Université de Montréal

Associations entre les consommations d'alcool et de cannabis et les variations volumétriques chez l'adulte et lors de l'adolescence, et évaluation des différences sexuelles potentielles

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Ce mémoire intitulé

Associations entre les consommations d'alcool et de cannabis et les variations volumétriques chez l'adulte et lors de l'adolescence, et évaluation des différences sexuelles potentielles

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Résumé

Objectifs : Les différences structurelles associées aux troubles d'usage d'alcool (TUA) et de cannabis (TUC) sont inconsistantes dans la littérature, et les chercheurs ont du mal à cerner si des différences entre les sexes (DS) structurelles observées chez des patients TUA et TUC existent. De plus, le lien longitudinal entre la consommation d'alcool et de cannabis durant l'adolescence et le développement cérébral est indéterminé. Le premier objectif est de caractériser les différences structurelles entre les patients TUA ou TUC et leurs témoins et de comparer ces différences cas-témoins à celles observées dans d'autres troubles psychiatriques. Le deuxième objectif est d'évaluer les DS structurelles chez les patients TUA et TUC par rapport à leurs témoins. Le troisième objectif est d'évaluer la relation entre la consommation d'alcool et de cannabis et le développement cérébral durant l'adolescence sur une période de cinq ans. **Méthodes :** Des méta-analyses sur des larges échantillons de TUA (k = 7, N = 798) et de TUC (k = 7, N = 447) ont été réalisées à partir de la base de données sur des adultes et des adolescents du groupe de travail ENIGMA-Addiction pour a) comparer les différences structurelles observées entre les cas et témoins dans les TUA et TUC à celles observées dans d'autres conditions psychiatriques et b) évaluer les DS structurelles dans les TUA et TUC en évaluant des termes d'interaction et en stratifiant les analyses par sexe. La base de données Neuroventure (N = 130), une cohorte d'adolescents âgés de 13 ans et suivis sur une période de cinq ans, a été utilisée afin d'évaluer comment la beuverie et le cannabis sont associés à des DS structurelles chez l'adolescent. Les résultats sur ces deux bases de données ne sont pas directement comparés puisqu'elles ne se concentrent pas sur la même population. **Résultats :** Des réductions volumétriques observées dans les TUA et TUC sont semblables à celles des autres conditions psychiatriques comparées. Des réductions volumétriques spécifiques à l'un des deux sexes et communes aux deux sexes ont également été observées pour les TUA et TUC. Finalement, des variations volumétriques sous-corticales et d'épaisseurs corticales ont été associées spécifiquement à la consommation simultanée et décalée d'alcool et de cannabis. **Conclusions :** Bien qu'aucune direction causale n'a pu être déterminée dans ces trois articles, ces résultats contribuent au développement des connaissances sur les DS structurelles et les mécanismes neurobiologiques impliquées dans les dépendances chez l'adulte et les effets de l'alcool et le cannabis sur le développement adolescent,

notamment dans l'hippocampe. Les DS structurelles observées sont importantes afin d'éviter de généraliser les différences structurelles observées entre les cas et témoins associées à la consommation de substance aux deux sexes.

Mots-clés : neuroimagerie, différences sexuelles, dépendance, alcool, cannabis, adultes, adolescents

Abstract

Objectives: Structural differences associated with alcohol use disorders (AUD) and cannabis use disorders (CUD) are inconsistent in the literature, and researchers have difficulty identifying whether structural sex differences (SDs) observed in AUD and CUD patients occur. In addition, the longitudinal relationship between alcohol and cannabis use during adolescence and brain development is unclear. The first objective is to characterize the structural differences between AUD or CUD patients and their controls and to compare these case-control differences with those observed in other psychiatric disorders. The second objective is to assess the structural SDs in AUD and CUD patients compared to their controls. The third objective is to assess the relationship between alcohol and cannabis use and brain development during adolescence over a five-year period. **Methods:** Meta-analyses were performed on large samples for alcohol (k = 7, N = 798) and cannabis (k = 7, N = 447) use disorders based on the ENIGMA-Addiction working group dataset that includes adolescents and adults to a) compare structural differences in AUD and CUD patients compared to controls to those reported in other psychiatric conditions, and b) evaluate SSD in AUD and CUD by evaluating interaction terms and by performing sex-stratified analyses. The Neuroventure dataset (N = 130), a cohort of 13 year-old adolescents followed one a five-year period, was used to evaluate how adolescent binge-drinking and cannabis use were associated with SSD in brain structures and cognitive performance. The results on these two datasets are not directly compared since they do not focus on the same population of interest. **Results:** Reduced volumes were observed in AUD and CUD with effect sizes in general similar to those reported in the other compared psychiatric disorders. Male- and female-specific and non-sex specific case-control differences were also observed in AUD and CUD. Finally, reduced subcortical volumes and cortical thickness were associated with drug- and sex-specific parameters through adolescence. **Conclusion:** Although no causal direction was evaluated in the three articles, these results contribute to a better understanding of the impact of alcohol and cannabis misuse on the SSD occurring in the adult and adolescent brain, notably in the hippocampus. The observed sex differences are important to avoid generalizing the substance use-related structural abnormalities to both sexes.

Keywords: neuroimaging, sex differences, addiction, alcohol, cannabis, adults, adolescents

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Liste des abbréviations

Abbréviations de termes français

TUS : Trouble d'usage de substance

TUA : Trouble d'usage d'alcool

TUC : Trouble d'usage de cannabis

ISFH : Institut de la santé des femmes et des hommes

DS : Différence entre les sexes

ARNm: acide ribonucléique messager

CB1: récepteur cannabinoide de type 1

THC: Δ9-Tetrahydrocannabinol

IRM: Imagerie par résonance magnétique

Abbréviations de termes anglais

SUD : Substance use disorder

DALYs : Disability-adjusted life years

AUD: Alcohol use disorder

CUD: Cannabis use disorder

SSD : Structural sex differences

MDD: Major depressive disorders

SCZ: Schizophrenia

BD: Bipolar disorders

ADHD : Attention-Deficit/Hyperactivity Disorder

ENIGMA: Enhancing Neuroimaging Genetics through Meta-Analysis

MRI : Magnetic Resonance Imaging

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Introduction

Troubles d'usage de substance

Les troubles liés à la consommation de substances (TUS) sont des troubles psychiatriques caractérisés par une consommation persistante d'une substance malgré les dommages et les conséquences aversives selon la dernière édition du Manuel diagnostique et statistique des troubles mentaux[1]. L'étude du «Global Burden of Disease» en 2010 a évalué le poids relatif de différents troubles psychiatriques et neurologiques à l'échelle internationale. Dans une perspective de pouvoir comparer le poids relatif sociétal et humain des différents troubles, les chercheurs ont estimé le nombre d'années de vie affectées pour chaque condition (DALY) [2]. La charge de morbidité des TUS a fait état de taux élevés de DALY associés aux troubles d'usages d'alcool (TUA) et d'autres TUS [3,4]. Bien que ces résultats soient influencés par les taux de prévalence pour les troubles psychiatriques[5], les taux de DALY liés aux TUS nous informent sur l'impact humain associé à ces conditions. Il est intéressant de noter que ce rapport a également observé que les hommes avaient taux de DALYs supérieurs à ceux des femmes pour les TUS, et ce dans tous les groupes d'âge[4]. Étant donné que l'alcool et le cannabis sont parmi les substances les plus consommées à travers le monde, une meilleure compréhension de l'étiopathologie des AUD et des troubles d'usage de cannabis (TUC) pourrait contribuer à comprendre les mécanismes sous-jacents à de telles disparités en termes de DALY entre les hommes et les femmes.

La consommation d'alcool et de cannabis chez les adolescents est un problème de santé publique qui a pris de l'ampleur au cours des dernières années puisque certaines études ont rapporté la transition potentielle de l'usage récréatif vers les troubles liés à la consommation de substance[6, 7]. L'alcool est l'une des substances les plus couramment utilisées par les adolescents et la prévalence de la consommation excessive d'alcool est de 14% au niveau mondial, avec des pourcentages de consommation d'alcool au cours du dernier mois plus élevé chez les adolescents en Amérique du Nord[8]. De récentes études épidémiologiques ont fait état d'une plus grande fréquence de consommation de cannabis chez un nombre accru d'adolescents ainsi que d'une hausse de la fréquence annuelle de consommation chez les adolescents [9, 10]. Ces observations

peuvent s'avérer inquiétantes face aux changements juridiques sur le statut accordé à la consommation de cannabis, ainsi que sa disponibilité, dans différentes régions d'Amérique du Nord au cours de la dernière décennie.

Différences sexuelles

Dans le contexte de ce mémoire, les différences entre les sexes (DS) chez les adultes et chez les adolescents ont un rôle central afin d'élucider comment les DS se manifestent dans ces deux groupes d'âge différent dans le contexte de consommations d'alcool et de cannabis.

Définition

Au cours des dernières années, les progrès récents en sciences sociales ont permis de mieux comprendre les différences entre le sexe et le genre en tant que caractéristiques distinctes d'un individu. Selon la définition de l'Institut de la santé des femmes et des hommes (ISFH) des Instituts de recherche en santé du Canada, le sexe réfère aux caractéristiques physiologiques et physiques quantifiables telles que les chromosomes, l'expression des gènes, les niveaux d'hormones et les organes reproducteurs qui définissent les hommes et les femmes chez les animaux et chez les humains[11]. Toujours selon l'ISFH, le genre est défini comme les constructions socioculturelles des rôles, des comportements, de l'expression et de l'identité des garçons/hommes et des filles/femmes et les individus qui expérimentent et expriment leur genre de diverses façons [11]. Cette distinction est importante car historiquement, le sexe était utilisé dans les études précliniques, alors que le genre était utilisé dans les études chez l'humain.

Observations des études pré-cliniques

Une revue de la littérature a examiné les DS dans la neurobiologie des AUD dans les études précliniques en se concentrant sur les mécanismes neurobiologiques et les comportements impliqués dans les trois stades du modèle de maladie cérébrale de l'addiction[12, 13].

En ce qui concerne la phase d'intoxication, l'alcool a été associé à des niveaux de dopamine plus élevés chez les rats femelles ainsi qu'à une sensibilité accrue aux propriétés de renforcement de l'alcool lorsqu'il est auto-administré dans la zone tegmentale ventrale, une région faisant partie

du système de récompense chez les rongeurs [14, 15]. Une autre étude a observé que la beuverie était associée à une expression plus faible d'acide ribonucléique messager (ARNm) des sous-unités α2 des récepteurs $GABA_A$ chez les rats femelles dans plusieurs régions des ganglions de la base et des voies mésocorticolimbiques, dont le noyau accumbens, le noyau du lit de la strie terminale et l'amygdale centrale [16]. Ces DSs au niveau neurobiologique sont intéressants puisque des DSs sont également observés dans les comportements liés à la consommation d'alcool. Alors qu'une étude a rapporté un plus grand appétit pour l'alcool chez les rats femelles que chez les rats mâles, une autre étude a observé une préférence moindre pour une récompense incertaine suite à une injection aiguë d'alcool chez les rats femelles par rapport à l'injection chez les rats mâles [17, 18]. Ces résultats pourraient suggérer que les rongeurs mâles sont moins susceptibles d'arrêter de boire et potentiellement plus enclins à la dépendance.

Concernant l'affect négatif pendant la phase de sevrage, une étude a observé qu'une excitabilité accrue des neurones préprodynorphines dans l'amygdale centrale était induite par le sevrage de la beuverie chronique chez les rats mâles seulement [19]. Une autre étude a observé que le retrait de l'abus d'alcool était associé à une hausse de la signalisation du glutamate dans le noyau du lit de la strie terminale et de l'amygdale basolatérale plus importante chez les rongeurs mâles adolescents que chez les rongeurs femelles adolescents [20, 21]. Ces résultats pourraient suggérer que l'amygdale est plus sensible au retrait de l'abus d'alcool chez les rongeurs mâles que chez les rats femelles. Ces études sur le rôle de l'amygdale dans le sevrage d'un point de vue neurobiologique convergent avec des observations comportementales. En effet une étude a rapporté que les rats mâles ne montraient des comportements anxieux accrus qu'après un sevrage de l'alcool [22-24].

Dans le contexte préoccupation et l'anticipation qui caractérisent la troisième phase du modèle de la maladie cérébrale de l'addiction, des études précliniques ont évalué l'impact de l'abus d'alcool sur le cortex frontal et l'hippocampe. Une étude a observé que la consommation excessive d'alcool était associé à une plus grande réduction du nombre de cellules et de la neurogenèse dans l'hippocampe chez les rats femelles par rapport aux rats mâles [25]. Une autre étude a observé que le stress ainsi que des antécédents de consommation d'alcool étaient associés à une hausse de récepteurs de glucocorticoïdes dans le cortex frontal ainsi qu'à une

augmentation des récepteurs de glucocorticoïdes et du récepteur 1 du facteur corticolibérine dans l'hippocampe des souris femelles uniquement [26]. Ces résultats suggèrent une adaptation neurobiologique associée à la consommation d'alcool excessive face au stress dans ces régions limbiques.

Ces études précliniques sont importantes afin de nous informer sur les mécanismes neurobiologiques sous-jacents aux différences structurelles chez les animaux exposés à des substances. En effet, des modèles animaux de la dépendance à l'alcool ont révélé que des bouffées phasiques d'activité des neurones GABAergiques et dopaminergiques de l'aire tegmentale ventrale vers l'accumbens sont induites par la consommation d'alcool[27]. Cette transmission signale les effets de renforcement positifs de l'alcool et est ensuite codée par des mécanismes dans les voies afférentes de l'accumbens au cortex préfrontal, qui deviennent plus sensibles à l'alcool au fil des expositions répétées et conduisent à une motivation accrue pour la consommation d'alcool[28]. Ces modifications induites par la consommation d'alcool de la structure corticale, qui sont associées aux taux d'expression de récepteurs GABAergiques et dopaminergiques, pourraient potentiellement indiquer les processus neurobiologiques impliqués dans les premiers stades de la dépendance à l'alcool.

Pour le cannabis, des DSs ont également été observées dans l'expression des récepteurs cannabinoïdes [29]. Des niveaux plus élevés d'ARNm de récepteur cannabinoide de type 1 (CB1) ont été observés chez les rats femelles adolescents par rapport aux rats mâles adolescents dans plusieurs régions limbiques, notamment le cortex préfrontal, l'amygdale et l'hippocampe [30]. Les études précliniques peuvent informer sur des différences métaboliques entre les sexes qui pourraient en partie sous-tendre les effets physiologiques propres à chaque sexe. Une étude a exposé des rongeurs au Δ9-Tetrahydrocannabinol (THC), l'une des principales molécules psychoactives du cannabis, et a observé des niveaux plus élevés de métabolites de THC chez les rats femelles par rapport aux rats mâles appariés selon l'âge. Ces résultats suggèrent que, comme pour l'alcool, les DSs pharmacocinétiques expliquent en partie les différences de vitesse à laquelle les rongeurs femelles métabolisent le cannabis par rapport aux rongeurs mâles. Ces résultats pourraient suggérer que les rongeurs femelles sont plus susceptibles que les rongeurs mâles de développer une addiction au cannabis ou une neurotoxicité[31].

En somme, des DS sont observées dans les études pré-cliniques de modèles de consommation d'alcool et de cannabis aux niveaux physiologique du cerveau et comportemental. Ces différences sont importantes pour notre compréhension des mécanismes neurobiologiques sous-jacents aux TUA et TUC observés chez l'humain. Dans une perspective translationnelle, ces études pourraient nous informer sur les SDs comportementales chez l'humain à la suite d'une consommation chronique d'alcool ou de cannabis.

Différences sexuelles dans l'épidémiologie clinique

Plusieurs études ont évalué le traitement des troubles liés à la consommation de substances et ont constaté que les femmes adultes recherchaient un traitement plus rapidement que les hommes après l'initiation à l'alcool et l'apparition de TUA [32, 33].

Au niveau national, une enquête nationale a révélé que 19% des participants de moins de 45 ans ayant un AUD au cours de leur vie ont sollicité des services liés à l'alcool [33]. Bien qu'une proportion plus faible de femmes adultes ait bénéficié de services liés à l'alcool par rapport aux hommes adultes, les femmes adultes ont montré un âge moyen plus jeune que les hommes adultes pour la première utilisation de services liés à l'alcool [33]. En ce qui concerne les DSs dans le type de traitement recherché par les adultes avec un TUA, les résultats d'une étude basée sur deux enquêtes nationales suggèrent que les hommes avec un TUA pourraient préférer un traitement spécialisé pour les TUA, tandis que les femmes avec un TUA semblent préférer un traitement de santé mentale plus général [34].

Alors que les taux d'admission pour des problèmes liés au cannabis ont augmenté de plus de 30% entre 1996 et 2006 selon une enquête nationale, la recherche de traitement pour les TUC signalés est relativement faible puisqu'environ 14 % des hommes et 12 % des femmes atteints de TUC ont cherché à obtenir un traitement[35].

En ce qui concerne les résultats du traitement, des résultats mitigés sont observés pour les différences entre les sexes en raison de la taille des échantillons et du nombre limité de femmes TUS incluses. Cependant, une étude a suggéré que la plupart des essais cliniques randomisés à grande échelle n'ont pas observé de différences entre les sexes pour les TUA et les TUC en ce qui

concerne les résultats du traitement, y compris la rétention du traitement [36]. Les résultats sont mitigés en ce qui concerne les différences sexuelles dans les traitements et la réponse à ces traitements spécifiques à un seul sexe, mais une étude a observé que les femmes participant à des programmes réservés aux femmes ont obtenu de meilleurs résultats en matière de traitement de la toxicomanie, non spécifique à l'alcool ou au cannabis, que les femmes participant à un programme non réservé aux femmes [37].

Des observations similaires ont été faites chez l'adolescent, puisque les adolescentes avaient plus de chance de recevoir un traitement que les adolescents du même âge[38]. En revanche, il est important de mentionner que des DSs dans les taux de prévalence peuvent contribuer à expliquer une telle observation. Bien que les résultats chez l'adulte mentionné précédemment résultats indiquent l'absence de DSs dans la recherche de traitement pour les TUC, une étude basée sur une enquête nationale a observé des taux de traitement pour les TUC plus élevés chez les adolescents par rapport aux adolescentes [38].

En somme, les femmes semblent chercher un traitement pour leur problème de consommation plus souvent que les hommes, mais cette DS n'a pas été observée de manière consistante chez les adolescents. Il est légitime d'émettre l'hypothèse que les DS dans la recherche de traitement entre les femmes et les adultes pourraient être induites par des SD structurelles dans certaines régions cérébrales impliquées dans le comportement ou la mémoire (face aux effets aversifs de la consommation). En effet, une différence structurelle plus importante que les femmes dépendantes que chez les hommes dépendants dans le cortex préfrontal et l'hippocampe pourraient encourager ces dernières à chercher un traitement plus fréquemment que leurs homologues masculins. En dehors des taux de prévalence qui varient selon les groupes d'âge, il est possible que ces différences observées entre les adultes et adolescentes soient liées à de potentiels des changements dans les taux de consommation au niveau populationnel.

Changements épidémiologiques et sensibilité biologique

Bien que les résultats d'une enquête nationale ont permis d'observer des différences entre les sexes dans la prévalence des TUA et des TUC au cours de la vie[39], l'écart entre les hommes et le femmes en termes de consommations d'alcool et de cannabis semblent se rétrécir. Alors que les

hommes déclarent généralement des niveaux de consommation d'alcool et de cannabis plus élevés que les femmes du même âge, des études épidémiologiques récentes ont observé une convergence des taux de consommations d'alcool et de cannabis entre les sexes, tant chez les adultes que chez les adolescents[10, 40].

Bien qu'une hausse des cas de TUA ait été observée chez les deux sexes chez l'adulte au cours des dernières décennies à l'échelle mondiale, une augmentation relativement plus importante a été observée chez les femmes par rapport aux hommes [5, 41]. Toutefois, une fréquence plus élevée de beuverie reste observée chez les hommes par rapport aux femmes à l'adolescence ainsi qu'à l'âge adulte dans le monde [8, 39, 42]. Des résultats similaires sont observés dans les échantillons d'adolescents puisque les différences entre les sexes dans la prévalence de la consommation d'alcool chez les adolescents ont diminué au cours des dernières années [10, 40]. Tel que discuté par Lees et coll. dans leur revue de la littérature sur les TUA en 2020[6], ces changements dans les taux de prévalence par sexe au cours des dernières années sont consistants avec les récentes baisses de la consommation d'alcool et de la beuverie. De plus, ces changements se produisent de manière concomitante avec les augmentations des taux d'adolescents qui s'abstiennent de consommer de l'alcool.

Il est important de surveiller ces changements épidémiologiques car des DSs biologiques quant à la sensibilité à l'alcool sont plausibles. Certaines études ont tenté d'évaluer ces DSs dans la sensibilité à l'alcool et le cannabis en étudiant l'activité fonctionnelle du cerveau et les scores auto-rapportés d'effets subjectifs induits par une substance chez l'humain. Pour l'alcool, une étude chez l'adulte a observé que des signaux de stress et d'alcool étaient associés à des activations plus importantes chez les hommes par rapport aux femmes dans le cortex préfrontal médian, l'insula postérieure, l'amygdale et l'hippocampe, qui sont des régions limbiques impliquées dans le modèle de maladie cérébrale de l'addiction [43]. Pour le cannabis, une étude[44] a observé une plus grande sensibilité au risque d'abus chez les femmes adultes par rapport aux hommes adultes qui ont été jumelés pour fumer du cannabis quotidiennement. En effet, les femmes ont rapporté des scores plus élevés d'effets subjectifs liés à l'abus quotidien. Néanmoins, la rareté des études sur l'évaluation des DSs dans la sensibilité biologique à l'alcool et le cannabis limitent la capacité de tirer des conclusions.

Différences métaboliques pour l'alcool et le cannabis

Les différences entre les sexes dans le métabolisme de l'alcool ont été observées dans les niveaux d'alcool déshydrogénase, qui est l'enzyme qui catalyse l'alcool. En contrôlant pour la quantité d'alcool, les femmes présentaient des niveaux d'alcool déshydrogénase plus faibles dans l'estomac, ce qui pourrait entraîner des concentrations d'alcool dans le sang plus élevées et des intoxications plus importantes que chez les hommes[45]. Plusieurs chercheurs ont également fait état de DSs dans l'évolution vers les TUA, les femmes progressant plus rapidement que les hommes en ce qui concerne la transition de consommation récréative vers les TUA ainsi que la recherche d'un traitement [46-48].

Bien que le nombre d'étude sur le sujet soit restreint, des DSs dans les effets physiologiques des cannabinoïdes ainsi que dans le métabolisme du cannabis ont été observés [29]. Si la consommation de cannabis est associée à une augmentation plus importante de la fréquence cardiaque chez les hommes que chez les femmes, les femmes ont fait état d'effets sédatifs et de vertiges plus importants induits par le cannabis que les hommes[49-53]. Bien que ces résultats suggèrent que les femmes expérimentent plus d'effets neurophysiologiques et que la fréquence cardiaque est plus sensible au cannabis chez les hommes, ces résultats sont à interpréter avec précaution puisque la quantité de cannabis par rapport au poids corporel n'a pas été contrôlée de manière consistante dans ces différentes études[49-53]. Deux études ont donné des résultats mitigés sur les taux de THC dans le plasma des femmes, car une étude a observé des taux plus élevés chez les femmes que chez les hommes, tandis que la seconde étude a fait état de taux de THC plasmatique plus faibles que ceux des hommes [54, 55]. Finalement, de même que l'effet télescopique observé pour l'alcool, une étude sur un échantillon national a rapporté une progression télescopique vers les TUC chez les femmes adultes seulement[35], ce qui suggère des DSs au niveau biologique dans les mécanismes de l'addiction.

Finalement, des études sur des petits échantillons sur des adultes sains suggèrent que les femmes pourraient ressentir davantage de symptômes de type dépressif induits par le cannabis, tel que la sédation et la suppression psychomotrice, par rapport aux hommes qui eux peuvent ressentir davantage d'analgésie[29, 52, 56]. Bien que ces résultats convergent partiellement avec les

observations mentionnées plus tôt, davantage d'études étant sont requises sur le sujet du fait des résultats mitigés rapportés dans la littérature sur les DSs sur dans les effets subjectifs induits par le cannabis. [29, 52, 56].

Ainsi, les différences métaboliques et dans les effets subjectifs observés chez l'adulte semblent impliquer des DS. Puisque le nombre d'études portant sur les différences métaboliques et d'effets subjectives lors de l'adolescence sont limitée, une meilleure compréhension du dimorphisme sexuel cérébral lors de l'adolescence pourraient nous informer sur la neurobiologie des DS observées à l'âge adulte.

Trajectoires neurodéveloppementales lors de l'adolescence

L'adolescence est une période de développement au cours de laquelle le cerveau subit d'importants changements microscopiques et macroscopiques. Des études longitudinales de neuroimagerie d'enfants en bonne santé ont observé une légère diminution du volume cérébral total et une augmentation du volume ventriculaire latéral tout au long de l'adolescence. En ce qui concerne la matière cérébrale, une trajectoire en forme de U inversé région a été observée pour le volume de matière grise dans les régions sous-corticales et corticales, tandis qu'une augmentation du volume de matière blanche dans le cerveau a été observée en suivant une trajectoire linéaire [57, 58]. Ces modifications macroscopiques du volume du cerveau sont dues à des mécanismes microscopiques impliqués dans la réorganisation du cerveau tout au long de l'adolescence, notamment l'élagage synaptique, l'arborisation dendritique et axonale, et la myélinisation [57].

Des DSs dans les trajectoires développementales sont observées dans les régions du cerveau tout au long de l'adolescence [59, 60]. Alors que le volume total du cerveau a atteint son maximum plus tôt chez les adolescentes que chez les adolescents, une augmentation plus importante du volume de la matière blanche a été observée chez les hommes que chez les femmes entre 3 et 27 ans[58]. On a observé que les processus de maturation s'achevaient un ou deux ans plus tôt dans les lobes corticaux et les régions sous-corticales des adolescentes par rapport aux adolescents, et ce tout en suivant une trajectoire en forme de U inversé [58]. Compte tenu des relations rapportées entre le développement pubertaire et les volumes sous-corticaux tout au long de l'adolescence, et que

le la puberté débute plus tôt chez les adolescentes, le rôle potentiel de la puberté dans ces DSs dans les trajectoires développementales a été évalué[61]. Compte tenu du rôle du cortex préfrontal dans le modèle de maladie cérébrale de l'addiction, il est intéressant de noter qu'un retard de maturation dans le cortex préfrontal a été observé chez les adolescents par rapport aux adolescentes dans un large échantillon d'adolescents de 14 à 16 ans[62]. Ces résultats suggèrent des DSs dans les rythmes de maturation dans le cortex préfrontal du cerveau adolescent

Associations entre les structures cérébrales et la consommation

Consommation d'alcool chez l'adulte et l'adolescent

Les adultes TUA, comparés à des sujets sains, ont présenté plusieurs différences d'intégrité structurelle et fonctionnelle altérées dans divers systèmes tels que les réseaux fronto-limbique, fronto-striatal et fronto-cérébelleux [63]. Les fonctions fronto-limbiques comprennent la mémoire et la motivation épisodiques, les fonctions fronto-striatales comprennent la régulation émotionnelle, l'inhibition, l'utilisation des récompenses et la motivation et les fonctions fronto-thalamo-cérébelleuses comprennent la démarche, l'équilibre, la mémoire de travail et les fonctions exécutives [63]. Bien que ces réseaux et ces fonctions soient vulnérables au TUA, la causalité entre les TUA, l'intégrité du cerveau et la cognition ne peut pas être facilement évaluée car de nombreuses études sont transversales et plusieurs facteurs sont impliqués l'étiologie de ces changements structurels tels que la variation structurelle ou fonctionnelle préexistante et l'excitotoxicité induite par l'alcool directement ou en combinaison avec des facteurs nutritionnels tels que la carence en thiamine [64]. Les régions frontales, y compris le gyrus frontal supérieur et précentral, et l'hippocampe ont montré des interactions entre l'âge et le TUA, avec des volumes réduits plus importants chez les alcooliques plus âgés par rapport aux alcooliques plus jeunes [63].

