs résiduels. Les consommations d’alcool seront évaluées à plusieurs reprises afin de déterminer s’il y a un effet du type de prise en charge sur le devenir addictologique.

Les rares études ayant examiné l’effet de la remédiation cognitive chez les patients TUAL ont montré qu’elle permet non seulement une amélioration du fonctionnement cognitif et sur le plan psychologique mais également une diminution du *craving* (Rupp *et al.*, 2012; Marceau *et al.*, 2017). De plus, les patients TUAL transposent les compétences acquises durant les programmes de remédiation lors des évaluations neuropsychologiques post-traitement ainsi qu’au cours des prises en charge addictologique de type TCC (Roehrich and Goldman, 1993). Ces résultats laissent penser qu’une prise en charge incluant de la remédiation cognitive permettra également aux patients TUAL d’être plus à même de maintenir leur contrat thérapeutique.

La remédiation cognitive cherche donc à restaurer ou renforcer les fonctions cognitives altérées chez les patients TUAL, et notamment celles qui sont impliquées dans le phénomène de rechute. En effet, les résultats de la première étude de cette thèse, ainsi que ceux de la littérature ont montré que la rechute serait liée aux déficits cognitifs et comportementaux observés après le sevrage.

4.1.3. Récupérer pour ne pas rechuter

Les résultats de la première étude de cette thèse montrent que les patients qui ont rechuté au moment du suivi à un an, avaient des déficits de mémoire épisodique à l’issue du sevrage. La différence entre les sujets contrôles et les patients ayant maintenu des consommations à faible risque n’est, quant à elle, pas significative, même s’il existe tout de même une forte tendance. Alors que ces troubles ne semblent pas être des déterminants de la rechute (Pitel *et al.*, 2009b), ils sont fréquemment observés chez les patients récemment sevrés et pourraient les empêcher d’intégrer correctement les notions fournies en psychoéducation (Pitel *et al.*, 2007b).

Certaines études rapportent que les capacités d’inhibition et de mémoire de travail des patients qui rechutent durant les premiers mois qui suivent le sevrage sont moins bonnes que

celles des patients qui maintiennent une abstinence durant cette même période (Noël *et al.*, 2002; Camchong *et al.*, 2013; Czapla *et al.*, 2016). Concernant les capacités d'inhibition, nos résultats ne vont pas dans le sens de ces études (étude 1). Comme nous l'avons déjà évoqué dans la partie 3.2 de cette discussion, cette discordance entre nos résultats et ceux des précédentes études pourrait résider dans le fait que le score d'interférence du *Stroop* n'est pas assez sensible. Les précédentes études utilisaient, en effet, le *Hayling test* ou encore le *go/no-go*. L'hypothèse d'un manque de sensibilité du *Stroop* est renforcée par le fait que nous trouvons tout de même des altérations cérébrales au sein des régions du réseau du contrôle exécutif. Nous avons effectivement mis en évidence une atrophie et un hypométabolisme des lobes frontaux, particulièrement marqués chez les rechuteurs. A contrario, chez les patients qui maintiennent des consommations à faible risque ces atteintes sont présentes mais de façon beaucoup plus restreinte.

Nos résultats mettent également en évidence un hypermétabolisme du cervelet, des gyri cingulaires antérieurs et des hippocampes, ainsi qu'une atrophie du cortex préfrontal ventromédian et des amygdales, ceci uniquement chez les patients qui ont rechuté au cours de l'année qui a suivi le sevrage (étude 1). Ces données suggèrent qu'un déséquilibre entre le système limbique, impliqué dans les comportements impulsifs, et le système de contrôle exécutif, permettant de réguler la prise de décisions, est associé à la rechute (Noël *et al.*, 2013). Dans une précédente étude, l'impulsivité et les déficits de prise de décision ont respectivement été associés à un taux de rechute élevé et à un arrêt prématuré de la prise en charge (Barreno *et al.*, 2019). Les déficits de prise de décision semblent également être de bons prédicteurs de l'augmentation des consommations d'alcool deux ans après l'évaluation neuropsychologique (Goudriaan *et al.*, 2011). Cependant, une autre étude n'a pas retrouvé de lien entre les performances de prise de décision et la rechute (Maurage *et al.*, 2018). Les auteurs suggèrent que la tâche utilisée, l'*Iowa Gambling Task*, n'est pas un outil clinique adapté pour identifier les troubles impliqués dans la rechute.

L'ensemble de ces résultats montre l'importance de l'évaluation neuropsychologique et notamment du choix des tâches. En effet, l'impossibilité de faire des examens IRM ou TEP à tous les patients TUAL nous incite à poursuivre des travaux de recherche afin d'identifier ou de développer des tâches qui permettraient de refléter les atteintes cérébrales mises en évidence comme facteur pronostique de la rechute. Ces tâches devraient notamment évaluer les déficits de contrôle inhibiteur, les troubles de la prise de décision et l'impulsivité comportementale.

Par ailleurs, tout comme les précédentes études (Witkiewitz and Villarroel, 2009; Berking *et al.*, 2011; Rupp *et al.*, 2017), nous avons montré que les difficultés émotionnelles, et notamment l’alexithymie, sont associées au phénomène de rechute, en lien avec une atrophie amygdalienne. Ces déficits sont également impliqués dans les problèmes de relations interpersonnelles (Hoffman *et al.*, 2019). Ainsi, l’évaluation neuropsychologique devrait également accorder une certaine importance à l’évaluation des processus émotionnels et de la théorie de l’esprit.

De plus, nos résultats sont en accord avec de précédentes études (Chiappetta *et al.*, 2014; Durazzo and Meyerhoff, 2017) indiquant que le tabac joue un rôle dans la rechute. Il a également été mis en évidence que l’usage de nicotine influence négativement la récupération cérébrale (Durazzo *et al.*, 2015). Il semble donc important d’en informer le patient afin de travailler avec lui sur un sevrage nicotinique en parallèle du sevrage d’alcool.

Enfin, nous montrons que seuls les patients rechuteurs présentaient à l’issue du sevrage une atrophie du mésencéphale. Cette structure cérébrale comprend l’aire tegmentale ventrale qui est impliquée dans le circuit de la récompense. Un dysfonctionnement de ce circuit serait à l’origine du *craving* (Koob, 2013; Galandra *et al.*, 2018), processus fortement mis en cause dans de nombreuses rechutes (Stohs *et al.*, 2019; Weinland *et al.*, 2019). Après le sevrage, il est crucial d’encourager les patients à réinvestir des activités plaisantes afin qu’ils aient des solutions alternatives en cas de survenue d’un *craving*. Ceci peut notamment passer par des prises en charge telles que l’activité physique (Ussher *et al.*, 2004) ou la méditation (Pang *et al.*, 2019; Witkiewitz *et al.*, 2019) qui ont montré des résultats prometteurs dans le TUAL.

4.2. Prise en charge des SK

Le SK reste une pathologie mal connue. L’histoire de la maladie ainsi que le tableau clinique sont à l’origine d’une orientation aussi bien vers les services d’addictologie, de psychiatrie que de neurologie, ce qui va souvent engendrer une errance diagnostique. Une fois le diagnostic posé, ces patients entrent alors dans un parcours de soins compliqué. En effet, comme nous l’avons vu dans l’introduction (Chapitre III, partie 5), la prise en charge des patients SK est problématique. Il y a très peu de structures qui peuvent les accueillir, et lorsqu’une solution d’accueil est enfin trouvée, elle n’est que rarement adaptée à cette

pathologie. Il est d'autant plus difficile de trouver une solution d'accueil lorsque les patients ont moins de 60 ans car l'accès en EHPAD nécessite alors une dérogation MDPH. De plus, cette solution est loin d'être idéale en termes de prise en charge.

Alors que chez les patients TUAL, la remédiation cognitive vise surtout à restaurer les déficits cognitifs légers et à renforcer les fonctions cognitives les plus altérées en s'appuyant sur les capacités préservées ; chez les patients SK, l'objectif de la prise en charge va surtout être d'aménager leur environnement afin d'améliorer leur qualité de vie et de les rendre le plus indépendants possible malgré la persistance de l'amnésie antérograde sévère mise en évidence par les résultats de l'étude 3 de cette thèse.

Nos résultats ont permis de montrer que, même si les déficits de mémoire épisodique persistent après une longue période sans alcool, une récupération partielle du fonctionnement exécutif est possible. Par ailleurs, une précédente étude a décrit une amélioration du tableau clinique de ces patients. Les auteurs ont notamment montré que contrairement à l'orientation temporelle, l'orientation spatiale des patients SK s'améliore rapidement (Fellgiebel *et al.*, 2003). Une autre étude a également indiqué que le fait de s'appuyer sur la mémoire visuospatiale pourrait être un levier thérapeutique intéressant dans la prise en charge des patients SK (Oudman *et al.*, 2019). Ainsi, une augmentation du nombre d'indices spatiaux dans l'environnement pourrait aider les patients à se repérer plus facilement, d'autant plus que le système de mémoire non déclarative des patients SK n'est pas ou peu altéré (Heyselaar *et al.*, 2017). Ces résultats montrent qu'il est possible de développer des prises en charge, se basant sur des apprentissages implicites, qui permettront aux patients SK d'être autonomes dans certaines activités de la vie quotidienne. En effet, dans le groupe de patientes SK qui ont été évaluées environ 10 ans après l'arrêt des consommations d'alcool, certaines sont, après quelques années à la Maison Vauban, en mesure d'aller seule à la banque pour retirer de l'argent, par exemple. Des techniques d'apprentissage sans erreur peuvent être utilisées pour permettre aux patients SK de réapprendre à réaliser des tâches de la vie quotidienne. Ainsi, ils récupéreraient un peu d'autonomie et d'indépendance dans la vie quotidienne ce qui aurait pour conséquence d'augmenter la qualité de vie de ces patients (Rensen *et al.*, 2017, 2019b) et de diminuer les symptômes affectifs et psychotiques (Rensen *et al.*, 2019a).

Les résultats de la littérature montrent ainsi que malgré les troubles sévères de la mémoire épisodique, une prise en charge adaptée peut-être bénéfique à ces patients. Comme nous l'avons évoqué précédemment, la prise en charge du SK passe avant tout par un environnement qui va protéger les patients des consommations d'alcool. De plus, cet environnement doit être

suffisamment stimulant car les patients SK ont tendance à être apathiques. La prise en charge va également passer par la remise en place de routines avec le support d'auxiliaires de vie qui seront là non pas pour faire à la place des patients mais avec eux, ainsi que pour veiller à ce qu'ils ne se mettent pas en danger, en oubliant d'éteindre le gaz par exemple.

Davantage de structures adaptées à l'accueil des patients SK sont nécessaires. Si les patients peuvent rester chez eux ou s'ils vivent en famille d'accueil, il est important de former les aidants pour qu'ils ne se sentent pas dépassés par la situation. De plus, il faudrait que des équipes mobiles pluridisciplinaires puissent intervenir pour aider à aménager l'environnement et à mettre en place les routines de vie.

Pour conclure, la meilleure prise en charge du SK reste tout de même la prévention, qui peut notamment se faire en repérant les patients à risque de développer un SK. En effet, un continuum de sévérité des atteintes a été décrit entre les patients TUAL et les patients SK (Ryback, 1971). Il est ainsi possible de repérer les patients qui présentent de sévères déficits et altérations de la mémoire épisodique (Pitel *et al.*, 2008) et des régions du CP (Sullivan and Pfefferbaum, 2009; Pitel *et al.*, 2012) afin d'adapter la prise en charge avant l'éventuel développement d'un SK caractérisé par une amnésie antérograde irréversible et handicapante.

5. Conclusion générale

Le TUAL est associé à des déficits cognitifs qui sont sous-tendus par des dysfonctionnements cérébraux. Ces atteintes cognitives et cérébrales vont avoir un retentissement sur la prise en charge addictologique et augmenter le risque de rechute. Les études de la littérature mettent en évidence une réversibilité de ces atteintes avec l'abstinence. En revanche, chez les patients SK, l'évolution cognitive et cérébrale est peu documentée. Dans ce travail de thèse, nous avons montré que :

- Des facteurs neurobiologiques et psychologiques peuvent permettre de distinguer les patients qui risquent de rechuter des patients qui réussiront à avoir des consommations à faible risque.
- Les tâches neuropsychologiques fréquemment utilisées ne semblent pas pertinentes pour repérer les futurs rechuteurs.

- Dès les premières semaines d'abstinence, le fonctionnement cognitif est significativement amélioré.
- La stimulation cognitive semble pouvoir « booster » la récupération cognitive.
- Dans le SK, les déficits de mémoire épisodique, sous-tendus par les dysfonctionnements du CP, persistent au cours du temps, alors que les déficits exécutifs sous-tendus par les altérations du CFC sont partiellement réversibles.

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ANNEXES

1. Chapitre « Neuropsychological deficits in alcohol use disorder: impact on treatment » (Maillard et al., 2020)

Neuropsychological deficits in alcohol use disorder: impact on treatment

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Introduction

Alcohol use disorder (AUD) is defined as a chronic, relapsing disease of the brain, which is characterized by a high rate of relapse (Koob and Volkow, 2016). Acute alcohol-induced intoxication transiently alters the brain functioning while ethanol is still present in the blood, whereas the effects of chronic alcohol misuse affect the brain in enduring ways even after withdrawals. In 2013, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5, American Psychiatric Association, 2013) has proposed to consider excessive alcohol drinking no more as a categorical phenotype (dependence vs. abuse, DSM-IV, American Psychiatric Association, 2000) but as an AUD lying along a continuum of severity, from mild to moderate to severe according to the number of criteria (out of 11) presented by the patient.

AUD is characterized by a 12-month prevalence of 13.9% in the worldwide population, whereas lifetime prevalence is 29.1% (Grant et al., 2015). Every year, 3.3 million deaths are partially attributable to excessive alcohol consumption. Life expectancy is reduced by 20 years for an alcohol-dependent person (John et al., 2013). Indeed, alcohol is the direct cause of more than 60 diseases from fetal alcohol syndrome to hepatic cirrhosis and psychotic manifestations. In addition, alcohol contributes to the development and the course of more than 200 diseases such as cancers, neuropsychiatric conditions, cardiovascular or neurological diseases, infectious diseases, etc. (World Health Organisation, 2014). For example, Schwarzinger et al. (2018) indicated that AUD is a major risk factor for early onset of all types of dementia. Even in absence of ostensible alcohol-related disease, chronic alcohol consumption can result in an invisible disability: AUD is not only associated with motor dysfunctions (gait and

balance) but also with a variety of cognitive disorders. After alcohol withdrawal, 50%–80% of the recently detoxified patients exhibit neuropsychological impairments (Ihara et al., 2000; Oscar-Berman et al., 2014 for review). The DSM-5 classification introduced a diagnosis of “alcohol-induced neurocognitive disorders” to describe these neuropsychological deficits observed in AUD patients even in absence of any neurological complications. Alcohol-induced neurocognitive impairments are also considered along a continuum of severity from mild to major deficits, comparable with those observed in patients with Korsakoff's syndrome (KS), depending on how they interfere with independence in everyday activities. Despite their prevalence and their potential harmful effects on social and occupational integration, as well as rehabilitation, these cognitive impairments remain frequently undiagnosed because neuropsychological abilities are not systematically assessed in AUD patients.

In this chapter, we will describe the cognitive impairments and brain abnormalities in AUD patients and the reversibility of these deficits with abstinence. We will then focus on the clinical implications of the cognitive deficits. And finally, we will provide some recommendations for clinicians and researchers who work in the field of alcohol addiction.

Altered brain structure and function in alcohol use disorder

During the last decades, many studies have shown that chronic alcohol consumption results in brain damage and associated heterogeneous cognitive deficits (Pitel et al., 2011), including impairments of executive functions, memory, visuospatial abilities, difficulties in emotional

processing, and theory of mind (ToM) abilities (Le Berre et al., 2017 for review).

Alcohol-related brain damage is characterized by a reduction of brain volume, an enlargement of the ventricles and sulci, and an increased cerebrospinal fluid quantity. Several brain regions, including the cerebellum, corpus callosum, hippocampus, thalamus, amygdala, and frontal cortices, are especially vulnerable (Oscar-Berman and Marinkovic, 2003; Sullivan, 2003). Thus, two brain networks seem particularly affected in AUD patients: the circuit of Papez (PC) and the frontocerebellar circuit (FCC), which share the thalamus as a key node (Fig. 8.1) (Pitel et al., 2015).

Attention, working memory, and executive functions

It is now well-known that attention, working memory, and executive functions rely notably on the prefrontal cortex. Indeed, patients with a frontal lobe lesion frequently have difficulties in behavioral control and regulation, potentially with harmful consequences in their daily life. Postmortem analyses have revealed decreased neuronal density in the frontal cortex of AUD patients (Harper and Matsumoto, 2005). Moreover, in vivo studies revealed alcohol-related gray matter volume deficits (Chanraud et al., 2007; Pitel et al., 2012), functional abnormalities during a spatial working memory task (Tapert et al., 2001), decreased cerebral blood flow (Gansler et al., 2000), and lower glucose metabolism (Dao-Castellana et al., 1998; Ritz et al., 2016b) in the frontal cortices.

Not only is the frontal cortex implicated in executive functioning but also other brain regions connected to the

frontal cortex. The cerebellum seems essential to the neural circuitry subserving cognition, particularly executive function and working memory. The cerebellum and the frontal cortex are connected through the pons (feedforward loop) and thalamus (feedback loop) within the FCC (Ritz et al., 2016b). The different nodes of the FCC are affected by heavy and chronic alcohol consumption (Fig. 8.1). MRI studies have shown atrophy in AUD patients compared with controls in the cerebellum (Antunez et al., 1998; Sullivan, 2003), pons (Chanraud et al., 2009b; Sullivan, 2003) and thalamus (Le Berre et al., 2014; Pitel et al., 2012). These regional volumes have been related to executive abilities in AUD patients (Chanraud et al., 2007; Sullivan, 2003; Zahr et al., 2010). Regarding white matter volume, brain abnormalities have been found in AUD patients in the cerebellum and midbrain (Mechtcheriakov et al., 2007; Pitel et al., 2012; Sullivan, 2003). An alteration of the white matter tracts within the midbrain and pons, characterized by 18% fewer fibers in AUD than in healthy controls, indicates a disconnection within the FCC (Chanraud et al., 2009b). The authors also found a correlation between these altered white matter fibers integrity and impaired results on a flexibility task (part B of Trail Making Test). Brain alterations in nodes and connections of the FCC seem to be better predictors of executive dysfunction than damage of the prefrontal regions solely (Chanraud et al., 2007; Sullivan, 2003).