La relation entre l'abus d'alcool chez les adolescents et plusieurs différences structurelles entre les consommateurs et les abstinents a été récemment examinée et a révélé une réduction du volume de matière grise dans les régions frontales et temporelles [6]. La consommation d'alcool a été associée à une altération de la trajectoire normale de croissance du cerveau pour la matière grise dans les régions frontale et temporale ainsi qu'à une densité anormale de la matière blanche

et à une intégrité des matières blanches [65-67]. Ces résultats suggèrent que l'abus d'alcool chez les adolescents pourrait être impliqué dans un processus de vieillissement accéléré du cerveau et associé aux mauvaises performances de la mémoire observées chez les adolescents [6, 68]. Des performances réduites en matière d'apprentissage, de visuospatiale et de mémoire de travail ont été observées chez les adolescents buveurs occasionnels par rapport aux témoins du même âge [6]. Des études de neuroimagerie fonctionnelle ont évalué l'association entre l'abus d'alcool chez les adolescents et la réaction dépendant du niveau d'oxygène dans le sang lors de tâches cognitives et les variations fonctionnelles des régions temporales lors de tâches neuropsychologiques [69, 70]. Ces différences entre les cas et témoins peuvent dépendre de la tâche cognitive car une réduction de l'activation cérébrale a été observée lors d'une tâche de sensibilité à la récompense alors qu'une augmentation de l'activation cérébrale a été signalée lors du fonctionnement exécutif [6]. Dans l'ensemble, l'abus d'alcool chez les adolescents a été associé à une réduction de la substance grise et de la substance blanche ainsi qu'à des déficits cognitifs.

En somme, l'abus d'alcool et le TUA ont été associés à plusieurs troubles du comportement et du cerveau chez les adultes et les adolescents [6, 63, 71].

Consommation de cannabis chez l'adulte et l'adolescent

Des déficits cognitifs subtils au niveau du fonctionnement exécutif, de la mémoire, de l'attention et de l'apprentissage sont observés chez les adultes au moins une semaine après une forte consommation de cannabis[72], mais la littérature sur les effets persistants à long terme a donné des résultats mitigés. En termes de variations structurelles, des variations du volume de l'hippocampe et de la densité de la matière grise ont été signalées de façon récurrente, tandis que des résultats incohérents sont signalés dans les variations volumétriques de l'amygdale, du noyau accumbens et du cortex orbitofrontal [72] . En ce qui concerne l'activité fonctionnelle du cerveau adulte suite à la consommation de cannabis, une activité réduite dans le cortex préfrontal dorsolatéral droit ainsi que dans le cortex cingulaire antérieur a été reproduite, et les études sur l'activité dans l'hippocampe sont incohérentes puisque différentes études ont observé soit une hyperactivation, soit une hypoactivation ou une activation similaire chez les consommateurs de cannabis par rapport aux non-utilisateurs [73-77]. Une connectivité fonctionnelle

accrue a été observée chez les consommateurs de cannabis et était plus importante chez les consommateurs dépendants par rapport aux consommateurs non dépendants [78, 79]. Dans l'ensemble, des anomalies cognitives et cérébrales des régions frontales et limbiques sont observées chez les consommateurs adultes de cannabis, mais les résultats sont mitigés et plusieurs facteurs de confusion peuvent être impliqués, ce qui limite l'association causale entre la consommation de cannabis et les troubles cognitifs et cérébraux.

Un autre article récent a passé en revue les variations structurelles associées à la consommation de cannabis chez les adolescents [80]. Des altérations structurelles ont été observées dans le volume et l'épaisseur corticale des régions frontales et pariétales chez les adolescents consommateurs de cannabis par rapport aux non-utilisateurs, mais les résultats ne sont pas cohérents puisque les variations à la hausse et à la baisse ont été observées dans toutes les études [80-84]. Dans l'ensemble, les résultats de la littérature sur les origines de la structure et de la fonction frontopariétales associées à la consommation de cannabis chez les adolescents sont mitigés, car les études transversales n'ont pas pu déterminer si ces variations structurelles sont dues à un ou à une interaction de multiples facteurs de confusion tels que le début précoce de la consommation de cannabis, les différences préexistantes dans les échantillons ou la chronicité de la consommation de cannabis [80]. Il est intéressant de noter qu'une étude prospective a observé que le début de la consommation de cannabis à la fin de l'adolescence était prédit par un volume réduit dans le cortex orbitofrontal des jeunes adolescents, ce qui suggère que des facteurs neurobiologiques peuvent être antérieurs à l'apparition du cannabis et pourraient être un facteur de risque de la consommation de cannabis chez les adolescents [85, 86].

Dans l'ensemble, les études et les revues de la littérature de neuroimagerie examinées ont largement mis en évidence les différences structurelles et fonctionnelles du cerveau chez les adultes atteints d'un TUC et les adolescents consommateurs de cannabis [72, 80].

L’importance des méta-analyses

Compte tenu des observations inconsistantes rapportées dans la littérature sur les anomalies structurelles associées à la consommation d’alcool et de cannabis chez les adolescents et les adultes, les chercheurs ont évalué comment l’utilisation de différentes méthodologies pouvait

partiellement expliquer l'inconsistance des résultats publiés. Une méta-analyse sur les variations structurelles observées chez les adultes TUA a rapporté que leurs résultats inconsistants pourraient s'expliquer par différents facteurs, incluant l'hétérogénéité des sujets dans les études incluses, les différentes méthodes de segmentation du cerveau et les différents types de scanner utilisés [87]. Un deuxième problème avec les études individuelles est la taille de l'échantillon qui limite la puissance statistique des analyses et donc la capacité à détecter un effet réel. Tel que mentionné plus haut, un autre problème est l'utilisation de différents cadres anatomiques par les différentes études, ce qui complique l'agrégation et la comparaison des résultats des différentes études sans l'aide de coordonnées prédéterminées. Un problème observé dans les études de neuroimagerie est l'étude sur quelques régions d'intérêt sélectionnée *a priori* au lieu d'effectuer des analyses sur le cerveau entier. Bien que la sélection *a priori* de régions peut être justifiée selon la question de recherche, une telle approche peut compliquer la comparaison entre les et contribue donc à l'hétérogénéité des résultats dans la littérature.

Pour faire face à ces défis méthodologiques, les chercheurs ont commencé à combiner les résultats des résultats publiés dans la littérature et à effectuer des méta-analyses pour évaluer les anomalies cérébrales à travers l'ensemble des échantillons inclus dans l'analyse, dont la puissance se voit accrue. Grâce à la combinaison des observations des études individuelles, les résultats de la méta-analyse fournissent des résultats généralisables à une plus grande population puisque l'une des forces de la méta-analyse réside en sa capacité à détecter des effets partagés à travers les études incluses. Si les différentes méthodes de traitement des images peuvent entraîner une hétérogénéité entre les études dans la méta-analyse en raison d'images non-standardisées, les méta-analyses sont néanmoins utiles pour généraliser les résultats à une plus grande population puisque les échantillons des différentes études sont regroupés à partir desquels on peut dériver des tailles d'effet pour quantifier l'ampleur d'un phénomène.

Évaluation des différences sexuelles

Les auteurs d'une étude récente ont recommandé deux approches analytiquement appropriées pour évaluer les DSs. La première consiste à tester l'interaction entre une variable liée à la substance et le sexe. Elle permet d'évaluer les différences hommes-femmes en fonction de la

variable liée à la substance, ainsi on pour évaluer les DSs pour chaque score de la variable de la consommation. La seconde consiste à effectuer des analyses stratifiées par sexe séparément, qui pourraient être utilisées, par exemple, pour comparer les cas de TUS à leurs homologues sains de même sexe. Bien que cette dernière approche analytique puisse détecter différents effets de la substance sur les volumes cérébraux, elle ne permet pas de comparer les hommes et les femmes parmi les cas lorsque les sujets sont classés par catégorie. Néanmoins, il est important d'évaluer cette deuxième option analytique, car une revue de la littérature a constaté qu'environ 85% des études qui ont effectué des analyses stratifiées par sexe ont observé différentes associations entre la consommation de substance et le volume de différentes régions du cerveau[88].

Études transversales et longitudinales

En l'absence de possibilités de réaliser des études expérimentales pour explorer les relations causales entre la consommation de substance et la structure cérébrale, les études longitudinales avec une approche analytique sur une cohorte de taille suffisante peuvent informer sur les théories de causalité entre la consommation de substances et le développement cérébral. Contrairement aux études transversales classiques, les approches longitudinales permettent également l'estimation de variables latentes, qui sont des variables qui n'ont pas été mesurées empiriquement, mais plutôt inférées à partir de variables qui elles furent mesurées. Il est important d'évaluer ces variables pour comprendre comment la consommation de substances chez les adolescents, par exemple, peut être associée à court et à long terme avec les variations structurelles cérébrales. Si deux études récentes sur un échantillon de plus de 3000 adolescents du grand Montréal ont informé sur les effets à court et à long terme potentiels de la consommation d'alcool et de cannabis sur les performances cognitives, on ignore encore comment la consommation d'alcool et de cannabis sont associées au développement des structures cérébrales du cerveau adolescent dans un cadre dynamique [89, 90].

Justification du mémoire

À la lumière des résultats rapportés dans la littérature révisée ci-dessus, les articles inclus dans ce mémoire tentent de répondre à trois questions de recherche suivantes. La première question de recherche est d'évaluer dans quelle mesure les différences structurelles cérébrales entre les patients et les témoins observés dans les TUA et TUC sont similaires à celles observées dans d'autres troubles mentaux. Le premier objectif de ce mémoire est de déterminer si les différences structurelles entre les patients TUA ou TUC et les témoins sont semblables aux différences structurelles rapportées dans d'autres conditions psychiatriques. Également, à partir des DS comportementales et neurophysiologiques qui sont observées dans les TUS, la deuxième question de recherche est de comprendre si des DS existent également au niveau des DS cérébrales dans les TUS. Le deuxième objectif du mémoire est d'évaluer les différences sexuelles potentielles dans les TUA et TUC. Finalement, du fait de la rareté des études longitudinales de neuroimagerie sur l'association entre le développement cérébral et la consommation de substances lors de l'adolescence, la troisième question de recherche est d'élucider dans quelle mesure les consommations d'alcool et de cannabis sont liées au développement cérébral adolescent, et si ce lien varie dans le temps. Le troisième objectif du mémoire est d'évaluer si l'association longitudinale entre la consommation d'alcool et de cannabis et le développement cérébral durant l'adolescence varie dans le temps sur une période de cinq ans. Nous émettons les hypothèses que a) les différences structurelles chez les patients TUA et TUC par rapport à leurs témoins seront similaires dans l'hippocampe à celles observées dans d'autres troubles psychiatriques, b) davantage de différences structurelles entre les patients et témoins seront observées chez les hommes dans le TUA et davantage de différences structurelles entre les patients et témoins chez les femmes seront observées dans le TUC et c) la consommation d'alcool et de cannabis lors de l'adolescence variera dans le temps.

Méthodes

Échantillons

Deux bases de données ont été utilisées dans les articles inclus dans ce mémoire: la base de données du groupe de travail ENIGMA-Addiction sur les TUA et TUC ainsi que la cohorte prospective Neuroventure. Les bases de données du groupe ENIGMA-Addiction ont été utilisées pour évaluer les anomalies structurelles observées chez les adultes atteints de TUA et TUC, tandis que la cohorte Neuroventure a été utilisée pour évaluer les corrélats cérébraux associés à l'usage de substances chez les adolescents dans une perspective longitudinale.

Le consortium Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) a été créé pour permettre aux chercheurs de partager leurs données de neuroimagerie et génétique afin d'effectuer des analyses statistiques puissantes et d'observer les anomalies cérébrales associées à différentes conditions psychiatriques. Le groupe de travail ENIGMA-Addiction a été créé en 2016 pour développer un ensemble de données internationales avec des données de neuroimagerie, génétiques et cliniques provenant de participants souffrant de TUS et de sujets sains afin d'effectuer des comparaisons cas-témoins en utilisant des protocoles de traitement et d'analyses statistiques standardisés. [91].

Le groupe de travail ENIGMA-Addiction est une branche du consortium ENIGMA qui comprend de 28 échantillons internationaux avec des données de neuroimagerie et des données cliniques provenant de patients dépendants et de témoins sains. De ces 28 études, huit sont sur les TUA et sept sont sur les TUC. Un article TUA n'a pas été inclus dans les deux premiers articles puisqu'aucun sujet contrôle n'a été recruté. Les deux premiers articles sont des méta-analyses basées sur sept sites internationaux de cas-témoins de TUA (N = 798, 54% sont des cas) et sept études internationales sur les TUC (N = 447, 45% sont des cas). Des 798 participants des sept études TUA, 435 (dont 127 femmes) sont des sujets contrôles et 363 (dont 136 femmes) sont des sujets TUA. Concernant les sept études sur les TUC, 200 contrôles (dont 61 femmes) ont été comparés à 247 sujets (dont 72 femmes) avec un TUC. Bien que des critères d'inclusion et d'exclusion spécifiques à chaque groupe de travail se concentrant sur différentes conditions

psychiatriques existent (comme la médication pour les troubles psychotiques), les différents groupes de travail tentent de recruter des participants sans comorbidités psychiatriques. Les participants ayant des antécédents de maladie neurologique et/ou de comorbidité psychiatrique (autres que les troubles dépressifs et anxieux) ont été exclus des analyses. Chaque étude incluse dans les méta-analyses a obtenu l'approbation du conseil institutionnel local et l'approbation éthique, et tous les participants ont donné leur consentement écrit pour l'étude originale sur le site local. Le CHU Sainte-Justine a également obtenu l'approbation éthique pour ces méta-analyses du Comité d'éthique de l'Hôpital Sainte-Justine de Montréal.

Le troisième article fait état des associations observées entre la consommation d'alcool et de cannabis chez les adolescents et le développement sous-cortical et cortical en utilisant l'ensemble de données Neuroventure. Neuroventure est une étude de cohorte prospective composée de 151 (dont 130 ont été inclus dans les analyses du troisième article) adolescents recrutés dans les écoles de Montréal à partir de l'essai Co-Venture vers l'âge de 13 ans afin d'évaluer les effets du retardement de la consommation de substances sur le cerveau et les performances cognitives des adolescents [92, 93]. Les participants ont été suivis à chaque année pendant cinq ans et étaient en 7e ou 8e année au premier temps de mesure, en 9e année au troisième temps de mesure et en 11e année au cinquième et dernier temps de mesure. Les adolescents ont été soumis à des scanneurs de neuroimagerie et à des évaluations neurocognitives aux trois moments de l'étude mentionnées ci-dessus à l'Institut neurologique de Montréal. Le CHU Sainte-Justine a obtenu l'approbation éthique pour cette recherche et le consentement écrit des parents ou du tuteur légal des participants, qui ont également activement consenti à participer.

Mesures de la consommation de substance

Dans les deux premiers articles, la quasi-totalité des participants des bases de données ENIGMA-Addiction sur les TUA et TUC étaient des patients ou des sujets sains classés sur la base d'entretiens diagnostiques structurés validés qui s'alignent sur la quatrième édition révisée du Manuel diagnostique et statistique des troubles mentaux [94]. Bien qu'ils n'aient pas reçu de diagnostic de TUC, les consommateurs chroniques de cannabis (qui consommaient entre cinq et

sept fois par semaine lors des deux dernières années et qui ont consommé au moins 500 joints dans leur vie au moment du recrutement) d'un site ont été considérés comme des cas dans les deux premiers articles pour augmenter la taille de l'échantillon après une analyse de sensibilité visant à évaluer la robustesse des résultats des méta-analyses. Les participants des études du groupe de travail ENIGMA-Addiction ont été classés selon leur consommation de manière dichotomique, de sorte à comparer les sujets cas aux témoins.

Dans le troisième article, les adolescents ont déclaré eux-mêmes leur consommation de substances à chacune des cinq années où ils ont été suivis en utilisant une version modifiée du Questionnaire de détection des problèmes d'alcool et de drogues chez les adolescents (DEP-ADO) sur une plateforme en ligne dédiée [95]. Les participants ont indiqué que la fréquence de beuverie correspondait au nombre d'épisodes où ils avaient bu cinq boissons alcoolisées ou plus à la même occasion au cours de leur vie. Pour la consommation de cannabis, les adolescents ont indiqué la fréquence de leur consommation sur une échelle de 0 à 5 (jamais, occasionnellement, une fois par mois, une ou deux fois par semaine, trois fois ou plus par semaine, tous les jours).

Données de neuroimagerie structurelles T1

Dans les deux premiers articles, des images cérébrales structurelles d'imagerie par résonance magnétique pondérées T1 ont été acquises à chaque site et la segmentation de sept volumes sous-corticaux de matière grise (noyau accumbens, amygdale, noyau caudé, hippocampe, pallidum, putamen et thalamus), de 34 régions corticales, des ventricules latéraux et du volume intracrânien total a été réalisée à l'aide de FreeSurfer. Il s’agit d’un logiciel de segmentation entièrement automatisé et validé qui est utilisé par les différents groupes de travail du consortium ENIGMA [96]. Le traitement des images a été effectué en utilisant les protocoles standardisés du consortium ENIGMA pour faciliter l'harmonisation de l'analyse des images entre les études (décrits en détail à la page 51). Les protocoles d’imagerie et d’analyses statistiques du consortium ENIGMA sont utilisés par l’ensemble des groupes de travail afin de faciliter les comparaisons entre les groupes de travail. Chaque étude recrutée par le groupe de travail ENIGMA-Addiction a également suivi le protocole de contrôle de qualité du consortium et une

inspection visuelle a été effectuée pour détecter les anomalies dans la segmentation ainsi que pour minimiser les effets potentiels du site dans les résultats de la méta-analyse.

Pour le troisième article capitalisant sur la cohorte Neuroventure, un scanneur d'imagerie par résonance magnétique (IRM) 3T Siemens Magnetom Trio/Prisma a été utilisé pour les séances d'imagerie aux trois moments mentionnés plus haut. Le pipeline de prétraitement longitudinal du consortium ENIGMA a été utilisé sur les données IRM structurelles pondérées T1 obtenues pour traiter les mesures cérébrales unilatérales des sept volumes de matière grise sous-corticale (noyau accumbens, amygdale, noyau caudé, hippocampe, pallidum, putamen et thalamus), des 34 régions corticales, des ventricules latéraux et du volume intracrânien total. Un contrôle de qualité et une inspection visuelle ont été effectués à chaque moment du suivi ainsi qu'avant la réalisation des analyses statistiques au CHU Sainte-Justine**.**

Analyses statistiques

Les variations structurelles observées dans les sujets atteints de TUS peuvent être analysées à l'aide de diverses méthodes de neuroimagerie et d'approches statistiques. Le consortium ENIGMA a développé ses propres protocoles de traitement et de statistiques afin d'harmoniser les analyses au sein des groupes de travail et entre eux. Cette uniformisation des analyses statistiques permet de réaliser des comparaisons entre les troubles psychiatriques en utilisant des statistiques tel que le *d* de Cohen[97], qui est une différence de moyenne standardisée entre deux groupes (détaillé ci-dessous). En capitalisant sur l'ensemble de données du groupe de travail ENIGMA-Addiction, deux séries d'analyses ont été effectuées, à savoir une pour les études TUA et une pour les études TUC. Les différences cas-témoins dans les volumes sous-corticaux et les différences d'épaisseur corticale ont été évaluées pour chaque site en utilisant une régression linéaire pour calculer le *d* de Cohen tout en ajoutant des covariables au modèle linéaire. Cette taille d'effet représente la différence entre deux moyennes (par exemple celle des cas et celle des contrôles) divisée par un écart-type combiné. [97]. Une taille d'effet peut ainsi être calculée pour chaque région d'intérêt pour chaque site, et une estimation méta-analytique de ces tailles d'effet peut être calculée pour évaluer les variations structurelles principales parmi les sites

inclus. Cette approche a été utilisée dans le premier article pour évaluer les différences cas-témoins dans les échantillons TUA et TUC.

Comme mentionné dans l'introduction, les différences entre les sexes peuvent être évaluées de différentes manières et il est important d'effectuer des analyses stratifiées par sexe même si les termes d'interaction liés au sexe ne sont pas significatifs. Comme pour le premier article, les DSs dans les échantillons de TUA et de TUC de l'ensemble de données du groupe de travail ENIGMA-Addiction ont été calculées en utilisant une approche méta-analytique pour observer les variations structurelles partagées par les différentes études en estimant les termes d'interaction sexe-par-diagnostic pour chaque site à partir desquels une taille d'effet a été dérivée afin de calculer ultérieurement un effet méta-analytique pour effectuer des comparaisons homme-femme au sein des patients TUA et au sein des patients TUC. Les effets principaux du sexe et du diagnostic ont également été estimés dans cette première série d'analyses. Ensuite, des analyses d'interaction entre le sexe et le statut du participant furent réalisées. Finalement, des analyses stratifiées par sexe ont été effectuées pour tous les sites qui comptaient suffisamment de participantes pour comparer les patients TUA aux témoins sains appariés par sexe. Des analyses similaires ont été réalisées pour l'échantillon TUC. Pour les besoins de ce mémoire, nous ferons référence aux DSs comme étant des différences entre hommes et femmes chez les participants adultes et adolescents plutôt que des différences de genre puisque le sexe n'était pas une variable systématiquement évaluée lors de la collecte des données par le groupe ENIGMA-Addiction.

En ce qui concerne les changements structurels au cours de l'adolescence dans le troisième article, l'objectif de ce troisième et dernier article de mémoire est d'informer sur les différences entre les sexes dans la préséance temporelle dans l'association entre la consommation de substances chez les adolescents et le développement des structures cérébrales dans le contexte d'un cadre d'inférence causale dynamique multiniveaux avec un estimateur bayésien[98]. En l'absence de possibilités de réaliser des études expérimentales pour explorer les relations causales, un cadre analytique multiniveau appliqué à l'étude longitudinale de la bonne cohorte peut être utilisé pour informer sur certaines théories de causalité, comme la préséance temporelle, et peut contribuer à constituer un ensemble de preuves pour ou contre la causalité.

Une telle analyse permet de distinguer les associations intra-sujet (les relations variables dans le temps) des associations inter-sujets (les caractéristiques au niveau du sujet) et la manière dont ces associations sont associées séparément à la valeur initiale ou à l'évolution dans le temps d'une variable dépendante. Les associations intra-sujet peuvent également être modélisées de différentes manières pour évaluer l'association simultanée entre un prédicteur sur une variable dépendante et l'association décalée d'un prédicteur à un certain moment sur une variable dépendante au moment suivant. Ces deux manières différentes de modéliser les associations intra-sujet pourraient être interprétées comme des associations à court terme ou durables d'un prédicteur sur la structure du cerveau, respectivement.

Dans les trois articles inclus dans ce mémoire, des corrections pour les comparaisons multiples ont été réalisées pour les volumes sous-corticaux et les épaisseurs corticales en employant une procédure de Benjamini-Hochberg[99] après avoir confirmé l'indépendance des tests.

L'apport original de XN fut de rédiger les manuscrits, réaliser les analyses statistiques ainsi que les figures et corriger les manuscrits selon les commentaires des co-auteurs et réviseurs.

Article 1

How do substance use disorders compare to other psychiatric conditions on structural brain abnormalities? A cross-disorder meta-analytic comparison using the ENIGMA Consortium findings.

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Abstract

Objective: Alcohol (AUD) and Cannabis Use Disorders (CUD) are associated with brain alterations particularly involving fronto-cerebellar and meso-cortico-limbic circuitry. However, such abnormalities have additionally been reported in other psychiatric conditions, and until recently there has been few large-scale investigations to compare such findings. The current study uses the ENIGMA Consortium method of standardising structural brain measures to quantify case-control differences and to compare brain-correlates of substance use disorders with those published in relation to other psychiatric disorders.

Methods: Using the ENIGMA protocols, we reported effect sizes derived from a meta-analysis of alcohol (seven studies, N = 798, 54% are cases) and cannabis (seven studies, N = 447, 45% are cases) dependent cases and age- and sex-matched controls. We conducted linear analyses using harmonised methods to process and parcellate brain data identical to those reported in the literature for ENIGMA case-control studies of major depression, schizophrenia, and bipolar disorder so that effect sizes are optimally comparable across disorders. The relation between subcortical grey matter volumes and cortical thickness with ICV, age and sex as covariates was evaluated.

Results: After correcting for multiple comparisons, AUD case-control meta-analysis of subcortical regions of interest indicated significant differences in the thalamus, hippocampus, amygdala and accumbens, with effect sizes generally equivalent to, or larger than |0.23|, those previously reported for other psychiatric disorders (except for the pallidum and putamen). On measures of cortical thickness AUD was associated with significant differences bilaterally in the fusiform gyrus, inferior temporal gyrus, temporal pole, superior frontal gyrus, and rostral and caudal anterior cingulate gyri. Meta-analysis of CUD case-control studies indicated reliable reductions in amygdala, accumbens and hippocampus volumes, with the former effect size comparable to, and the latter effect size around half of that reported for alcohol and schizophrenia. CUD was associated with lower cortical thickness in the frontal regions, particularly the medial orbitofrontal region, but this effect was not significant after correcting for multiple testing.

Conclusions: This study allowed for an unbiased cross-disorder comparison of brain correlates of substance use disorders and showed alcohol-related brain anomalies equivalent in effect size to that found in schizophrenia in several subcortical and cortical regions and significantly greater alterations than those found in major depression in several subcortical and cortical regions. Although modest, CUD results overlapped more with findings reported for AUD and other psychiatric conditions but appear to be specifically related to reduced thickness of the medial orbitofrontal cortex.

Introduction

The Global Burden of Disease Studies[2] have been critical in developing methods to study health outcomes and have proven invaluable when advocating for health equity, both cross-nationally and across diseases. The 2010 update[3] systematically quantified prevalence of 1,160 sequelae of 289 diseases and injuries across 21 geographical regions. Results for specific diseases and impairments have highlighted the high rates of disability from mental disorders (particularly depression) and substance use disorders[4]. Alcohol and cannabis are among the most widely abused substances globally, and second only to tobacco use in terms of frequency of use. [100, 101]

Harmful alcohol use and dependence have long been associated with cognitive impairments in multiple neuropsychological domains, including evidence from the very earliest case-control studies employing standardised test batteries, such as the Luri-Nebraska Battery or the Wechsler Adult Intelligence Scale[102, 103]. However, a long-standing challenge in these and successive studies is the multifactorial aetiology of such impairments, including pre-existing variation, fetal alcohol effects, and both direct alcohol-induced excitotoxicity in the brain and indirect toxicity related to factors such as impaired nutrition (e.g., thiamine deficiency[64]), head injury, liver disease, psychiatric comorbidity, and complex interactions between these factors[104]. Cognitive deficits have also been recognized in social drinkers[105], with the suggestion that there is a continuum of deficits related to intensity of alcohol use, including impairments in verbal and non-verbal performance, learning, memory, abstract reasoning, and speed of information processing and efficiency[106]. Finally, recent studies have focused on more selective and aetiologically relevant impairments in emotion and reward processing[107, 108].

Multiple structural imaging studies have shown generalised cortical atrophy particularly for measures of gray[109] and white matter integrity[110] in alcohol dependence[111]. Other reports of brain-related abnormalities include the disruption of white matter tracts[112] and abnormal functional activity[113]. Functional imaging studies in alcohol dependence have identified lower cerebral metabolism in frontal brain regions that show a correlation with executive neuropsychological deficits[114]. Studies in the alcohol-related Wernicke-Korsakoff Syndrome have shown prominent fronto-striatal impairment[115].

Recent attempts to reconcile inconsistent findings across neuroimaging studies with alcohol dependent patients have led to the proposal that, despite alcohol's widespread acute effects on brain function, brain deficits due to chronic and severe alcohol consumption might be limited to frontocerebellar and mesocorticolimbic circuitry, while other brain circuits might be spared or might even undergo compensatory changes[116]. However, prior studies may simply not have been sufficiently powered to reliably detect brain-related impairments and compensatory processes due to small sample sizes, variability across neuroimaging methods, and failure to distinguish disease-specific neurological abnormalities. Standard meta-analysis across neuroimaging studies has proven difficult, mainly due to heterogeneity in the methods used to collect, quality control and parcellate brain data. These limitations also apply to any potential comparisons with other psychiatric conditions. Structural brain abnormalities have also been observed in adults with heavy or problematic cannabis use[117]. Heavy cannabis users have been shown to have lower gray matter density in the right parahippocampus and greater gray matter density in the precentral gyrus and right thalamus[118], and anterior cerebellum[119]. Other studies reported cannabis use and misuse associated with bilateral volumetric reductions in the hippocampus[118, 120, 121,] and amygdala[121 119]. However, findings have not always been replicated, so further studies are needed to confirm these observations[122].

One approach used by researchers to see beyond inconsistent findings in human substance dependence is the meta-analysis. Recent meta-analyses on alcohol use disorder observed grey matter abnormalities in corticostriatal-limbic circuits, such as prefrontal cortical regions, thalamus, striatum and hippocampus[123-125]. Even if several meta-analyses were performed to determine general impacts of a single drug on the adult brain, to our knowledge no meta-analyses compared two widely consumed drugs to other major psychiatric conditions to evaluate the relative volumetric variations observed between cases and controls among psychiatric disorders. Similarly, a recent meta-analysis observed that the hippocampus and the orbitofrontal cortex were most consistently identified as having structural alterations in regular cannabis users[126].

Quantifying brain anomalies across disorders:

There is a recent trend in psychiatric epidemiology to create standardised metrics for the purpose of cross-jurisdiction and cross-disorder comparisons[4, 127] However, until recently, such harmonised approaches have not been used in the field of psychiatric neuroimaging. The development of such methods would help to quantify the subtle and specific brain-related correlates of major psychiatric conditions, which may contribute to, or reflect, an individual's specific symptom profile, general quality of life, and disability. More objective measures of brain impairment may help to identify disorder-specific processes and quantify brain-related impairment and may also help to reduce the effect of social stigma when evaluating disease-related impairment, or when addressing gaps in access to services. In the case of substance use disorders, brain structural measures have been linked to the duration and severity of the disorder, as well as likelihood of relapse[128]. However, research on other psychiatric conditions, such as mood disorders, psychosis, and attention-deficit/hyperactivity disorder (ADHD) has reported abnormalities in similar brain structures[129-131]. Despite potential similarities in brain-related outcomes, public health policies on how these conditions are managed dramatically differ across cultures and across disorders. Alcohol use disorders are detrimentally under-treated in most parts of the world, relative to other psychiatric conditions[132]. However, it is not clear if the treatment gaps observed across disorders can be justified based on objective indicators of impairment.

The current study aims to capitalise on the methods developed in the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium to use standardized protocols for quantifying and comparing the brain-related correlates of various psychiatric conditions for the purpose of promoting health equity. Using standardized protocols to harmonise neuroimaging data and conduct meta-analyses for cross-disorder comparisons[133-135], we report, for the first time, effect sizes derived from meta-analysis involving alcohol dependent and cannabis dependent cases and age- and sex-matched controls worldwide. Results of this analysis will be compared to effects found in large-scale international studies of major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BD), and Attention-Deficit/Hyperactivity Disorder (ADHD) using identical brain parcellation methods and covariates[129-131].

The ENIGMA network[133] was formed to address the need for replicability and increased sample sizes and to increase power for genome-wide association studies of brain measures. With the development of standard anatomical templates and coordinate-based reference systems, researchers worldwide can now relate their new findings to previous results in a consistent way. The pooling of datasets across sites and clinical samples now allows us to study uncommon or complex phenomena and compare findings across disorders. The most commonly used statistical approach in ENIGMA is a meta-analysis, in which evidence for association is combined using effect sizes for each separate site, which are weighted to adjust for each site's sample size and error variance.

Several disease-specific working groups have been formed, focusing on performing meta-analysis of case-control disease differences of measures extracted using the ENIGMA protocols. This approach also allows for the unification of both case-control and cohort datasets with a standard protocol and allows for the largest imaging studies of the human brain to be performed while focusing on a particular disease process. To date, ENIGMA working groups such as Major Depression, Bipolar Disorder and Schizophrenia have reported small to moderate effect sizes in terms of brain-related abnormalities[129-131], such as alterations in hippocampus (except for ADHD), amygdala (except for MDD) and thalamus (except for ADHD and MDD).

The combined datasets contain participants with structural brain data and addiction phenotyping and involves both cohort and case-control designs, representing individuals with ages ranging from 12- 60 years and a number of different addiction phenotypes. For the purpose of the current study, we omit cohort studies and focus on case-control samples representing alcohol use disorder (AUD) and cannabis use disorder (CUD) since these substances are among the most consumed worldwide [100, 101, 136]. To be able to compare effect sizes for addiction subgroups to published results from other ENIGMA disease groups, we focused our first set of analyses on structural measures of subcortical and cortical brain regions[129-131].

ENIGMA provides quality control procedures for harmonising neuroimaging and genetic data, available online through http://enigma.loni.ucla.edu/ongoing/gwasma-of-subcortical-structures. While many working groups within ENIGMA are now moving toward the 'mega-

analysis' strategy, where all phenotypic and genotypic data are sent to a centralised site for pooling and analysis, the first ENIGMA studies used a "meta-analysis" approach. Meta-analyses circumvent barriers associated with data sharing across sites and countries and allows sites to maintain responsibility for their data and its integrity since studies can share site-level summary statistics instead of individual data. This approach also has advantages when the purpose of the study is to make cross disorder comparisons. ENIGMA-Addiction recently evaluated the subject-specific volumetric variations in drug-specific groups using innovative methods[137, 138]. These approaches observed subcortical and cortical variations in alcohol-dependent participants but not in cannabis-dependent participants, which is interesting given the fact that a recent meta-analysis observed an association between cannabis use and reduced volumes in subcortical regions and thinning of cortical thickness in the orbitofrontal cortex[139]. Similar case-control differences were observed in ADHD, MDD, SCZ and BD but have never been compared to drug-specific variations using common metrics.

Subjects and Methods

Samples

The ENIGMA-Addiction Working Group includes international samples with neuroimaging and clinical data from substance dependent patients and healthy controls. This is an ongoing collection of data sets and new research groups continue to join the consortium regularly. Inclusion criteria for study enrolment were that sites must agree to their data being processed using the ENIGMA scripts and basic information on dependence criteria and patterns of early use are available for cases and controls. Demographic details for seven international samples of alcohol-dependent subgroups and seven international samples of cannabis use that were available in April 2019 are presented in Table 1. The number of participants included vary from the sample of the mega-analysis performed by Mackey et al., (2019) on the substance-specific association between dependence and grey matter volume because sites that did not include a control group could not derive a comparable effect size. Most participants were classified as having substance use disorder, or not, using validated structured diagnostic interviews that conform to Diagnostic and Statistical Manual of Mental Disorders-Fourth-TR Edition[94] criteria.

One site included chronic cannabis users for whom DSM criteria could not be confirmed [140], and two adolescent sites were included in the sample. Similarly to the mega-analysis of the ENIGMA Addiction working group, subjects with a lifetime history of neurological disease and/or a current DSM-IV axis I diagnosis (other than depressive and anxiety disorders) were excluded from the analyses of the current article. AUD and CUD cases were mostly lifetime dependence cases[138]. Participants with a co-occurring substance use disorder were removed from the analyses from the current article. All control participants were confirmed with similar interviews to be free of any substance use disorder. All participating studies obtained approval from local institutional review boards and ethics committees. All study participants provided written informed consent at their local institution for the local study. CHU Ste Justine provided ethical approval for this meta-analysis. This study includes 435 cases with primary alcohol use disorder (AUD) and 363 matched healthy controls; and 200 cases of CUD and 247 controls.

Tableau 1. – **Table 1 (Article 1).** Demographic details for each study.

Substance of Dependence	Number of Studies	Groups	N	Female	Age
All	14	Case	635	188	28.12
		Control	610	208	29.23
Alcohol	7	Case	435	127	32.43
		Control	363	136	33.58
IRC [1-3]		Case	43	11	28.05
		Control	84	21	37.49
Effects of heavy alcohol abuse on adolescent brain structure and function [4]		Case	60	34	14.81
		Control	56	31	14.94
NIAAA [5-7]		Case	212	57	31.11
		Control	140	67	38.48
Neuro-ADAPT [8]		Case	18	6	19.35
		Control	23	11	18.72
NESDA-AD [9]		Case	42	19	48.6
		Control	20	6	48.29
ADPG study [10-12]		Case	28	0	43.43
		Control	24	0	37.17
TrIP Study [13]		Case	32	0	41.69
		Control	16	0	39.94
Cannabis	7	Case	200	61	23.80

	Control	247	72	24.88
Trinity-THC [14]	Case	15	2	23.27
	Control	15	4	22.4
Orr [15]	Case	13	1	16.00
	Control	14	1	16.77
Cannabis Prospective [16-18]	Case	38	12	21.85
	Control	40	15	21.39
ADS	Case	7	6	18.96
	Control	93	44	19.00
Chronic cannabis users (Barcelona) [19-21]	Case	16	1	35.00
	Control	18	2	38.98
Chronic cannabis [22-25]	Case	81	39	30.47
	Control	38	6	33.21
Chronic Cannabis-Memory [26-29]	Case	30	0	21.03
	Control	29	0	22.41

Image processing and analysis

Structural T1-weighted magnetic resonance imaging brain scans were acquired at each study. Using the fully automated and validated segmentation software FreeSurfer[96], the segmentations of seven subcortical gray matter regions (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus), 34 cortical regions, lateral ventricles, and total ICV were derived following standardized protocols designed to facilitate harmonized image analysis across multiple studies (http://enigma.ini.usc.edu/protocols/imaging-protocols). Image acquisition parameters and software descriptions for each sample are similar to those in previous ENIGMA studies[129-131], to facilitate the between-disorder comparison. A majority of the datasets were prepared using CBRAIN, a network of high-performance computing facilities in Canada[141]. Studies followed the ENIGMA protocols for quality control http://enigma.ini.usc.edu/protocols/imaging-protocols/. The detection of outliers and visual inspection were performed in a series of standard planes to avoid the inclusion of poorly segmented and mislabeled structures. Quality control procedures at each study were conducted according to standardized protocols to minimize potential site effects. Additional visual inspection was performed on a randomly selected sub-sample of participants centrally at the University of Vermont to ensure uniformity of quality control across studies.

Statistical framework of meta-analysis

Consistent with other ENIGMA working groups, multiple linear regression analyses derived case versus control group differences within each study-specific sample using the mean volume of bilateral subcortical ROIs ((left+right)/2) along with left and right thickness and surface area for each cortical ROI as the outcome measures and control/case as the binary grouping independent variable. In order to make results comparable with those of yielded from the schizophrenia, MDD, BD, and ADHD working groups, models for subcortical ROIs covaried for age, sex and total intracranial volume (ICV), and models for cortical ROIs covary for age and sex. In order to be consistent with the reported findings of the other working groups, we did not covary for past 30-day alcohol and nicotine use in the analyses. Furthermore, because past 30-day substance use is so highly correlated with dependence scores, co-varying for this variable in meta-analysis would likely lead to underestimation of main differences between cases and controls. Regression models were fit for each study separately and t-statistics were used to estimate effect sizes. A Cohen's d-effect size estimate was obtained using an inverse variance-weighted random-effect meta-analysis model in R (metafor package[142]). Uncorrected and False Discovery Rate (FDR) corrected *p* values are reported and, are indicated as significant effect sizes by an asterix in figures below. I-square indices were calculated to provide a measure of heterogeneity. Significance level was determined with a $p_{FDR} < 0.05$ for all regions of interest. Differences between effect sizes were considered significant if confidence intervals (or standard errors) did not overlap, which is appropriate when Cohen's d is derived based on sample sizes above 20[143]. We performed a *posthoc* sensitivity analysis on the meta-analytic results for the alcohol and cannabis subgroups excluding the two adolescent studies using a leave-one-out approach (Viechtbauer W, 2010). The inclusion of adolescent studies in the AUD and CUD analyses might lead to greater variability and inconsistent findings due to the volumetric variations that occur during the adolescence[144]. Because the confidence intervals for the adolescent studies overlap with the adult-only studies for all regions of interest, it did not significantly differ from the rest of the sample. The Results section include significant variations when the adolescent studies are included because the volumetric case-control differences were consistent (i.e., overlap between confidence intervals) to those observed with the adult sites for subcortical volumes and cortical

thickness (Supplementary Figures 1-4). The Cohen's d values were obtained after adjustment for age, the adolescent studies were included in final AUD and CUD sample sizes in order to increase the sample size.

Results

Figure 1 shows the forest plot with effect sizes and 95% confidence intervals for subcortical volumes when comparing AUD cases to their matched controls: FDR corrected significant differences are shown in the thalamus, (*d* = −0.23, CI = [−0.42, −0.04]), putamen (*d* = -0.27, CI = [-0.45, -0.08]), hippocampus (*d* = -0.50, CI = [-0.76, -0.24]), amygdala (*d* = −0.39, CI = [−0.63, −0.16]) and the accumbens (*d* = -0.30, CI = [-0.49, -0.12]). The caudate (*d* = −0.04, CI = [−0.22, 0.15]) and the pallidum (*d* = −0.10, CI = [−0.24, 0.04]) were not significant following the FDR correction.

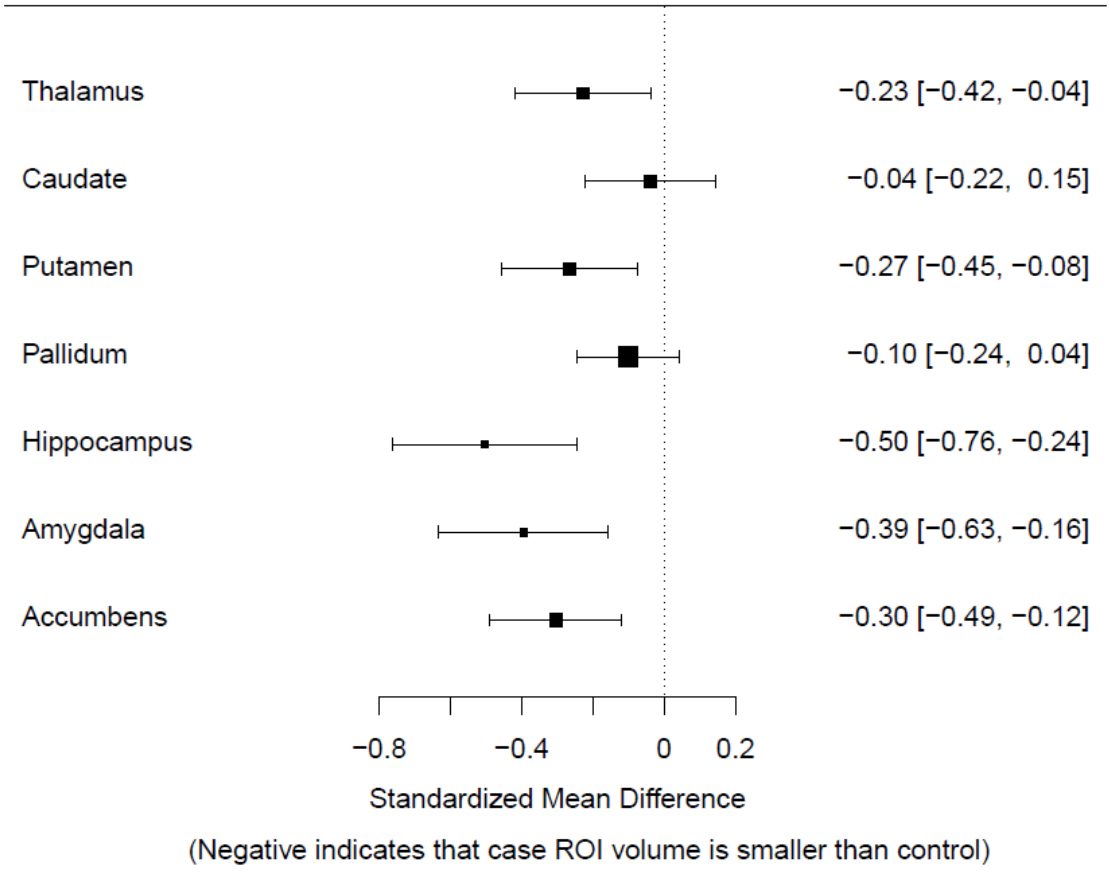

Figure 1. – **Figure 1 (Article 1).** Forest plot with effect sizes and confidence intervals for bilateral subcortical volume for the alcohol use disorder versus controls comparison controlling for

age, sex when females were included, and ICV. Error bars represent 95% confidence intervals. The caudate and the pallidum were not significant following the FDR correction.

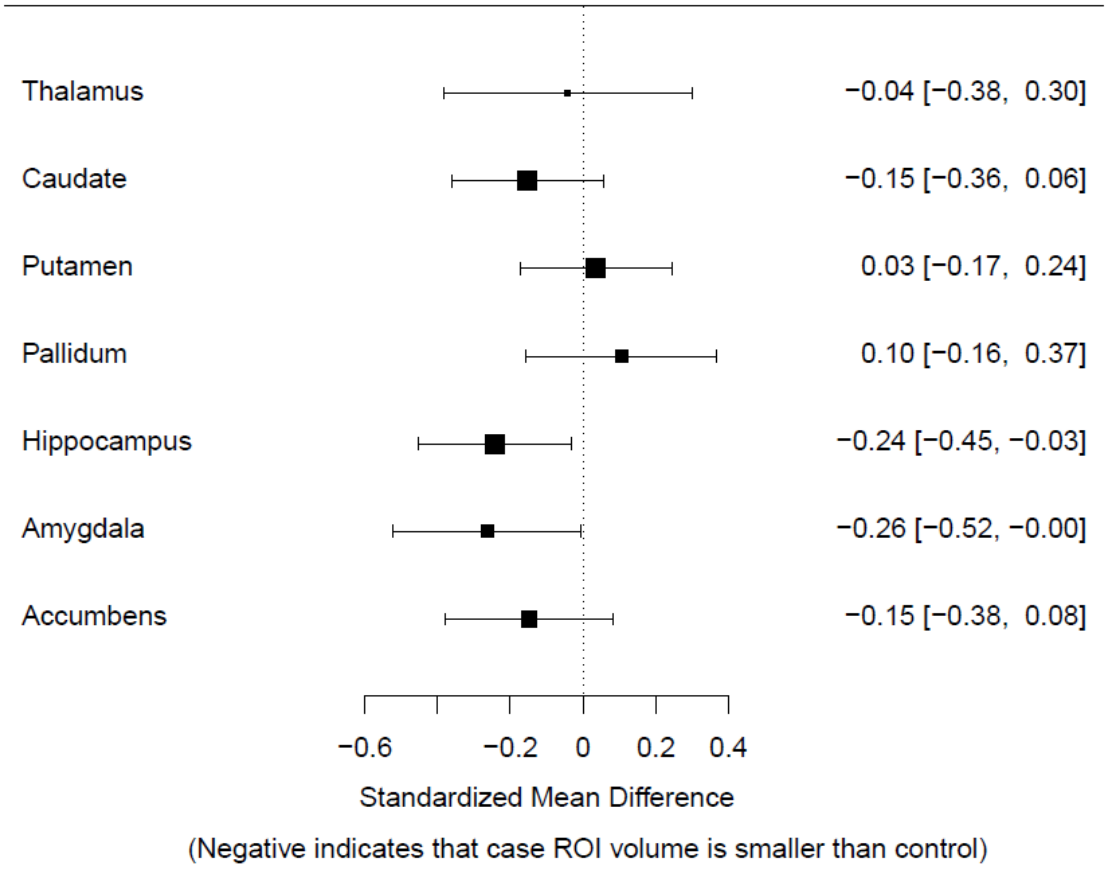

Figure 2. – **Figure 2 (Article 1).** Forest plot with effect sizes and confidence intervals for bilateral subcortical volume for the cannabis use disorder versus controls comparison controlling for age, sex when females were included, and ICV. Error bars represent 95% confidence intervals. All results are non-significant following FDR correction.

Figure 2 presents the case control comparisons for CUD, showing non-significant case-control differences after correcting for multiple comparisons.

Figure 3 presents a comparison of subcortical results for AUD and CUD and previously published ENIGMA meta-analyses on major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BD), and ADHD. If confidence intervals overlap between groups for a region of interest,

no significant difference was observed. The magnitude of effect sizes for case-control AUD comparisons appear larger than effect sizes reported for MDD, BD, and ADHD except for the caudate and the pallidum. However, these effect sizes do not differ significantly from the other psychiatric conditions since the confidence intervals overlap. In comparison to effects reported for SCZ, confidence intervals overlapped between AUD and SCZ on all subcortical ROIs. When comparing other subcortical regions across AUD and MDD, confidence intervals did not overlap for the putamen, hippocampus, amygdala and accumbens, with AUD associated with significantly smaller volumes in these regions. When comparing AUD and BD, confidence intervals overlap for all regions but the amygdala, with significantly greater differences evident in AUD case control comparison (AUD associated with smaller volume). The effects reported for CUD in the amygdala and accumbens appear comparable to those reported for AUD and SCZ, but due to large confidence intervals, these effects were not shown to significantly differ from non-effect line and the other disorders. CUD observations also overlapped with AUD and SCZ findings. These CUD results suggest considerable heterogeneity or variability in the CUD studies (Supplementary Figure 5).

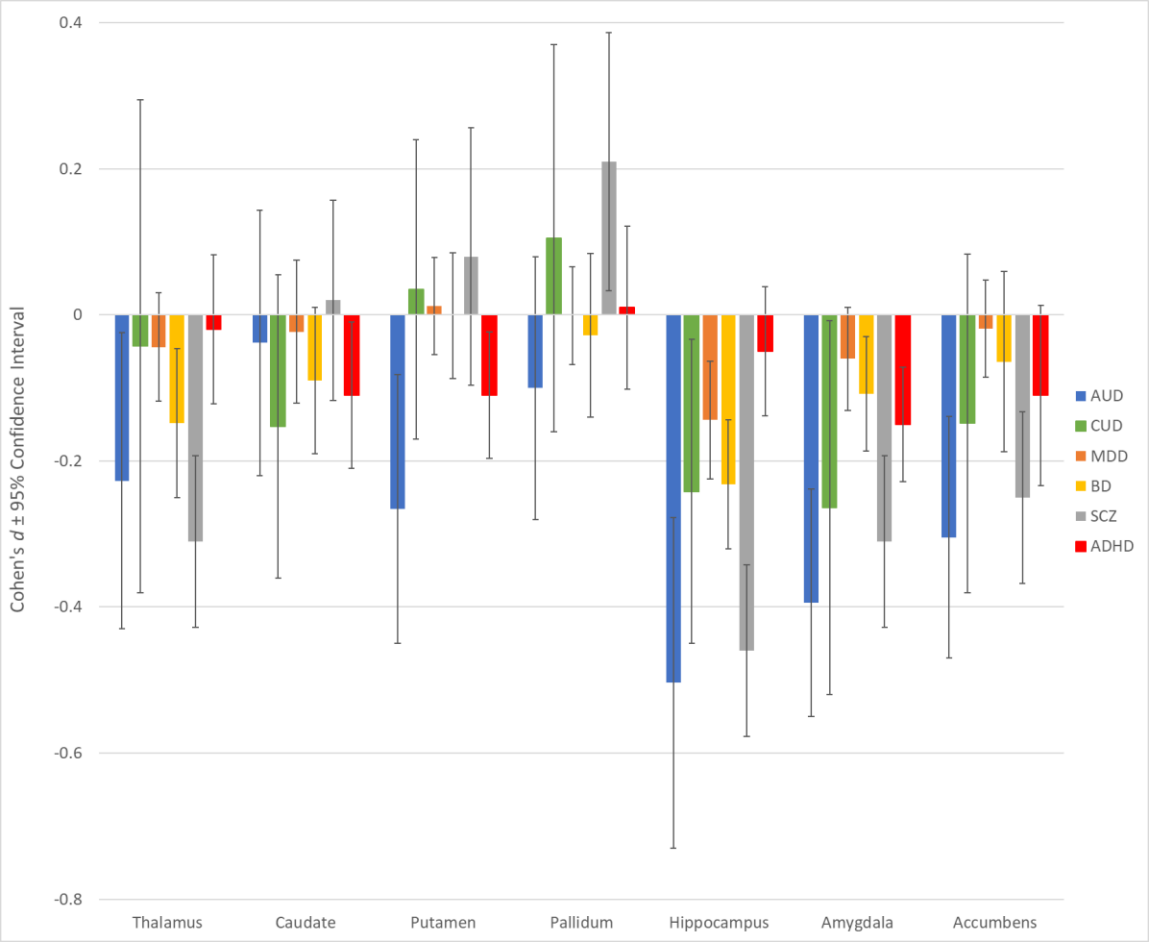

Figure 3. – **Figure 3 (Article 1).** Comparison between bilateral subcortical results for alcohol use disorder (AUD), cannabis use disorder (CUD), depression (MDD), psychotic disorder (SCZ), bipolar disorder (BPD), and ADHD. Error bars represent 95% confidence intervals. Significant volumetric variations when compared to age-, sex- and disorder-matched controls was observed when the confidence intervals did not overlap with non-effect line at 0 and survived FDR correction. While significant reductions are observed in the ADHD for the putamen, amygdala and the caudate, none of these results remained in ADHD adult-specific analyses

Analysis of cortical thickness by AUD case-control comparisons shows FDR-corrected significant bilateral differences in the caudal anterior cingulate, fusiform, inferior temporal, parahippocampal, posterior cingulate, superior frontal and temporal pole. Table 2 presents effect sizes and confidence intervals for cortical thickness in each ROI for alcohol use disorder. Table 3

presents effect sizes and confidence intervals for cortical thickness for cannabis use disorder in each ROI. None of the CUD-control comparisons on cortical thickness were shown to survive FDR correction for multiple testing across all ROIs, but marginal, FDR-corrected effects were revealed for the medial orbitofrontal cortex ($p_{FDR} < 0.1$), caudal middle frontal ($p_{FDR} = 0.1$), precentral gyrus ($p_{FDR} = 0.1$) and insula ($p_{FDR} = 0.1$).