Attention is defined by Mesulam (1999) as “a preferential allocation of limited processing resources to events that have become behaviorally relevant.” Usually, three main higher order attentional processes are distinguished: (a) selective attention, the ability to focus cognitive set on relevant information and inhibit distracting stimuli;

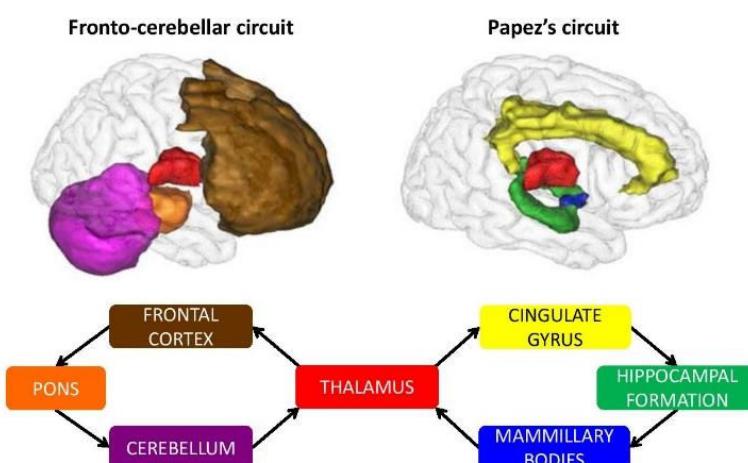


FIGURE 8.1 The two brain circuits mainly affected in alcohol use disorder (AUD). From Pitel, A.L., Segobin, S.H., Ritz, L., Eustache, F., Beaunieux, H., 2015. Thalamic abnormalities are a cardinal feature of alcohol-related brain dysfunction. *Neurosci. Biobehav. Rev.* 54, 38–45. <https://doi.org/10.1016/j.neubiorev.2014.07.023>.

(b) sustained attention, the aptitude to maintain a consistent response for a long time; and (c) divided attention, the capacity to treat simultaneously two tasks. Selective and sustained attention seems to be preserved in AUD patients, while divided attention abilities are impaired (Tedstone and Coyle, 2004). Regarding processing speed, sometimes considered as reflecting low-level attention, results are more heterogeneous. Noël et al. (2001) reported that recently detoxified AUD patients had preserved performance on parts A of the Trail Making Test and Hayling Test, or color-naming part of the Stroop Task, and presented normal latency time on the Tower of London test. On the contrary, Nowakowska-Domagala et al. (2017) found that AUD patients were slower than healthy controls on parts A of the Trail Making test.

Working memory is a short-term memory system that allows temporary storage and manipulation of the information necessary for complex cognitive tasks such as language comprehension, learning, and reasoning. Working memory, which requires the simultaneous storage and processing of information, is composed of three slave systems under the control of a central executive (Baddeley, 2000; Baddeley and Hitch, 1974). The slave systems are short-term storage systems comprising the phonological loop, which processes verbal information, the visuospatial sketchpad, which processes visuospatial information, and the episodic buffer, which links information across domains and maintains such multimodal information. The storage of both verbal and nonverbal components can be impaired in AUD patients (Beatty et al., 1996; Kopera et al., 2012; Pitel et al., 2007b), although the nonverbal working memory component is typically observed as more severely affected than the verbal one (Sullivan et al., 2000). The episodic buffer was also found to be impaired in AUD (Pitel et al., 2007b). Finally, the central executive, which is regarded as being similar to executive functions, is classically described as compromised in AUD patients.

Executive functions are cognitive abilities that control and regulate the cognitive system to coordinate thoughts and actions toward a goal. They enable us to face complex and nonroutine situations (Alvarez and Emory, 2006). These functions permit a behavioral adaptation to environmental changes. Executive functions are not a unitary construct, they are a multifactorial system composed of several components, presenting specific characteristics, which are interacting with each other (Hull et al., 2008; Jurado and Rosselli, 2007). Executive functions include mental flexibility, abstraction, planning, problem-solving, shifting of mental states, monitoring and updating of working memory representations, organization, rules deduction, and categorization.

While two-thirds of AUD patients exhibit executive function impairments (Ihara et al., 2000), there is heterogeneity in the profile of executive dysfunction. Several

studies have shown that AUD patients perform worse than healthy controls on part B of Trail Making Test, which assesses set shifting and mental flexibility (Ihara et al., 2000; Loeber et al., 2009; Moriyama et al., 2002; Noël et al., 2001). The Wisconsin Card Sorting Test is frequently used to evaluate executive functions in AUD patients. It indicates that recently abstinent patients present an inability to conceptualize, be flexible, and consider feedback information from the experimenter (Chanraud et al., 2007; Ratti et al., 2002; Salgado et al., 2009). The number of categories found and error rate are especially sensitive to the effects of chronic alcohol consumption (Stephan et al., 2017). AUD patients also present a deficit of inhibition when evaluated with the Stroop Task (Konrad et al., 2012; Pitel et al., 2007a; Schulte et al., 2012; Tedstone and Coyle, 2004) and the part B of the Hayling Test (Noël et al., 2001). Stephan et al. (2017), in their metaanalyses, indicated that the Hayling Test is very sensitive to the effects of alcohol. AUD patients also presented organization difficulties and deficits in self-generation of strategies as revealed by verbal fluency and Ruff Figural Fluency Tests (Oscar-Berman et al., 2009). Updating abilities, assessed with n-back tasks, are impaired in AUD patients (Pitel et al., 2007a, 2009). The use of the Tower of London test suggests that planning abilities are impaired as well (Goudriaan et al., 2006), but such finding could also be related to the deficits of flexibility and inhibition. In impulsivity tests such as in a go/no-go task, AUD patients responded too quickly and did not inhibit responses when a stop signal appeared (Pandey et al., 2012). Executive functions are also impaired when examined with the Behavioral Assessment of Dysexecutive Syndrome (BADS), a battery of executive tests designed to have an ecologic validity (Ihara et al., 2000). In this battery, the temporal judgment and the modified six elements subtests seemed particularly affected.

All together, these data suggest that chronic and excessive alcohol consumption results in executive dysfunction. Despite the variety of executive deficits observed in AUD, several studies (Kamarajan et al., 2005; Noël et al., 2007) suggested that an impairment of inhibition could be a central feature in the neuropsychological profile of the patients. In accordance, Brion et al. (2017) investigated whether the impurity and multidetermined nature of the executive tasks previously used could explain the variety of the deficits observed. They explored the three main executive components (shifting of mental sets, monitoring and updating of working memory representations, and inhibition of prepotent responses) described by Miyake et al. (2000) and conducted specific tasks to selectively evaluate these components in AUD patients. For each task, they used accuracy and reaction time indexes as dependent variables, and they found that reaction time was relatively preserved, whereas AUD patients were

significantly less accurate than the healthy control participants. They also found a moderate deficit of inhibition, while shifting and updating were more severely impaired. The authors concluded that alcohol-related executive deficits did not include only an inhibition deficit but also other executive alterations.

Episodic memory

Mnemonic functions and notably episodic memory mainly rely on PC. PC involves gray matter nodes of the limbic system including the hippocampus, thalamus, mammillary bodies, and cingulate cortex, interconnected by bundles of white matter fibers (Fig. 8.1). The anterior thalamus receives inputs from the mammillary bodies via the mammillothalamic tract and projects to the cingulate cortex via the internal capsule. Then, the cingulum bundle connects the cingulate cortex to the entorhinal cortex and hippocampus, which projects to the mammillary bodies through the fornix. Studies in AUD patients reported volume loss in mammillary bodies (Pitel et al., 2012; Sheedy et al., 1999; Sullivan et al., 1999), hippocampus (Sullivan et al., 1995), thalamus (Cardenas et al., 2007; Chanraud et al., 2007), and cingulate cortex (Pitel et al., 2012) but failed to show any correlation between gray matter macrostructural abnormalities and episodic memory impairments. Rather, episodic memory disorder may be associated with alteration of gray matter microstructure in the medial temporal lobes (Chanraud et al., 2009a) or damage of white matter bundles and tracts, in particular, the cingulum and the fornix (Pfefferbaum et al., 2009; Schulte et al., 2010; Trivedi et al., 2013), leading to a disruption of the PC. Segobin et al. (2015) found lower episodic memory performance in AUD patients with the most severe alterations of the microstructure within the cingulum and fornix.

Episodic memory is currently described as the memory system in charge of the encoding, storage, and retrieval of personally experienced events, associated with a precise spatial and temporal context of encoding. Episodic memory allows the conscious recollection of personal events from one's past and the mental projection of anticipated events into one's subjective future (Wheeler et al., 1997). Recollection of episodic events requires autonoetic awareness, which is the impression of reexperiencing or reliving the past and mentally traveling back in subjective time (Tulving, 2001). Episodic memory is not only hierarchically the most sophisticated memory system but also the most sensitive to pathology, trauma, and toxicity.

Most studies investigated episodic memory in AUD with classical learning tasks such as learning a list of words (Sherer, 1992), face-name associations (Beatty et al., 1995), or delayed recall of a complex figure (Sullivan et al., 1992). Learning abilities were impaired for both verbal and nonverbal information. Although AUD patients performed

lower than healthy controls on the Free and Cued Selective Reminding Test (Pitel et al., 2007a), they seemed to improve their performance at the same rate. They can indeed show evidence of some learning over trials (Ryan and Butters, 1980). Pitel et al. (2007a) investigated episodic memory in accordance with the current and comprehensive definition of this skill: encoding, storage, and retrieval of factual information located in a precise space-time context associated with autonoetic recollection. AUD patients showed impairment on a recognition task test after a spontaneous encoding as well as on a free recall task after a deep encoding. These results suggest an impairment of both encoding and retrieval abilities in AUD. However, authors did not find any storage impairment in AUD patients, in accordance with a previous research (Sherer, 1992). Moreover, the spatiotemporal context of encoding was also altered, with a deficit in spatial and temporal contexts (Pitel et al., 2007a; Salmon et al., 1986). Patients tended not to recall complete episodes, i.e., correct factual information associated with the correct spatiotemporal context of encoding, suggesting incomplete episodic memories. AUD patients also present difficulties identifying the source of remembered information (Schwartz et al., 2002) and a deficit of autonoetic consciousness (Pitel et al., 2007a).

Noel et al. (2012) indicated that patients perform better on cued-recall and recognition testing conditions, which are less dependent on strategic retrieval operations. In AUD patients, impaired learning abilities could be related to executive dysfunctions and notably impoverished generation of spontaneous strategies. However, another study found very little relationship between episodic memory performance and executive results, and suggested rather a genuine episodic memory impairment that could not be interpreted solely as the consequence of executive dysfunctions (Pitel et al., 2007a).

Another component of episodic memory is prospective memory, which is the ability of remembering to carry out an intended action at some future point in time (Brandimonte et al., 1996). The Prospective Memory Questionnaire, based on self-report measures, revealed prospective memory complaints in AUD (Heffernan et al., 2002; Ling et al., 2003), suggesting that prospective memory may be impaired in AUD patients (Heffernan, 2008 for a review). The severity of the complaints was associated with the total amount of alcohol consumption (Ling et al., 2003). Moreover, patients who reported prospective memory difficulties also complained about impaired executive functioning (Heffernan et al., 2005). They did not appear to use sufficient internal or external memory strategies to compensate for prospective memory deficits (Heffernan et al., 2002).

Autobiographical memory (AM) refers to remote memory, comprising the specific personal events (episodic

component) as well as general knowledge about one-self (semantic component) (Conway, 2001). Compared with healthy controls, AUD patients recalled specific memories less frequently and general memories more frequently, which is a phenomenon of overgenerality (D'Argembeau et al., 2006). However, when a specific past event was provided, AUD patients subjectively experienced as many sensory and contextual details as controls. AUD patients may encode and/or access fewer episodic memories than controls, but when they do, the richness of the memories seems qualitatively equivalent to that of controls. Nandrino et al. (2016) compared semantic and episodic dimensions of AM in AUD patients after a short-term (STA, nearly 5 weeks) and long-term (LTA, at least 6 months) abstinence and healthy controls. On the overall, the two groups of AUD patients were especially impaired for recall of both episodic and semantic recent events and knowledge, corresponding to the drinking period. However, no significant differences were observed between the AUD and control groups for childhood semantic events. Concerning episodic events from childhood, STA provided fewer memories than healthy controls and LTA. First, these results suggest encoding alteration during the drinking period. Second, the semantic component of AM may be less affected by heavy chronic drinking than the episodic component. Third, the preservation of episodic memories from childhood may be preserved in LTA because of cognitive and brain recovery with sobriety.

Although AUD patients are impaired on most of the episodic memory components, they seem to present a limited awareness of those deficits. AUD patients may thus exhibit a deficit of metamemory, which refers to personal knowledge about one's own memory abilities (Flavell, 1971). Metamemory is related to monitoring and control processes. Indeed, to improve performance during a memory task, it is necessary to adjust strategies according to this one. Monitoring concerns the capacity to assess future performance before a memory task and the skills to evaluate performance retrospectively (Nelson and Narens, 1990). The most frequently used measure of metamemory is the feeling-of-knowing (FOK) (Hart, 1965), characterized by the ability to accurately predict the future performance on tasks requiring recognition of newly learned information. The FOK judgment is recorded on a Likert-type scale (from 0% "definitely will not recall" to 100% "definitely will recall"). A FOK accuracy index is calculated to evaluate the agreement between predictions of the future recognition performance and real recognition performance (Goodman-Kruskal Gamma statistic; Nelson, 1984). Le Berre et al. (2010) found that AUD patients were impaired in this task as they obtained a FOK index significantly lower than that of the control group (not better than chance level). Patients had a tendency to overestimate their memory skills: they predicted that they would be

capable of recognizing the correct word while they actually failed to do so. An explanation of this metamemory deficit is that AUD patients fail to update information about their level of memory and, as a consequence, assess their memory skills regarding earlier functioning in life (Le Berre and Sullivan, 2016). This metamemory impairment may be considered as a mild form of anosognosia, a lack of insight of the disease frequently observed in KS.

Semantic memory

Semantic memory is sustained by relatively preserved lateral temporal lobes in AUD. Semantic memory refers to the memory of meaning, understanding, general knowledge about the world, and other concept-based knowledge unrelated to specific experiences. The level of consciousness associated with semantic memory is noetic (giving rise to feelings of familiarity or knowing) because it is independent of encoding context (Tulving, 1985, 2001). Fama et al. (2011) studied remote semantic memory processes in three clinical groups: AUD group, patients infected with the human immunodeficiency virus (HIV), and patients comorbid for both conditions (AUD + HIV group), compared with healthy controls. AUD and HIV groups exhibited performance below healthy controls, but these differences were not statistically significant, whereas AUD + HIV group appeared impaired compared with healthy controls. Although remote semantic memory has been found preserved in AUD patients (Fama et al., 2011), recently detoxified patients may experience difficulties to acquire new semantic information. Pitel et al. (2007b) studied the ability to acquire new semantic concepts including, for each concept, a label, a superordinate category, and three features associated with a picture. The learning protocol comprised eight daily sessions. AUD patients were able to acquire the category and features of the semantic concepts, albeit slowly, but they presented impaired label learning. AUD patients invoked different and inefficient cognitive strategies to attempt to compensate for impaired episodic and working memory. The use of errorless learning may be relevant for AUD patients with cognitive deficits to learn new complex semantic knowledge, and more particularly, new labels (Pitel et al., 2010). Moreover, information acquired with errorless learning was flexible, i.e., it may be generalized and or transferred to other situations. This learning condition allows preventing that patients repeat their errors in the course of the acquisition, learning them instead of the correct answers, and leading to learning impairments.

Procedural memory

Hubert et al. (2007) highlighted a specific brain network involved in procedural learning and memory. Procedural

learning is a dynamic process involving different phases (cognitive, association, and autonomous) and resulting in the automation of the procedure that underlie motor, visuospatial, or cognitive skills (Anderson, 1992). During the cognitive phase, brain structures such as the prefrontal cortex, anterior cingulate cortex, right angular cortex, and posterior cerebellar regions are activated. The associative phase is mainly underlined by caudate nucleus and occipital regions. The posterior brain is also found activated during the autonomous phase with the anterior cerebellum (Hubert et al., 2007).

Although remote procedural memory seems to be preserved, the acquisition of a new cognitive procedure may be affected by chronic alcohol consumption. Pitel et al. (2007b) tested procedural learning with the Tower of Toronto task (TT task) during four daily sessions. AUD patients and healthy controls performed 10 trials in each learning sessions (40 trials in total). The TT task consists of a rectangular base with three pegs and four colored disks on the leftmost peg. Participants are required to rebuild the initial disk configuration on the rightmost peg, following some rules. Early in abstinence, AUD patients were slower than controls and made more moves to achieve the task, but they managed to reach the same level of performance as controls at the end of the 40 trials (Pitel et al., 2007b). The between-group difference regarding the learning dynamics may be related to the fact that cognitive procedural learning requires episodic memory and working memory in the initial stage of learning (Beaunieux et al., 2006). Alcohol-related episodic and working memory deficits may have prevented patients from completing the cognitive and associative stages at the same pace as controls, making it difficult to automate the new cognitive procedure. An MRI investigation reinforced this hypothesis as it indicated that procedural learning performance correlated with gray matter volume of the angular gyrus and caudate nucleus, not only during the first learning trials but also after 40 trials of the TT task (Ritz et al., 2014). Another explanation of these altered cognitive procedural learning abilities may be related to the visuospatial deficits frequently reported in AUD (Beatty et al., 1996; Fama et al., 2004).

Perceptive memory and visuospatial abilities

There is no specific brain region involved in perceptive memory but several neural networks including sensory areas. Perceptive memory is in charge of the encoding and the storage of perceptual features of physical objects. This memory system includes both conscious and nonconscious processing of sensoriperceptual information (Tulving and Schacter, 1990). Perceptive memory is assumed to be involved in perceptual priming, which refers to the effect in which exposure to the form of a stimulus influences a response to a later stimulus. It can be considered as the root

of human memory because it is through perceptual memory that information is subsequently and progressively transferred into the different representation memory systems. This memory component depends on sensory modalities, notably on sight. In this vein, perceptual memory is linked to three visuospatial abilities: visuoperceptual skills, which concern abilities to classify stimuli such as objects or faces; visuospatial skills, which include localization in space, navigation, and the conceptualization of the distance; and visuoconstruction, which is the ability to organize elements into correct spatial relationships.

In AUD, several structural brain abnormalities have been related to visuospatial deficits. A decreased volume in the parietal lobes has been observed (Chanraud et al., 2007; Fein et al., 2002) and associated with poor performance in spatial processing (Fein et al., 2009). However, cerebellar hemispheric white matter may be a better predictor of visuospatial abilities than parietal lobes volume (Sullivan, 2003).

Impairments in perceptual abilities have been reported in AUD patients by many studies using the embedded figures test (Sullivan et al., 2002; Fama et al., 2004), mental rotation test (Beatty et al., 1996), block design subtest from Wechsler Adult Intelligence Scale (Beatty et al., 1996; Oscar-Berman et al., 2009; Sullivan et al., 2002), and Rey-Osterrieth Complex Figure Test (Beatty et al., 1996; Sullivan et al., 2002). All these tasks are complex, they require different visuospatial components and the integrity of other cognitive functions. For example, poor performance in Rey-Osterrieth Complex Figure copy could be explained by a deficit in visuoperceptual skills, visuoconstruction, or executive functioning. When using an implicit perceptual learning paradigm (assessed with a picture fragment completion task, for example), AUD patients were impaired on the primary components of visuo-perception and explicit memory for visuospatial stimuli but obtained preserved results on the perceptual learning task (Fama et al., 2004). These findings suggest that visuospatial perception is impaired in AUD but patients can take advantage of prior exposure to enhance performance based on preserved implicit memory. Although AUD patients performed at the same level as healthy controls on the perceptual learning task, groups used different strategies: visuoperceptual abilities predicted perceptual learning performance in the control group, whereas in the AUD group, performance was predicted by executive abilities.