Tableau 2. – **Table 2 (Article 1).** Full meta-analytic results for volume and thickness of each bilateral structure for the alcohol use disorder versus controls comparison controlling for age, sex and ICV (for subcortical regions only).

ROI	ES	SE	95% CI.LB	95% CI.UB	I^2	p	p-fdr	Controls	Cases
Thalamus	-0.2272	0.0976	-0.4184	-0.0359	28.84	0.0199	**0.0279**	359	345
Caudate	-0.0382	0.094	-0.2225	0.1461	28.12	0.6844	0.6844	361	437
Putamen	-0.2656	0.0966	-0.455	-0.0762	30.53	0.006	**0.0105**	361	436
Pallidum	-0.1002	0.0727	-0.2427	0.0423	0.01	0.1681	0.1961	365	437
Hippocampus	-0.5037	0.1325	-0.7634	-0.244	60.85	0.0001	**0.0010**	362	437
Amygdala	-0.3942	0.1215	-0.6323	-0.156	53.99	0.0012	**0.0031**	364	437
Accumbens	-0.3044	0.0948	-0.4901	-0.1187	28.27	0.0013	**0.0031**	362	436
Bankssts	-0.15	0.147	-0.43	0.14	68.609	0.319	0.5784	360	436
Caudal anterior cingulate	-0.24	0.073	-0.38	-0.09	0.00	0.001	**0.0067**	365	437
Caudal middle frontal	-0.1	0.154	-0.4	0.2	71.767	0.517	0.7563	365	437
Cuneus	-0.03	0.142	-0.31	0.25	66.9	0.817	0.9496	364	437
Entorhinal	-0.22	0.137	-0.48	0.05	62.843	0.115	0.3001	362	431
Fusiform	-0.47	0.084	-0.64	-0.31	14.048	0.00	**0.0001**	365	436
Inferior parietal	-0.01	0.149	-0.3	0.29	70.21	0.965	0.9647	365	437
Inferior temporal	-0.36	0.081	-0.52	-0.21	10.367	0.00	**0.0001**	365	437
Isthmus cingulate	-0.22	0.103	-0.43	-0.02	37.955	0.029	0.0997	364	436
Lateral occipital	-0.16	0.119	-0.39	0.08	52.71	0.188	0.4576	365	437
Lateral orbitofrontal	-0.29	0.119	-0.53	-0.06	52.526	0.014	0.0531	365	436
Lingual	-0.01	0.143	-0.29	0.27	67.39	0.942	0.9647	365	437
Medial orbitofrontal	-0.13	0.116	-0.36	0.1	49.999	0.265	0.5630	364	436
Middle temporal	-0.23	0.137	-0.49	0.04	63.939	0.1	0.2833	361	437
Parahippocampal	-0.25	0.073	-0.39	-0.1	0.003	0.001	**0.0053**	364	437
Paracentral	-0.19	0.196	-0.58	0.19	82.825	0.323	0.5784	365	437
Pars opercularis	-0.01	0.131	-0.27	0.24	61.005	0.921	0.9647	365	437
Pars orbitalis	-0.06	0.109	-0.28	0.15	43.834	0.556	0.7563	365	437
Pars triangularis	-0.03	0.167	-0.36	0.29	76.22	0.839	0.9496	365	437
Pericalcarine	0.05	0.166	-0.28	0.37	75.831	0.781	0.9496	365	436
Postcentral	0.05	0.203	-0.35	0.45	84.059	0.809	0.9496	365	437
Posterior cingulate	-0.29	0.115	-0.51	-0.06	49.129	0.012	**0.0498**	365	437

Precentral	-0.13	0.189	-0.5	0.24	81.542	0.503	0.7563	365	437
Precuneus	-0.15	0.14	-0.43	0.12	66.082	0.284	0.5686	365	437
Rostral anterior cingulate	-0.31	0.073	-0.45	-0.17	0.001	0.000	**0.0002**	365	437
Rostral middle frontal	-0.03	0.178	-0.38	0.32	79.1	0.866	0.9496	365	437
Superior frontal	-0.18	0.073	-0.33	-0.04	0.002	0.011	**0.0498**	365	436
Superior parietal	-0.11	0.186	-0.47	0.25	80.83	0.549	0.7563	365	436
Superior temporal	-0.21	0.182	-0.57	0.14	79.566	0.242	0.5483	360	435
Supramarginal	-0.14	0.148	-0.43	0.15	69.05	0.344	0.5853	361	436
Frontal pole	0.06	0.073	-0.08	0.2	0.00	0.408	0.6611	365	437
Temporal pole	-0.32	0.073	-0.46	-0.17	0.00	0.00.	**0.0002**	365	437
Transverse temporal	0.05	0.152	-0.25	0.34	71.255	0.76	0.9496	365	437
Insula	-0.21	0.12	-0.45	0.03	53.324	0.08	0.2471	363	436

Note. Bankssts: Banks of the superior temporal sulcus, ROI: Region of Interest, ES: Effect size, SE: Standard Error, CI.LB: Confidence Interval Lower Bound, CI.UB: Confidence Interval Upper Bound, p-fdr: adjusted p-value for the seven studies following a BH correction.

Tableau 3. – **Table 3 (Article 1).** Full meta-analytic results for volume and thickness of each bilateral structure for the cannabis use disorder versus controls comparison controlling for age, sex and ICV (for subcortical regions only).

ROI	ES	SE	95% CI.LB	95% CI.UB	I^2	p	p-fdr	Controls	Cases
Thalamus	-0.0425	0.1744	-0.3844	0.0821	58.47	0.8074	0.8074	249	200
Caudate	-0.1526	0.1062	-0.3608	0.0556	0.00	0.1508	0.3519	250	200
Putamen	0.0349	0.1062	-0.1732	0.2431	0.00	0.7421	0.8074	250	199
Pallidum	0.1049	0.1333	-0.1563	0.3662	30.98	0.4312	0.6037	250	200
Hippocampus	-0.2416	0.1071	-0.4515	-0.0318	0.00	0.024	0.1608	249	196
Amygdala	-0.2638	0.1322	-0.5229	-0.0048	29.6	0.0459	0.1608	249	200
Accumbens	-0.1483	0.1175	-0.3787	0.0821	14.28	0.207	0.3623	250	200
Bankssts	-0.12	0.11	-0.34	0.09	0.00	0.259	0.4797	229	186
Caudal anterior cingulate	0.01	0.107	-0.2	0.22	0.005	0.952	0.9783	247	200
Caudal middle frontal	-0.26	0.106	-0.47	-0.05	0.00	0.015	0.1031	248	200
Cuneus	-0.14	0.143	-0.42	0.14	39.02	0.325	0.5017	248	200
Entorhinal	-0.1	0.154	-0.4	0.2	41.499	0.512	0.6217	230	175
Fusiform	-0.14	0.127	-0.39	0.11	25.048	0.277	0.4797	250	200
Inferior parietal	-0.17	0.123	-0.41	0.07	20.127	0.173	0.3667	246	199
Inferior temporal	-0.07	0.133	-0.33	0.19	30.497	0.609	0.6681	248	200
Isthmus cingulate	0.00	0.128	-0.25	0.25	25.557	0.978	0.9783	246	200
Lateral occipital	-0.11	0.134	-0.37	0.16	31.126	0.43	0.5727	247	199

Lateral orbitofrontal	-0.2	0.128	-0.45	0.05	25.254	0.12	0.3667	250	200
Lingual	-0.16	0.118	-0.4	0.07	14.98	0.165	0.3667	248	200
Medial orbitofrontal	-0.33	0.107	-0.54	-0.12	0.00	0.002	0.0672	248	199
Middle temporal	-0.01	0.108	-0.22	0.2	0.00	0.918	0.9749	239	192
Parahippocampal	-0.19	0.141	-0.47	0.09	37.631	0.18	0.3667	250	200
Paracentral	-0.23	0.109	-0.44	-0.01	3.011	0.037	0.2075	249	200
Pars opercularis	-0.06	0.108	-0.28	0.15	0.00	0.549	0.6436	243	197
Pars orbitalis	-0.09	0.107	-0.3	0.12	0.00	0.382	0.5414	249	199
Pars triangularis	-0.18	0.107	-0.39	0.03	0.00	0.093	0.3221	249	197
Pericalcarine	-0.29	0.144	-0.57	-0.01	39.396	0.043	0.2076	248	200
Postcentral	-0.23	0.161	-0.55	0.08	51.628	0.15	0.3667	249	200
Posterior cingulate	-0.12	0.138	-0.39	0.15	35.024	0.382	0.5414	248	200
Precentral	-0.3	0.121	-0.54	-0.06	17.566	0.013	0.1031	244	200
Precuneus	-0.16	0.123	-0.41	0.08	20.083	0.183	0.3667	246	200
Rostral anterior cingulate	-0.08	0.107	-0.29	0.13	0.00	0.456	0.5738	246	200
Rostral middle frontal	-0.06	0.107	-0.27	0.15	0.00	0.594	0.6681	249	199
Superior frontal	-0.16	0.106	-0.37	0.05	0.00	0.129	0.3667	248	200
Superior parietal	-0.21	0.126	-0.46	0.04	23.49	0.095	0.3221	250	200
Superior temporal	-0.15	0.145	-0.43	0.14	38.979	0.312	0.5017	239	193
Supramarginal	-0.11	0.137	-0.37	0.16	32.748	0.438	0.5727	244	200
Frontal pole	-0.11	0.106	-0.32	0.09	0.007	0.282	0.4797	250	200
Temporal pole	-0.3	0.107	-0.5	-0.09	0.00	0.006	0.0955	250	200
Transverse temporal	-0.2	0.106	-0.41	0.01	0.00	0.061	0.2580	249	200
Insula	-0.29	0.119	-0.53	-0.06	15.824	0.014	0.1031	250	200

Note. Bankssts: Banks of the superior temporal sulcus, ROI: Region of Interest, ES: Effect size, SE: Standard Error, CI.LB: Confidence Interval Lower Bound, CI.UB: Confidence Interval Upper Bound, p-fdr: adjusted p-value for the seven studies following a BH correction.

Figure 4 presents the comparison between bilateral cortical thickness results for AUD, CUD and previously published ENIGMA meta-analysis comparing MDD cases to controls on comparable cortical thickness measures. ROIs reported in Figure 4 were significantly different between cases and controls for MDD, AUD, or both of them. There is an overlap in confidence for most ROIs except temporal pole, where AUD and CUD showed greater reductions in cortical thickness when compared to MDD. However, the temporal pole for CUD did not survive FDR correction, so it is not a reliable finding. Relative to MDD effects, greater AUD-related reductions are observed in the fusiform since the confidence intervals do not overlap. Even if reduced cortical thickness in the medial orbitofrontal cortex for CUD is greater than in MDD since the intervals do not overlap, the large confidence intervals for CUD suggest using caution interpreting this finding.

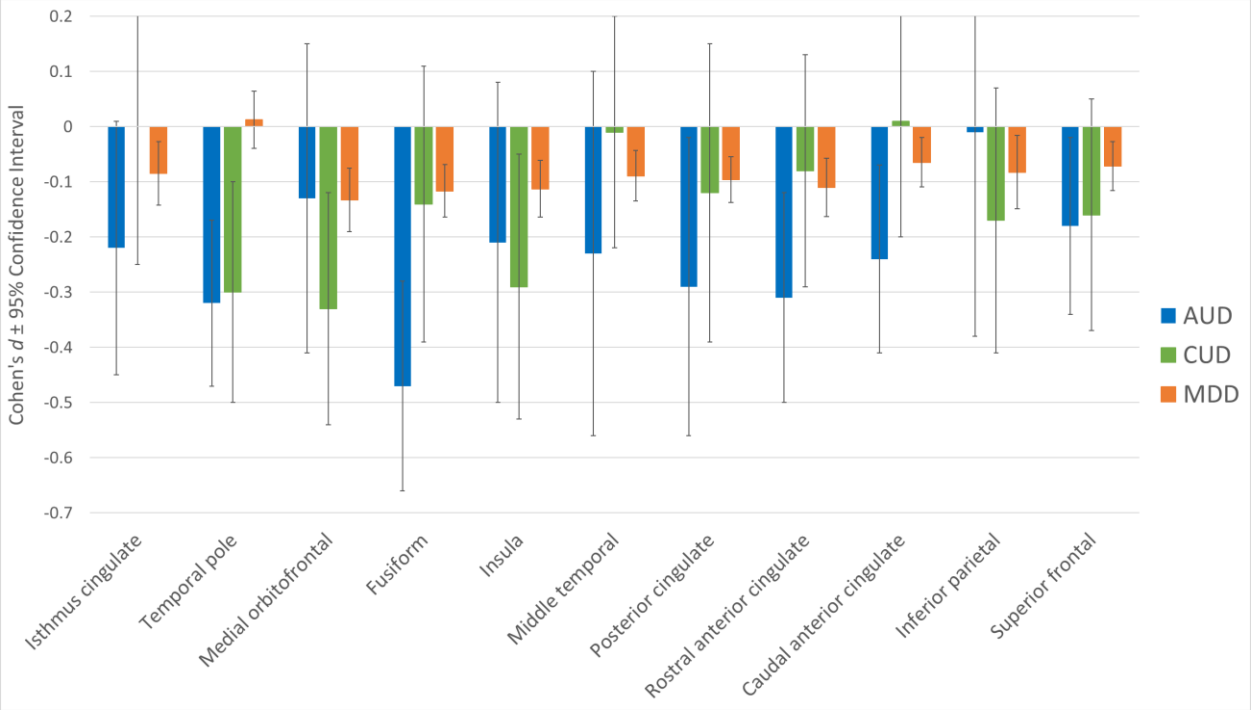

Figure 4. – **Figure 4 (Article 1).** Comparison between bilateral cortical thickness results for alcohol (AUD), cannabis use disorder (CUD) and depression (MDD) on ROIs. Bilateral effects represent mean unilateral effect for each region. Error bars represent 95% confidence intervals. Significant volumetric variations when compared to age-, sex- and disorder-matched controls was observed when the confidence intervals did not overlap with non-effect line at 0 and survived FDR correction

Figure 5 compares AUD and CUD effects to the results reported for bipolar disorder[145, 146] and schizophrenia[130, 147] . Most regions identified in the AUD cortical thickness analyses were also reported to be significant for BD and SCZ, with the exception of the rostral anterior cingulate and the temporal pole, which were not reported as significant for BD but were significant for SCZ. However, most of the effect sizes showed overlapping confidence intervals, suggesting no discernible differences. The confidence intervals do not overlap for temporal pole between AUD and BD, with greater case-control differences (smaller volumes) in AUD. Of interest, the four regions that marginally discriminated CUD from controls showed overlap with AUD, BD and SCZ findings (medial orbitofrontal, caudal middle frontal, precentral gyrus and insula). This figure also

shows that relative to other disorders, there was considerable heterogeneity in AUD and CUD findings (large confidence intervals) for cortical thickness measures.

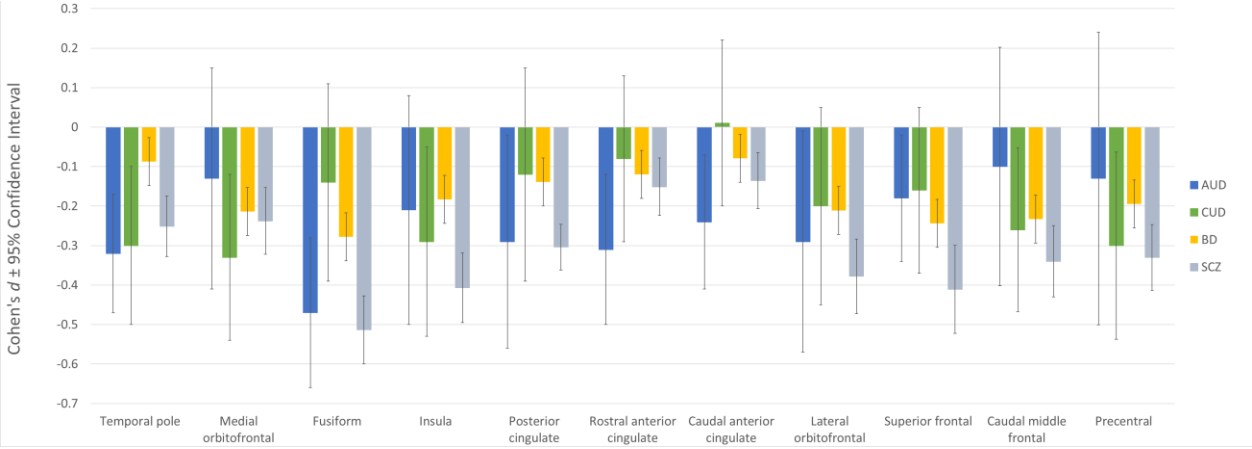

Figure 5. – **Figure 5 (Article 1).** Comparison between bilateral cortical thickness results for alcohol use disorder (AUD), cannabis use disorder (CUD), bipolar disorder (BD) and schizophrenia (SCZ) on ROIs. Bilateral effects represent mean unilateral effect for each region. Significant volumetric variations when compared to age-, sex- and disorder-matched controls was observed when the confidence intervals did not overlap with non-effect line at 0 and survived FDR correction. Error bars represent 95% confidence intervals.

Conclusion and Context

Health outcomes of various neurological and psychiatric conditions are currently compared using models such as global burden of disease, focusing on years of life lost, or severe indicators of disability. However, less developed are the models focusing on the quantification of brain-related impairment. This study represents a first step in developing and validating a method for comparing brain health/impairment for which the next steps will necessarily require association with quality of life or disability measures. In this transversal meta-analysis study we observed reduced bilateral volumes in the thalamus, putamen, hippocampus, amygdala in alcohol-dependent participants. Additionally, AUD subjects showed reduced cortical thickness in the rostral and caudal anterior cingulate gyri, fusiform, inferior temporal, parahippocampal,

posterior cingulate, superior frontal and temporal pole. No significant subcortical volume or cortical thickness variation was observed in cannabis-dependent subjects. The AUD variations mentioned above are consistent with previous meta-analytic findings[123, 124], which support the proposal that alcohol dependence consistently impacts specific subcortical and cortical regions in the adult brain. The altered subcortical and cortical regions in AUD reported could give some insight into the pathophysiology of alcohol dependence. The amygdala, accumbens, hippocampus and cingulate regions showed reduced volumes in AUD. These observations are interesting since these regions are part of the mesocorticolimbic system, which has been shown to be central to addictive behaviors in pre-clinical studies[148]. This meta-analysis of human neuroimaging studies confirms reliable alcohol-related brain impairment in this brain system.

The current findings suggest that AUD is associated with significant alterations in subcortical brain structures and at a magnitude that is comparable to or larger than other major psychiatric disorders. Furthermore, results for alcohol were comparable to those previously reported for patients with psychosis, at least within the thalamus, hippocampus, amygdala and accumbens and were significantly larger than MDD in the hippocampus, amygdala and accumbens. When comparing AUD findings to MDD findings on cortical thickness across all ROIs of the brain, AUD was generally associated with reductions in cortical thickness across many of the same brain regions that were associated with MDD, but alcohol produced larger effect sizes, with two regions showing significantly smaller volumes in AUD participants compared to MDD participants: fusiform gyrus and temporal pole. Compared to schizophrenia and bipolar disorder, AUD-related differences in brain volume overlapped with those reported for these other disorders, but there was evidence that AUD might be particularly linked to abnormalities in the cingulate.

The absence of significant differences that survived FDR correction between CUD patients and controls is interesting given the debate on the potential neurotoxic impact of cannabis dependence on the hippocampus and the medial orbitofrontal cortex[139, 149]. This could be partly explained by the substantial heterogeneity observed within the included studies (Supplementary Figure 5). Even if the reduced thickness observed in the medial orbitofrontal and the insula

cortices is consistent with previous findings in long-term users[139, 150], further studies are required to determine if these observations are part of the structural signature of the CUD pathophysiology.

The current findings suggest that AUD is associated with significant alterations in subcortical brain structures and at a magnitude that is comparable to or larger than other major psychiatric disorders. Furthermore, results for alcohol were comparable to those previously reported for patients with psychosis, at least within the thalamus, hippocampus, amygdala and accumbens and were significantly larger than MDD in the hippocampus, amygdala and accumbens. When comparing AUD findings to MDD findings on cortical thickness across all ROIs of the brain, AUD was generally associated with reductions in cortical thickness across many of the same brain regions that were associated with MDD, but alcohol produced larger effect sizes, with two regions showing significantly smaller volumes in AUD participants compared to MDD participants: fusiform gyrus and temporal pole. Compared to schizophrenia and bipolar disorder, AUD-related differences in brain volume overlapped with those reported for these other disorders, but there was evidence that AUD might be particularly linked to abnormalities in the cingulate. By contrast, cortical thickness analyses on CUD case-control studies suggest convergent findings with a previous study from the ENIGMA-Addiction working group[138]. The regions that most distinguished CUD cases from controls (though only achieving marginal statistical significance) also significantly discriminated BD and SCZ cases from controls. Hibar et al. and Van Erp et al. both previously reported reduced cortical thickness in medial orbitofrontal, insula, caudal middle frontal and precentral gyrus in BD and SCZ, which were not observed for AUD in the current study but appear marginally significant for CUD in the current study[146, 147]. Recognizing that these findings require further investigation due to the non-significance revealed for cannabis after FDR correction, they are worth pursuing considering that cannabis and psychosis show a strong relationship in clinical and epidemiologic studies (reviewed by Gage[151]). This relationship has been shown to be independent of other substance use and other mental health symptoms [152]. These effects should also be further investigated to determine if they reflect a potential unexamined effect of substance misuse in the bipolar and schizophrenia studies, or a potential common underlying vulnerability toward cannabis use and psychotic disorders.

Using this preliminary study as a proof-of-concept, future meta-analyses focusing on pooling across disease groups will help to identify brain attributes that are common to mental disorders and those that are more disease-specific, using multi-level analytic strategies. These findings could then guide more focused, region of interest analyses incorporating behavioral, genetic, or brain diffusion/connectivity measures. There might also be some value in linking these findings to other global measures of disability, for example, Global Assessment of Functioning measures, to help identify the brain regions that most affect disability across disorders and within specific disorders.

The current findings of smaller volumes and cortical alteration in the hippocampus, amygdala, accumbens, temporal pole, fusiform of AUD patients relative to patients with MDD (and comparable to patients with SCZ or BD are consistent with the observation that alcohol dependence is associated with specific impairment in memory encoding and recall[116]. However, effect sizes for all subcortical regions (including pallidum and putamen) along with alterations in the anterior cingulate, indicate that alcohol dependence is potentially associated with impairment in brain regions implicated in affect regulation, mood, attention/concentration, motivation, processing speed, behavioral control and executive functions[153]. These functions are not typically measured on brief tests of general intellectual functioning or memory and require more elaborate neuropsychological and repeated behavioral assessments in order to be detected. The current findings suggest a need for investment in cognitive rehabilitative services for patients with AUD that are comparable in terms of specificity and intensity to those available to patients with schizophrenia, and focusing on more subcortically mediated functions.

Disability measures can be confounded by factors such as social desirability, stigma, education and socioeconomic status, and might explain the inequities in treatment gap observed across the mental and neurologic disorders. The current findings, using an objectively-derived brain metric, allow for a cross-disorder comparison that is free of culturally-influenced biases and places AUD in the same class as schizophrenia, and far above Major Depression, in terms of brain-related impairment.

Substance use disorders are detrimentally under-treated in society, despite their demonstrated social and health costs[154]. For example, one community-based psychiatric epidemiology study conducted by the Global Burden of Disease consortium examined standardized diagnostic instruments and statistics on percentage of individuals receiving care across various WHO regions. This study found that the treatment gap was not equitable across mental disorders and that the largest treatment gap was reported for alcohol use disorders: 92% of alcohol-dependent individuals in Europe were recognized as not having received services, while only 17% of individuals with schizophrenia were not receiving services[132]. The findings from the current study provide some context for understanding the level of brain-related impairment that alcohol-dependent patients experience relative to people suffering from other mental disorders and could eventually be used to inform policy to promote health equity in addition to brain-based rehabilitative services.

The available data from CUD case-control comparisons suggests that there is significant heterogeneity in these studies, limiting the confidence around possible case-control differences. While effect sizes in some subcortical and cortical regions were similar in magnitude to those revealed for alcohol and other psychiatric conditions, the confidence intervals around these effect sizes were so large that no conclusions could be drawn regarding whether such differences were statistically significant. This variation could be partly explained by the methodological differences among the included studies for assessing cannabis abuse.

Another limitation was related to the historical variation in diagnostic criteria for SUD, which changed between 2000 and 2014 in order to better capture the nature of addiction to a variety of substances of abuse. Therefore, in the current meta-analysis, some studies used more conservative inclusion criteria than others, and this is particularly the case for cannabis studies. However, heterogeneity *within* CUD studies appear just as evident as *across* CUD studies. More research is required to evaluate the brain alterations in heavy and problematic cannabis use, potentially placing greater attention on severity of CUD or quantity or type of substance abused, in order to reduce variability within and across studies. Recognizing that the current study did not control for severity substance use disorder, in order to be optimally comparable with

published results on other psychiatric conditions, it is recommended that future ENIGMA studies attempting to compare and contrast brain correlates of substance use and psychiatric conditions derive global (harmonized) severity measures to further reduce variability within and across studies.