Emotional processes and theory of mind

Emotions

The amygdala plays a key role in emotional regulation and behavioral control (McBride, 2002 for review). Wrage et al. (2002) found a reduction of gray matter volume in the

limbic system of AUD patients, notably in amygdala. In addition, Marinkovic et al. (2009) identified abnormal activation of the amygdala and hippocampus during a task of facial emotions identification in AUD.

Chronic and heavy alcohol consumption alters emotional processing. AUD patients present a tendency to alexithymia, i.e., they have difficulties to experiment, characterize, and express their own internal emotional state (Maurage et al., 2017; Uzun et al., 2003). They also exhibit deficits in detection and interpretation of others' emotions (de Timary et al., 2010). Several studies have shown that AUD patients do not succeed in identifying emotions of faces (Kornreich et al., 2002; Philippot et al., 1999), prosody (Brion et al., 2018; Maurage et al., 2009; Monnot et al., 2001), and body postures (Maurage et al., 2009). Moreover, AUD patients do not seem aware of their difficulties in interpreting facial emotions (Philippot et al., 1999). D'Hondt et al. (2015) indicates that AUD patients would need higher intensity in emotion expressing to make efficient identification. Comorbidity between AUD and mood disorders is well established. Moreover, most AUD patients exhibit heightened sensitivity to negative emotions during early withdrawal, especially when they present anxious or depressed symptoms (Schuckit, 2006).

Maurage et al. (2017) conducted a cluster analysis in AUD patients, taking into consideration two types of highly prevalent socioemotional difficulties: alexithymia (three subscales' scores of Toronto Alexithymia Scale-II) and interpersonal problems (six subscales' scores of the Inventory of Interpersonal Problem). They identified five distinct subgroups of patients showing different specific patterns of emotional and interpersonal difficulties. These findings are in line with the idea that cognitive deficits observed in AUD are heterogeneous and suggest that classical group comparisons can be misleading and should be completed by subgroup explorations.

Social cognition

Social cognition concerns the cognitive processes, such as emotion decoding, ToM, and empathy, that enable individuals to take advantage of being part of a social group (Frith, 2008). Several regions, including notably the pre-frontal cortex, anterior cingulate cortex, the temporal pole, and the striatum, have been found to be involved in ToM. Abu-Akel and Shamay-Tsoory (2011) presented a model in which these cortical and subcortical regions are subdivided and functionally organized into networks that subserve the ability to represent cognitive and affective mental states to both self and others. A few studies have examined brain dysfunction related to ToM. They report that in AUD, social cognition deficits are related to prefrontal (Uekermann and Daum, 2008) and temporoparietal dysfunction (Samson, 2009).

ToM is defined as the capacity to infer mental states from others' social signals to predict their behaviors, desires, intentions, and beliefs. Several studies have reported ToM impairments in AUD patients (Bosco et al., 2014; Maurage et al., 2015; Onuoha et al., 2016; Thoma et al., 2013). Maurage et al. (2015) specified that 50% of the AUD patients may present ToM impairments, and in most cases, the deficit concerns the tracking of other people's mental states. Maurage et al. (2016) highlighted a dissociation between impaired affective ToM (i.e., the ability to understand and experience others' feelings and emotions) and relatively preserved cognitive ToM (i.e., the ability to identify others' intentions and thoughts).

Empathy is defined as the ability to understand and share others' feelings and emotions. AUD patients may present a dissociation between an impaired emotional component of empathy (capacity to feel other people's emotions) and a preserved cognitive empathy (capacity to understand other people's mental states such as thought and opinions) (Maurage et al., 2011). Overall, deficits of social cognition observed in AUD patients (Kornreich et al., 2002; Maurage et al., 2017) could disturb interpersonal relationships within the context of a vicious cycle with alcohol consumption as a coping mechanism to overcome social isolation.

Reversibility of cognitive deficits and cerebral damage with abstinence

Many studies provided evidence of the brain and cognitive recovery after drinking cessation (Mulhauser et al., 2018; Rosenbloom et al., 2004; van Eijk et al., 2013) even in the absence of any stimulation. Goldman (1990) refers to time-dependent recovery to describe this phenomenon; the phrase "spontaneous recovery" is also used. Recovery of the brain structure and function has been reported in cross-sectional investigations that compare groups of patients with different length of sobriety or in longitudinal studies of a single AUD group to assess within-subject changes in the course of abstinence.

Brain recovery

Improvement of brain structural integrity (Stavro et al., 2013) is related to the length of abstinence and varies according to the cerebral regions. After a long abstinence period (4 years of sobriety), the blood flow in the frontal lobe seems to increase and even return to normal (Gansler et al., 2000). One year of abstinence is also associated with improved fractional anisotropy of the corpus callosum (Alhassoon et al., 2012). Cardenas et al. (2007) highlighted that recovery of temporal lobes, cerebellum, and anterior cingulate among others brain structures was more limited in relapses than in abstainer AUD patients at 8-month

follow-up. A short period of sobriety (1 month) has been found to result in increased white matter volume and decreased cerebrospinal fluid (Agartz et al., 2003). Interestingly, even a short-term period without alcohol induces noticeable changes in gray matter volume (20 days in Pfefferbaum et al., 1995; 2 weeks in van Eijk et al., 2013). More recently, Segobin et al. (2014) evaluated brain recovery within 6 months with an original and novel method. In this longitudinal study, patients examined at follow-up were not classified into relapsers versus abstainers. The authors analyzed the relationship between regional brain changes and the total amount of alcohol consumed over the 6-month follow-up. They found that interim drinking correlated with the volume of different brain regions (cerebellum, striatum, and cingulate gyrus notably): heavy interim drinking was related to lower recovery. In addition, the degree of recovery was not the same for the entire brain, indicating that the dynamics of neural plasticity may be regionally specific. Interestingly, the findings also revealed that very limited alcohol consumption (<10 g of pure alcohol per day) between baseline and follow-up did not prevent brain recovery.

Neuropsychological recovery

Apparent discrepancies

In accordance with the brain recovery observed with sobriety, neuropsychological deficits described early in abstinence can also be reversible. According to Fein et al. (2006), AUD patients can even perform as well as healthy controls after 7 years of sobriety, in agreement with Stavro et al. (2013) who found that AUD patients sober for up to 1 year exhibit cognitive performance in the normal range. On the contrary, others studies showed that cognitive dysfunctions are still observed after 1 year of abstinence (Nowakowska-Domagata et al., 2017). There are also discrepancies in the findings regarding recovery after 6 months of sobriety. Several studies showed that performance returns to normal (Bell et al., 2016; Pitel et al., 2009), whereas others indicated that impairments can still be observed 6 months after alcohol withdrawal (Munro et al., 2000). The same pattern of heterogeneous results is found for short-term recovery. Wegner et al. (2001) and Stavro et al. (2013) reported that 1 month of abstinence is not enough to recover from alcohol-related cognitive deficits, whereas other authors showed that, after the first weeks of sobriety, the recovery is sufficient for AUD patients to fully benefit from therapeutic activities (Kish et al., 1980; Mann et al., 1999; Petit et al., 2017). These apparent inconsistent results can notably be explained by the fact that recovery of the different cognitive functions evaluated in these studies can require different length of sobriety (Petit et al., 2017).

Episodic memory

Generally, episodic memory deficits are no longer observed following prolonged abstinence (Fein et al., 2006; Reed et al., 1992; Rourke and Grant, 1999). Episodic memory recovery may thus occur within a 6-month abstinence period (Bell et al., 2016) with a potential normalization of memory performance (Pitel et al., 2009). There is also evidence of episodic memory improvements early in abstinence (3 weeks, Manning et al., 2008; 10 days, Mulhauser et al., 2018) possibly through the reduction of lateral ventricle volume (Rosenbloom et al., 2007).

Executive functions

Fein et al. (2006) found that, after several years of sobriety, inhibition, abstraction, flexibility, updating, and working memory results were similar to those of healthy controls. Six months of sobriety may be long enough to observe a return to normal for inhibition, flexibility, and updating abilities (Loeber et al., 2010; Pitel et al., 2009). In the study conducted by Pitel et al. (2009), patients were considered as "relapsers" as soon as they had a single drink during the 6-month follow-up. "Relapsers" exhibited more severe flexibility deficits at follow-up than early in abstinence, suggesting deterioration of executive abilities with even limited interim drinking. Regarding STA, there are discrepancies in the findings. Several studies found improvements of executive abilities during the first month of abstinence (Kish et al., 1980; Mann et al., 1999; Manning et al., 2008; Petit et al., 2017) except for inhibition and for flexibility and planning. However, according to Mulhauser et al. (2018), executive dysfunctions persist after 2 weeks of sobriety. Taken together, these data suggest that inhibitory control remain impaired in AUD early in abstinence.

Other functions

Deficits of visuospatial processing may be particularly persistent even after long-term sobriety (Fein et al., 2006). However, in a cross-sectional study, Munro et al. (2000) showed that low visuospatial performance observed after 6 months of sobriety on the Rey-Osterrieth Complex Figure may reflect impairments of executive functions (such as organization and planning abilities) rather than visuospatial deficits per se. In effect, when visuospatial abilities were evaluated with other tests (e.g., Benton Visual Form Discrimination Test) unrelated to executive functions, AUD patients abstinent for 6 months had preserved results, contrary to those early in abstinence. These findings suggest an improvement of visuospatial abilities with sobriety.

Altered emotional processing and ToM abilities can still be observed 2 months after drinking cessation but in a less

severe form (Foisy et al., 2007; Kornreich et al., 2001). Although episodic memory and executive recovery has been relatively well studied, further studies are required to explore changes in visuospatial processing and social cognition over the course of abstinence. It is worthwhile noting that the absence of recovery or very persistent neuropsychological alterations may reflect premorbid cognitive risk factor to develop AUD.

Factors influencing the recovery

A critical factor possibly modulating recovery is the number of previous detoxifications (Loeber et al., 2010). For example, AUD patients with fewer than two previous detoxifications had better set shifting and flexibility recovery than AUD patients with more than two detoxifications. The heterogeneity in the findings can also be explained by the experimental designs of the studies: cross-sectional (e.g., Fein et al., 2006; Munro et al., 2000) versus longitudinal (e.g., Mulhauser et al., 2018; Pitel et al., 2009). Another factor that influences recovery is the age of the patients when they stop drinking (Rourke and Grant, 1999; Pitel et al., 2009), with alcohol-related deficits being more persistent in elderly AUD patients (Munro et al., 2000). Finally, it is important to take account of the smoking status of AUD patients as it seems to influence the cognitive and brain recovery (Durazzo et al., 2015, 2014).

Clinical implication and relapse factors

While cognitive functions appear to be responsive to abstinence, they often remain severely impaired in recently detoxified patients. The neuropsychological impairments observed early in abstinence could have negative consequences on the patients' capacity to benefit fully from treatment (Fein et al., 1990; Tapert et al., 2004). Because of their cognitive deficits, they may be unmotivated or unable to maintain abstinence or decrease alcohol consumption. Indeed, episodic memory deficits, executive dysfunctions, and impaired social cognition can alter motivation to change behavior, decision-making abilities, new complex learning, or interpersonal relationships. They can also influence the treatment compliance and quality of life (Fig. 8.2).

Motivation

Cognitive impairments can slow down the motivational process to abandon excessive drinking behavior. Motivation to change drinking behavior is crucial for engagement in alcohol treatment (DiClemente et al., 1999). Motivational interview can help to assess the degree of the patient's readiness to change and to encourage patients exploring and resolving their ambivalence toward changing

their behavior. It favors the development of internal motivation to change drinking habits (Miller and Rollnick, 1991). According to the Transtheoretical Model of motivation (Prochaska and DiClemente, 1983), behavior changes involve an evolution of motivation along five stages (Precontemplation, Contemplation, Preparation, Action, Maintenance, and additionally Relapse). The motivation process to abandon maladjusted behavior in favor of a healthier lifestyle requires becoming aware of one's own drinking problem, solving ambivalence, deciding drinking cessation, and applying strategies to act differently. Episodic memory impairments, executive dysfunction, and decision-making deficits have been linked to readiness to change alcohol habits (Blume et al., 2005; Le Berre et al., 2013, 2012). Patients with lower motivation level would present lower cognitive abilities and lower gray matter volume, whereas patients with preserved cognitive abilities and brain integrity would be at a more advanced motivational stage. A set of complementary cognitive abilities is needed to achieve awareness and resolve ambivalence toward alcohol addiction, which is essential for activating the desire to change problematic behavior. Some AUD patients may not be cognitively able to be motivated (Le Berre et al., 2012).

Decision-making

When AUD patients experience alcohol craving, i.e., an irrepressible and unwanted desire to drink, they tend to favor instant gratification of alcohol use and ignore the future negative consequences of their choice. This phenomenon, named "myopia" for the future (Le Berre et al., 2014), is close to the psychopathological concept of denial (Verdejo-García and Pérez-García, 2008). Indeed, patients continue drinking despite devastating consequences on their social relations, work, health, and finances, suggesting decision-making deficits in AUD. Using the Iowa Gambling Task, several studies revealed impaired performance in AUD patients (Brevers et al., 2014; Fein et al., 2004; Goudriaan et al., 2005) related to brain shrinkage in regions involved in the emotional and cognitive components of decision-making (Le Berre et al., 2014).

Galadra et al. (2018) described two theories developed in the literature that could explain for a decision-making disorder in addictions. The first theory, the control-related deficit theory, hypothesizes that decision-making deficits result from imbalance between two separate but interactive brain networks: an impulsive system underlined by the striatum and the amygdala considered as exciter, and a reflective system underlined by the anterior cingulate and prefrontal cortex, which play an inhibitory control role. The hyperactive impulsive system (impulsive, automatic, and emotional processes) would lead to overestimate the impact of the immediate outcomes. On the other hand, the



FIGURE 8.2 Altered neuropsychological abilities limiting the benefit of alcohol treatment.

weakening of the reflective system (highly controlled) would lead to underestimate the future consequences of a decision. In response to an alcohol cue, this imbalance accounts for rapid decision-making, prioritizing short-term reward irrespective of the long-term consequences. This imbalance would result in a bias in decision-making abilities, which would increase the risk of relapse. Noël et al. (2013) stated that the insula may play a regulatory role between these two systems, by translating bottom-up, interoceptive signals into subjective output, such as craving.

The second theory is the reward deficit theory that highlights the key role played by the motivational brain network. This network promotes behaviors that provide anticipated or experienced pleasure/reward versus stressing stimuli or events. AUD is characterized by a compulsion to seek and take alcohol, loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug (alcohol) is prevented. The theory argues that AUD is a reward deficit disorder, and the emergence of a negative emotional state plays an important role in defining and perpetuating chronic heavy drinking. The development of AUD would reflect the evolution from impulsivity (positive reinforcement) to compulsivity mainly driven by negative reinforcement (i.e., by the need to avoid craving). Craving is considered as a result of a hypoactive reward system desensitized by repetitive alcohol intake and a hyperactive stress system activated by acute excessive alcohol intake and sensitized during repeated withdrawal (Galadra et al., 2018; Koob, 2013).

New complex learning

Psychoeducational therapy aims at providing information and knowledge about alcohol and addictions to patients.

The overall hypothesis is that when patients know, understand, and learn what ethanol is, its action on the body and brain, and the consequences of chronic and heavy drinking, they should be more motivated to change their behavior and more active during treatment. Psychoeducational therapy requires thus the acquisition of new and numerous complex general (semantic) pieces of information presented during workshops. Moreover, cognitive behavioral therapy is based on modification of alcohol habits. Caregivers encourage patients to identify situations at risk of alcohol consumption. They propose new avoidance behavior or refusal skills. Such therapies, classically proposed to AUD patients during the first weeks of sobriety, require the acquisition and implementation of new procedures, skills, and habits without alcohol. As previously mentioned, Pitel et al. (2007b) reported that learning new complex semantic concepts and cognitive procedures are altered in AUD patients early in abstinence because of episodic memory deficits and executive dysfunctions. Patients could acquire new semantic concepts or new procedures but more slowly than healthy controls, suggesting that new complex learning conducted early after detoxification would require more repetitions and expositions to the new material. To benefit fully from treatment, high-level cognitive abilities are crucial. Consequently, such therapies may not be relevant, at least early in abstinence, in AUD patients with impaired neuropsychological performance. They must be personalized to the neuropsychological profile of patients.

Interpersonal relationships

Social integration constitutes a primary human need, but AUD leads to social alterations and interpersonal impairments such as ostracism, defined by the lack of awareness

and exclusion by others. Seventy percent of alcohol relapses are consecutive to negative emotional and social exclusion feelings (Zywiak et al., 2003). Rupp et al. (2017) have confirmed previous results showing that emotion recognition is still impaired after 3 months of abstinence in AUD patients (Foisy et al., 2007). They also indicated that patients who had relapsed at follow-up presented lower emotion recognition performance at baseline than healthy controls and patients who had maintained abstinent. Poor performance on a facial emotion recognition task seems to be related to interpersonal difficulties in daily life (Kornreich et al., 2002) and could thus also be predictive of treatment outcome. In a longitudinal study, Moriyama et al. (2002) showed that poor performance on two subtests of the BADS (temporal judgment and zoo map) was related to lower social outcome (job status) in AUD patients. Efficient executive function that involved, for example, being able to use feedback may contribute to successful employment.

Functional MRI studies have provided novel insights on the brain network associated with ostracism. During a cyberball task that induces social exclusion feelings, activations in the dorsal anterior cingulate cortex and insula have been linked to negative feelings and social distress in healthy controls. In addition, the middle frontal gyrus and inferior frontal gyrus have been involved in the regulation and inhibition of this emotional response (Eisenberger et al., 2003; Gunther-Moor et al., 2010). Maurage et al. (2012) revealed that AUD patients present a different pattern of brain activations during a cyberball task, a virtual ball toss game where the participant is led to believe he is playing with two others partners. The cyberball task includes “inclusion” phases during which the two other partners play with the participant and “exclusion” phases during which they throw the ball only to each other. Activation of the cerebral network related to social exclusion feelings was increased, whereas the ability to regulate such feelings was reduced. Interestingly, these social exclusion feelings persisted even after reinclusion in the social context (Maurage et al., 2012) suggesting negative ruminations (Zadro et al., 2006). Moreover, interpersonal difficulties could be accentuated by alexithymia traits (Maurage et al., 2017): it is especially difficult for AUD patients to identify others’ emotions and intentions as they present reduced ability to describe and communicate their own emotions and feelings.