Similarly, in order to be optimally comparable with the published results for other psychiatric disorders, the effects of tobacco use were not controlled for[155]. Considering that psychiatric conditions and substance use disorders have different patterns of co-occurrence with nicotine dependence, future studies could explore the role of this confounding variable and other co-variates to begin to explain disorder-specific and disorder-general volumetric variations.

Sex-specific results were also not reported by all working groups that cover other psychiatric disorders, therefore complete comparisons of the sex-related differences would have been limited. Future studies should consider making sex-specific results available in a consistent way in order to compare sex-specific variations across psychiatric disorders. Although the presence of other substance use disorders (other than nicotine dependence) were exclusion criteria for inclusion in each of the AUD and CUD studies, the analyses did not control for concurrent and recreational substance use. Efforts to develop harmonized quantitative measures of quantity and frequency of drug use are underway within the ENIGMA-Addiction working group and will be investigated in the future.

Finally, the number and sample sizes of substance use disorder studies were generally smaller than those reported for MDD, SCZ and BD, which also likely contributed to the greater variance in effects in the SUD studies (AUD studies also showed high heterogeneity). These findings, suggest the need for further investment in research on brain correlates of substance use disorders, considering their demonstrated role in global health[1] and the magnitude of the effects reported in this study.

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Article 2

Sex-specific Volumetric Variations in Alcohol and Cannabis Use Disorders: an ENIGMA-Addiction Meta-Analysis

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Abstract

Objectives: Although numerous studies have compared brain volumes of cortical and subcortical regions in participants with a substance use disorder, there is a lack of consensus regarding how brain correlates of alcohol and cannabis misuse differ by sex. Meta-analysis is a methodology that can investigate reliability of neuroanatomic variations across available studies. The current study investigated sex differences regarding the association between alcohol and cannabis misuse and structural brain abnormalities, using a harmonized method for quality control and parcellating structural brain measures across research neuroimaging studies.

Methods: Based on an ENIGMA-Addiction working group dataset that was developed by combining neuroimaging data from 14 primary studies, random-effect meta-analysis was performed on the bilateral subcortical volumes and cortical thickness from seven case-control studies (N = 798, 54% are cases) comparing participants with alcohol use disorder (AUD) to age and sex-matched controls and seven case-control cannabis use disorder (CUD) studies (N = 447, 44% are cases). Cohen's d-effect size estimates were calculated to evaluate the sex-by-diagnosis interaction and main effects of sex and diagnosis for bilateral grey matter volumes of seven subcortical regions and 34 cortical regions for each study. Sex-stratified analyses were performed and reported to highlight sex-specific case control differences and non sex-specific variations were evaluated when case control differences occurred in both sex-stratified analyses.

Results: While sex-by-diagnosis interactions were significant in three subregions of the cingulate, none remained significant after correcting for multiple comparisons. Shared and sex-specific effects were revealed by FDR-corrected sex-stratified case-control meta-analysis for AUD. Reduced volumes in the thalamus and putamen were observed in AUD males relative to controls, and reduced volumes in the hippocampus, amygdala and accumbens were observed in AUD females relative to controls. While thinner cortices in frontal and temporal regions were only observed in AUD males relative to their study-level matched controls, reduced thickness in the fusiform, inferior temporal and temporal pole were observed in both AUD males and females. Although no volumetric differences between CUD males and CUD females in subcortical regions were observed for CUD when examining the interaction, reduced cortical thickness in the medial orbitofrontal, posterior cingulate and insula were observed in CUD females only in sex stratified analyses. Power analysis based on current effect sizes are reported to guide future studies.

Conclusion: These results give some insights on sex-specific brain correlates of substance use disorders, but also highlight the need for larger samples that are more balanced with respect to sex representation to provide conclusive results on sex-specific effects.

Introduction

Sex disparities in biomedical research were systematic and widespread until the National Institute of Health announced in 2014 its intentions to address the sex bias in basic science studies [1-3]. Such sex disparities are particularly uneven in substance misuse research, in which alcohol studies have been reported to be the most biased in terms of male sampling[3]. While sex differences have been observed across pre-clinical and clinical outcome studies for alcohol and cannabis use behaviors and disorders, the nature of sex differences in the brain correlates of addiction remains under studied. Such evaluation could potentially shed light on differences in biological sensitivity to addiction or substance-related harms[3, 4]. A better understanding of the sex differences in neurobiological mechanisms underlying substance use disorders (SUDs) is crucial given the rate of alcohol use disorder in females has increased by 84% over the past 10 years, which is relatively larger to the 35% increase observed in males[5].

A recent review[6] of the findings from pre-clinical studies on sex differences in behavioural and biological processes linked to addiction concluded that adolescent female rodents are more prone to drinking behaviours compared to males in the context of stress, negative affect and increased cue -reactivity. There was also some evidence that female rodents show more sensitivity to the aversive effects of intoxication, whereas male rodents might be less likely to stop drinking and consequently more prone to heavier consumption patterns [6-8]. Sex differences in rodents were also observed on measures of brain structures most affected by substances of abuse use, where alcohol-exposed male rodents showed greater reduction in cortical thickness in the prefrontal cortex whereas alcohol-exposed female rodents showed greater alcohol-induced reduction in the hippocampal neurogenesis[6]. In another review that focused on cannabis[9], sex differences were observed in how THC was metabolized in rodents. These results suggested indeed that, like alcohol, sex differences in pharmacokinetics partly explain the different rates at which female rodents metabolize cannabis compared to male rodents[10].

Sex differences in pre-clinical studies mentioned above are interesting given the human epidemiologic data that suggest a greater risk for addiction for males compared to females[7, 8]. Although preclinical studies give insights on potential sex differences in the brain correlates of

substance misuse, there is an obvious gap in the literature that precludes translating pre-clinical findings to aetiologic theories and intervention approaches that are sex-specific.

Based on findings from various scientific fields, a multi-dimensional brain disease model of addiction was proposed [11]. However, this model does not consider sex differences, for the most part, due to a limited number of human studies investigating sex differences in brain-related addiction processes, and to the different methodological approaches used to study human sex-related effects across studies. In particular, many studies used sex-stratified analyses to explore sex differences, which do not necessarily address questions on how sex and gender are related to substance use outcomes. This lack of consistency in methods and findings also applies to the literature on brain correlates of alcohol and cannabis use disorders in males and females. There is a need for a more systematic approach to determine if there are reliable differences between males and females in terms of how brain processes are implicated in substance-related outcomes. Nonetheless, there is a growing body of literature suggesting that female cannabis users show a greater co-morbid symptomatology related to anxiety, schizophrenia and depression compared to male users[9]. In addition, greater anxiety and depressive symptoms were correlated with an increase in right amygdala volume in female cannabis users[9].

With a recent trend towards sex-balanced research designs, newer studies are providing an opportunity to investigate sex differences in brain correlates of addiction. This applies in particular to alcohol and cannabis, where sex biases in prevalence of the behaviour have narrowed in recent decades[4]. Recent reviews on the sex-related brain correlates of alcohol (AUD) and cannabis use disorders (CUD) have suggested mixed results on the most frequently studied brain structures, such as the hippocampus and the medial orbitofrontal cortex [9, 12, 13]. Two major limitations of these studies are that they are not designed *a priori* to detect sex-related effects and inconsistently reported whole-brain analysis versus *a priori* brain regions of interest. For instance, by comparing 60 chronic alcoholics (30 males) to 60 healthy controls (29 males), Sawyer et al. (2017) evaluated the total volume of the reward system in both sexes and observed an alcoholism-by-sex interaction. Reduced total reward volumes in alcoholic males compared to healthy males and greater total reward volumes in alcoholic females compared to healthy females were observed [14]. Significant interaction terms between AUD and sex were also observed

in the dorsolateral prefrontal cortex and ventral diencephalon. However, this study did not evaluate the whole brain since their purpose was to evaluate sex differences in the reward system in AUD patients. These results remain interesting since sexual dimorphism was observed in brain regions identified as being implicated in the addictive behaviors according to the brain disease model of addiction,[15] however, such differences are difficult to put into context relative to other studies involving whole brain analyses. Three studies with greater than average sample sizes might inform this research question. One study[16] involving 130 substance dependent participants recruited from the National Institute on Alcohol Abuse and Alcoholism reported significant sex differences when comparing alcohol dependent cases to controls: alcoholic males had thinner insula and medial frontal gyrus in the right hemisphere compared to control males. Alcoholic females showed thinner precentral and postcentral gyri in the right hemisphere compared to control females. However, alcohol-dependent males did not exhibit any significant structural differences compared to alcohol-dependent females[16]. Overall, case control analyses were only significant for female alcoholics and not for males. However, because an interaction term was not included in the analysis, this study was not able to provide statistical evidence of sex differences in brain correlates of alcohol dependence that go beyond general sex differences or substance-related differences. Another study evaluated the relationship between grey matter volume and alcohol use in a sample of 436 adults using both voxel- and surface-based morphometry approaches[17]. The authors evaluated interactions between sex and alcohol use using Alcohol Use Disorders Identification Test scores as a secondary analysis and observed a significant interaction, suggesting greater reduction in the cortical thickness in the left lateral orbitofrontal cortex in heavy-drinking females compared to heavy-drinking males and non-heavy drinkers[17]. In another study, Morris et al., (2019) used data from the Human Connectome Project[18] to investigate sex-related brain correlates of alcohol in a sample of 706 young adults and reported that number of drinks consumed in the past week was negatively associated with male-specific reduced cortical thickness in temporal and frontal regions. Such sex-specific differences were not observed in females, but no significant sex-by-region interaction was associated with the heavy drinking frequency. Together these latter two studies suggest that AUD females showed greater reduction in brain structures compared to AUD males, but due to the

variability in the approach to studying sex differences in across studies, further investigation is required.

Reporting the interaction term and the main effects of sex and substance-related variables in a consistent way may be a methodological adjustment that could contribute to clarifying the similarities and the sex differences in the brain correlates of substance dependence. [19, 20]. The absence of interaction terms reported among the studies mentioned above contrasts with the significant sex-by-AUD interactions reported by two studies[21, 22] based on the DSM-III-R criteria for alcohol dependence. In the first study, researchers reported significantly marked reductions in brain gray matter volume in 36 alcoholic females compared to 19 control females, and relative to case-control comparisons between the 43 alcoholic males and 20 alcoholic males[21]. The second study reported a sex-by-diagnosis interaction as an increased cortical gray matter in alcoholic males compared to healthy control males that was not observed between case-control comparisons for females[22]. These results are consistent with three previously described large samples studies , according to which AUD females show greater volumetric reductions. While these studies did provide information on sex differences, larger studies are needed in order to test such effects across all regions of the brain and to properly control for multiple multiple testing.

A potential solution to resolving inconsistency across these studies could be the meta-analytic approach provided by the ENIGMA consortium for processing brain data and harmonizing statistical protocols across neuroimaging studies[23]. This standardized methodological approach could also allow the comparison of sex differences in brain correlates of different substances of abuse.

The literature on sex differences in brain correlates of cannabis use disorder are also limited. To evaluate the consistent neuroanatomic case-control and male-female differences across studies, a recent meta-analysis reported cannabis-related reduced volumes in the hippocampus and orbitofrontal cortex, but did not investigate sex-related effects [24]. While, cannabis-related brain volumetric variations were reported in adult and adolescent samples, a limited number of cannabis studies addressed the interaction term between cannabis use/diagnosis and sex[9, 25-31]. Two adolescent studies reported this interaction and observed greater volumes in the prefrontal

cortex in female marijuana users than in males, as well as a female-specific increased volume in the right amygdala in cannabis users compared to non-users[32, 33]. Considering the limited neuroimaging literature on sex differences in cannabis use in adults, preliminary work from the ENIGMA-Addiction working group evaluated sex-by-group interactions and reported reduced cortical thickness in orbitofrontal cortex in cannabis-dependent females compared to non-dependent female users and control females, while no effects were observed in males[34]. Although these results were on a priori selected regions of interest rather than investigating whole brain analysis, these interaction results align with the findings in adolescent samples, suggesting a potential greater variability in CUD females' brain compared to CUD males' [25, 35].

These imaging findings are consistent with the findings of sex differences in cannabis-related cognitive impairment in a large adolescence cohort[36]. This population-based study showed that adolescent females between exhibited greater cannabis-related working memory deficits compared to their male counterparts[36]. And another study on a smaller sample of young adults reported findings that are consistent with this large sample study[37]. Although these two studies suggest a sex-specific association between age of cannabis use initiation and neuropsychological functioning, further investigations involving direct brain measures are necessary as cognitive consequences of cannabis use can also be a attributed to missed opportunities resulting from school disengagement, failure or exclusion [38-40].

As evident from the studies reviewed above, the literature is limited to studies of small samples, that often fail to directly test for sex differences and from a whole brain perspective. [3] Two analytic methods can be used to evaluate sex differences in SUDs. First, evaluating the interaction term between SUD status and sex allows to determine male-female differences among the cases over and above main effects of sex or substance-related variable. Another strategy is the analysis of sex-stratified outcomes allowing to compare male and female cases to their sex-matched controls. While this latter approach allows for the evaluation of SUD-related case-control neuroimaging differences, it does not inform on potential male-female differences *among* the cases. Neuroimaging studies are notoriously underpowered and sex differences are often investigated as post hoc analyses. Therefore these effects are inconsistently reported and rarely reported using a design which is designed, a priori, to test the interaction between sex and

substance use diagnosis, involving equal cell sizes and comparable inclusion and exclusion criteria. [41]. In this context, a systematic and harmonised sex-stratified case-control analysis can give insights on sex-specific effects. While considering the unique characteristics of each study, these two analytical approaches (sex differences and sex stratified), when used synergistically and systematically reported, could minimize the inconsistency in findings reported in the literature.

Addressing a number of additional methodological factors could also lead to more clarity on this topic . The single study nature of studies and relatively small sample size have several potential implications. First, these factors cannot be easily included in analyses as covariates. Second, the limited statistical power of models in conventional studies might lead to limited generalizability and restricted reproducibility of the results and an inability to detect real sex-differences, particularly within the context of an interaction term. Third, single site studies may use different standardized anatomical frameworks to parcellate the regions of interest, which could limit the comparison with other studies. Fourth, some studies may only report results in *a priori* selected regions of interest, which introduces more heterogeneity, and potential bias, in the literature.

Meta-analysis is a way to circumvent issues mentioned above by finding consistent neuroanatomic variations across included studies. By increasing the statistical power, this analytic approach can detect small effects that would not be considered significant in a single study and can also quantify heterogeneity across included studies. A main advantage of the meta-analysis is the generalization of common findings across studies to a larger population, where possible heterogeneity of effects across studies can be explored by investigating their relationship to differences in methodology or sample characteristics that would not be captured in a single controlled study. With improved precision around the confidence intervals of derived estimates, both type I and type II errors are minimized relative to both small and large sample studies. Finally, over-represented studies in the literature can be identified through the distribution of the effect sizes of the studies included in the model [42].

The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) network developed standardized anatomical templates and statistical protocols to help create a standard method for conducting meta-analyses across existing neuroimaging and genetics studies[23]. This harmonized

approach addresses some important issues conventional meta-analysis can not fully address. A traditional meta-analysis is likely to encounter methodological issues since single-site studies may use different brain templates during the processing. Such unstandardized images may be a source of variability that can increase the heterogeneity between studies in the meta-analytic results. Through the ENIGMA consortium, a number of existing neuroimaging addiction databases have been re-analysed using these standard data processing pipelines to allow for standardized structural brain measures. The aim of the current study was to compare sex-related effects in AUD and CUD since alcohol and cannabis are among the most consumed substances [43, 44]. Specifically, the objective of this study is to address examine sex differences in a systematic way, assuring that sex, substance of abuse and their interaction are systematically investigated across studies. We also aim to standardize such analyses across studies focusing on alcohol and cannabis use disorders, to allow for opportunities to make comparisons in brain correlates, not only across sex, but across substance use disorder as well Capitalizing on the ENIGMA-Addiction dataset, the current study performed a structural meta-analysis to quantify case-control subcortical volumetric and cortical thickness differences in regions of interest and compare effect sizes across alcohol and cannabis, with a focus on sex-related effects and their interaction.

Subjects and Methods

Samples

Demographic details for seven AUD sample and seven CUD studies, that were the same samples used in the first article of this master thesis, are presented in Table 4 . We excluded studies that did not include controls and/or females in order to perform statistical analyses at the study-level which included interactions. All substance use participants were confirmed to be regular heavy users during structured clinical interviews, as defined by each study protocol. Healthy control participants were similarly confirmed with interviews to be free of any type of substance use disorder. Subjects with a lifetime history of neurological disease and/or a current DSM-IV axis I diagnosis (other than depressive and anxiety disorders) were excluded from the analyses. Most of the cases were classified as having a substance use disorder based on validated structured diagnostic interviews that conform to the Diagnostic and Statistical Manual of mental Disorders-

Fourth-TR Edition criteria. Chronic cannabis users from one study, for whom DSM-IV-TR criteria could not be confirmed, were included in the analyses since subjects in the cannabis group consumed regularly cannabis for the two past years and smoked at least 500 joints in their lifetime [45]. AUD and CUD cases were mostly lifetime dependence case. Subjects with a co-occurring substance use disorder, other than nicotine, were excluded by all original studies. The included studies obtained approval from local institutional review boards and ethics committees, and all participants provided written informed consent at their local institution for the local study. The University of Vermont were exempt from obtaining approval from their ethics research board and the CHU Ste Justine provided ethical approval for this meta-analysis. Here we focus on the sex-specific differences in 435 AUD cases compared to 363 age- and sex-matched controls, and 200 CUD cases compared to 247 age- and sex-matched matched controls. Two studies (one AUD study[46] and one CUD study[47]) included adolescent substance users. Although including adolescent studies may increase between-study heterogeneity in the analyses, confidence intervals for the adolescent studies overlapped with the adult-only studies in case-control analysis for all regions of interest with age as covariate. We investigated whether age of sample affected results in a sensitivity analysis (described below).

Image processing

Structural T1-weighted magnetic resonance imaging brain scans were acquired for all included study and the segmentation was performed using FreeSurfer34. Seven subcortical regions (thalamus, caudate, pallidum, putamen, hippocampus, nucleus accumbens and amygdala), 34 cortical regions, lateral ventricles, and total intracranial volume were automatically segmented. The extracted information from the segmentation was acquired following the ENIGMA standardized protocols. The image acquisition parameters and software descriptions for the included studies are akin to those in previous ENIGMA studies[48-51]. To ensure uniformity of quality control across studies, a visual inspection was completed on a randomly subsample participants at the University of Vermont. The inclusion of poorly segmented and mislabeled structures was avoided by outliers' detection and visual inspection. To curtail potential study effects, the quality control procedures were conducted at each study according to the ENIGMA standardized protocols. Many studies decided to send deidentified and anonymized, processed data or

summary scores to the University of Vermont and CHUSJ in order to centralize and standardize data analysis.

Statistical framework of meta-analysis

Multiple linear regression analyses were used to be consistent with the other ENIGMA working groups meta-analyses. We examined the sex differences for all included studies using the mean subcortical volume and cortical thickness of each region of interest (left+right/2) as the dependent variable, with sex as a binary independent predictor. To make results comparable across drugs and with results, models for subcortical ROIs covary for case-control status, age and intracranial volume, while models for cortical ROIs covaried for age and case-control status. First, two independent models for alcohol and cannabis included main effects of sex and diagnosis. Second, a sex-by-diagnosis interaction term was added to the models to identify significant sex differences in patients compared to age and sex matched controls over and above main effects of sex and diagnosis. Results of models that are uncorrected and corrected for multiple testing across brain regions are reported. To explore significant interactions, uncorrected main effects analyses of sex and diagnosis are reported for ROIs that revealed significant interactions. Third, for the purpose of contributing to open science, we performed sex-stratified analyses for each drug and report case-control adjusted effect sizes. Regression models were performed for each study independently to derive t-statistics that were used to estimate Cohen's d-effect size estimate (*d*). An inverse variance-weighted random-effect meta-analysis model was performed for each region of interest with the *metafor* package in R[52]. Using the false discovery rate (FDR), the significance level was determined at a p_{FDR}-value of 0.05 after correcting for multiple comparisons. Because of the inconsistent volumetric case-control and male-female differences across single-site studies in the literature, statistical heterogeneity was calculated using the I^2 statistic with an $I^2 \geq 20\%$ indicating a moderate heterogeneity, an $I^2 \geq 50\%$ substantial heterogeneity and $I^2 \geq 75\%$ considerable heterogeneity. Two AUD studies and one CUD study were removed from the analyses in which a male-female comparison was performed since no females were included at the study level (See Table 1). A planned sensitivity analysis was conducted to determine whether the inclusion of adolescent studies would impact the observed effect sizes and the significance level, or not. Because the confidence intervals overlapped with

the adult-only studies for all regions of interest, and the effect sizes with and without the adolescent studies for AUD and CUD samples were comparable, they were included in the analyses to increase sample size (Supplementary Figures 1-8). While positive mean differences suggest increased volumes in cases compared to controls, negative mean differences values suggest reduced volumetric measures in cases when compared to their healthy counterparts.

Results

Main effects of diagnosis were reported previously[53], so in this study, we report only main effects of sex and sex-by-diagnosis interactions, while including diagnosis as a main effect in the models.

Sex main effects in alcohol and cannabis use disorders

For AUD studies, significant main effects of sex that survived FDR correction were observed in subcortical volumes in the putamen (*d*=0.24, CI= [0.07, 0.41]), pallidum (*d*=0.22, CI= [0.06, 0.37]) and the accumbens (*d*= 0.25, CI= [0.10, 0.41]). Significant main effects of sex were also observed at the cortical level in the pars orbitalis (*d*= −0.24, CI= [−0.39, −0.09]), pericalcarine (*d*= 0.28, CI= [0.12, 0.43]) and insula (*d*=0.26, CI= [0.11, 0.41]) after correcting for multiple testing.

For CUD studies, when all seven subcortical and 34 cortical regions of interest were analysed, a significant main effect of sex was observed in the superior frontal (*d*= -0.37, CI = [-0.60, -0.14]).

Analysis of Sex Differences

Significant sex-by-diagnosis interaction terms were observed in the caudal anterior cingulate (*d*= - 0.16, CI = [−0.31, −0.01], p = 0.038) and in the rostral anterior cingulate (*d*=-0.20, CI = [−0.36, −0.05], p = 0.009) in AUD subjects, but neither of these interaction terms remained significant after correcting for multiple comparisons (p_{FDR}>0.05).

Similarly, a unique significant interaction was observed in CUD subjects in the posterior cingulate (*d* = 0.24, CI = [0.02, 0.47], p = 0.036), which also did not survive the FDR correction (p_{FDR}>0.05).

Sex-stratified analyses for alcohol use disorder

Figure 1 shows the subcortical differences between AUD cases and controls when stratified by sex. For the comparison between AUD males and controls, differences in volumes survived FDR correction in the thalamus (*d* = -0.25, CI = [-0.41, -0.09]) and the putamen (*d* = -0.29, CI = [-0.47, -0.17]). For the comparison between AUD females and controls, differences survived FDR correction in the the hippocampus (*d* = -0.46, CI = [-0.62, -0.30]), amygdala (*d* = -0.26, CI = [-0.48, -0.04]) and accumbens (*d* = -0.21, CI = [-0.36, -0.06])

As shown in **Figure 2**, reduced cortical thickness in AUD males was observed in the caudal anterior cingulate (*d* = -0.31, CI = [-0.46, -0.16]), entorhinal (*d* = -0.28, CI = [-0.49, -0.07]), fusiform (*d* = -0.40, CI = [-0.55, -0.25]), inferior temporal (*d* = -0.30, CI = [-0.44, -0.15]), lateral orbitofrontal (*d* = -0.28, CI = [-0.49, -0.06]), parahippocampal (*d* = -0.22, CI = [-0.36, -0.07]), posterior cingulate (*d* = -0.29, CI = [-0.53, -0.06]), rostral anterior cingulate (*d* = -0.37, CI = [-0.52, -0.22]), superior frontal (*d* = -0.21, CI = [-0.36, -0.07]) and temporal pole (*d* = -0.20, CI = [-0.35, -0.05]) when compared to sex and study matched controls, after the FDR correction. Compared to their control counterparts, AUD females showed reduced cortical thickness in the fusiform (*d* = -0.34, CI = [-0.49, -0.18]), inferior temporal (*d* = -0.30, CI = [-0.45, -0.14]), and temporal pole (*d* = -0.28, CI = [-0.43, -0.13]) after correcting for multiple comparison.

Sex-stratified analyses for cannabis use disorder

Figure 3 shows the subcortical differences between CUD cases and controls when stratifying males and females, and no regions remained significant after the FDR correction for either sex.

As shown in **Figure 4**, reduced cortical thickness in females with CUD was observed in the medial orbitofrontal (*d* = -0.53, CI: [-0.82, -0.25]), posterior cingulate (*d* = -0.45, CI: [-0.70, -0.19]) and the insula (*d* = -0.52, CI: [-0.82, -0.22]) after correcting for multiple comparison. No effect survived FDR correction in CUD males.

Discussion

This study evaluated sex-related brain structural case-control differences in AUD and CUD samples from the ENIGMA-Addiction working group by combining the findings from seven

studies focusing on AUD and seven studies on CUD. To circumvent the heterogeneity and methodological differences in the MRI data acquisition across studies, we performed meta-analyses to quantify sex-related effects in case-control comparisons on brain structures in AUD and CUD participants. First, main effects of sex and drug without sex-by-group interactions were processed. Second, sex-by-diagnosis interactions were evaluated in AUD and CUD cases and age- and sex-matched controls for seven bilateral subcortical volumes and the cortical thickness of 34 bilateral regions. Third, sex-stratified analyses were performed to evaluate simple main effects of sex and diagnosis. .

In AUD subjects, main effects of sex were observed in putamen, pallidum and accumbens, which indicates larger subcortical volumes in males compared to females. Main effects were also found at the cortical level, which indicated reduced cortical thickness in the pars orbitalis and thicker cortices in the pericalcarine and insula in males compared to females. Significant sex-by-diagnosis interaction terms were observed in the rostral and caudal anterior cingulate. Although these interactions did not survive the correction for multiple testing, the evaluation of simple main effects revealed significant case control differences in the rostral and caudal anterior cingulate in males, which did survive FDR correction. The effects were consistently not significant for females, indicating that there is some confidence in the conclusion that males with AUD show greater reductions in cortical thickness in the anterior cingulate compared to females with AUD. As shown in Figure 2, cortical thickness reductions found in the anterior cingulate for AUD males partly align with the findings of two meta-analytic studies based on both regions of interest and voxel-based morphometry approaches [54, 55]. Implicated in reward responding and drug craving, the anterior cingulate is now becoming a target in novel neurotherapeutic interventions for addiction, including neural implants, deep brain stimulation and repeated transcranial magnetic stimulation (via stimulation of the dorsal lateral prefrontal cortex[56]). The current findings suggest that there might be important sex differences in the relevance of such therapeutic approaches. This sex differences was not observed for CUD, despite previous studies showing that anterior cingulate is equally implicated in brain reactivity and craving in response to cannabis and alcohol cues[57]. Indeed, clinical studies reported indeed that cue-induced craving increased both the activation and the release of dopamine and opioid peptides in the anterior cingulate gyrus, a

region that seems involved in the preoccupation/anticipation stage from the brain disease model of addiction[58].