These emotional and social disabilities contribute to the vicious circle of AUD: difficulties in perceiving the consequences of alcohol consumption, or conversely, difficulties in perceiving the benefit of abstinence, on others. AUD patients with cognitive deficits misinterpret their own emotional states as well as others’ emotions and intentions (altered ToM), potentially resulting in inappropriate social behavior and interactions as well as social stress (Maurage et al., 2011). Alcohol consumption is

frequently used by AUD patients as a coping strategy to overcome interpersonal difficulties, but leading to conflicts (Zeichner et al., 1994) and violence (Brismar and Bergman, 1998). And in turn, emotional and social cognition abilities are even more severely affected by heavy drinking. As a consequence, ToM disabilities and emotion recognition deficits can be regarded as a risk factor of relapse in AUD patients.

Alcohol-related neurocognitive complications

The assessment of cognitive function should not only target the harmful effects of severe and chronic alcohol use but also look for associated nutritional deficiency or liver disease as these factors can result in exacerbated brain damage (Hayes et al., 2016; Ritz et al., 2016a).

Wernicke’s encephalopathy

Wernicke’s encephalopathy (WE) results from severe thiamine deficiency or depletion and is clinically characterized by the classical triad of confusion (particularly disorientation to time and place), ataxia, and oculomotor abnormalities, including nystagmus and ophthalmoplegia (Wernicke, 1881). Mental status change is the most common symptom at WE presentation. The outcome of WE is poor, around 80% of cases resulting in KS.

AUD patients are at special risk for thiamine deficiency because of poor diet, compromised thiamine absorption from the gastrointestinal tract, impaired thiamine storage, and reduced thiamine phosphorylation (Thomson, 2000). Indeed, 30%–80% of AUD patients exhibit such deficiency (Thomson, 2000). Postmortem studies of large samples of AUD cases have indicated that WE is underdiagnosed *in vivo* (Harper, 2006). It is the reason why “operational criteria” for identifying WE have been proposed by Caine et al. (1997). They suggest that WE is associated to the presence of, at least, two of the following four criteria: (1) history of dietary deficiencies, (2) oculomotor abnormalities, (3) cerebellar dysfunction defined by instability of gait and static posture and contributed to cognitive impairment by FCC dysfunctions, and (4) either an altered mental state or mild memory impairment. Preclinical signs of WE can thus be diagnosed *in vivo*, enabling the identification of AUD patients who are at risk for neuropsychological complications. Retrospectively using these criteria in a sample of AUD patients not diagnosed with neurological complications, Pitel et al. (2011) found that there were graded effects in cognitive and motor performance between patients meeting zero criteria (27%) not differing from controls, those meeting one criterion (57%, at risk for WE) presenting mild-to-moderate deficits, and those meeting two or more criteria (16%, with signs of WE),

having the most severe deficits on each of the domains examined. In addition, thiamine levels were selectively related to memory performance in the AUD patients. These findings suggest that the presence of signs of WE may explain, at least partially, the heterogeneity of alcoholism-related neuropsychological deficits. From a more clinical perspective, the use of these operational criteria may help identifying *in vivo* and clinically AUD patients at risk to develop WE. Treatment of WE consists of thiamine administration, preferably by intravenous route. While there are no universally accepted guidelines, recommended doses range from 200 to 500 mg tds for 5–7 days, followed by oral administration (Latt and Dore, 2014).

Korsakoff's syndrome

Although KS can result from different etiological causes, it is most frequently observed in AUD patients. Alcohol-related KS results from the combination of chronic and excessive alcohol consumption with thiamine (B1 vitamin) deficiency. It usually occurs after the acute stage of WE but can also develop insidiously.

In the early stage of the disease, KS includes anosognosia, confabulations, false recognition, and a profound impairment of episodic memory, the latter persisting even at a chronic stage (Kopelman et al., 2009 for review). The DSM-5 refers to “alcohol-induced major neurocognitive disorder, amnestic-confabulatory type, persistent.” Indeed, KS patients exhibit severe and persistent anterograde amnesia associated to variable retrograde amnesia and mild-to-moderate working memory impairments and executive dysfunction (Oscar-Berman, 2012 for review; Van Oort and Kessels, 2009). A continuum of cognitive impairments has been proposed between AUD and KS patients (Parsons, 1998; Ryback, 1971). AUD without neurological complication and KS patients mainly distinguish themselves on the severity of episodic memory deficits (Pitel et al., 2008) and more precisely by the disproportionate impairment of encoding abilities in KS patients. In addition, contrary to what is reported in AUD, episodic memory deficits observed in KS do not recover with abstinence, resulting in difficulties in daily life and autonomy loss. Interestingly, analyses of individual episodic memory results revealed an unexpected partial overlap between AUD patients with the worst performances and KS patients with the best ones. Those AUD with equivocal episodic memory performances, similar to those of KS, may be regarded as AUD patients at risk of developing KS and should receive particular attention and preventive action.

A gradient of brain volume deficits from AUD to KS patients has also been found notably in the hippocampus, thalamus, and mammillary bodies (Sullivan and Pfefferbaum, 2009) (Fig. 8.3). Moreover, Pitel et al. (2012) found

that some AUD patients present as severe thalamus atrophy as KS patients, suggesting that these AUD patients may be at risk of developing KS. Similar results have been found in a diffusion tensor imaging investigation. Segobin et al. (2015) described graded effects of white matter microstructural abnormalities in the fornix and cingulum. Taken together, these data suggest that the severity of the brain abnormalities within the PC and the associated enduring amnesia can be considered as a specificity of KS. The neurotoxicity of ethanol for the PC may be exacerbated by the thiamine deficiency resulting in the pathophysiology of KS. It seems possible and clinically relevant to identify AUD patients at risk of developing KS based on episodic memory results and integrity of PC. As the amnesia in KS is irreversible, prevention is the main therapeutic option. The keys to prevent the occurrence of KS in AUD subjects are the early identification of memory impairments through a cognitive follow-up and, when appropriate, the prompt diagnosis and thiamine supplementation in WE.

Marchiafava–Bignami disease

Marchiafava–Bignami disease (MBD) is a rare complication of chronic alcohol consumption characterized by a demyelination and necrosis of the corpus callosum (Fig. 8.3). Because the MBD mimicks other common etiologies such as WE, corpus callosum glioma, demyelination, and vascular lesions (Parmanand, 2016), this encephalopathy is difficult to diagnose. Hillbom et al. (2014) reported the symptoms frequently presented by patients of studies cases among the literature, such as altered mental state, confusion, delirium, impaired memory, dysarthria, impaired walking, primitive reflexes, incontinence, and rigidity. Although no specific proven treatment is available for MBD, steroids and parenteral thiamine treatment are often reported in case reports (Hillbom et al., 2014; Nemlekar et al., 2016; Sehgal et al., 2013). Authors also indicate that repeated neuropsychological assessment could allow following the recovery, which appears to be slow.

Hepatic encephalopathy

Hepatic encephalopathy (HE) covers an extensive spectrum of neuropsychiatric abnormalities induced by liver dysfunction (Ferro et al., 2016). HE may occur in the setting of acute liver failure, mostly due to infectious or toxic liver causes, or of chronic portosystemic shunting as a consequence of cirrhosis (Ferro et al., 2016). In rare cases, chronic liver dysfunction may result in a syndrome called acquired hepatocerebral degeneration (Fig. 8.3), which manifests itself by cognitive changes together with motor symptoms such as tremor, rigidity, speech disorders, and reflex modifications (Blei and Córdoba, 2001).

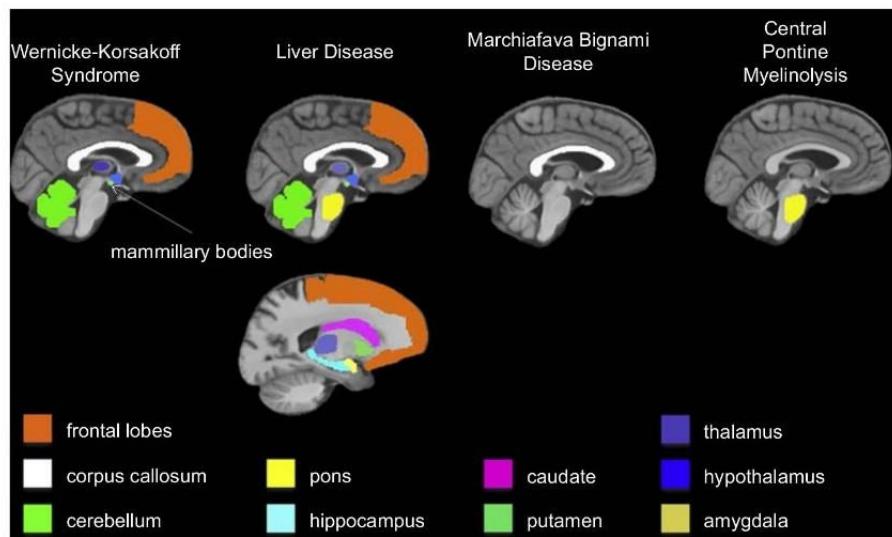


FIGURE 8.3 Brain regions targeted by alcohol-related neurological complications. Alcohol's effects on the brain: Neuroimaging results in humans and animal models. *Alcohol Research: Current Reviews* 38:e–1–24. Adapted from Zahr and Pfefferbaum (2017). Figure modification courtesy of Pfefferbaum, A., Zahr, N.M., Sullivan, E.V., SRI International, CA and Stanford University School of Medicine, USA.

In cirrhotic portosystemic shunting, which is by far the most common mechanism of HE in AUD subjects, the disease course may be either chronic, episodic, or recurrent (Ferro et al., 2016). Most importantly, it is now known that in such cases, the cognitive impairment may be subtle, a condition referred to as minimal hepatic encephalopathy (MHE), which can go unnoticed in the absence of a thorough neuropsychological assessment (Randolph et al., 2009). It is thus of utmost importance to detect MHE, which can significantly impair daily activities and quality of life (Arria et al., 1991). Patients at risk of MHE should be submitted to relevant tests (see Randolph et al., 2009 for review) to take the appropriate actions and prevent further worsening or complications.

It is now well-known that an elevated level of gamma-glutamyltransferase (GGT), although nonspecific, can be regarded as a biomarker of alcohol-related liver disease (Mancinelli and Ceccanti, 2009). Twenty percent of AUD patients present liver steatosis, which may lead to hepatitis and potentially ultimately cirrhosis. 30%–45% of AUD patients with cirrhosis develop HE (Vilstrup et al., 2014) characterized by cognitive impairments related to brain abnormalities in frontal cortices (Lockwood et al., 2002) as well as thalamus and cerebellum (Kril and Butterworth, 1997). MHE has also been shown to induce changes in the structure and connectivity of the hippocampus (García-García et al., 2018), which adds to the direct impact of alcohol and thiamine deficiency on memory.

Well before the development of a full-blown HE, altered liver function may affect brain structure and function. Ritz et al.'s results (2016a) indicated that chronic

liver disease associated with liver fibrosis may partially explain executive dysfunction in AUD patients without clinically detectable HE. In agreement, Junghanns et al. (2004) showed that the GGT level was related to mental flexibility abilities. These results indicate that associated liver function may predict the severity of executive impairments in AUD patients.

Central pontine myelinolysis

Central pontine myelinolysis (CPM) is an osmotic demyelination syndrome, a condition in which the myelin sheath of central nervous system neurons is damaged. The mechanism of demyelination is not inflammatory, like in multiple sclerosis, but is thought to be due to vasogenic and intramyelinic edema, cerebral dehydration, and oligodendrocyte damage (Costin and Miles, 2014). CPM was first described by Adams et al. (1959). At first associated to alcoholism, which remains a significant risk factor, CPM was later shown to be connected in most cases with overly rapid correction of hyponatremia, and other less frequent causes as well (Alleman, 2014).

Myelinolysis may extend well beyond the central pons (Fig. 8.3), to involve a number of other brain structures, of which are, by decreasing order of frequency, the cerebellum, lateral geniculate body, external and extreme capsules, hippocampus, putamen, cortex, thalamus, caudate nucleus, and others (Gocht and Colmant, 1987), always in a symmetric pattern. CPM is isolated in 50% of cases, it is associated to extrapontine myelinolysis (EPM) in 30%, and EPM occurs in isolation in the remaining 20%

(Martin, 2004). In all cases, the diagnosis is confirmed by magnetic resonance imaging, showing diffusion restriction, with decreased apparent diffusion coefficient. Microstructural changes of white matter, which can be reversible with abstinence (Alhassoon et al., 2012), have been demonstrated in AUD patients (Pfefferbaum et al., 2000). AUD subjects may thus be particularly vulnerable to myelin damage induced by electrolytic disturbances. Hyponatremia is found as a causative factor in 80%, and AUD is the most common comorbidity (50% of cases).

The most common presentation of CPM is encephalopathy, followed by paresis and epileptic seizures. In many cases, the encephalopathy and seizures are associated to hyponatremia, and resolve as it is being corrected, before the appearance of the specific symptoms of myelinolysis, in a characteristic biphasic clinical course. The neurological picture then depends on the anatomical location of demyelination. In CPM, the corticospinal tract involvement induces quadriplegia, dysarthria, dysphagia, and sometimes locked-in syndrome, while in EPM, many other symptoms may occur, including movement disorders, behavioral disturbances, encephalopathy, and depression (Alleman, 2014). In a metaanalysis of clinical studies from 1985 to 2013, Singh et al. found that one-fourth of subjects died, one-fourth were left with disability, and half recovered. Myelinolysis is also a complication of liver transplantation, in which case the prognosis is much worse, with a rate of combined death and disability of 77% (Singh et al., 2014).

CPM and EPM thus stand as another cause of neurological complications of AUD and should be considered whenever an AUD subject develops neurological symptoms, particularly encephalopathy, and paresis or seizures, all the more in the presence of hyponatremia.

Recommendations for researchers and clinicians

It is now clear that chronic and excessive alcohol consumption affects directly and indirectly brain and cognition. The nature and severity of these brain structure and function alterations are very heterogeneous, but in some cases, they can limit the benefit of treatment and be predictive of poor treatment outcome. Cognitive assessment of AUD patients is crucial for the detection of impaired and preserved neuropsychological functions and then the adaption of treatment. Moreover, a neuropsychological assessment is crucial to make a differential diagnosis. Finally, the neuropsychological profile is very informative to implement a relevant rehabilitation program.

Modalities of screening and assessment

Given the potential impact of neuropsychological deficits presented by AUD patients on patients' ability to remain

abstinent, it is recommended to screen their cognitive functioning at treatment entry. Because of the limited financial and human resources in addiction departments that do not permit a systematic comprehensive evaluation, two screening tools can be used to detect alcohol-related cognitive deficits.

The **Montreal Cognitive Assessment** (MoCA; Nasreddine et al., 2005) is constituted by subtests assessing visuospatial/executive abilities, memory, attention, language, abstraction, and orientation. Although the MoCA has initially been developed for the assessment of mild cognitive impairment related to neurodegenerative diseases, this screening tool has satisfactory psychometric properties to distinguish KS and AUD patients from healthy controls (Alarcon et al., 2015; Copersino et al., 2009; Oudman et al., 2014). More precisely, the MoCA seems to have good specificity and sensitivity to discriminate KS patients from healthy controls, whereas MoCA's specificity to discriminate AUD patients from healthy controls is limited (Wester et al., 2013b). That could be explained by the fact that the MoCA evaluates cognitive functions that are not impaired in AUD while other cognitive abilities altered in AUD are not evaluated.

The **Brief Evaluation of Alcohol-Related Neuropsychological Impairment** (BEARNI; Ritz et al., 2015) has been specifically designed to assess the semiology of alcohol-related cognitive and motor deficits in AUD. It is intended to be short and easy to score, making it useable by nonpsychologists. This screening tool is composed of five subtests (verbal memory, working memory, executive functions, visuospatial abilities, and ataxia), with a total score and a "cognitive" subscore that allows interpreting the results even when the patient cannot perform the ataxia subtest. BEARNI has a high sensitivity and gauges the severity of cognitive impairments from mild to moderate to severe cognitive deficits. The main limitation of the BEARNI is its relative low specificity for the detection of patients with mild impairments. Indeed, patients may be classified as having mild deficits on BEARNI, while an extensive neuropsychological battery does not reveal any cognitive deficits. BEARNI should be used especially for the detection of moderate-to-severe impairments.

Recently, Pelletier et al. (2018) compared these two screening tools for the detection of cognitive impairments in AUD patients. Although both tools exhibited a high sensitivity, BEARNI's sensitivity was even higher than the MoCA's one. Concerning specificity, the MoCA was much better than BEARNI. Almost all AUD patients without cognitive deficits on a comprehensive neuropsychological battery had a BEARNI score below the normal cutoff (< or = to 16 for cognitive subscore or 19 for total score). The proportion of well-classified patients was significantly better with the MoCA than with the BEARNI test. In addition, a previous study found that the MoCA is a reliable tool for monitoring cognitive improvement during

hospitalization for rehabilitation (Pelletier et al., 2016). The authors concluded that the MoCA appears to be more appropriate than BEARNI in clinical settings.

Whenever it is possible, and particularly when patients exhibit poor performance on screening tools, patients should be referred to a neuropsychologist to conduct an in-depth assessment based on gold standard tests. AUD patients do not exhibit systematic deviation from the normal range in the reference neuropsychological tests while they encounter problems in daily life. Indeed, day-to-day level of function is better determined by ecologically valid assessments than by laboratory-based neuropsychological tests. Several studies have reported executive and memory dysfunctions, respectively, assessed with the BADS (Ihara et al., 2000; Maharasingam et al., 2013; Moriyama et al., 2002), and the Rivermead Behavioral Memory Test (RBMT) (Wester et al., 2013b). Moriyama et al. (2002) also found that executive dysfunction evaluated by the BADS were associated to alcohol-unrelated outcomes (job performance) but not to alcohol-specific outcomes (control drinking). Using the RBMT allows detecting more severe memory impairments in KS than in AUD patients (Wester et al., 2013a). This pattern of difference was also found in executive performance assessed with the BADS (Maharasingam et al., 2013) while laboratory-based measures mainly revealed a difference in memory.

According to Stephan et al. (2017), some neuropsychological tests are more sensitive to the effects of alcohol than others. According to these authors, it would be more relevant to use the Wisconsin Card Sorting Test, Iowa Gambling Task, and Hayling Test than a verbal fluency task or a Stroop Color–Word interference test.

Finally, it is important to specify that benzodiazepines impair memory functioning (Bacon et al., 1998) and affect mood states (Curran, 1991). A neuropsychological assessment must be conducted when clinicians consider that the benzodiazepines commonly used during withdrawal no longer have an effect. It is also crucial to keep in mind that AUD patients frequently exhibit psychiatric, neurological, and addictive comorbidities that can exacerbate neuropsychological impairments and hamper spontaneous recovery after drinking cessation (Yang et al., 2018).