Sex-stratified case-control whole brain analyses indicated that AUD cases showed thinner fusiform, inferior temporal and temporal pole cortices for both sexes, but also revealed reduced volumes in the thalamus and putamen in AUD males, whereas reduced volumes in the hippocampus, amygdala and nucleus accumbens in AUD females. These latter findings correspond with findings reported in the animal literature following alcohol exposure[6] and are interesting since these subcortical regions are implicated in emotion processing and reactivity [59, 60]. However, as there was little evidence of a significant interaction between sex and AUD diagnoses in these brain regions, these sex-specific effects might not represent meaningful and reliable sex differences in alcohol related morphology, and instead differences in sample size or heterogeneity in male and female samples.

Our results could not confirm previously reported sex-by-diagnosis interactions in the anterior cingulate cortex in AUD and in the posterior cingulate in CUD, since no significant region of interest survived correction for multiple testing[14, 16, 18]. This may be partly explained by the heterogeneity observed between and within studies (Supplementary Figures 9-12), the sample size and underpowered analyses However, these non-significant results are valuable information to reduce the gap in the literature on sex differences in SUDs. Indeed, a very limited number of studies with a large sample size performed both sex differences and sex-stratified analyses in the context of a whole-brain analysis. Because the model revealed significant simple main effects of sex in cingulate subregions, these results suggest that any comparison of male and female substance users must include an appropriate model of general sex differences in brain morphology. More studies are required to determine the robustness of the results of this work since our interaction results in the cingulate were not consistently reported in previous studies on AUD and CUD[14, 16-18].

A better understanding of the sex differences in the biological sensitivity to alcohol dependence might shed light on the relationship between structural abnormalities and alcohol-related cognitive impairment. A review of 27 studies on the neuropsychological correlates of binge

drinking in youth highlighted that, among the 17 studies that examined sex-specific effects, only five studies reported significant interactions between sex and binge-drinking[62]. Poorer performance in spatial working memory [63], cognitive flexibility[64] and visual search[65] were observed in binge-drinking females compared to non binge-drinking females. On the other hand, impaired inhibition[66] and visuospatial memory[67] were observed in binge-drinking males compared to non binge-drinker males. While these functional differences do appear to parallel the differences reported above, there is a need for more studies designed to detect sex differences to evaluate the robustness of these neuropsychological correlates of alcohol misuse and their neural correlates, since four of the five studies that reported significant interactions used small sample sizes.

As presented in Figure and 4, sex-stratified whole brain analyses of CUD subjects showed reduced thickness in the medial orbitofrontal, posterior cingulate and insula in CUD females compared to healthy females. These results contribute to the debate since cannabis-related brain abnormalities are not consistent in the literature, notably in the hippocampus and medial orbitofrontal cortex [12, 24, 29, 68-70]. Future studies should explore factors that might explain why females with AUD show more reliable morphologic changes in these subcortical regions, but considering that this study did not confirm a sex difference, such investigations should not exclude males, and instead attempt to identify factors that moderate the drug-brain relationship across both sexes. A better understanding of the underlying mechanisms of sex-specific relationship between these cortical regions and cannabis use could explain the role of sex-related effects in the emotional dysregulation associated with chronic cannabis use[71].

Concerned about the possibility of rejecting false negatives in the current study, a retrospective power analysis was performed. Results revealed that the random-effect meta-analysis has a power of 25.26% for the meta-analytic effect size of the caudal anterior cingulate in sex-by-AUD diagnosis interaction term analysis, suggesting a high probability of incorrectly accepting the null hypothesis and making a type II error. The power analysis was performed on the caudal anterior cingulate for AUD interaction because it was the smallest significant effect observed. Similar observations were found in the sex-by-CUD diagnosis interaction analyses for which a power of

30.30% was obtained. Accordingly to sample size calculations, 1300 additional cases and a similar number of controls, with a similar number of participants per group from 19 additional studies would be necessary to complement our five studies to reach a power of 80% for the AUD interaction term in the caudal anterior cingulate, which is considered sufficient by convention[72]. To reach a power of 80% for the interaction analysis in the posterior cingulate in CUD, at least 574 new cases and a similar number of controls, with a similar number of participants by group, from 17 new studies would be required to complement our six studies. Considering that the recruitment of such a large number of participants precisely distributed among new studies is unlikely, the addition of new studies with large samples may be a more viable strategy for sex differences research. However, the numbers of additional participants required to reach a sufficient analytic power described above should be carefully interpreted considering the heterogeneity for a specific region can vary large samples. Indeed, any increase in the heterogeneity would likely decrease the power and therefore more studies and participants would be necessary to reach a power of 80%. Another factor to consider is the variation in meta-analytic effect size for a given region of interest as the number of studies included in the analyses increases, since a larger effect size requires fewer samples to achieve sufficient power. Since we observed small effect sizes in the sex simple main effects and in the interaction terms analyses (rather than moderate or large effect sizes), a large number of additional participants is required to assess the robustness of the current sex-related results with sufficient statistical power. Finally, the moderator tests (e.g., the sex-by-diagnosis interaction term) are especially likely to be underpowered, therefore such retrospective power analysis could allow to put the non-significance in perspective[73]. Such retrospective analysis is highly relevant in our study since the included studies were not designed to be appropriately powered to detect moderated effects of sex at the study level. Although this retrospective analysis revealed that our random-effect meta-analyses were underpowered, it allowed to define criteria for which a sufficient statistical power is reached, which we hope will inform future studies on this subject.

As with any meta-analysis, this study has some limitations. False negative results may be reported when the FDR correction masked significant results due to the large number of regions of interest we evaluated. Substantial within-study heterogeneity was observed in cannabis studies, which

could be partly explained by differences in diagnostic routines due to the historical changes in diagnostic criteria for alcohol and cannabis use disorders between 2000 and 2014. However, within-study heterogeneity was greater than across studies (Supplementary Figure 13). Another limitation is that we could not associate grey matter reduction with specific patterns of consumption because of the binary classification of subjects. Moreover, this study has only focused on sex-related effects on the adult brain in AUD and CUD samples. However, AUD and CUD cases are more likely to consume recreationally other drugs that were not controlled for in the analyses [74]. For example, we did not control for nicotine use in order to be consistent with previous ENIGMA findings[48, 50, 51]. Harmonized severity measures of drug consumption should be used in further meta-analyses to reduce heterogeneity. The inclusion of adolescent studies in the samples is arguable based on the sexual dimorphism in the developing brain, which could increase the noise in our analyses[75]. To address this issue, all effect sizes were adjusted for age.

Finally, our meta-analysis on the interaction between sex and diagnosis showed a possible interaction in the anterior cingulate for AUD and in the posterior cingulate for CUD. However, a retrospective power analysis revealed high probabilities of incorrectly accepting the null hypothesis and making a type II error for these interaction term. Our power analysis indicated that samples with thousands of participants are required to evaluate sex differences using a meta-analytic approach with adequate power. This finding will hopefully raise awareness among researchers to more systematically assess statistical power in meta-analyses. Sex-stratified analysis in AUD and CUD showed more structural changes in subcortical and cortical regions in AUD males compared to healthy subjects than in AUD females compared to controls. Abnormal cortical thickness was only observed in CUD females. The posterior cingulate was thinner in AUD males and in CUD females in similar magnitude. Further studies are encouraged to include both sex-by-diagnosis interaction terms and sex-stratified analyses in their analytic plan to avoid generalizing observations in one sex to both. A better understanding of the sex differences in substance use disorders could lead to better treatments based on the sex-specific neural mechanisms that seems to differ between males and females for addictive behaviors[15].

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Tableau 4. – **Table 1 (Article 2).** Demographic details for each study.

Substance of Dependence	Number of Studies	Groups	N	Female	Age
All	14	Case	635	188	28.12
		Control	610	208	29.23
Alcohol	7	Case	435	127	32.43
		Control	363	136	33.58
IRC [1-3]		Case	43	11	28.05
		Control	84	21	37.49
Effects of heavy alcohol abuse on adolescent brain structure and function [4]		Case	60	34	14.81
		Control	56	31	14.94
NIAAA [5-7]		Case	212	57	31.11
		Control	140	67	38.48
Neuro-ADAPT [8]		Case	18	6	19.35
		Control	23	11	18.72
NESDA-AD [9]		Case	42	19	48.6
		Control	20	6	48.29
ADPG study [10-12]		Case	28	0	43.43
		Control	24	0	37.17
TrIP Study [13]		Case	32	0	41.69
		Control	16	0	39.94
Cannabis	7	Case	200	61	23.80
		Control	247	72	24.88
Trinity-THC [14]		Case	15	2	23.27
		Control	15	4	22.4
Orr [15]		Case	13	1	16.00
		Control	14	1	16.77
Cannabis Prospective [16-18]		Case	38	12	21.85
		Control	40	15	21.39
Adolescent Development Study		Case	7	6	18.96
		Control	93	44	19.00
Chronic cannabis users (Barcelona) [19-21]		Case	16	1	35.00
		Control	18	2	38.98
Chronic cannabis [22-25]		Case	81	39	30.47
		Control	38	6	33.21
Chronic Cannabis-Memory [26-29]		Case	30	0	21.03
		Control	29	0	22.41

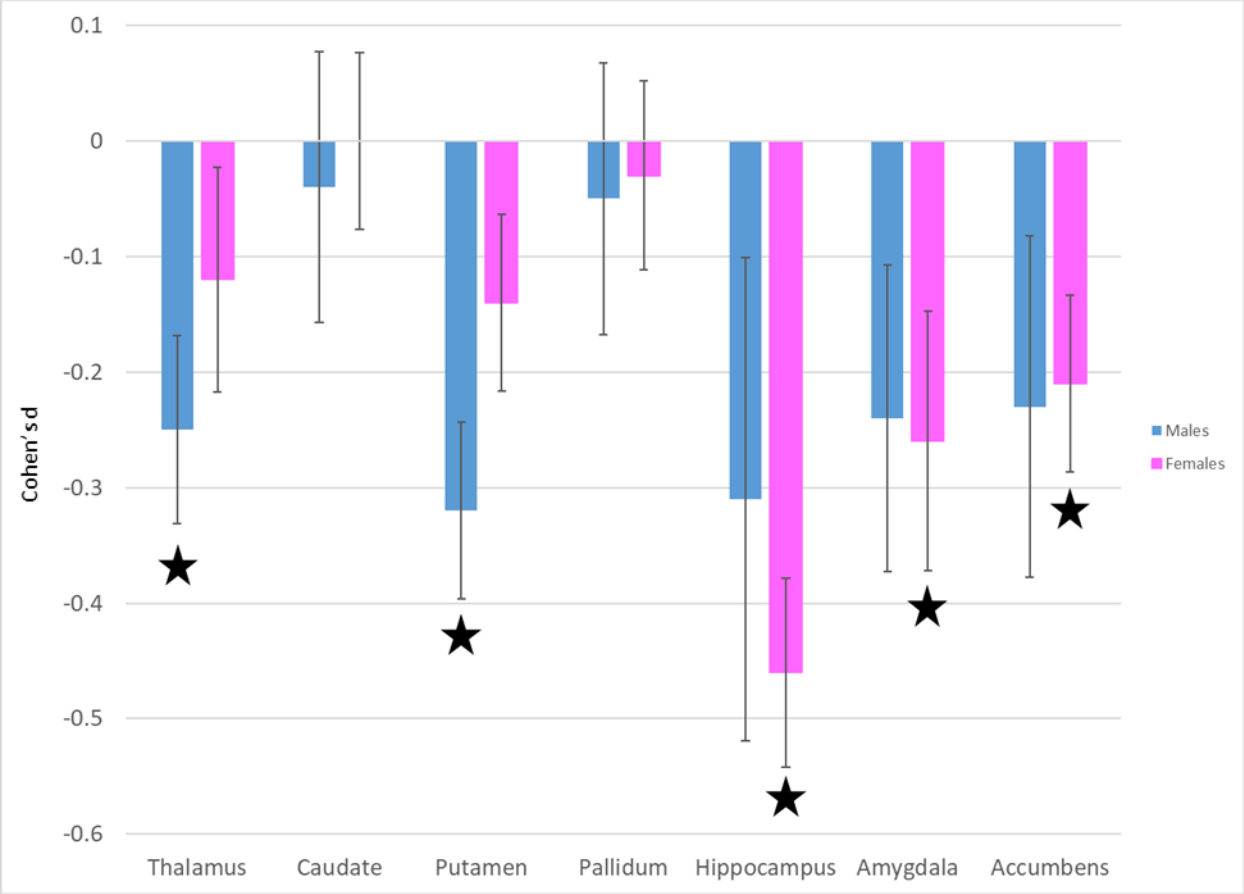

Figure 6. – **Figure 1 (Article 2).** Summary of sex-by-diagnosis interaction terms and diagnosis main effect within each sex structural brain differences in AUD participants compared to controls. Negative values suggest reduced volumes in cases when compared to controls. Subcortical models covaried for age and total intracranial volume. Error bars represent standard errors and stars indicate significant effect sizes after correcting for multiple comparisons. Stars indicate effects that survived FDR correction, and square brackets indicate regions in which a pre-FDR significant sex-by-group interaction was observed.

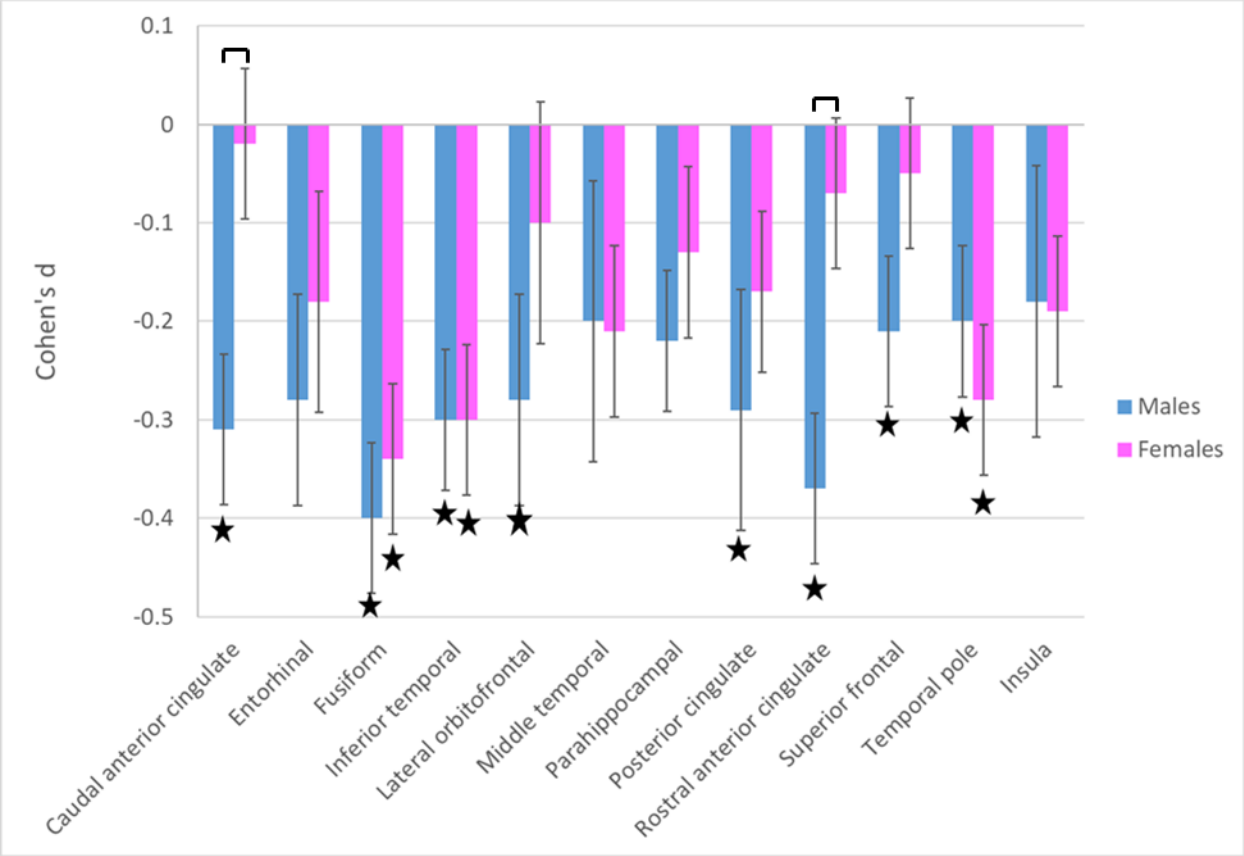

Figure 7. – **Figure 2 (Article 2).** Summary of sex-by-diagnosis interaction terms and diagnosis main effect within each sex structural brain differences in AUD participants compared to controls. Negative values suggest reduced volumes in cases when compared to controls. Cortical models covaried for age and stars indicate significant effect sizes after correcting for multiple comparisons. Error bars represent standard errors and stars indicate significant effect sizes after correcting for multiple comparisons. Stars indicate effects that survived FDR correction, and square brackets indicate regions in which a pre-FDR significant sex-by-group interaction was observed.

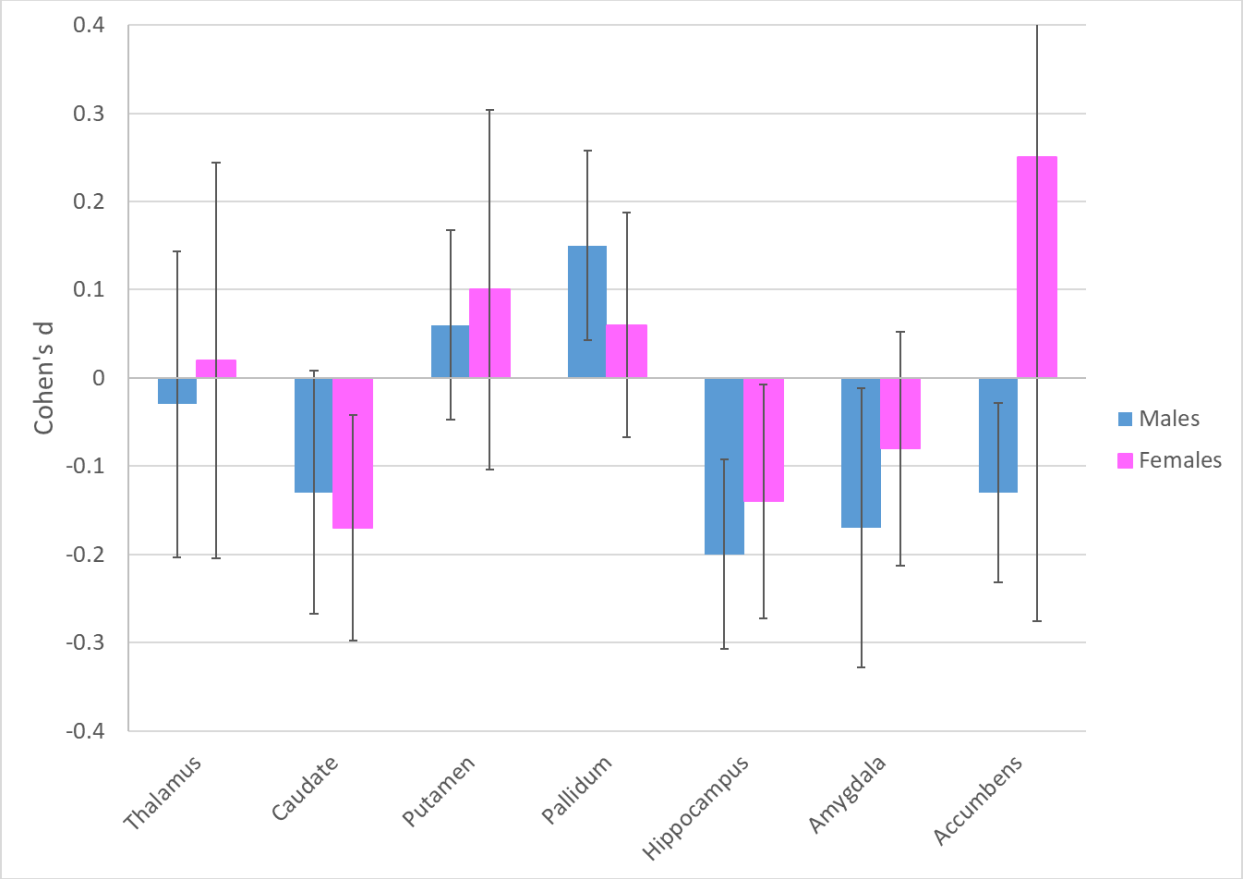

Figure 8. – **Figure 3 (Article 2).** Summary of sex-by-diagnosis interaction terms and diagnosis main effect within each sex structural brain differences in CUD participants compared to controls. Negative values suggest reduced volumes in cases when compared to controls. Subcortical models covaried for age and total intracranial volume. Stars indicate effects that survived FDR correction, and square brackets indicate regions in which a pre-FDR significant sex-by-group interaction was observed. Error bars represent standard errors and no effects survived FDR correction.

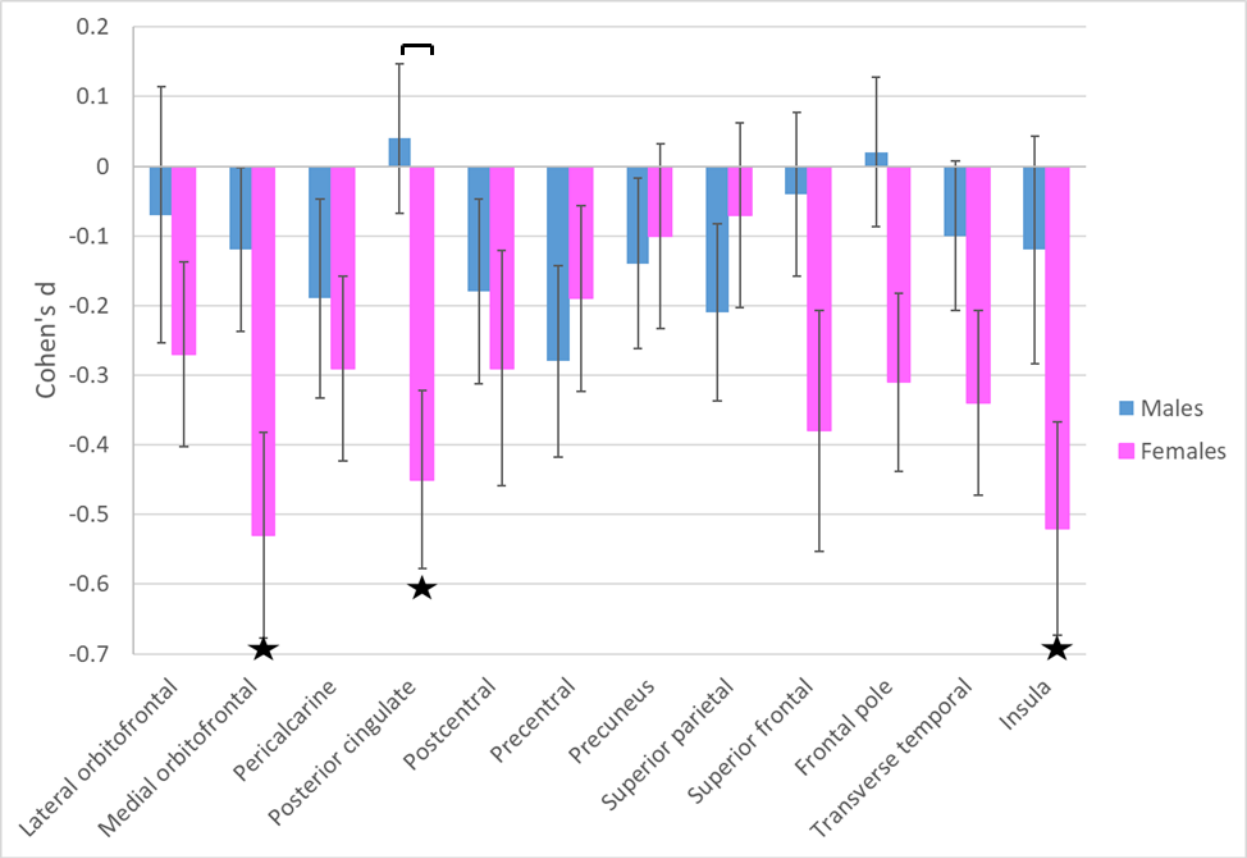

Figure 9. – **Figure 4 (Article 2).** Summary of sex-by-diagnosis interaction terms and diagnosis main effect within each sex structural brain differences in CUD participants compared to controls. Negative values suggest reduced volumes in cases when compared to controls. Cortical models covaried for age, and error bars represent standard errors and stars indicate significant effect sizes after correcting for multiple comparisons. Stars indicate effects that survived FDR correction, and square brackets indicate regions in which a pre-FDR significant sex-by-group interaction was observed.

Article 3

Time-varying relationships between cannabis use and changes in brain structure over a 5-year period during adolescence: A multi-level analysis of common vulnerability, concurrent and one-year lagged associations and potential sex differences.

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Abstract

Background: Adolescence is a time of important brain maturation which may be vulnerable to neurotoxic agents. Yet the literature on longitudinal impact of alcohol and cannabis on cortical and subcortical maturation remains inconclusive. The objectives of the study were to inform potential neurotoxic impacts of adolescent substance use on its impact on the developing brain structure by exploring the associations between binge drinking and cannabis use frequency and brain structure in the other parts of the brain (i.e. temporal, parietal and occipital regions) and potential sex differences.

Methods: A sample of adolescents (N = 130, 52.3% females) from the Neuroventure cohort was followed longitudinally across three repeated assessments of behavioral and neuroimaging measures between 13 and 17 years of age. Adolescent binge-drinking and cannabis use frequencies were assessed annually using the DEP-ADO questionnaire. Neuroimaging data were acquired every two years on a 3T Siemens scanner and preprocessed using the longitudinal pipeline from the ENIGMA consortium. A primary analysis on frontal and subcortical regions of interest was performed to identify the effects of substance use on changes in brain structure and then a secondary analysis investigated potential sex differences in this relationship, while controlling for age. In the context of open science, a similar analysis on the remaining cortical regions was performed and reported in the supplementary content. Multilevel models with a Bayesian estimator were used to estimate between-person predictors and both concurrent and lagged within-person predictors to inform on temporal precedence.

Results: Few between-person relationships were revealed, but cortical thickness in frontal, temporal and parietal regions showed concurrent and negative associations with binge-drinking frequency at the within-person level in the caudal and rostral middle frontal, pars orbitalis, pars triangularis and superior frontal, without evidence of lagged relationships. Concurrent negative associations between cannabis use frequency and parietal and occipital thickness were observed at the within-person level, but not in frontal or subcortical regions. However, a lagged and negative relationship between cannabis use frequency and bilateral nucleus accumbens volume

was observed. An interaction between sex and binge-drinking frequency was observed in the hippocampus. Sex-by-cannabis use interactions at the within-person level were revealed in the caudate, putamen, pallidum, hippocampus, amygdala and thalamus, and sex-by-cannabis use interactions at the lagged within level were revealed in the caudate and thalamus.

Conclusions: We did not find significant associations between binge drinking or cannabis use frequency and brain structure at the between-subject level, suggesting that there was limited evidence for a common vulnerability to substance use and abnormal brain structure during adolescence. All significant relationships between substance use and brain structure revealed in this study appeared to be time-varying, meaning that, as substance use increased from one year to the next, and over the individual's mean level of use (throughout the full follow-up period), important structural brain changes were also observed and shown to covary with changes in substance use. Furthermore, this study showed that some of the changes in brain structure that covaried with substance use lasted beyond the period of the increase in substance use. Therefore, this study findings are consistent with neuroplasticity and neurotoxicity hypotheses.

Introduction

The global burden of substance use disorders (SUD) is well documented[1, 2], and considering the important relationship between adolescent-onset substance use and risk for adult SUDs [3], research on the impact of adolescent substance use on brain development has become a major focus of addiction research. With alcohol being one of the most commonly used substances in adolescents[4], the global prevalence of current alcohol use and binge drinking among adolescents are 27% and 14%, respectively. Higher percentages were reported in Europe and North America in 2018 [4], where 38-44% of adolescents report consuming alcohol in the past month, and there is much debate and research on how recent changes in drug policy in some jurisdictions might be impacting these trends[5, 6]. While national surveys in North America, including Canada, are being widely used to examine time-varying relationships between drug policies and the prevalence and severity of adolescent alcohol and cannabis use, relatively few studies have used the same approach to investigate hypotheses on the relationship between substance use adolescent developing brain.

Adolescence is an important period of brain maturation and reorganization, described at the micro-structural level as synaptic pruning, dendritic and axonal arborization, and myelination (for a review[7], Lenroot & Giedd, 2006). Prior neuroimaging research has shown that global grey matter volume maturation follows a regionally-specific inverted U-shape trajectory while the global white matter volume increases throughout adolescence[7]. The development of subcortical regions before the development of prefrontal regions is described as a mismatch in the timing of structural brain maturation that leads to adolescent behavior often characterized by increased risk taking[8]. Moreover, adolescent brain maturation varies according to sex due to early puberty onset in adolescent females[9, 10]. Adolescent females present an earlier maturational peak followed by a steeper grey matter volume decrease rate, compared to adolescent males, particularly in limbic regions such as the hippocampus, amygdala, and the prefrontal cortex[11]. Therefore, the influence of substance use on brain maturation may be dependent on the maturational stages underlined by sex differences. Although the development and sexual

dimorphism in the adolescent brain are well studied, it remains unclear how adolescent alcohol and cannabis use may impact sex-specific brain development.

Previous cross-sectional studies have reported relationships between prefrontal volume reductions as well as subcortical volume reductions, such as, in the hippocampus and thalamus, and adolescent-onset alcohol use disorders [12, 13]. Unlike cross-sectional studies, longitudinal studies allow to evaluate the impact of substance use on brain developmental trajectories through adolescence and inform on temporal precedence, but they are in limited number in the literature. The few longitudinal studies conducted thus far suggest that alcohol misuse may alter normal adolescent brain growth by accelerating the decrease in overall grey matter volume [14]. Interestingly, these studies also suggest that there are pre-existing volumetric differences.[12] For example, one study reported abnormal neurodevelopmental trajectories[13] in frontal and temporal regions in future adolescent heavy drinkers, which suggests a potential effect of alcohol on neural pruning that would amplify cortical volume reductions through adolescence [15, 16]. One study involving 134 young participants (ages 12-24) who completed between two and six assessments were followed across two time points over about 3.5 years compared brain measures of 75 youth who became heavy drinkers and 59 who remained light drinkers [16] This study also evaluated sex differences in the relationships between substance use and changes in brain structure over a follow-up period that was up to eight years in duration: reduced temporal lobe volumes were reported in male heavy drinkers compared to female heavy drinkers. Overall heavy alcohol drinking during adolescence was associated with accelerated grey matter volume reduction in cortical frontal and temporal regions that were also observed in alcohol dependent adults and normal brain aging, which suggest that alcohol may accelerate brain aging [17, 18]. Although inconsistent findings are reported regarding the association between brain structure or activity and heavy alcohol drinking and binge-drinking (defined as more than four drinks for females and more than five drinks for males within two hours[16]), in 2020 a review of adolescent studies suggested that adolescent alcohol misuse was associated with reduced grey matter volume in frontal and temporal regions in a dose-dependent relationship, and a reduced brain activation during reward sensitivity tasks[19, 20]. One longitudinal study[14] included in the review previously mentioned stood out methodologically since it evaluated alcohol-related abnormal

brain developmental on a large sample of adolescents with no/low alcohol consumption. This study on 483 adolescents (ages 12–21) reported steeper grey matter volume reductions in frontal regions were associated with initiation of heavy drinking during adolescence[14], but the methodology was not able to determine whether adolescents prone to steeper reductions were simply prone to alcohol use, or whether alcohol use caused these brain-related changes. This study illustrates the limitations of observational studies in making any causal inferences about the effects of substances of abuse on brain development. Presently, the literature consistently associates adolescent alcohol use and misuse with reductions in cortical frontal thickness, and subcortical abnormalities, but much of this literature is based on cross-sectional designs or limited longitudinal studies that fail to account for potential developmental processes that might be causally implicated in risk for substance use.

Similarly several volumetric variations have been observed in early onset and heavy chronic cannabis users on the adolescent brain structure in cross-sectional studies, but such studies have also revealed a number of inconsistent findings, particularly when comparing across and within studies that use longitudinal designs[21-25]. For example, the longitudinal examination of relationships between neurodevelopmental trajectories and cannabis use in adolescence showed reduced cortical thickness in frontal regions of interest in cannabis users, and such differences predated onset of cannabis use, suggesting brain anomalies observed were associated with risk for cannabis use, rather than consequences of cannabis use[26, 27]. Another longitudinal study[28] on 79 adolescents aged 16 at baseline tracked the 18-month brain recovery in three distinct groups of adolescents: those with with cannabis use disorder, those with cannabis use disorder and early-onset schizophrenia, and healthy controls. This study reported an attenuated thickness loss in the frontal, temporal and parietal lobes in subjects with cannabis use disorders, across diagnostic groups, compared to non-users. These results suggest that the trajectory of normal grey matter cortical development may be altered by heavy cannabis use through adolescence.

Sex differences in the relationship between adolescent cannabis use and brain structure were reported in two cross-sectional studies on the same sample of adolescent cannabis users after

28 days of monitored abstinence. Medina et al (YEAR) showed sex-by-group interactions in prefrontal cortex volumes, where adolescent female cannabis users showed larger prefrontal volumes than adolescent male cannabis users compared to sex-matched controls. McQueeny et al[29] reported sex differences in the amygdala: larger right amygdala volumes were observed in female cannabis users compared to adolescent female non-users, but no volumetric differences were observed between male cannabis users and male non-users. Together these two studies suggest abnormal frontal and subcortical brain structures in adolescent female cannabis users compared to sex-matched non-users and male users, but it remains unknown whether these structural abnormalities persisted or disappeared after the 28-day abstinence period according to adolescent cannabis use. Overall, these cross-sectional and longitudinal studies suggest a cannabis-related maturational delay with attenuated cortical thickness loss in cannabis-using adolescents, and sex-specific patterns of differences between cannabis users and non-users in key subcortical regions such as the amygdala.

While early onset, frequent and heavy alcohol and cannabis use are associated with risk of developing SUD[30, 31], it remains unclear whether such risk is conferred through a process of common vulnerability, or through potential lasting association between adolescent substance use and brain development. Despite a growing number of studies on adolescent substance misuse, longitudinal studies nonetheless represent a minority, particularly those involving cohorts whose brain structure was assessed prior to the onset of substance use. Even fewer are sufficiently powered to study sex differences in the neural markers and consequences of substance misuse. Better designs are needed to investigate the relationship between substance use and brain development and, considering important sex differences in the pace and nature of brain development, these studies should be done while paying close attention to sex-specific processes. A better understanding of binge-drinking and cannabis use on the developing brain could lead to more targeted and effective prevention and intervention programs and potentially better gender-specific interventions [32 33].

In the absence of opportunities to perform experimental studies to explore causal relationships, a multilevel analytic framework applied to the right cohort longitudinal study can be used to

examine hypotheses that are relevant to causal theories, such as, directionality and temporal precedence and can contribute to mounting a body of evidence for, or against, causality [34, 35]. Such time series analyses can distinguish within-subject parameters (e.g., time varying relationships) from between-subject parameters (e.g., subject-level characteristics) and how such parameters are separately associated with the initial value or the change over time of a dependent variable. Within-subject parameters can also be modeled in different ways to evaluate the concurrent association between a predictor and a dependent variable and the lagged relationship between a predictor at a certain time point and a dependent variable at a later time point. These two methods to modelling within-subject time-varying relationships allow to dissociate the short term/transient from the longer-term/lasting associations between a predictor and a brain outcome. By contrast, between-subject associations can be interpreted as a common vulnerability to higher substance use and a particular brain profile over the course of adolescence. Modeling pre-morbid vulnerability in this way is important, because in some longitudinal designs, children will be assessed before being exposed to substances. A simple pre-post analysis in which baseline differences in substance use are controlled, will not account for common vulnerability (e.g., slower brain growth and early onset substance use). Finally, interaction terms can be computed for between-level covariates and within- subject parameters to evaluate potential covariate-related differences in the relationship between a time-varying or subject-level characteristics. A unique feature of multi-level modeling is that it permits the study of within- and between-subject parameters as distinct predictors. Finally, studies that include multiple time points can also inform on temporal precedence and changes through time, and test hypotheses about the directionality of the association between substance use and brain changes.

Using this analytic framework, two recent studies evaluated the relationships of adolescent alcohol and cannabis use to cognitive development over a 5-year period, and potential sex differences in such associations [36, 37]. The first population-based study used a sample of 3826 adolescents (47% female) who were assessed annually on substance use and cognitive performance [36]. Using a multilevel modeling framework, this study modeled between-, concurrent within- and lagged within-person relationships, with the former testing a common cognitive *vulnerability* hypothesis, the second testing a *neuroplasticity* hypothesis as the short-

term cognitive impairment related to substance use that can subside if substance use diminishes, and third testing a *neurotoxicity* hypothesis reflecting potential lasting cognitive impairment following early onset substance use. The study found evidence of associations between vulnerability towards lower performance on working memory and inhibitory control over the course of adolescence and vulnerability to more frequent and earlier alcohol and cannabis use. Over and above these significant between-subject associations, any further increases in cannabis use predicted greater impairment in working memory and response inhibition within the same year and one year later. While the random effects of cannabis on cognition were significant, they were not significant for alcohol. Quantity or dose of cannabis exposure could not be assessed in terms of standard units in this study, but this study stands out methodologically as one of the few studies on humans that can inform on the temporal precedence between adolescent substance use and brain development. The second study on the same sample of 3826 adolescents reported sex-related neurotoxic and negative effects of yearly fluctuations of cannabis use on working memory performance, with stronger associations in females compared to males[36]. However, further investigations involving direct measurement of brain are required to confirm theories of neurotoxicity, as relationships between substance use and cognitive outcomes could be mediated by school and other psychosocial outcomes (e.g., verbal IQ[38]). No study to date has investigated the relationships between substance use and adolescent brain development using this analytic framework, which is often used in other disciplines to attribute causal relationships between interventions or policies and human outcomes (e.g., drug-related arrests in youth[39]).

Using a data modeling strategy that dissociates the brain correlates implicated in risk for addiction from those that are consequential to early onset substance use, the goal of this study was to study the temporal precedence in the association between adolescent substance use and brain structure development in the context of a multi-level dynamical causal inference framework. The primary aim of this longitudinal study was to explore relationships between adolescent binge-drinking and cannabis use on cortical frontal and subcortical changes through development where the brain correlates of vulnerability to adolescent substance use are dissociated from the short and long-term brain correlates of random substance use events in time that are unrelated to an individual's general vulnerability to early onset substance use and

other measured covariates. This study will also uniquely compare findings for alcohol and cannabis using identical analytic strategies, to optimise comparability. Furthermore, with important sex differences in risk for and clinical outcomes of substance use and misuse[6, 40, 41], the second aim was to evaluate sex-related differences in the relationship between alcohol, cannabis use and structural brain measures within this longitudinal multi-level framework. In light of the literature reviewed above, we hypothesized that binge-drinking and cannabis use would be distinctly associated with subcortical and frontal sex-specific trajectories. Based on results from Medina et al[42], we also hypothesized that drug-specific relationships between alcohol and cannabis use and brain-related changes in cortical regions would be observed, and such associations would be particularly pronounced in adolescent females. We also hypothesized that binge-drinking would be associated with greater cortical thickness reduction in adolescent females compared to their male counterparts based on a review by Verplaetse et al in 2020[43].

Methods

Participants

Neuroventure is a prospective cohort study composed of 151 adolescents recruited in schools of Montreal from the Co-Venture trial[44] at 13.6 ± 0.64 years of age to evaluate the impact of delaying substance use on the adolescent brain and cognitive performance . The recruitment and data collection at all timepoints finished. Participants were in Grade 7 or 8 at the first time point (T1), in Grade 9 at T2 and in Grade 11 at T3. Inclusion and exclusion criteria for the Neuroventure cohort were previously described [44, 45] and included major neurodevelopmental disorders (e.g., autism), visual impairment or hearing deficits, uninterruptible central nervous system medication, and any MRI contraindications (e.g., pregnancy, braces, etc.) for the individual magnetic resonance imaging assessment. Participants underwent neuroimaging scans three times across five years at the Montreal Neurological Institute (MNI). The final sample in the analyses included 130 participants (52.3% females) who completed the neuroimaging sessions (detailed in the Image Processing section). The mean age of participants at the three timepoints were 13.6 ± 0.64, 14.8 ± 0.4 and 17.2 ± 0.5 years, respectively. The CHU Sainte-Justine obtained

ethics approval for this research from the Sainte-Justine's Hospital Ethics Committee in Montreal. Written consent was obtained from the parents or legal guardian of the participants, who also actively assented to participate to the study (reference number: 3678).

Image Processing

The scanning session was implemented on a 3T Siemens Magnetom Trio/Prisma MRI scanner at the three time-points. High-resolution three-dimensional T1-weighted structural scans were acquired for all participants with a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters at the three time-points: TR = 2.3 s, TE = 2.96 ms, 1 mm thickness, 1 x 1 x 1 mm voxel size resulting in a 256x256 matrix.

The ENIGMA longitudinal preprocessing pipeline (http://enigma.ini.usc.edu/protocols/imaging-protocols/) computed the brain measures of unilateral cortical thickness and subcortical volumes for the 41 regions of interest on structural T1-weighted MRI data. The segmented brain images were parcellated into AAL mapped regions of interest with the Nilearn Python package's AAL tool NiftiLabelMasker[46].

Visual inspection and quality control of the segmentation were completed for all participants at each time point at the MNI and at the CHU Sainte-Justine to detect abnormalities among the sample. Out of 151 participants scanned at T1, 21 were excluded from the analyses. 1 participant was excluded due to epilepsy, 8 participants were excluded due to incidental findings on MRI including enlarged ventricles (6) and arachnoid cysts (2), 1 was excluded due to an artefact, 3 had excessive motion, 4 had poor Freesurfer segmentation and 4 had missing data (T1 sample for the analyses n=130). Out of 133 participants scanned at T2, 15 were excluded from the analyses. 1 participant was excluded due to epilepsy, 6 participants were excluded due to incidental findings on MRI including enlarged ventricles (4), arachnoid cyst (1) and right temporal abnormality (1), 1 was excluded due to an artefact, 2 had excessive motion and 5 had poor Freesurfer segmentation (T2 sample for the analyses n=118). Out of 129 participants scanned at T3, 19 were excluded from the analyses. 1 participant was excluded due to epilepsy, 7 participants were excluded due to incidental findings on MRI including enlarged ventricles (4), arachnoid cyst (1), right temporal

abnormality (1) and small corpus callosum (1), 3 were excluded due to an artefact, 1 had excessive motion, 6 had poor Freesurfer segmentation and 1 was excluded due to brain truncation (T3 sample for the analyses n=110).

Predictors

Self-reported alcohol and cannabis use were assessed using modified digital version of the Detection of Alcohol and Drug Problems in Adolescents (DEP-ADO) questionnaire validated for use across all schools in the Province of Quebec to screen for adolescent substance use disorders which includes a binge-drinking measure [47]. Participants were asked to report the frequency of binge-drinking as the number of times they had five or more drinks on the same occasion in their lifetime. Cannabis use was reported by the participants as the frequency of their consumption on a scale of 0-5 (never to everyday). Additional information regarding the sex-specific lifetime frequencies of binge-drinking and cannabis use are presented in Tables 1 and 2.

Brain Outcomes

To compare the drug-specific relationships between substance use and subcortical volumes and cortical thickness through adolescence, seven subcortical bilateral volumes (nucleus accumbens, caudate, putamen, pallidum, hippocampus, amygdala and thalamus) and the bilateral cortical thickness for 13 frontal regions of interest (superior frontal, rostral and caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral and medial orbitofrontal, precentral, paracentral and frontal pole) were the brain measures of the primary analysis based on previous findings in the literature on the relationships between alcohol and cannabis misuse and brain measures[48]. A secondary analysis on 21 cortical regions distributed in the temporal, parietal and occipital lobes are also reported (superior parietal, inferior parietal, supramarginal, postcentral, precuneus, posterior cingulate, superior parietal, middle parietal, inferior temporal, banks of the superior temporal sulcus, fusiform, transverse temporal, entorhinal, temporal pole, parahippocampal, lateral occipital, lingual, cuneus, pericalcarine and isthmus cingulate), for the purpose of open science, were not primary regions of interest and were included as

supplementary materials. The mean bilateral measure was obtained by summing the two unilateral measures then dividing by two [(left+right)/2]. We adjusted for age in all analyses. Sex was a binary variable that was included in the model as a non-time varying variable to detect sex differences in the adolescent brain and was this included in the models as time-invariant covariate. Time was a numeric variable to observe brain changes through the three time points. We covaried for intracranial volume for the subcortical volumes only since cortical thickness does not scale proportionally with brain size[49].

Statistical Analysis

Figure 1 shows the multilevel model using dynamic structural equation modelling (DSEM) in MPLUS software for the time series analysis [50]. Unlike traditional multilevel models, DSEM allows for random effects for both predictors and outcomes, and lagged associations are modeled using latent variables. Such considerations are important to avoid alleged dynamic panel bias [51]. Bayesian estimator processed the parameters through 5000 iterations with two Markov chain Monte-Carlo (MCMC) and a MCMC convergence criterion of 0.5 was used. Two multilevel models were performed independently on two dependent measures: one for binge-drinking, and one for cannabis use. The predictors were person-mean centered in both models. A first model was performed to evaluate the impact of substance use on the bilateral cortical thickness of each region of interest. After estimating the time parameters, a second model evaluated the contribution of six predictors: a) average substance use over the three time points (between-subject differences in consumption), b) average brain structure over the three time points (between-subjects differences in cortical development), c) change in substance use this time point compared with the participant's mean use (within-subject difference in consumption), d) substance use the time point before compared with the participant's mean use (lagged within-subject difference in consumption), e) change in brain structure this time point compared to the participant's mean use (within-subject difference in cortical development), and f) brain structure the time point before compared with the participant's mean use (lagged within-subject difference in cortical development). This second model covaried for age and sex for the between-level predictors and ICV for subcortical volumes. A final model added sex-specific predictors at

the between-level with the four within-subject associations, and two interaction parameters: interaction of average substance use over the three time points and sex, and interaction of average brain structure over the three time points and sex.

Between-subject associations were interpreted as a common vulnerability between substance use and deviant neurodevelopment. Within-subject relationships were interpreted as potentially neurotoxic effects of substance use, with concurrent associations interpreted as neuroplasticity and lagged relationships as neurotoxicity[33]. The interaction of sex with within-person associations were interpreted as a potential sensitivity in one sex relative to the other with respect to the neurotoxic effects of substances on brain development. The moderator role of sex in between-subject associations was interpreted as a sex differences in the common vulnerability between substance use and deviant neurodevelopment.

Missing data on the predictors and outcomes were handled through Bayesian estimation. While correcting for multiple testing does not always apply to multilevel models[52], our independent models require a correction since they were developed separately for each region of interest. To correction for multiple testing, a false discovery rate (FDR) correction was applied using the Benjamini-Hochberg procedure following a verification of the independency structure between the tests. While statistical significance threshold was determined using $p_{FDR} = 0.05$, marginal significant results were reported when zero was outside of the confidence interval and a $p_{FDR}<0.1$.

Results

Alcohol model

Binge-drinking frequency on frontal cortical thickness and subcortical volumes

Tables 3 and 4 show estimated parameters for multilevel models assessing the association between binge-drinking and brain structures. At the between-person level there was no significant associations between binge-drinking and cortical thickness scores or subcortical volumes**.** Several frontal regions showed marginal significant concurrent associations between

increased binge-drinking frequency and reduced cortical thickness at the within-subject level. Indeed, marginal significant concurrent negative associations for binge-drinking were observed in the caudal middle frontal (Estimate=-0.119, 95% CI=[-0.23, -0.029], p_{FDR}=0.060), rostral middle frontal (Estimate =-0.118, 95% CI=[-0.236, -0.016], p_{FDR}=0.062), pars orbitalis (Estimate =-0.128, 95% CI=[-0.27, -0.005], p_{FDR}=0.096), pars triangularis (Estimate =-0.127, 95% CI=[-0.244, -0.019], p_{FDR}=0.062) and superior frontal (Estimate =-0.126, 95% CI=[-0.239, -0.033], p_{FDR}=0.060). No significant associations for the lagged within-subject binge-drinking frequency variable was significant for any of the frontal and subcortical structural measures.

Sex differences in the relationship between binge-drinking frequency and brain cortical frontal and subcortical structure

No significant moderator role of sex on the concurrent relationship between binge-drinking and the hippocampus and amygdala were observed at the between-subject level.

Cannabis model

Cannabis use frequency on cortical frontal thickness and subcortical volumes

Table 5 shows estimated parameters for multilevel models assessing the association between cannabis and subcortical brain structures. At the between-person level there were no significant associations between cannabis use frequency and brain structures in cortical frontal and subcortical regions**.** No significant associations were revealed for cannabis use frequency and frontal and subcortical regions at the concurrent within-subject level. However, a significant within-subject lagged association was observed for the accumbens, which revealed that any further increases in cannabis use frequency was marginally associated with further increases in bilateral volume in the accumbens one timepoint (i.e. two years) later (Estimate=0.261, 95% CI=[0.070, 0.443], p_{FDR} =0.070). No lagged associations between cannabis use frequency and any cortical frontal regions were observed.

Sex differences in the relationship between cannabis use frequency and brain cortical frontal and subcortical structure

Analyses revealed a significant moderator role of sex on the concurrent time-varying relationship between cannabis and subcortical volume in the thalamus (Estimate=0.480, 95% CI=[0.158, 0.698], p_{FDR}=0.019), caudate (Estimate=0.390, 95% CI=[0.046, 0.638], p_{FDR}=0.035), putamen (Estimate=0.389, 95% CI=[0.041, 0.634], p_{FDR}=0.035), pallidum (Estimate=0.828, 95% CI=[0.170, 0.983], p=0.035), hippocampus (Estimate= 0.603, 95% CI=[0.214, 0.834], p_{FDR}=0.019) and amygdala (Estimate= 0.564, 95% CI=[0.166, 0.810], p_{FDR}=0.019). No post-FDR significant moderator role of sex was observed on the lagged relationship between cannabis frequency use and two-year volumetric changes.

Exploratory analyses

Supplementary Tables 1 and 2 shows estimated parameters for multilevel models for the association between cortical parietal, temporal and occipital regions and binge-drinking and cannabis use, respectively. No FDR-corrected significant interactions between sex and cannabis use frequency were observed at the between-subject level.

Discussion

In this study we first aimed to evaluate the between, concurrent and lagged associations between binge-drinking or cannabis use with subcortical and frontal regions using a unique longitudinal neuroimaging cohort, which was assessed every two years on substance use and neuroimaging outcomes over a 5-year period. The second aim was to identify sex differences in these drug-specific relationships on the development of brain structure. The third aim was to explore the associations between binge drinking and cannabis use frequency and brain structure in the other parts of the brain (i.e. temporal, parietal and occipital regions) and potential sex differences.

While the lack of between-person relationships between substance use and brain structure are surprising considering a previous literature linking abnormal brain structure to future substance

use, [14, 25, 53] no study has investigated this relationship over the full course of adolescent brain development, controlling for sex differences in brain development and using a multilevel approach, so it will be important to investigate the replicability of these findings in other ongoing cohort studies[14, 25].

With respect to the time-varying relationships between substance use and developing brain structure, several frontal regions marginally confirmed our hypotheses about significant concurrent associations between binge-drinking frequency and cortical thickness since no associations survived the FDR correction, and exploratory analyses showed similar marginal relationships within parietal and temporal regions (see supplementary material). The relationships between concurrent binge-drinking and cortical thickness in our study are consistent with a study based on a large sample of adolescents, in which steeper reductions in grey matter volume in frontal and parietal regions were observed in adolescents who reported heavy drinking over the course of a follow-up period, compared to moderate and low drinking adolescents[14]. Our study extends this literature to confirm that such changes in frontal cortical thickness are closely linked to year-to-year changes in binge drinking, and not related to between person differences in brain structure or growth in brain structure. Inherent in a significant concurrent within-person effect is the test that when substance use increases or reduces from one year to the next (relative to the participant's mean level of use), any observed brain changes increase or decrease in relation to the participant's mean cortical thickness, providing a strong test of covariance between two variables. The results reported here suggest that adolescent binge drinking is marginally associated with reductions in cortical thickness in the frontal lobes, consistent with a neuroplasticity model, in that we also showed that if such increases in binge drinking subside, so do the observed reductions in cortical thickness. Such time-varying relationships are important to understand since animal models of alcohol dependence have revealed that phasic bursts of activity from the tegmental ventral area GABAergic and dopaminergic neurons to the accumbens are induced by alcohol consumption[54]. This transmission signals alcohol positive reinforcing effects and is later encoded through neuroplastic mechanisms in the afferent connections of the accumbens to the prefrontal cortex, which become more sensitive to alcohol over repeated measure and lead to an increased motivation

for alcohol consumption[55, 56]. The changes in cortical structure revealed to be associated with alcohol use could potentially index neurobiologic processes implicated in early stages of alcohol addiction. However, no associations survived the FDR procedure for the alcohol model so further studies are required to validate these post-FDR non-significant results.