Heterogeneity of the neuropsychological profile

Several factors that may contribute to the heterogeneity of alcohol-related cognitive impairments have been identified (Fig. 8.4). The continuum hypothesis postulated that alcohol-related cognitive deficits range from mild to moderate to severe, comparable to those observed in KS, depending on the severity of alcohol history. Some studies confirmed a relationship between neuropsychological

impairments and the total amount of alcohol consumed over a lifetime (Ryback, 1971) or duration of AUD (Sullivan et al., 2000), but these relationships are not systematically found. The number of withdrawals (Duka et al., 2003), length of sobriety (Zinn et al., 2004), associated malnutrition (Pitel et al., 2011; Ritz et al., 2016a), and biological factors such as liver complications and thiamine deficiencies (Fama et al., 2017; Ritz et al., 2016a) may also contribute to the presence and profile of cognitive impairments. The age at first drinking is significantly correlated with the decrease in gray matter volume in the frontal cortex, the cerebellum, and the brainstem (Charnaud et al., 2007), structures previously described as supporting impaired neuropsychological functions in AUD. In addition, it is well known that sleep participates in the brain and cognitive integrity, particularly in memory consolidation, and that sleep disturbances are frequently reported in AUD patients. Junghanns et al. (2009) showed that chronic and excessive alcohol consumption is associated with impaired sleep-dependent memory consolidation, suggesting that sleep disorders may also contribute in the heterogeneity of cognitive deficits.

This heterogeneity in the nature and the severity of the deficits observed in AUD patients sometimes leads to difficulties in differential diagnostic. In effect, the differential diagnosis can be challenging especially with respect to KS, as described in the previous section, but also with “normal” aging, Alzheimer’s disease (AD), and frontotemporal lobar degeneration.

Differential diagnosis

Age–alcohol use disorder interaction

Cognitive deficits observed in AUD may be similar to those observed in healthy subjects as a result of normal aging (Oscar-Berman et al., 1997). The interaction between age and AUD may be explained by the premature aging hypothesis, suggesting that AUD patients exhibit neuropsychological and brain changes typical of aging. Indeed, a longitudinal imaging study comparing AUD to healthy subjects revealed that chronic alcohol consumption increases volume of gray matter loss observed in frontal regions during aging (Pfefferbaum et al., 1998). Chronic and excessive alcohol consumption leads to accelerated cortical aging, even when alcohol misuse develops later in life (Sullivan et al., 2018).

Alzheimer’s disease

AD is a neurodegenerative disease that develops in elderly subjects and is mainly characterized by episodic memory impairments (McKhann et al., 2011). Although executive function and visuospatial abilities are similarly impaired in AUD and AD, AD patients exhibit more severe episodic

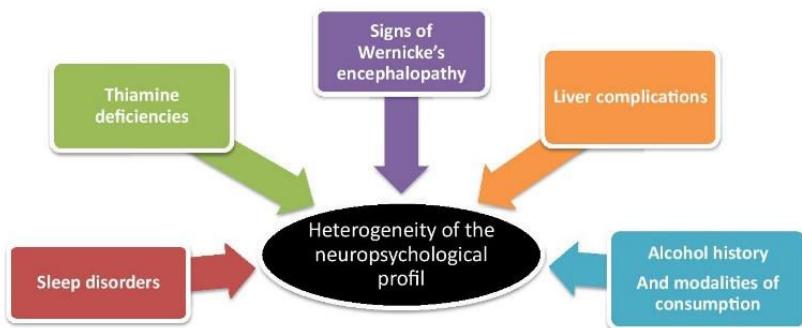


FIGURE 8.4 Factors explaining the heterogeneity of the neuropsychological profile in alcohol use disorder (AUD) patients.

memory impairments than AUD patients (Liappas et al., 2007). AD patients are also impaired in a recognition task, which is usually relatively preserved in AUD patients. In elderly subjects, the diagnosis between AUD and AD can thus be relatively easily and reliably made.

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease that develops in middle age adults and initially consists notably of behavioral disturbances. Among behavioral disturbances, abnormal alcohol consumption can be observed in 30%–41% of cases (Lebert and Pasquier, 2008). These consumptions are characterized by specific features such as a recent onset of alcohol abuse, an appetite for sugary alcoholic drinks that may never have been consumed before, and quantities and hours of consumptions becoming gradually ritualized. Moreover, patients with FTLD do not exhibit withdrawal syndrome as they do not experience genuine alcohol dependence. Neuropsychological disorders observed in later stages of the FTLD are similar to those observed in AUD: executive and emotional deficits as well as altered decision-making processes (Mendez et al., 2005). Because alcohol-related deficits recover with abstinence, whereas there is a global deterioration of performance in FTLD patients, a follow-up neuropsychological evaluation in detoxified patients is very useful for an accurate diagnosis. In effect, cognitive recovery is expected in AUD after drinking cessation, while the clinical diagnosis of FTLD is supported by persistent and worsening cognitive and behavioral deterioration even with sobriety.

Treatment modifications

As previously mentioned, severe deficits of episodic memory, executive functions, and social cognition may result in poor treatment outcome. A systematic screening conducted early in abstinence would allow clinicians to identify patients who are not cognitively able to enter

treatment and would rather benefit from a recovery period (Fig. 8.5). For these patients, the hospitalization could last longer to protect them from short-term relapse and favor spontaneous recovery. Ideally, treatment options (timing and methods) could be adjusted for each and every patient according to the neuropsychological profile. For example, repetition of materials or procedures to be learned could be a useful strategy for some AUD patients in educational program, wherein they are expected to acquire new complex information (Nixon et al., 1998). To increase even more the efficiency of treatment, adjustments could also be based on the cognitive functions identified as preserved during the neuropsychological assessment. For example, errorless learning (Pitel et al., 2010) allows compensating for the deficits of episodic memory and executive dysfunction.

Neuropsychological rehabilitation

Another way to adjust treatment is to conduct neuropsychological rehabilitation programs. According to Sofuoğlu et al. (2013), enhancement of executive control may increase behavioral treatment efficacy in AUD. Neuropsychological rehabilitation aims at facilitating cognitive recovery or compensating for cognitive deficits. Roehrich and Goldman (1993) found that AUD patients transferred what they had learned during experience-dependent recovery (i.e., cognitive remediation or rehabilitation) to a wide range of tasks that went well beyond the trained tasks. This transfer could thus occur to material that relates directly to AUD treatment as required in educational treatment, suggesting that such experience-dependent recovery could be valuable for AUD treatment.

Other interventions have been developed to improve cognitive functioning in AUD patients. For example, treatments validated in other diseases for the rehabilitation of executive function, such as Goal Management Training (GMT) (Levine et al., 2011) and a combination of GMT with mindfulness-based meditation, improve working memory, inhibition, and decision-making abilities in AUD

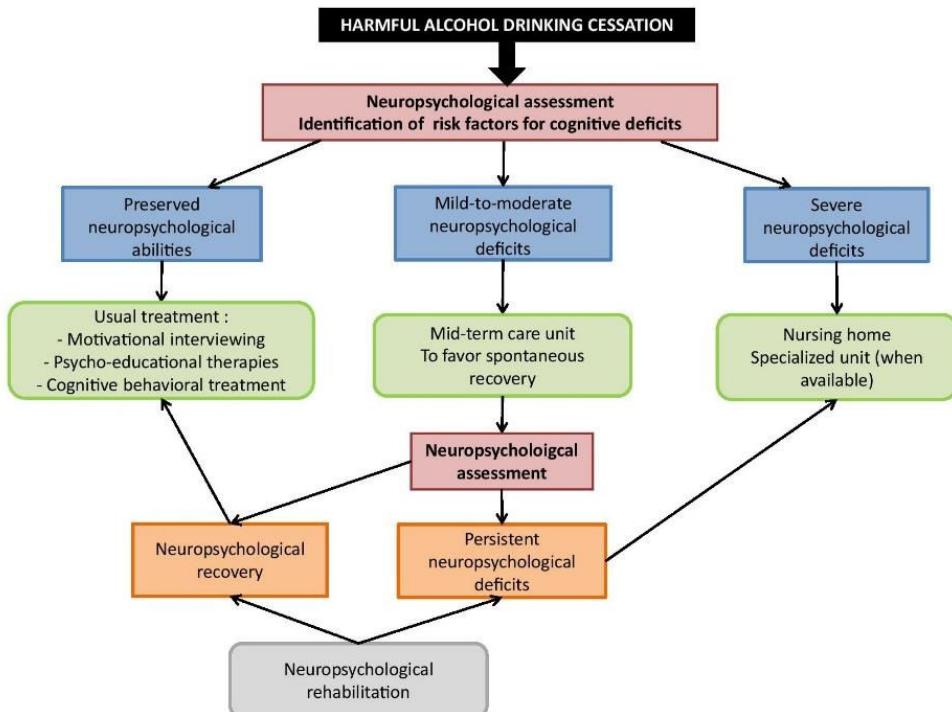


FIGURE 8.5 How to integrate the neuropsychological assessment as key information for relevant clinical decisions in AUD treatment? Early after the cessation of alcohol drinking, a neuropsychological assessment enables clinicians to offer AUD patients the best treatment options according to their neuropsychological profile. When neuropsychological abilities are preserved, patients can benefit from usual treatment. When patients exhibit mild-to-moderate neuropsychological deficits, they can be referred to midterm care units to permit spontaneous cognitive recovery without drinking potentially favored by neuropsychological rehabilitation. After several weeks, they can be reevaluated: a significant neuropsychological recovery would allow attending usual treatment, while persisting neuropsychological deficits would require specialized care, just as patients with severe neuropsychological deficits, including neuropsychological rehabilitation programs.

patients compared with treatment as usual (Alfonso et al., 2011; Valls-Serrano et al., 2016). In the same vein, studies showed that patients in such rehabilitation group not only improve cognitive functioning but also present decreased craving, affective distress, and psychological symptoms compared with patients who received usual treatment (Marceau et al., 2017; Rupp et al., 2012).

In 2011, Houben et al. examined the relationship between neurocognitive functioning and alcohol outcomes. People presenting AUD were recruited via the Internet. They performed working memory training or control tasks during 25 sessions. The authors found an improvement of working memory, which persisted 1 month after the end of the protocol, in the working memory training group. Moreover, alcohol consumption measured with the Timeline Followback questionnaire (Sobell and Sobell, 1992) decreased by approximately 10 drinks per week from pretest to posttest in the training group, and this reduction was still present 1 month after. The improvement of working memory could help restoring control over automatic impulses and thus reducing drinking.

Wiers et al. (2011) focused on a bias observed in AUD patients in the action tendency to approach alcohol-related stimuli. They used a cognitive bias modification method, based on the alcohol approach/avoidance task (Wiers et al., 2010). This task aims at inhibiting alcohol habits that are notably based on the attentional bias toward alcohol stimuli observed in AUD. During this task, AUD patients were instructed to respond to pictures of alcohol drink or soft drink, with an approach movement (pulling a joystick) or an avoidance movement (pushing a joystick). The pulling and pushing were accompanied by a zooming feature that made the picture increase in size consistent with approach or decrease with avoidance. Patients performed four training sessions on four consecutive days. AUD patients trained to “avoid” alcohol stimuli during the task showed better drinking outcomes than those in other conditions when interviewed 1 year later.

Regarding interpersonal difficulties, the development of therapeutic programs that target social abilities to regulate interpersonal relationships is required (Maurage et al., 2012) and could be inspired by what is currently proposed

in schizophrenia (Veltri et al., 2011). Self-esteem could also be a therapeutic target as low self-esteem is related to increased social difficulties (Trucco et al., 2007), interpersonal deficits, and high risks of relapse (Maurage et al., 2012).

Conclusion

AUD patients recently detoxified present altered brain structure and function resulting in mild-to-moderate cognitive impairments that are the most severe right at the time neuropsychological abilities are required for alcohol treatment. Although cognitive impairments have the potential to limit the benefit of treatment, they remain underestimated in clinical practice. It is thus essential to identify risks factors for cognitive dysfunction or to evaluate alcohol-related cognitive deficits early after detoxification not only to adjust treatment options for impaired patients but also for early detection of patients at risk for developing neurological complications. Further well-designed studies are necessary to evaluate the benefit of neuropsychological rehabilitation in accelerating cognitive recovery and favoring the benefit of alcohol treatment. From a more fundamental perspective, the physiopathology of alcohol-related cognitive deficits and brain damage remains unclear and requires further longitudinal and multimodal investigations including clinical, biological, neuropsychological, and neuroimaging examinations. The impact of the alcohol neurotoxicity *per se* and/or associated liver disease, sleep disorders, or nutritional deficiency needs also to be clarified.

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2. Collaboration : Lanier et al., Brain Communication 2020

Title: The effect of alcohol withdrawal syndrome severity on sleep, brain and cognition

Running title: The harmful effects of drinking cessation

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Abstract:

In alcohol use disorder, drinking cessation is frequently associated with an alcohol withdrawal syndrome. Early in abstinence (within the first two months after drinking cessation), when patients do not exhibit physical signs of alcohol withdrawal syndrome anymore (such as nausea, tremor or anxiety), studies report various brain, sleep and cognitive alterations, highly heterogeneous from one patient to another. While the acute neurotoxicity of alcohol withdrawal syndrome is well known, its contribution to structural brain alterations, sleep disturbances and neuropsychological deficits observed early in abstinence has never been investigated and is addressed in this study. We included 54 alcohol use disorder patients early in abstinence (from 4 to 21 days of sobriety) and 50 healthy controls. When acute physical signs of alcohol withdrawal syndrome were no longer present, patients performed a detailed neuropsychological assessment, a T₁-weighted MRI, and a polysomnography for a subgroup of patients. According to the severity of the clinical symptoms collected during the acute withdrawal period, patients were subsequently classified as mild alcohol withdrawal syndrome (mild-AWS) patients (Cushman score ≤ 4 , no benzodiazepine prescription, N=17) or moderate alcohol withdrawal syndrome (moderate-AWS) patients (Cushman score > 4 , benzodiazepine prescription, N=37). Patients with severe withdrawal complications (delirium tremens or seizures) were not included. Mild-AWS patients presented similar gray matter volume and sleep quality as healthy controls, but lower processing speed and episodic memory performance. Compared to healthy controls, moderate-AWS patients presented non-rapid eye movement sleep alterations, widespread gray matter shrinkage and lower performance for all the cognitive domains assessed (processing speed, short-term memory, executive functions and episodic memory). Moderate-AWS patients presented a lower percentage of slow wave sleep, gray matter atrophy in fronto-insular and thalamus/hypothalamus regions, and lower short-term memory and executive performance than mild-AWS patients. Mediation analyses revealed both direct and indirect (via fronto-insular and thalamus/hypothalamus atrophy) relationships between poor sleep quality and cognitive performance. Alcohol withdrawal syndrome severity, which reflects neurotoxic hyperglutamatergic activity, should be considered as a critical factor for the development of non-rapid eye movement sleep alterations, fronto-insular atrophy and executive impairments in recently detoxified alcohol use disorder patients. The glutamatergic activity is involved in sleep-wake circuits and may thus contribute to molecular mechanisms underlying alcohol-related brain damage, resulting in cognitive deficits. Alcohol withdrawal syndrome severity and sleep quality deserve special attention for a better understanding and treatment of brain and

cognitive alterations observed early in abstinence, and ultimately for more efficient relapse prevention strategies.

Keywords: alcohol use disorder; alcohol withdrawal syndrome; sleep; brain structure; cognition

Abbreviations:

- AASM: American Association of Sleep Medicine
ACME: Average Causal Mediation Effect
ADE: Average Direct Effects
AHI: Apnea-Hypopnea Index
AUD: Alcohol Use Disorder
AUDIT: Alcohol Use Disorder Identification Test
AWS: Alcohol Withdrawal Syndrome
BDI: Beck Depression Inventory
DSM: Diagnostic and Statistical Manual of Mental Disorders
ESS: Epworth Sleepiness Scale
FWE: Family wise error
FWHM: Full Width at Half Maximum
GM: Gray Matter
HC: Healthy Controls
MNI: Montreal Neurological Institute
NREM: Non Rapid Eye Movement
N1: stage 1
N2: stage 2
N3: stage 3
PSG: Polysomnography
PSQI: Pittsburgh Sleep Quality Index
REM: Rapid Eye Movement
SE: Sleep Efficiency
SPM: Statistical Parametric Mapping
STAI: State-Trait Anxiety Inventory
TST: Total sleep time

INTRODUCTION

In Alcohol Use Disorder (AUD) patients, cessation of alcohol consumption is frequently associated with several clinical symptoms (tremor, nausea, anxiety, insomnia, etc.) that constitutes the alcohol withdrawal syndrome (AWS; American Psychiatric Association, 2013). The severity of AWS is variable in AUD patients, ranging from a mild clinical form to severe neurological complications such as seizures and *delirium tremens*, potentially leading to death (Jesse *et al.*, 2017). From a neurobiological perspective, AWS results from a brain hyperexcitability due to increased glutamate transmission combined with decreased GABA transmission (De Witte *et al.*, 2003). This excessive brain glutamate release is neurotoxic and has important consequences on brain functioning, mainly underlying the acute symptomatology of AWS (Tsai and Coyle, 1998; Lukyanov *et al.*, 1999; Kühn *et al.*, 2014; Frischknecht *et al.*, 2017).

This cerebral hyperexcitability is also known to be related to sleep abnormalities, which can persist several months after alcohol cessation and increase the risk of relapse (Begleiter and Porjesz, 1979; Chakravorty *et al.*, 2016). Early in abstinence (from 2 to 8 weeks after detoxification, when acute physical symptoms of alcohol withdrawal are no more present), sleep abnormalities can be observed and consist of increased sleep latency and fragmentation, decreased sleep duration and sleep efficiency (defined as the ratio between time spent asleep and time in bed) as well as a decreased percentage of stage 3 (N3) of Non Rapid Eye Movement (NREM) sleep, also named slow-wave sleep (Heilig *et al.*, 2010; Angarita *et al.*, 2016). The potential alteration of Rapid Eye Movement (REM) sleep is still debated (Gillin *et al.*, 1990; Chakravorty *et al.*, 2016).

Structural brain alterations and cognitive deficits have been well-described (Zahr *et al.*, 2017) in recently sober AUD patients. Neuroimaging studies reported gray matter (GM) alterations mainly affecting two brain networks: the fronto-cerebellar (Kelly and Strick, 2003) and Papez circuits (Aggleton, 2012), which are involved in motor and executive abilities, and episodic memory respectively. As a result, a large number of recently detoxified AUD patients present neuropsychological deficits including executive, working memory and episodic memory impairments (Stavro *et al.*, 2013; Le Berre *et al.*, 2017). The extent of these cognitive alterations is extremely variable. Some patients have preserved abilities, others exhibit mild-to-moderate deficits and others present severe impairments. This heterogeneity observed in the severity of AUD-related brain and cognitive deficits could be explained by several factors, such as demographical variables (Bates *et al.*, 2002; Nolen-Hoeksema, 2004; Oscar-Berman *et al.*,

2004), alcohol-related history (Zahr and Sullivan, 2008; Ritz *et al.*, 2016), malnutrition and thiamine deficiency (Zahr and Sullivan, 2008; Pitel *et al.*, 2011), liver disease (Junghanns *et al.*, 2004; Ritz *et al.*, 2016), and repeated alcohol withdrawals (Kouimtsidis *et al.*, 2019).

Several studies reported that AUD patients who experienced multiple detoxifications (two or more) have more severe executive and decision making deficits (Duka *et al.*, 2003, 2011; Loeber *et al.*, 2009), emotional impairments (Townshend and Duka, 2003; O'Daly *et al.*, 2012), increased craving and anxiety-levels (Loeber *et al.*, 2010), brain functional connectivity abnormalities (O'Daly *et al.*, 2012) and altered cognitive recovery (Loeber *et al.*, 2010) compared to patients with none or only one previous withdrawal. Beyond the frequency of alcohol-withdrawal experiences, AWS severity may contribute to the heterogeneity of altered brain structure and function observed in AUD patients. To date, studies mainly focused on the identification of clinical predictors to prevent the development of severe AWS (Goodson *et al.*, 2014; Kim *et al.*, 2015; Silczuk and Habrat, 2020). These investigations highlighted the role of the alcohol consumption level and the number of previous detoxifications (Duka *et al.*, 2004) in the development of seizures and/or *delirium tremens*. To our knowledge, little is known regarding the effect of mild to moderate AWS on cognitive performance, GM volume and sleep quality in recently detoxified AUD patients.

The aim of the present study was thus to explore whether, even in absence of *delirium tremens* and/or seizures, AWS severity contributes to the heterogeneity of cognitive deficits, brain alterations and sleep changes observed in recently detoxified AUD patients.

MATERIALS & METHODS

Participants

One hundred and four participants were included in this study: fifty-four AUD inpatients and fifty healthy controls (HC). None of them had a history of neurological, endocrinial, infectious diseases, depression (assessed using both the Beck Depression Inventory (BDI (Beck *et al.*, 1961) and a psychiatric assessment) nor other forms of substance use disorder (except tobacco). All participants were informed about the study approved by the local ethics committee of Caen University Hospital (CPP Nord Ouest III, no. IDRCB: 2011-A00495-36) prior to their inclusion and provided their written informed consent. The study was conducted in France from 2016 to 2019.

AUD patients were recruited by clinicians while they were receiving withdrawal treatment

as inpatients at Caen University Hospital. AUD patients met “alcohol dependence” criteria according to the DSM-IV-TR (American Psychiatric Association (APA), 2000) or “severe AUD” criteria according to the DSM-5 (Harper, 2014) for at least 5 years. HC were recruited to match the demographics (age, sex and education) of the AUD patients. They were interviewed with the Alcohol Use Disorder Identification Test (AUDIT; (Gache *et al.*, 2005) to ensure that they did not meet the criteria for alcohol abuse (AUDIT < 7 for men and <6 for women). None of the controls had a BDI (Gache *et al.*, 2005) score > 29 and a Mini-Mental State Examination (Folstein *et al.*, 1975) score < 26. Demographical data are presented in **Table 1**.

Experimental design

Assessment of alcohol withdrawal syndrome (AWS)

All AUD inpatients included in this study underwent a symptom-triggered approach to the treatment of alcohol withdrawal, which requires to provide medication only when patients present alcohol-withdrawal symptoms (Saitz *et al.*, 1994; Daepen *et al.*, 2002). The Cushman score was used to monitor the severity of AWS (Cushman *et al.*, 1985), as recommended by the French Addiction Medicine Society and recognized by the European Federation of Addiction Societies (Société Française D’Alcoologie, 2017). This score takes the following clinical variables into account: hearth rate, systolic blood pressure, respiratory rate, tremor, sweating, agitation, and sensorial disorders. Each variable is scored from 0 to 3 according to the severity of the symptom. The Cushman score refers to the sum of these subscores.

Alcohol withdrawal symptoms were systematically assessed every four hours by the nursing staff supervised by a physician specialized in addiction medicine. When the Cushman score was, for the first time, superior or equal to 4, it was assessed a second time 30 minutes later to avoid false positive (caused by anxiety for example). When the Cushman score was higher than 4 twice in a row and/or when a history of severe alcohol withdrawal complications (seizure, *delirium tremens*) was known, a long-acting benzodiazepine with active metabolites (e.g. diazepam) was orally administered in order to alleviate AWS and prevent the development of a more severe AWS (Daepen *et al.*, 2002). In patients with hepatocellular or respiratory insufficiency, oxazepam was preferred to avoid over sedation or respiratory depression. A decrease in the benzodiazepine dosage was decided when the Cushman score was lower or equal to 2 for at least 24 hours, at a rate of 15 to 30% of the total dose every 24 to 48 hours.

AUD patients were classified into two groups according to the severity of AWS:

- *mild-AWS*: a maximum Cushman score ≤ 4 and no benzodiazepine treatment required during the acute alcohol withdrawal period according to the symptom-triggered approach.
- *moderate-AWS*: a maximum Cushman score > 4 and/or the presence of a history of severe alcohol withdrawal complications resulting in a benzodiazepine administration during the acute alcohol withdrawal period.

None of the patients had undergone severe AWS defined by neurological complications such as *delirium tremens* or seizures during the acute withdrawal period examined in the course of the present study.

For all AUD patients, the maximum Cushman score and the number of previous detoxifications were collected. For patients whom benzodiazepines were prescribed, we also recorded the number of days and the total amount of benzodiazepines received during alcohol withdrawal. Alcohol-related variables and withdrawal history are summarized in **Table 1**.

Neuropsychological assessment

All participants underwent a detailed neuropsychological examination focusing on processing speed, short-term memory, executive functioning, and episodic memory. Processing speed was measured with a composite score including the part A (time in seconds) of the Trail Making Test (Reitan and Wolfson, 1985) and the denomination condition (time in seconds) of the Stroop Test (Stroop, 1935). Short-term memory was assessed using verbal spans of the WAIS-III (Wechsler, 1997). For executive functions, a composite score was computed including performance on 3 tests assessing manipulation of information (verbal backward spans of the WAIS-III; Wechsler, 1997), inhibition (Stroop Test; Stroop, 1935) with the time in seconds needed to complete the interference condition minus time needed for the denomination condition, and mental flexibility (Modified Card Sorting Test, Cianchetti *et al.*, 2005) with the number of perseverative errors. Two patients had missing data for one measure; their composite score assessing executive functions was therefore computed using remaining scores. Episodic memory was examined through the sum of the 3 free recalls of the French version of the Free and Cued Selective Reminding Test (Van der Linden *et al.*, 2004). Neuropsychological data

were transformed into z-scores using the mean and standard deviation obtained from the HC. The sign of all variables for which high scores were in the impaired direction (such as completion time or number of errors) was reversed so that all the z-scores had the same direction: higher z-scores reflecting better performance.

Magnetic Resonance Imaging Data Acquisition and preprocessing

Brain imaging examinations were conducted in 31 HC and 43 AUD patients (13 mild-AWS and 30 moderate-AWS) within the same week as the neuropsychological assessment. HC and the two subgroups of AUD patients were matched for age, sex and education level. All neuroimaging examinations were performed at Cyceron center (Caen, France).

A high-resolution T1-weighted anatomical image was acquired for each subject on a Philips Achieva 3T scanner (Philips Health-care/Philips Medical Systems International B.V., Eindhoven, the Netherlands) using a 3-dimensional fast-field echo sequence (sagittal; repetition time, 20 ms; echo time, 4.6 ms; flip angle 10°; 180 slices; slice thickness: 1 mm; field of view 256 x 256 mm²; matrix, 256 x 256). The volumetric magnetic resonance imaging (MRI) data were analyzed using the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Preprocessing steps included segmentation of the MRI data into gray matter (GM) and spatial normalization to the Montreal Neurological Institute (MNI) template (voxel size = 1.5 mm³, matrix = 121 x 145 x 121). The normalized GM images were modulated by the Jacobian determinants to correct for nonlinear warping so that the resulting brain volumes were corrected for brain size. The resulting images were smoothed by a Gaussian kernel of 8 mm full width at half maximum (FWHM). A GM mask was obtained taking the unmodulated GM images of HC normalized to the MNI space, averaging them, and thresholding the resultant mean image at 0.5. The resulting GM mask was applied to GM data analyses.

Sleep

A subgroup of 21 AUD (8 mild-AWS and 13 moderate-AWS) and 15 HC, matched for age, sex and education, underwent one night of polysomnography (PSG) using a portable recording device (Siesta®, Compumedics, Australia), allowing AUD patients to sleep at the addiction department and HC at their home. The PSG was conducted within the same week as the neuropsychological and MRI examinations. The PSG acquisition consisted of twenty EEG electrodes (Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, P3, P4, O1, O2, FZ, CZ, PZ, vertex ground

and a bi-mastoid reference) placed over the scalp according to the international 10-20 system, with impedances kept below 5 kΩ. We also recorded the electrooculogram (EOG), chin EMG, ECG, respiratory movements using abdominal and thoracic belts, respiratory airflow using nasal and oral thermistor, and oxygen saturation with a finger pulse oximeter. The EEG signal was digitalized at a sampling rate of 256 Hz. High-pass and low-pass filters were applied, respectively at 0.3 Hz and 35 Hz. PSG recordings were scored in 30-s epochs according to the American Association of Sleep Medicine (AASM, 2017) standard criteria. The following parameters were obtained: total sleep time (TST; in minutes), sleep efficiency (SE (%), corresponding to time spent asleep/ time in bed), sleep onset latency (in minutes, referring to the time from lights-off to the first three epochs of any stage of sleep), wake after sleep onset (in minutes), time spent in each sleep stage (N1, N2, N3, and REM sleep, expressed as percentages of TST), arousal index (number of arousals/ TST), stage shifts index (number of sleep stage transitions to N1/TST) and the Apnea-Hypopnea Index (AHI, corresponding to the number of respiratory events per hour of sleep). We also calculated a composite score to assess sleep fragmentation including the micro-arousal index, the arousal index and the number of stage transitions to N1.

All participants underwent a self-assessment of their sleep quality using the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) in its initial version (previous month) for HC and with an adapted version (previous week, to better reflect the different stages of alcohol treatment) for AUD patients. The Epworth Sleepiness Scale (ESS; Johns et al., 1991) was proposed to assess signs of daytime sleepiness in all participants.

Statistical analysis

To test the differences between HC and the two subgroups of AUD patients (mild-AWS and moderate-AWS), non-parametric Kruskall-Wallis's tests were conducted on demographical variables (age and education) and a Chi² test was performed to compare the sex ratio in each group. Mann-Whitney's tests were performed between mild-AWS and moderate-AWS for alcohol- and withdrawal-related variables. Non-parametric Kruskall-Wallis's tests were conducted on neuropsychological data and sleep measures followed by *post-hoc* comparisons (Mann-Whitney's tests) when appropriate. The statistical threshold was set to p <0.05.

Neuroimaging data were analyzed using SPM12 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). More precisely, we conducted voxel-based ANCOVAs to compare

GM volume between HC, mild-AWS and moderate-AWS patients, controlling for the intracranial volume. We corrected for multiple comparisons (family wise error (FWE), $p < 0.05$) with a minimal cluster size (k) of 60 voxels (200 mm^3). Then, comparisons between the two-subgroups of AUD patients were reported at $p < 0.001$ with a minimal cluster size (k) of 60 voxels (200 mm^3). Only results surviving a cluster-level correction are reported.

Finally, the relationships between GM volume, sleep variables and cognitive performance were examined in the entire group of AUD patients with Spearman's correlations. Only the variables for which we found a significant difference between mild-AWS and moderate-AWS were entered in the analyses. When we observed significant relationships between a sleep variable on the one hand and both a GM volume and a cognitive variable on the other hand, we performed causal mediation analyses to assess the directionality of the relationships. Mediations analyses allow to test whether the causal effect of an independent variable (X) on a dependent variable (Y) is explained by a mediating variable (M). In other words, X exerts its effects on Y because X affects M, which in turn, affects Y (Goldstone *et al.*, 2018). Applied to our study, two models were tested to determine i) whether GM volume mediates the relationships between sleep and cognitive performance or ii) whether sleep mediates the relationships between GM volume and cognition. These analyses were performed using the "mediation" R package (Tingley *et al.*, 2014). We reported the average direct effects (ADE) and average causal mediation effect (ACME) estimated using nonparametric bootstrapping (5000 simulations, $p < .05$) for each model.

Data availability

All data and materials used within this study will be made available, upon reasonable request, to research groups wishing to reproduce/confirm our results.

RESULTS

Comparisons between HC, mild-AWS and moderate-AWS patients

Demographical variables and anxiety-depression levels: Kruskall-Wallis tests with Group as a between-subject factor (HC, mild, moderate-AWS) did not reveal any significant effect of group for age ($H_{(2,104)} = 2.48$, $p = 0.29$) and education ($H_{(2,104)} = 4.24$, $p = 0.12$). A Chi²-test showed that sex ratio was similar between groups ($\chi^2 = 2.85$, $p = 0.24$). Kruskall-Wallis tests

showed a significant effect of group for depression ($H_{(2,103)} = 42$, $p < 0.0001$), anxiety-state ($H_{(2,102)} = 8.55$, $p = 0.01$) and anxiety-trait ($H_{(2,102)} = 32.83$, $p < 0.0001$). Mild-AWS and moderate-AWS were both more depressed than HC (all p -values < 0.0001) but did not differ from each other ($p = 0.85$). Only moderate-AWS differed from HC on the anxiety-state questionnaire ($p = 0.004$). Mild-AWS and moderate-AWS exhibited higher levels of anxiety-trait compared to HC (all p -values < 0.0001), but did not differ from each other ($p = 0.14$). Results are presented in **Table 1**.

Alcohol-related variables: A Kruskall-Wallis test showed a significant effect of group for the AUDIT score ($H_{(2,103)} = 76.97$, $p < 0.0001$). *Post-hoc* comparisons revealed, as expected, that mild-AWS and moderate-AWS patients presented higher AUDIT scores than HC (all p -values $= 0.0001$) but did not differ from each other ($p = 0.41$). Mann-Whitney U tests did not show any significant difference between mild-AWS and moderate-AWS for the duration of alcohol misuse ($U = 279,5$, $p = 0.73$) and dependence ($U = 265$, $p = 0.44$), but moderate-AWS reported a higher daily alcohol consumption than mild-AWS patients ($U = 191,5$, $p = 0.05$; **Table 1**).

Alcohol withdrawal variables: Mild-AWS and moderate-AWS patients had an equivalent number of previous detoxifications ($U = 265,5$, $p = 0.44$). As expected, compared to mild-AWS patients, moderate-AWS patients had experienced a higher maximum Cushman score ($U = 35,5$, $p < 0.0001$), had received more diazepam ($U = 0$, $p < 0.0001$) and during a longer period ($U = 0$, $p < 0.0001$; **Table 1**).

Pattern of cognitive alterations Kruskall-Wallis tests revealed a significant effect of group for processing speed ($H_{(2,104)} = 29.7$, $p < 0.0001$), short-term memory ($H_{(2,103)} = 12.68$, $p = 0.002$), executive functions ($H_{(2,104)} = 23.38$, $p < 0.0001$) and episodic memory ($H_{(2,104)} = 22.32$, $p < 0.0001$). *Post-hoc* comparisons indicated that mild-AWS patients presented lower performance than HC for episodic memory ($U = 148$, $p < 0.0001$) and processing speed ($U = 177$, $p = 0.0004$), but not for short-term memory ($U = 422$, $p = 0.97$) and executive performance ($U = 384.5$, $p = 0.56$). Compared to HC, moderate-AWS patients presented lower performance for all cognitive measures (all p -values < 0.001). Compared to mild-AWS patients, moderate-AWS patients had lower executive ($U = 154$, $p = 0.003$) and short-term memory performance ($U = 178.5$, $p = 0.01$), but did not differ for processing speed and episodic memory (all p values > 0.05 ; **Table 2** and **Fig. 1**).

Pattern of GM alterations: Mild-AWS patients did not differ from HC regarding GM volume

($p_{(FWE)} < 0.05$; **Fig. 2A**). Compared to HC, moderate-AWS patients had significantly lower GM volume in frontal and prefrontal areas, insula, lateral and medial temporal cortices (including the hippocampus and parahippocampal gyrus), cingulate and occipital cortices, cerebellum, and in subcortical regions including the thalamus, putamen, and caudate nuclei ($p_{(FWE)} < 0.05$; **Fig. 2B**). Compared to mild-AWS patients, moderate-AWS patients had significantly lower GM volume in the right inferior frontal cortex (Broadman area 44), the bilateral insula, a cluster encompassing the anterior cingulate cortex and the medial superior frontal cortex, occipito-parietal regions and limbic structures including the anterior part of the thalamus and the hypothalamus. All regions listed above are significant at $p < 0.001$ (uncorrected) threshold and survived the cluster-level correction $p < 0.05$; **Fig. 2C**). The reverse comparison (mild-AWS patients < moderate-AWS patients) did not reveal any significant result.

Pattern of sleep alterations: Non-parametric Kruskall-Wallis tests revealed a significant effect of group for both percentage of sleep stages N1 ($H_{(2, N=36)} = 11.81$ $p = 0.003$) and N3 ($H_{(2, N=36)} = 15.87$ $p = 0.0004$). *Post-hoc* comparisons (Mann-Whitney U tests) showed that compared to HC, mild-AWS patients had similar percentage of N1 ($p = 0.24$) and N3 sleep ($p = 0.52$). Compared to HC, moderate-AWS patients showed higher percentage of N1 ($p = 0.0006$) and lower percentage of N3 sleep ($p = 0.0002$). Compared to mild-AWS patients, moderate-AWS patients showed lower percentage of N3 sleep ($p = 0.004$; **Table 2** and **Fig. 3**).

A significant effect of group was observed for the apnea-hypopnea index (AHI) ($H_{(2, N=36)} = 7.99$ $p = 0.02$). *Post-hoc* comparisons showed that mild-AWS patients and moderate-AWS patients exhibited a higher AHI compared to controls ($p = 0.03$ and $p = 0.01$ respectively) but did not differ from each other ($p > 0.05$). No group differences were observed for sleep latency, duration, efficiency and wake after sleep onset (all p -values > 0.05). Results remained unchanged when controlling for the AHI (data not shown).

A significant effect of group was observed for the PSQI score ($H_{(2, N=30)} = 11.19$, $p = 0.004$). *Post-hoc* comparisons showed that compared to HC, moderate-AWS patients had a higher score ($p = 0.001$). Mild-AWS patients did not differ from HC and moderate-AWS patients (all p -values > 0.05). No group difference was observed on the ESS score (p -value > 0.05 ; **Table 2**).

Relationships between GM volume, sleep and cognitive performance in the entire group of AUD patients.

Signal values within the significant clusters obtained from the comparison mild-AWS > moderate-AWS were extracted. Then, we conducted Spearman's correlations between GM volumes, sleep variables and cognitive performance in the entire group of patients. Only variables for which we found a significant difference between mild-AWS and moderate-AWS patients were entered in these analyses (i.e. short-term memory performance, executive abilities and N3 sleep). Short-term memory performance positively correlated with GM volume in the insula ($\rho = 0.51$, $p = 0.01$), occipito-parietal cortex ($\rho = 0.62$, $p = 0.003$), inferior frontal gyrus ($\rho = 0.45$, $p = 0.04$) and thalamus/hypothalamus ($\rho = 0.45$, $p = 0.04$), but not in the anterior cingulate cortex ($p > 0.05$). Executive performance positively correlated with all significant clusters of GM volume (insula: $\rho = 0.7$, $p = 0.0004$; occipito-parietal cortex: $\rho = 0.66$, $p = 0.001$; anterior cingulate cortex: $\rho = 0.57$, $p = 0.007$; inferior frontal gyrus: $\rho = 0.53$, $p = 0.01$; thalamus/hypothalamus: $\rho = 0.64$, $p = 0.002$). GM volume in all significant clusters positively correlated with the percentage of N3 sleep (insula: $\rho = 0.52$, $p = 0.01$; occipito-parietal cortex: $\rho = 0.55$, $p = 0.009$; anterior cingulate cortex: $\rho = 0.43$, $p = 0.05$; inferior frontal gyrus: $\rho = 0.56$, $p = 0.008$; thalamus/hypothalamus: $\rho = 0.51$, $p = 0.02$). Moreover, the percentage of N3 sleep positively correlated with short-term memory ($\rho = 0.48$, $p = 0.03$) and executive performance ($\rho = 0.44$, $p = 0.04$).

To better understand the directionality of the relationships between GM volume, N3 sleep and cognitive performance, we conducted mediation analyses and tested two models for each cluster. In the first one (Model 1), N3 sleep was the independent variable (X) and GM volume in the 5 significant clusters reported in the previous analysis was the mediator (M). In the second model (Model 2), GM volume was the independent variable (X) and N3 sleep was the mediator (M). In both models, cognitive variables (short-term memory or executive scores) were entered as the dependent variable (Y). First, considering short-term memory performance as the dependent variable, mediation analyses referring to both Model 1 and 2 were not significant ($p > 0.05$; **Supplementary Table 1**). Second, considering executive functions performance as the dependent variable, mediation analyses revealed that the volume of the bilateral insula ($p=0.006$), right inferior frontal cortex ($p=0.02$), occipito-parietal cortex ($p=0.01$) and the cluster including the anterior thalamus and the hypothalamus ($p=0.02$) significantly mediated the relationships between the percentage of N3 sleep and executive performance. None of the analyses referring to Model 2 was significant. Results of these mediation analyses are detailed in **Table 3 and Fig. 4**.

DISCUSSION

The present study aimed at determining whether AWS severity contributes to the heterogeneity of sleep changes, brain alterations and cognitive deficits observed in AUD patients early in abstinence. We showed that AWS severity contributes to the pathophysiology of NREM sleep abnormalities, decrease GM volumes in fronto-insular and thalamus/hypothalamus regions as well as short-term memory and executive deficits in AUD patients early in abstinence. We also found that lower percentage of N3 sleep related to cognitive deficits (short-term memory and executive functions) both directly and indirectly via GM shrinkage in AUD patients.

We showed that 68% of AUD patients exhibited a moderate AWS, which is a higher prevalence than the one reported in a previous study (Mirijello *et al.*, 2015). In the present study, all patients were recruited in a special unit for alcohol detoxification. They were thus potentially at risk for AWS complications. Contrary to a previous study (Duka *et al.*, 2004) in which only patients with severe alcohol withdrawal complications were included, we did not observe any association between multiple detoxifications and the severity of the current AWS. We also found that AUD patients with moderate AWS reported higher alcohol consumption during the month preceding withdrawal than those with mild AWS. This result suggests that during withdrawal, the brain hyperexcitability resulting from increased glutamate transmission combined to decreased GABA transmission may be related to the quantity of recent alcohol drinking (De Witte *et al.*, 2003; Jesse *et al.*, 2017).

Our study first confirms the pattern of sleep alterations observed in recently detoxified AUD patients, consisting of increased light sleep (N1), a lower percentage of N3 sleep (Gillin *et al.*, 1990; Junghanns *et al.*, 2009; de Zambotti *et al.*, 2014, Irwin *et al.*, 2016a; Singh *et al.*, 2018) and the presence of a sleep complaint (Laniepce *et al.*, 2019). It also specifies that only patients with moderate AWS presented these objective sleep alterations, as well as self reported sleep difficulties. The difference observed between moderate- and mild-AWS patients for N3 sleep is in accordance with a previous study showing that the number of alcohol withdrawal symptoms was negatively related to the percentage of N3 sleep (Gillin *et al.*, 1990). Sleep changes may be directly related to AWS severity since N3 sleep has been associated with lower glutamate levels (Dash *et al.*, 2009). Even when the clinical symptoms of AWS have faded, a hyper-glutamate activity may persist and alter brain regions involved in the generation and

maintenance of sleep rhythms, resulting in lower percentage of N3 sleep (Dang-Vu, 2012). Sleep abnormalities observed in our group of moderate-AWS patients may thus be interpreted as a persistent subacute alcohol withdrawal symptom (Brower, 2001; Feige *et al.*, 2007).

AWS severity was also related to structural brain alterations in the right inferior frontal cortex, the bilateral insula, the anterior cingulate cortex and the thalamus/hypothalamus, which are brain regions known to be affected in AUD patients (Pitel *et al.*, 2012; Yang *et al.*, 2016). Regarding the effect of AWS severity on the anterior cingulate cortex, studies using magnetic resonance spectroscopy reported increased glutamate levels in this brain region during alcohol withdrawal in both humans and rats (Lee *et al.*, 2007; Hermann *et al.*, 2012). Several studies suggested that the extent of structural brain abnormalities in AUD patients may be partially explained by alcohol withdrawal-related toxicity (De Witte *et al.*, 2003; Duka *et al.*, 2011; O'Daly *et al.*, 2012; Trick *et al.*, 2014; Frischknecht *et al.*, 2017). During alcohol withdrawal, the glutamate-mediated excitotoxicity induces neuronal death, which may explain structural brain alterations observed early in abstinence in AUD patients (Tsai and Coyle, 1998). The frontal lobes being particularly rich in glutamatergic pathways (Kril *et al.*, 1997), they are likely to be especially vulnerable to the severity of AWS. However, we do not exclude that these brain alterations may have been present before alcohol cessation because of the effects of chronic and heavy alcohol consumption or a family history of AUD or comorbidities such as liver disease or thiamine deficiency (Harper, 2009; Chen *et al.*, 2012; Filippi *et al.*, 2019). In this case, altered brain structure would constitute a vulnerability factor for exhibiting more severe AWS. Further studies including longitudinal measures of glutamate levels combined with structural MRI at different stages of the disease (active drinking, withdrawal period and abstinence) are now required.

Regarding cognitive abilities, our findings indicate that AWS severity may have deleterious effects on short-term memory and executive performance. While short-term memory deficits have previously been reported in AUD patients (Pitel *et al.*, 2007), we suggest here that AWS may contribute to this alteration. Executive dysfunctions are frequent in AUD patients early in abstinence (Stavro *et al.*, 2013) and could notably be influenced by alcohol history (Sullivan *et al.*, 2000; Zinn *et al.*, 2004; Maurage *et al.*, 2014), associated liver disease (Ritz *et al.*, 2016) and multiple detoxifications (Duka *et al.*, 2004; Loeber *et al.*, 2009). The present study suggests that beyond the repetition of alcohol withdrawals, the severity of AWS itself may represent another factor influencing the heterogeneity of executive impairments in AUD patients. By contrast, AWS severity does not appear to modulate processing speed and episodic memory deficits. Indeed, episodic memory was affected to the same extent in the two

subgroups of patients. Previous studies suggested that episodic memory abilities may rather be influenced by thiamine metabolism (Pitel *et al.*, 2011; Ritz *et al.*, 2016).

Mediation analyses enabled us to deepen our understanding of the relationships between sleep, brain and cognition considering the severity of AWS. For the first time, we showed that poor restorative sleep (reflected by a lower percentage of N3 sleep) is related to cognitive deficits both directly and indirectly through GM shrinkage. In line with a previous study in sleep-deprived individuals (Chengyang *et al.*, 2017), we demonstrated that poor restorative sleep is associated with short-term memory deficits in AUD patients. This relationship was not mediated by GM alterations, suggesting the potential contribution of other mechanisms such as altered functional activity of hippocampal-cortical circuits (Chengyang *et al.*, 2017). Interestingly, we found that poor restorative sleep contributes to fronto-insular shrinkage that in turn results in executive deficits. Our results suggest a potential role of sleep in the pathophysiological mechanisms of alcohol-related GM alterations in AUD patients. Poor sleep quality may result from alcohol-related brain damage such as increased glutamate levels (Cortese *et al.*, 2010), neuroinflammation (Irwin *et al.*, 2016b) and oxidative stress (Villafuerte *et al.*, 2015). These mechanisms may contribute to fronto-insular and thalamic/hypothalamic abnormalities in AUD patients recently detoxified. Fronto-insular regions, such as the right inferior frontal gyrus, have been related to executive deficits, notably during inhibition tasks (Levy and Wagner, 2011; Aron *et al.*, 2014; Wiers *et al.*, 2015). The insula promotes the integration and representation of interoceptive information into conscious feelings and viscerosensory signals leading to decision making (Craig, 2009). The insula being also a neuronal substrate of craving, insular shrinkage may underpin the relationship between sleep alterations and relapse (Brower, 2003). Thus, these analyses seem to explain, at least partially, the potential associations existing between sleep, brain and cognition in AUD patients, by showing that N3 sleep contributes to GM shrinkage in fronto-insular and thalamus/hypothalamus regions resulting in executive deficits. We do not exclude that, on the contrary, alterations in other brain regions may induce sleep abnormalities that, in turn, underlie cognitive functioning.

The present study has several strengths, including a meticulous collection of information about AWS severity associated with a detailed cognitive assessment, an MRI scan and an objective sleep assessment in AUD patients examined early in abstinence. However, several limitations should be mentioned. First, the results of the present study were obtained in AUD

patients without comorbidities nor other forms of substance use disorder (except tobacco). They cannot therefore be generalized to all AUD patients in Addiction departments given the frequency of comorbidities and multiple drug use. Second, all participants performed only one night of PSG-recording, which did not allow to control for “the first-night effect”. Third, although none of the AUD patients included in the present study fulfilled diagnostic criteria for current anxiety disorder and/or depression, higher self-report anxiety and depressive levels were reported by AUD patients compared to HC. Psycho-affective factors may influence sleep quality and cognitive performance in AUD patients as these factors are known to have a negative impact on neuropsychological abilities (Gualtieri and Morgan, 2008) and sleep quality (Baglioni *et al.*, 2016). Nevertheless, the two groups of AUD patients did not differ from each other on these variables and results remained unchanged when psycho-affective factors (BDI, STAI-A, STAI-B scores) were added as covariates (data not shown). Finally, the current clinical measure of AWS severity makes it difficult to disentangle the direct effect of pathophysiological mechanisms underlying AWS (hyperglutamatergic) from the potential effect of AWS-related benzodiazepine treatment. AWS severity was treated with benzodiazepines, corresponding to the gold-standard for AWS treatment (Amato *et al.*, 2010). Benzodiazepines are known to alter objective sleep quality and cognitive functions after an acute administration (Huron *et al.*, 2001; Deakin *et al.*, 2004; Roux and Kryger, 2010) and/or after a chronic consumption (Barker, 2004; Doghramji and Jangro, 2016; Fond *et al.*, 2018). In the present study, AUD patients with benzodiazepine dependence prior the hospitalization were not included and patients who needed benzodiazepines during withdrawal were prescribed for only a few days (4-17 days). In addition, patients were included at least 48 hours after the last benzodiazepine prescription (according to the half-life of the benzodiazepine used), after a progressive decrease of the benzodiazepine dosage starting when the Cushman score was lower or equal to 2 for at least 24 hours, at a rate of 15 to 30% of the total dose every 24 to 48 hours. Since prolonged diazepam intake may increase its terminal elimination time, we conducted supplementary analyses that did not show any correlation between the number of days since the last benzodiazepine prescription and our main results (**Supplementary Table 2**). This absence of relationship suggests that the differences observed between mild- and moderate-AWS patients do not result from the residual effects of benzodiazepines. However, further studies are required to specify the effects of short-term prescription of benzodiazepines on sleep quality, GM volumes and cognition in AUD patients.

Taken together, our results bring new insights on the pathophysiological mechanisms of sleep, structural brain alterations and cognitive deficits observed in recently detoxified AUD patients, showing the contribution of AWS severity. Moreover, we added novel evidence that poor sleep quality may contribute to cognitive deficits directly or indirectly through increased GM shrinkage in AUD patients early in abstinence. Further studies aiming at exploring brain, sleep or cognition in AUD patients should consider AWS severity to limit the heterogeneity of the AUD sample. For clinicians, these results suggest that a careful monitoring of AWS is not only useful to prevent the development of severe AWS complications, but also to predict sleep alterations, brain damage and cognitive deficits associated with a poor treatment outcome.

Acknowledgments:

The authors are grateful to the Cyceron MRI staff members for their help with patients and imaging examination acquisition, and Coralie Lannuzel, Stéphane Rehel, Ludivine Ritz and Hélène Beaunieux for their help at various stages of the study. We would also like to thank all the participants.

Funding:

This work was supported by the French National Institute for Health and Medical Research (INSERM), the French National Agency for Research (ANR), and Conseil Regional de Normandie. Alice Lanepce's doctoral fellowship was co-funded by European Union in the framework of the ERDF-ESF Operational Programme 2014-2020 and Lundbeck.

Competing interests:

The authors report no competing interests.

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Figures legends:

Figure 1: Neuropsychological performance according to the severity of the alcohol withdrawal syndrome.

Z-scores were computed based of the mean and standard deviation of the HC (mean=0; standard deviation=1).

*: significant difference compared to HC.

†: significant difference compared to mild-AWS patients.

Figure 2: Structural brain abnormalities in AUD patients with mild and moderate alcohol withdrawal syndrome (AWS) compared to controls.

A: Absence of gray matter (GM) atrophy in mild-AWS patients compared to healthy controls (HC). B: Pattern of GM atrophy in moderate-AWS patients compared to HC. Results are presented at $p < 0.05$ corrected for family-wise-error (FWE). C: Brain areas showing lower GM volume in AUD-moderate patients compared to AUD-mild patients. Results are presented at $p < 0.001$ (uncorrected) but only results surviving a cluster-level correction are reported. Minimum cluster size: > 60 voxels.

Figure 3: Time spent in each sleep stage expressed as a percentage of total sleep time according to the severity of the alcohol withdrawal syndrome

*: significant difference compared to HC.

†: significant difference compared to mild-AWS patients.

Figure 4: Results of mediation analyses showing that brain volume mediates the relationships between sleep and executive functions in recently detoxified AUD patients.

Direct effects in filled arrows and indirect effects were represented in dotted arrows (when the effect of brain volume is partially out).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. n.s, non-significant.

Tables legends:

Table 1: Demographic, clinical and alcohol-related data in healthy controls and AUD patients.

Abbreviations: HC, Healthy Controls; AUD, Alcohol Use Disorder patients; mild-AWS (Cushman \leq 4), moderate-AWS (Cushman $>$ 4 or the presence of a history of severe alcohol withdrawal history); BDI, Beck Depression scale

Data were analyzed using non-parametric tests for demographic, alcohol- and withdrawal related variables and cognitive functions. Groups effects were tested with Kruskall-Wallis tests and *post-hoc* comparisons were performed using Mann-Whitney U tests. We used a Chi² test to compare the sex ratio in each group.

^a: correlations between daily alcohol consumption on the one hand, and sleep quality, brain volume, and cognitive abilities on the other hand were not significant neither in the entire group of AUD patients, nor in the two subgroups (data not shown).

*: Missing value for one patient

**: Missing value for two patients

NS: non-significant ; \dagger : $p < 0.05$; \ddagger : $p < 0.01$; $\ddagger\ddagger$: $p < 0.001$

Table 2: Cognitive performance and sleep variables in healthy controls and AUD patients.

Abbreviations: see legend of Table 1. PSQI : Pittsburg Sleep Quality Index; ESS : Epworth Severity Scale.

^a: For sleep analyses, subgroups consisted of 15 HC, 8 mild-AWS and 13 moderate-AWS patients. Data were analyzed using non-parametric tests: groups effects were tested with Kruskall-Wallis ANOVAs and *post-hoc* comparisons were performed using Mann-Whitney U test.

*Missing data for one patient ; **Missing data for six AUD patients.

NS: non-significant; \dagger : $p < 0.05$; \ddagger : $p < 0.01$; $\ddagger\ddagger$: $p < 0.001$

Table 3: Mediation analyses between %N3 sleep, GM volumes and executive functioning in AUD patients.

Abbreviations: ADE: average direct effect; ACME: average causal mediation effect; CI: confidence interval.

For the 5 GM clusters, two models were tested. In the first one (Model 1), the percentage of N3 sleep was the independent variable and the GM volume was the mediator. In the second model (Model 2), GM volume was the independent variable and the percentage of N3 sleep was the mediator. In all models, executive functions were entered as the dependent variable. Values in bold accompanied by a “*” indicate the significance of the model.

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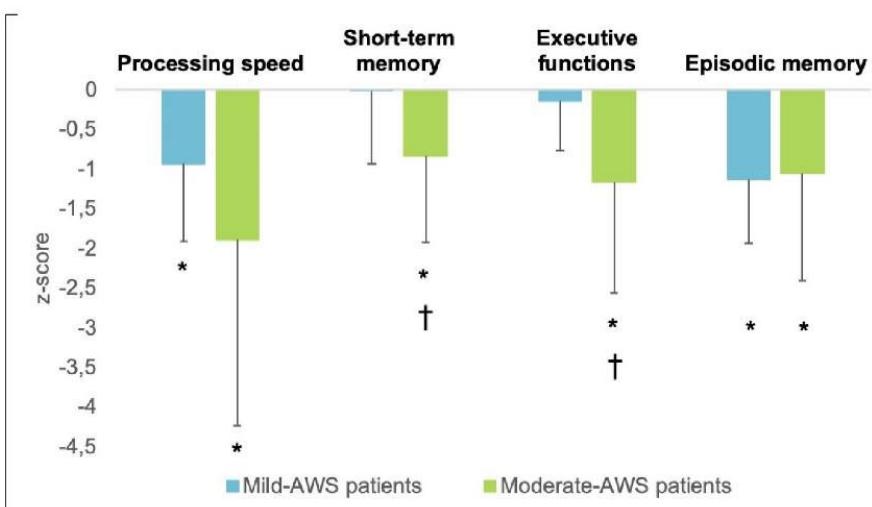


Figure 1: Neuropsychological performance according to the severity of the alcohol withdrawal syndrome.

Z-scores were computed based of the mean and standard deviation of the HC (mean=0; standard deviation=1).

*: significant difference compared to HC.

†: significant difference compared to mild-AWS patients.

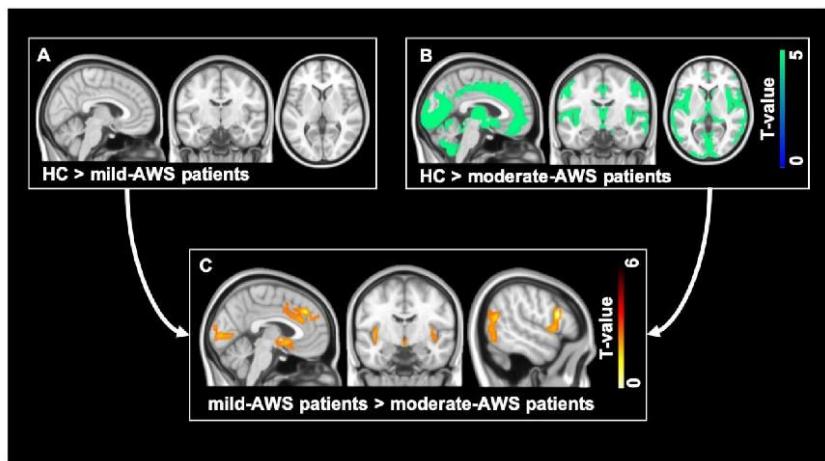


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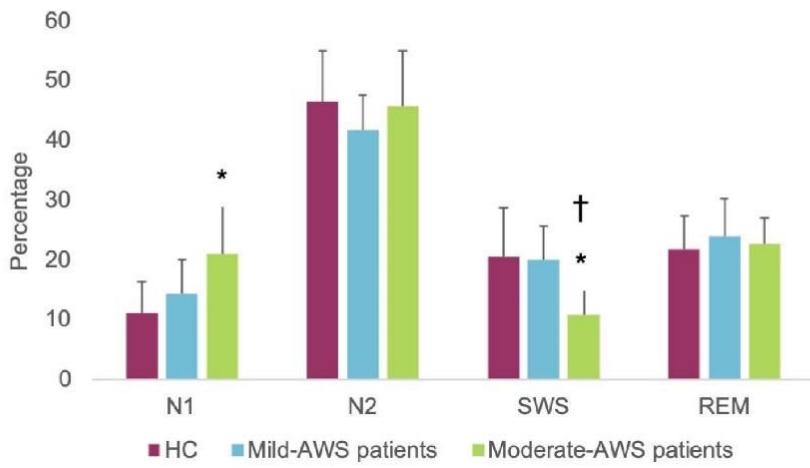


Figure 3: Time spent in each sleep stage expressed as a percentage of total sleep time according to the severity of the alcohol withdrawal syndrome

*: significant difference compared to HC.

†: significant difference compared to mild-AWS patients.

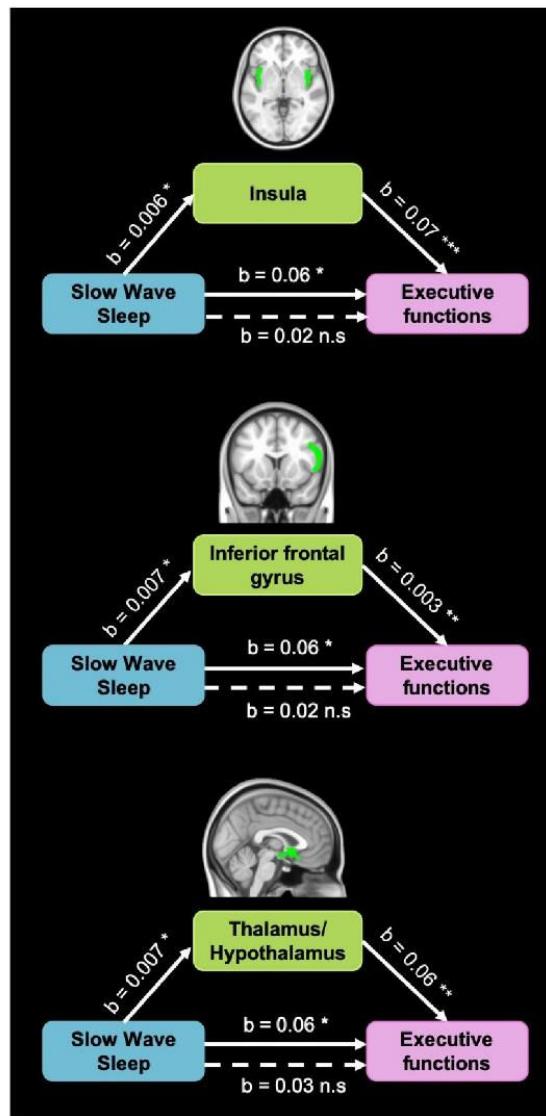


Figure 4: Results of mediation analyses showing that brain volume mediates the relationships between sleep and executive functions in recently detoxified AUD patients.

Direct effects in filled arrows and indirect effects were represented in dotted arrows (when the effect of brain volume is partially out).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. n.s, non-significant.

Table 1: Demographic, clinical and alcohol-related data in healthy controls and AUD patients.

	Healthy controls			Alcohol Use Disorder patients			Between-group comparisons
	HC (N=50)	mild-AWS (n=17)	moderate-AWS (n=37)				
Demographics							
Age (years)	44.02 ± 7.79	45.53 ± 11.36	46.86 ± 8.12				NS
Education (years)	12.30 ± 2.07	11.5 ± 2.18	11.69 ± 2.13				NS
Sex ratio (M/F)	34/16	13/4	31/6				NS
Anxiety and depression factors							
BDI score ^a	3.52 ± 3.99	12.29 ± 8.15	13.28 ± 8.96	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS			
STAI A (state anxiety) ^{**}	26.53 ± 5.72	31.82 ± 11.97	32.05 ± 10.59	HC < mild-AWS ^{††} , HC < moderate-AWS ^{††} , mild-AWS = moderate-AWS			
STAI B (trait anxiety) ^{**}	32.22 ± 6.84	49.18 ± 12.21	43.59 ± 11.28	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS			
Alcohol history							
Abstinence before inclusion (days) [*]	-	8.76 ± 3.73	11.22 ± 3.48	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
AUDIT [*]	2.60 ± 1.81	28.06 ± 5	28.89 ± 6.24	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Daily alcohol consumption (units)	-	15.63 ± 7.67	20.34 ± 8.39	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Alcohol misuse (years)	-	21.37 ± 10.16	20.62 ± 10.17	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Alcohol dependency (years)	-	13 ± 10.03	11.94 ± 11.47	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Alcohol withdrawal history							
Number of days between last benzodiazepines administration and inclusion	-	-	2.78 ± 1.24	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Number of previous detoxifications	-	1.94 ± 0.82	2.53 ± 1.70	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Highest Cushman score	-	2.88 ± 0.92	5.86 ± 1.81	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Total amount of benzodiazepine (equivalent diazepam) received (mg)	-	0 ± 0	294.83 ± 221.82	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			
Number of days of benzodiazepine prescription	-	0 ± 0	9.05 ± 3.26	HC < mild-AWS ^{†††} , HC < moderate-AWS ^{†††} , mild-AWS = moderate-AWS [†]			

Abbreviations: HC, Healthy Controls; AUD, Alcohol Use Disorder patients; mild-AWS (Cushman ≤ 4), moderate-AWS (Cushman > 4 or the presence of a history of severe alcohol withdrawal history); BDI, Beck Depression scale

Data were analyzed using non-parametric tests for demographic, alcohol- and withdrawal related variables and cognitive functions. Groups effects were tested with Kruskall-Wallis tests and *post-hoc* comparisons were performed using Mann-Whitney U tests. We used a Chi² test to compare the sex ratio in each group.

^a: correlations between daily alcohol consumption on the one hand, and sleep quality, brain volume, and cognitive abilities on the other hand were not significant neither in the entire group of AUD patients, nor in the two subgroups (data not shown).

*: Missing value for one patient

**: Missing value for two patients

NS: non-significant; [†]: p < 0.05; ^{††}: p < 0.01; ^{†††}: p < 0.001

Table 2: Cognitive performance and sleep variables in healthy controls and AUD patients.

	Healthy controls (HC)		Alcohol Use Disorder patients (AUD)		Between-group comparisons
	HC (N=50)	mild-AWS (n=17)	mild-AWS (n=27)	moderate-AWS (n=27)	
Cognitive functions (z-score)					
<i>Processing speed</i>	0 ± 1	-0.62 ± 1.13	-0.97 ± 1.49	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>Short term memory</i>	0 ± 1	-0.007 ± 0.93	-0.82 ± 1.09	HC = non-significant; HC > moderate-AWS ^{††}	
<i>Executive functions</i>	0 ± 0.64	-0.13 ± 0.62	-1.15 ± 1.40	HC = non-significant; HC > moderate-AWS ^{††}	
<i>Episodic memory*</i>	0 ± 1	-1.12 ± 0.80	-0.95 ± 1.25	HC = non-significant; HC > moderate-AWS ^{†††} ; HC > moderate-AWS ^{††} ; HC = non-significant	
Sleep architecture^a					
<i>Sleep latency (min)</i>	29.07 ± 17.71	14.06 ± 14.18	24.81 ± 15.11	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>Total sleep time (min)</i>	384.57 ± 53.75	376.87 ± 61.48	381.73 ± 69.30	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>Sleep efficiency, %</i>	80.95 ± 6.87	88.54 ± 8.72	80.78 ± 7.54	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>Wake after sleep onset (min)</i>	61.03 ± 31.53	37.19 ± 34.14	64.23 ± 40.65	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>NP%</i>	11.15 ± 5.22	14.31 ± 5.72	20.91 ± 8.19	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>N2%</i>	46.49 ± 8.53	41.7 ± 5.78	45.63 ± 9.39	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>N3%</i>	20.56 ± 8.15	20.08 ± 5.55	10.71 ± 4.60	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>REM%</i>	21.79 ± 5.50	23.85 ± 6.41	22.75 ± 4.19	HC > mild-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>Apnea-hypopnea index (AHI)</i>	13.59 ± 8.16	24.82 ± 13.57	26.77 ± 10.71	HC < mild-AWS ^{†††} ; HC < moderate-AWS ^{†††} ; HC = non-significant	
<i>Composite sleep fragmentation</i>	0 ± 0.85	-0.33 ± 0.96	-0.85 ± 1.18	HC < mild-AWS ^{†††} ; HC < moderate-AWS ^{†††} ; HC = non-significant	
<i>Subjective sleep assessment^a</i>					
<i>PSQI total score^{a,b}</i>	2.13 ± 1.35	7 ± 4.9	5.9 ± 2.64	HC = non-significant; HC < moderate-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	
<i>ESS total score</i>	4.78 ± 2	6.37 ± 2.33	3.92 ± 2.56	HC = non-significant; HC < moderate-AWS ^{†††} ; HC > moderate-AWS ^{†††} ; HC = non-significant	

Abbreviations: see legend of Table 1. PSQI : Pittsburgh Sleep Quality Index; ESS : Epworth Severity Scale;

Data were analyzed using non-parametric tests; groups effects were tested with Kruskall-Wallis tests and *post-hoc* comparisons were performed using Mann-Whitney U test.^a: For sleep analyses, subgroups consisted of 15 HC, 8 mild-AWS and 13 moderate-AWS patients.^b: Missing data for one patient. **Missing data for six AUD patients. NS: non-significant; [†]: p < 0.05; ^{††}: p < 0.01; ^{†††}: p < 0.001

Table 3: Mediation analyses between %N3 sleep, GM volumes and executive functioning in AUD patients.

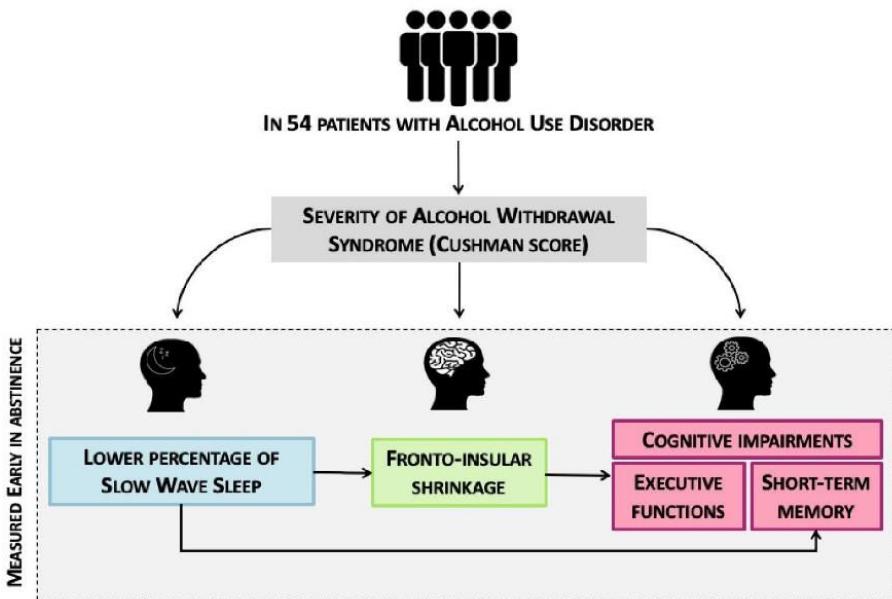
Brain areas	Model	ADE			ACME		
		Estimate	CI95%	P-value	Estimate	CI95%	P-value
Bilateral insula	Model 1	0.02	-0.03-0.09	0.47	0.04	0.01-0.09	0.006*
	Model 2	7.05	3.01-9.91	0.003	0.69	-1.18-3.61	0.46
Right inferior frontal gyrus	Model 1	0.02	-0.05-0.10	0.51	0.04	0.004-0.10	0.02*
	Model 2	5.98	0.92-10.95	0.02	0.99	-3.06-4.34	0.56
Cingulate anterior gyrus	Model 1	0.04	-0.02-0.11	0.22	0.02	-0.007-0.07	0.11
	Model 2	3.57	-0.83-7.37	0.08	1.15	-1.01-4.13	0.24
Anterior thalamus/hypothalamus	Model 1	0.02	-0.04-0.10	0.47	0.03	0.004-0.10	0.02*
	Model 2	5.71	1.56-10.23	0.008	0.90	-2.16-3.23	0.47
Occipito-parietal cortex	Model 1	0.02	-0.04-0.09	0.56	0.05	0.008-0.10	0.02*
	Model 2	7.77	1.82-12.74	0.02	0.96	-2.95-4.98	0.54

Abbreviations: ADE: average direct effect; ACME: average causal mediation effect; CI: confidence interval.

For the 5 GM clusters, two models were tested. In the first one (Model 1), the percentage of N3 sleep was the independent variable and the GM volume was the mediator. In the second model (Model 2), GM volume was the independent variable and the percentage of N3 sleep was the mediator. In all models, executive functions were entered as the dependent variable. Values in bold accompanied by a “*” indicate the significance of the model.

Abbreviated summary

Even in the absence of severe alcohol withdrawal syndrome, moderate alcohol withdrawal syndrome was associated with a lower percentage of slow-wave sleep, which related to cognitive deficits both directly and indirectly via gray matter shrinkage. Alcohol withdrawal syndrome severity seems to contribute to the pathophysiology of brain, sleep and cognitive damage in alcohol use disorder patients.



Graphical abstract

71x48mm (300 x 300 DPI)

Titre : Atteintes cognitives et cérébrales dans le trouble de l'usage d'alcool et le syndrome de Korsakoff : valeur pronostique, évolution et prise en charge.

Résumé : Le trouble de l'usage d'alcool (TUAL) est associé à des atteintes cérébrales et cognitives. Ces altérations empêchent les patients de bénéficier des prises en charges psychosociales et augmentent le risque de rechute. Une réversibilité de ces atteintes est possible avec l'abstinence et a été mise en évidence dans le TUAL. En revanche, les patients présentant un syndrome de Korsakoff (SK) ont une amnésie antérograde sévère qui est considérée comme irréversible, même si l'évolution cognitive et cérébrale de ces patients est peu documentée. L'objectif de cette thèse est donc d'étudier la valeur pronostique, l'évolution ainsi que la prise en charge des atteintes cognitives et cérébrales dans le TUAL et le SK. Nos résultats montrent que l'alexithymie et les altérations des systèmes limbique et fronto-cérébelleux observés post-sevrage sont des facteurs de mauvais pronostic du statut addictologique au cours de l'année post-sevrage. Nous montrons qu'après le sevrage, un court séjour en soins de suite et de réadaptation permet une amélioration, voire même une normalisation des fonctions cognitives. Une prise en charge intensive, incluant des ateliers de stimulation cognitive pendant ce séjour, semble favoriser la récupération. Nos résultats ont mis en évidence que chez les patients SK, les déficits sévères de mémoire épisodique sous-tendus par des altérations du circuit de Papez, persistent avec le temps. Les atteintes des fonctions exécutives et du circuit fronto-cérébelleux peuvent récupérer de manière limitée. Ces résultats soulignent la nécessité d'évaluer les atteintes cognitives et cérébrales ayant une valeur pronostique pour la rechute. Ils indiquent également l'importance d'adapter la prise en charge afin de favoriser la récupération cognitive dans le TUAL ou de compenser les troubles mnésiques persistants et invalidants dans le SK.

Title: Cognitive impairments and brain alteration in alcohol use disorder and Korsakoff's syndrome: prognostic value, changes over time, and rehabilitation.

Abstract: Alcohol use disorder (AUD) is characterized by brain damage and cognitive deficits. These alterations hinder AUD patients to benefit from psychosocial treatment and increase the risk of relapse. It is now clear that cognitive deficits and brain abnormalities can be reversible with drinking cessation in AUD. However, patients with Korsakoff's syndrome (KS) are described as exhibiting a severe anterograde amnesia supposed to persist over time, even though longitudinal studies in KS patients are very rare. The objective of this thesis is to examine the prognostic value, changes over time, and rehabilitation of the cognitive impairments and brain alterations in AUD and KS. Our results suggest that alexithymia, as well as alteration of limbic and frontocerebellar systems observed early in abstinence, contribute to a poor prognosis regarding alcohol status within the year following detoxification. We highlight that, after detoxification, a short stay as inpatient in a convalescent home favors cognitive improvement, and even a return to a normal level of performance. During this stay, an intensive care including neuropsychological training seems to favor the recovery. Finally, our results indicate that in KS patients, severe memory impairments, sustained by Papez circuit alterations, persist over time. Executive deficits and damage of the fronto-cerebellar circuit may recover but to a limited extent. These results emphasize the need to assess cognitive and brain alteration that have a prognostic value regarding treatment outcome. Results also encourage adapting treatment to favor recovery in AUD, or to compensate for persisting memory impairments in KS.

Mots clés : Trouble de l'usage d'alcool ; Syndrome de Korsakoff ; Neuroimagerie ; Cognition ; Longitudinal

Discipline : Psychologie

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