In the alcohol model, sex marginally interacted with the between-person relationship between amygdala volume and binge drinking, which indicated greater bilateral volume in adolescent males compared to adolescent females through the three timepoints. This sex-related difference in the brain morphometry is consistent with previous findings in the literature on the sexual dimorphism in the amygdala[57, 58]. A marginal interaction between sex and the concurrent within-person relation between binge-drinking and hippocampus volume, was also revealed. The hippocampus is a key limbic structure involved in memory, navigation and cognition[59]. Sex differences are reported in hippocampal plasticity, neurogenesis, and in a number of disorders that target integrity of the hippocampus (for review, Yagi & Galea[60]) including alcohol use disorder that leads to dramatic effects on the hippocampus[61]. These sex differences are important since accelerated alcohol-induced brain changes may be related to cognitive impairments observed in both heavy drinking adolescents and adults, particularly memory impairments [20, 62, 63]. Several small sample studies reported female sensitivity to the effects of alcohol on cognitive functioning, with poorer performance in spatial working memory before controlling for age of alcohol onset[64], cognitive flexibility[65] and visual search[66] reported in binge-drinking young adult females compared to non binge-drinking young female adults. However, a previous study examining sex differences in the relationship between alcohol use and cognitive function, using a multi-level longitudinal design similar to the current study, did not reveal that female adolescents experienced more alcohol-related impairment in cognitive function compared to males based on a sample of 3826 adolescents[37]. The sex-specific relationship between binge drinking and hippocampal volume should be investigated using other behavioural domains in order to be able to understand the clinical relevance of this finding.

In a similar way to the alcohol results, the absence of between-subject associations between cannabis use and brain structures are unexpected in view of previous studies associating deviant

brain structures to subsequent cannabis use[27, 67]. However, no study evaluated this relationship between 13 and 17 years of age while controlling for sex differences using a multilevel framework. Therefore, further investigations are needed to evaluate the replicability of our results in ongoing cohort studies. A review of cannabis-related structural abnormalities in adolescent studies reported important structural abnormalities in the frontal lobe are linked to cannabis[25]. However, we did not observe any significant association between cannabis use frequency and cortical thickness in frontal regions. It is important to point out that not all longitudinal studies performed whole-brain analysis, but rather studied *a priori* selected regions of interest in the frontal lobe. This limits the comparison between studies and introduces more heterogeneity in the literature. Among the longitudinal studies that evaluated cannabis-related structural abnormalities in adolescents, the few studies that did perform whole-brain analysis reported structural variations in other regions of interest, including the parietal and occipital lobes[22, 68]. Combined with our findings, this suggests that more studies using a whole-brain analysis approach are required to develop a better understanding of the cannabis-related structural variations observed through adolescence.

However, the current study did reveal a marginal lasting association between of cannabis use and the bilateral accumbens volume, suggesting that cannabis use during adolescence is associated with a significant reduction in accumbens volume that lasts beyond the period of heavier cannabis consumption. This finding establishes temporal precedence in the relationship between cannabis and subcortical brain structure changes, and also suggest a robust and repeatable effect, because this relationship was tested across two time-lagged periods. A multilevel study based on data from the Co-Venture trial on 3826 adolescents revealed that average cannabis use over four years was associated with lower inhibition and that any increase in cannabis use predicted subsequent inhibition impairment one year later[36]. These results are interesting since inhibitory control is regulated by a balanced activity between the prefrontal cortex and the accumbens[69]. Greater activity in the accumbens, or lower prefrontal activity, would likely result in disrupted inhibitory control, which seems to contribute to risk-taking behaviors and impulsivity[69, 70]. Our results showed that cannabis use frequency predicted increased accumbens volume two years later. This lasting effect is interesting since repeated THC

exposure seems to weaken glutamate inputs from the medial prefrontal cortex to the accumbens, resulting from a reduced glutamate release probability and a decreased proportion of high-conductance calcium-permeable AMPA receptors in mice[71]. Such a weakening of these glutamatergic inputs, induced by chronic cannabis exposure, could contribute to the accumbens volumetric variation and ultimately, to the imbalanced activity that likely contributes to the reduced inhibitory control in adolescent cannabis users. Further investigations are required to translate these pre-clinical observations to aetiologic theories of adolescent substance misuse.

Consistent with findings[25] from previous cross-sectional studies, the current study revealed that sex modified the concurrent relationships between cannabis use and changes in subcortical volumes in the thalamus, caudate, putamen, pallidum, hippocampus and amygdala. While the sexual dimorphism in the developmental trajectories of these subcortical regions of interest is recognized[57, 58], it remains unclear how cannabis use interacts with normal brain development through adolescence. Since these subcortical regions are part of the cortico-basal ganglia-thalamic circuitry, which is involved in addiction, such time-varying associations between these subcortical volumes and cannabis might inform on the neurobiological mechanisms that underlie sex differences in adolescent cannabis misuse[72, 73]. They may also explain the findings of sex differences in the relationship between adolescent cannabis use and cognitive development[37] , which were most pronounced on the development of working memory for girls. Nevertheless, it remains unclear what biologic or behavioural measures might explain these sex differences in sensitivity the long-lasting relationships between cannabis use and brain structure. A growing body of literature suggests that males and females respond differently to cannabinoids a various levels of central nervous system measurement[74].Furthermore, adolescent females present an earlier maturational peak followed by a steeper grey matter volume decrease rate in hippocampus and amygdala[75], compared to adolescent males. Therefore cannabis use might differently affect brain regions according to the maturational stage of the individual. Another plausible explanation might be the interaction between female hormones and cannabis to produce effects on the brain. Because preclinical studies indeed observed THC-induced variations in the secretion of luteinizing hormones, which might be associated with total grey matter volume, further investigations on the potential interaction between cannabis psychoactive

molecules and gonadal hormones are needed [76, 77]. Interestingly, caudate and thalamus volumes were the only two regions that showed both concurrent and lagged significant sex-by-cannabis interactions, which might suggest a potential greater sensitivity of these subcortical regions in adolescence.

One of the strengths of the current study is the use of multilevel modeling to estimate the different ways in which substance use might be related to brain outcomes within one model[35]. Moreover, by covarying out the relationship between brain structure and general vulnerability to high levels of substance use, as well as other covariate, what is being modeled at the within-person level are the random occurrences of substance use that cannot be explained by common vulnerability or other co-variates. In essence, the within-group effect can be modeled like a random assignment, which is why such models are becoming more widely accepted as being able to inform causal hypotheses. Since the analytical approach used can only partially inform causal hypotheses (e.g., co-variance and temporal precedence) between substance use and adolescent brain development, the results were presented in terms of an association/relationship instead of potential causal effects. Nevertheless, this work represents a significant advance, since dynamic relationships were distinguished from common vulnerability among participants in a sample that was nearly free of substance use at baseline. Further longitudinal studies using a multilevel approach are required to evaluate the robustness of these neuroplastic structural changes and whether the lagged relationships between cannabis use and nucleus accumbens volume are linked to important addiction outcomes.

Despite major strengths in the longitudinal design and analyses, this study has several limitations. First, data collection involved self-reported measures of retrospective substance use that could not be confirmed by more objective observation methods such as biological tests. Considering the sensitive nature of substance use in adolescents, this might have led to underreported behaviors by the participants. However, the guaranteed confidentiality provided to the Neuroventure participants (unless there was a risk of harm to self or others) can lead self-reports on adolescence substance use to greater accuracy than biological measures that lack sensitivity to episodic substance use [78]. Second, the application of a FDR procedure limited the

interpretation of marginally significant results, especially for the relationships between alcohol and cortical frontal regions. Third, the limited sample size restricts our ability to determine the reliability of the observed results. Further larger adolescent cohorts are encouraged to perform such analysis in order to evaluate the robustness of our findings. Finally, the three time points at which the participants underwent imaging scans did not represent exact Tanner stages[79] of pubertal development, which limits the interpretation of sex differences related to puberty in brain measures observed.

Finally, this study carried out one of the first sex differences analysis on the patterns of adolescents' brain development using a dynamic structural equation modelling design across three time points. The multilevel approach made it possible to distinguish time-varying relationships between substance use and brain development from between-subject associations, as well as to evaluate the moderating role of sex in these different relationships. Although no common vulnerability to alcohol and cannabis was observed in all regions of interest, results suggest that binge-drinking is associated with greater structural abnormalities than cannabis use for the concurrent associations between alcohol and cortical thickness, but cannabis showed more important lasting relationships, particularly in the nucleus accumbens. Furthermore, important cannabis-related sex differences in subcortical regions were observed and were the most significant results in the current study. These results contribute to characterizing the sex- and drug-specific associations between adolescent substance use and brain development through adolescence, and therefore provides new insights into the potential role of early onset substance use in the emergence of addictive behaviors. The results may be used to inform public health messaging and targeted drug and alcohol interventions for youth[80]. It will be important to associate these results to other meaningful clinical and psycho-educational outcomes to understand the functional consequences of substance-related abnormalities in adolescent brain development.

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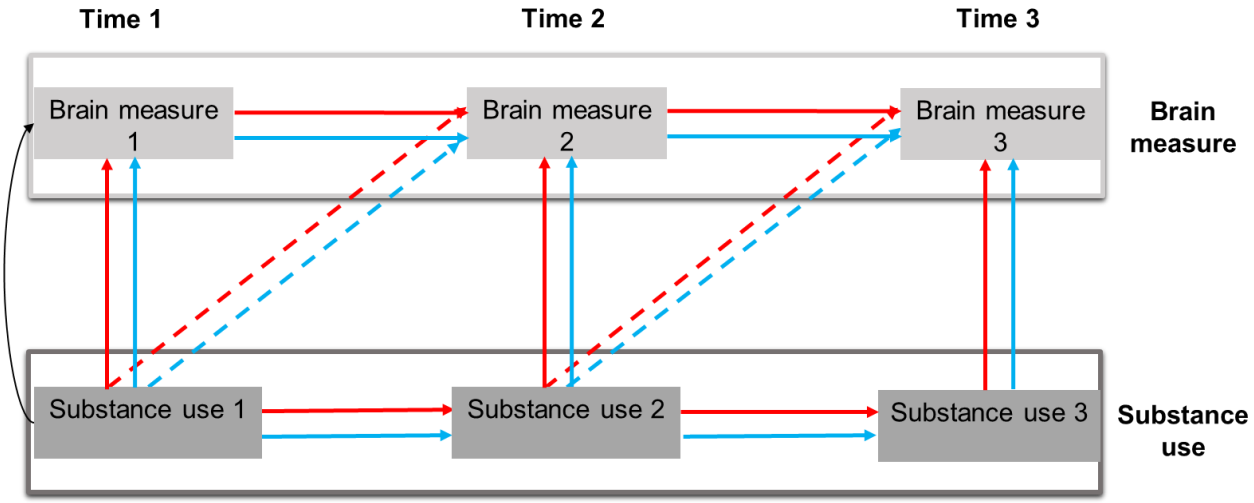

Figure 10. – **Figure 1 (Article 3).** Dynamic structural equation modelling of the sex-specific association between substance use and structural measures at the three timepoints at which participants underwent neuroimaging scans. The substance use variables were the lifetime frequency of binge-drinking (continuous variable) and the category of cannabis use (0-5, never to everyday). Cortical thickness 1-3 represents the bilateral subcortical volumes and cortical thickness. Red and blue lines represent sex-specific associations between each variable for adolescent females and males at the between-person level, respectively. Vertical lines represent concurrent associations (e.g., the neuroplasticity hypothesis), and hashed lines represent the lag associations (e.g. the neurotoxicity hypothesis).

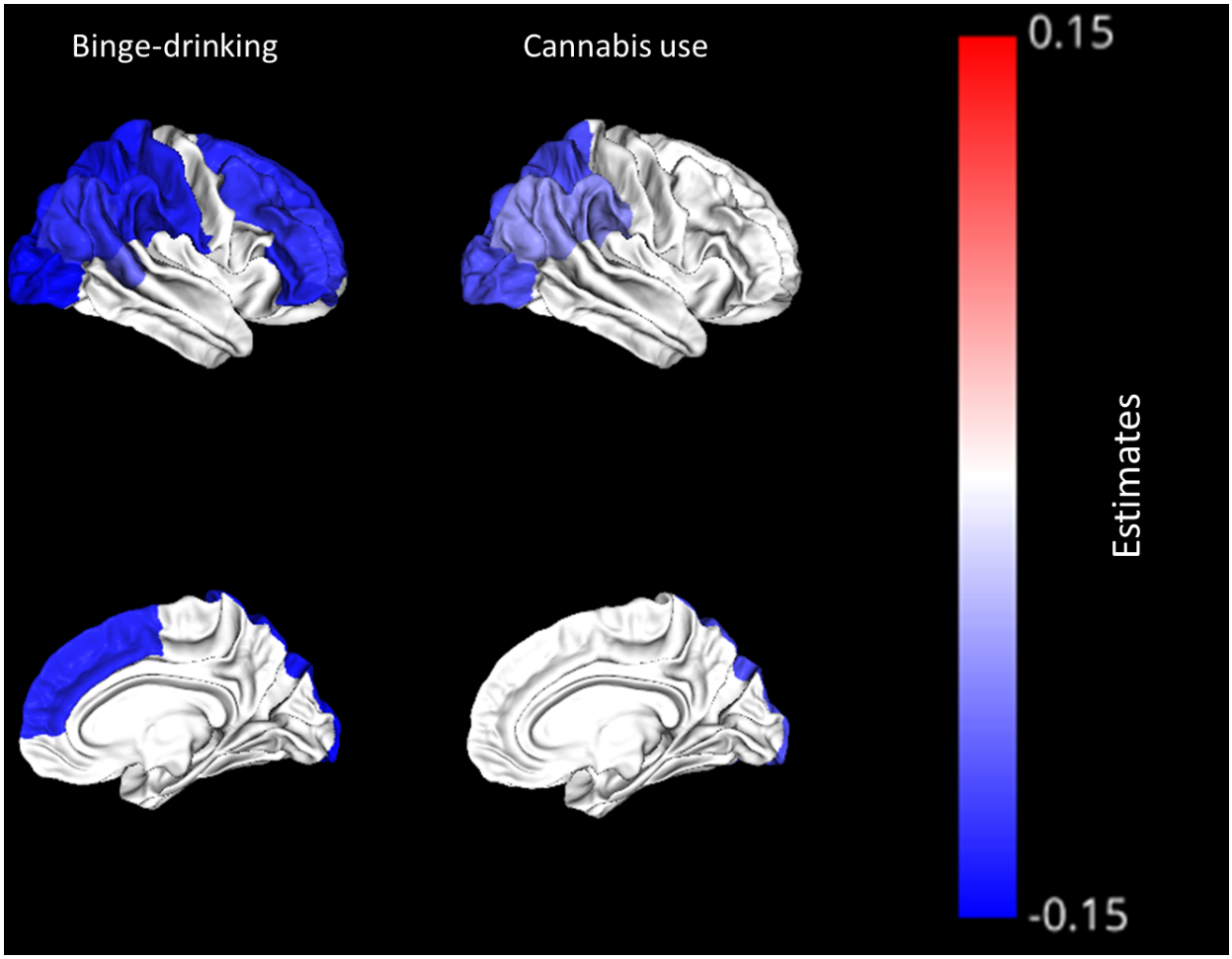

Figure 11. – **Figure 2 (Article 3).** Comparison of the significant within-subject concurrent (neuroplastic) associations between binge-drinking (brain on the left) or cannabis use (brain on the right) and cortical thickness through the three timepoints. A more diffuse decrease in cortical thickness is observed for binge drinking frequency compared to cannabis use frequency.

Tableau 5. – **Table 1 (Article 3).** Frequency distribution for substance use variables in adolescent females at the three time points.

Substance and assessment for girls [a]	Frequency or quantity					
Frequency	Never	Occasionally	Once a month	Once or twice per week	Three times or more per week	Every day
Cannabis use						
Time 1	95.46%	3.03%	0.00%	0.00%	0.00%	1.51%
Time 2	78.80%	13.64%	3.03%	1.51%	1.51%	1.51%
Time 3	51.51%	27.27%	6.06%	9.10%	0.00%	6.06%
	Number of episodes where more than five standard drinks were consumed in their lifetime					
Quantity [b]	<1	1-2	3-5	6-8	>8	
Binge-drinking						
Time 1	89.39%	4.55%	3.03%	0.00%	3.03%	
Time 2	68.18%	18.18%	7.58%	1.51%	4.55%	
Time 3	34.85%	12.12%	21.21%	13.64%	18.18%	

a. Time 1 represents assessment in 7th or 8th grade, Time 2 in 9th grade, and Time 3 in 11th grade.

b. Alcohol use quantity variables were categorized here for presentation purposes; in the analyses, alcohol use quantity was used as a continuous variable

Tableau 6. – **Table 2 (Article 3).** Frequency distribution for substance use variables in adolescent males at the three time points.

Substance and assessment for boys [a]	Frequency or quantity					
Frequency	Never	Occasionally	Once a month	Once or twice per week	Three times or more per week	Every day
Cannabis use						
Time 1	95.00%	3.33%	1.67%	0.00%	0.00%	0.00%
Time 2	88.33%	6.67%	0.00%	3.33%	0.00%	1.67%
Time 3	61.29%	19.35%	4.84%	8.06%	3.23%	3.23%
	Number of episodes where more than five standard drinks were consumed in their lifetime					
Quantity [b]	<1	1-2	3-5	6-8	>8	
Binge-drinking						
Time 1	96.67%	3.33%	0.00%	0.00%	0.00%	
Time 2	73.33%	15.00%	10.00%	0.00%	1.67%	
Time 3	29.03%	16.13%	20.97%	6.45%	27.42%	

a. Time 1 represents assessment in 7th or 8th grade, Time 2 in 9th grade, and Time 3 in 11th grade.

b. Alcohol use quantity variables were categorized here for presentation purposes; in the analyses, alcohol use quantity was used as a continuous variable

Tableau 7. – **Table 3 (Article 3).** Estimated Parameters for the Alcohol Model in Significant Subcortical Regions in a Sample of Adolescents (N = 130) Assessed Three Times Over 4 years

	Hippocampus				Amygdala			
Predictor	Estimate	Std. Er	Pr(>|t|)	95% CI	Estimate	Std. Er	Pr(>|t|)	95% CI
Intercept	-5.267	65.06	0.972	[-134.2, 113.9]	-23.160	75.522	0.972	[-160.7, 135.6]
Time	**0.854**	**0.086**	**<0.001**	**[0.676, 1.020]**	**0.588**	**0.147**	**0.008**	**[0.224, 0.807]**
ICV	**0.674**	**0.063**	**<0.001**	**[0.534, 0.778]**	**0.588**	**0.080**	**<0.001**	**[0.413, 0.727]**
Age	0.017	0.347	0.970	[-0.630, 0.567]	0.098	0.351	0.970	[-0.608, 0.647]
Sex (male)	0.046	0.105	0.775	[-0182, 0.239]	**0.259**	**0.112**	**0.294**	**[0.015, 0.462]**
Alcohol, B	-0.026	0.486	0.948	[-0.394, 0.520]	-0.059	0.256	0.948	[-0.414, 0.539]
Alcohol, W	0.074	0.082	0.884	[-0.097, 0.228]	0.098	0.095	0.884	[-0.081, 0.281]
Alcohol, W (lagged)	0.049	0.211	0.936	[-0.322,0.491]	0.153	0.149	0.936	[-0.155, 0.423)
Sex (male) x alcohol, Between	0.254	0.274	0.966	[-0.365, 0.639]	0.027	0.343	0.966	[-0.574, 0.641]
Sex (male) x alcohol, Within	**0.439**	**0.166**	**0.182**	**[0.060, 0.700]**	0.390	0.192	0.287	[-0.049, 0.687]
Sex (male) x alcohol, Within (lagged)	0.118	0.308	0.978	[-0.563, 0.636]	0.551	0.286	0.910	[-0.172, 0.908]

Note. When the confidence intervals did not overlap with zero, associations are bolded. Pr(>|t|): two-tailed FDR-corrected p-values.

Tableau 8. – **Table 4 (Article 3).** Estimated Parameters for the Alcohol Model in Significant Frontal Cortical Regions in a Sample of Adolescents (N = 130) Assessed Three Times Over 4 years

	Caudal middle frontal				Rostral middle frontal				Pars orbitalis				Pars triangularis				Superior frontal			
Predictor	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**
Intercept	31.348	78.321	0.764	[-148.1, 192.7]	28.565	75.828	0.764	[-134.2, 176.1]	33.01	74.431	0.764	[-125.8, 185.8]	32.341	71.682	0.764	[-103.1, 175.5]	42.240	74.587	0.764	[-114.8, 191.5]
Time	**-0.965**	**0.045**	**<0.001**	**[-1.077, -0.898]**	**-0.949**	**0.049**	**<0.001**	**[-1.06, -0.871]**	**-0.884**	**0.051**	**<0.001**	**[-0.979, -0.774]**	**-0.945**	**0.041**	**<0.001**	**[-1.033, -0.871]**	**-0.955**	**0.042**	<0.001	**[-1.047, -0.883]**
Age	-0.204	0.383	0.726	[-0.779, 0.581]	-0.198	0.392	0.726	[-0.861, 0.556]	-0.211	0.381	0.726	[-0.800, 0.616]	-0.188	0.397	0.726	[-0.824, 0.621]	-0.289	0.395	0.726	[-0.903, 0.574]
Sex (male)	-0.095	0.125	0.954	[-0.329, 0.150]	-0.067	0.124	0.954	[-0.298, 0.183]	-0.221	0.111	0.728	[-0.424, 0.005]	-0.02	0.117	0.954	[-0.243, 0.207]	-0.128	0.113	0.954	[-0.336, 0.097]
Alcohol, B	-0.07	0.37	0.988	[-0.756, 0.663]	-0.057	0.384	0.988	[-0.728, 0.656]	0.047	0.425	0.988	[-0.722, 0.759]	0.068	0.417	0.988	[-0.722, 0.737]	0.031	0.379	0.990	[-0.735, 0.707]
Alcohol, W	**-0.119**	**0.052**	**0.060**	**[-0.23, -0.029]**	**-0.118**	**0.055**	**0.062**	**[-0.236, -0.016]**	**-0.128**	**0.067**	**0.096**	**[-0.270, -0.005]**	**-0.127**	**0.056**	**0.062**	**[-0.244, -0.019]**	**-0.126**	**0.053**	**0.060**	**[-0.239, -0.033]**
Alcohol, W (lagged)	-0.063	0.124	0.890	[-0.269, 0.210]	-0.03	0.138	0.890	[-0.281, 0.243]	-0.044	0.142	0.890	[-0.346, 0.224]	-0.079	0.131	0.890	[-0.340, 0.162]	-0.090	0.115	0.890	[-0.305, 0.138]
Sex (male) x alcohol, B	0.538	0.283	0.520	[-0.280, 0.873]	-0.04	0.235	0.520	[-0.499, 0.394]	0.438	0.349	0.520	[-0.505, 0.841]	0.482	0.332	0.520	[-0.373, 0.887]	0.489	0.280	0.520	[-0.225, 0.850]
Sex (male) x alcohol, W	-0.085	0.227	0.904	[-0.516, 0.341]	-0.054	0.393	0.904	[-0.827, 0.645]	0.148	0.235	0.904	[-0.332, 0.545]	0.082	0.229	0.904	[-0.377, 0.489]	0.150	0.220	0.904	[-0.301, 0.529]
Sex (male) x alcohol, W (lagged)	-0.158	0.404	0.990	[-0.865, 0.601]	0.56	0.277	0.990	[-0.206, 0.894]	-0.186	0.396	0.990	[-0.850, 0.671]	-0.268	0.401	0.990	[-0.873, 0.562]	-0.005	0.396	0.990	[-0.757, 0.673]

Note. When the confidence intervals did not overlap with zero, associations are bolded. B: between-subject level, W: within-subject-level, Pr(>|t|): two-tailed FDR-corrected p-values.

Tableau 9. – **Table 5 (Article 3).** Estimated Parameters for the Cannabis Model in Significant Frontal Cortical Regions in a Sample of Adolescents (N = 130) Assessed Three Times Over 4 years

	Thalamus				Caudate				Putamen				Pallidum				Hippocampus				Amygdala				Accumbens			
Predictor	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**
Intercept	-3.396	74.164	0.992	[-144.0, 138.3]	12.749	81.217	0.992	[144.5, 179.2]	47.587	79.748	0.992	[-142.3, 203.8]	1.144	86.613	0.992	[-176.9, 155.1]	-2.454	78.448	0.992	[-159.9, 134.7]	-21.741	88.241	0.992	[-181.6, 158.0]	44.113	93.409	0.992	[-151.6, 229.8]
Time	0.136	0.203	0.616	[-0.283, 0.464]	**-0.429**	**0.123**	**0.028**	**[-0.621, 0.124]**	-0.167	0.205	0.583	[-0.443, 0.312]	**0.850**	**0.036**	**<0.001**	**[0.776, 0.920]**	**0.748**	**0.056**	**<0.001**	**[0.634, 0.861]**	**0.546**	**0.094**	**<0.001**	**[0.343, 0.727]**	**0.714**	**0.067**	**<0.001**	**[0.573, 0.843]**
ICV	**0.779**	**0.044**	**<0.001**	**[0.677, 0.849]**	**0.677**	**0.059**	**<0.001**	**[0.539, 0.776]**	**0.494**	**0.09**	**<0.001**	**[0301, 0.649]**	0.629	0.067	**<0.001**	**[0.479, 0.741]**	**0.656**	**0.065**	**<0.001**	**[0.510, 0.766]**	**0.572**	**0.083**	**<0.001**	**[0.385, 0.712]**	**0.432**	**0.099**	**<0.001**	**[0.214, 0.606]**
Age	0.018	0.334	0.988	[-0.573, 0.538]	-0.066	0.356	0.988	[-0.666, 0.603]	-0.333	0.388	0.988	[-0.813, 0.500]	-0.008	0.382	0.988	[-0.706, 0.632]	0.01	0.391	0.988	[-0.715, 0.601]	0.098	0.407	0.988	[-0.737, 0.690]	-0.268	0.408	0.988	[-0.830, 0.546]
Sex (male)	-0.012	0.082	0.912	[-0.178, 0.146]	0.011	0.094	0.912	[-0.168, 0.193]	0.206	0.118	0.329	[-0.043, 0.425]	-0.033	0.099	0.912	[-0.225, 0.166]	0.041	0.104	0.912	[-0.182, 0.234]	0.208	0.113	0.329	[-0.036, 0.419]	0.128	0.128	0.780	[-0.145, 0.362]
Cannabis, B	-0.06	0.101	0.784	[-0.250, 0.149]	0.15	0.118	0.714	[-0.087, 0.383]	0.200	0.151	0.714	[-0.094, 0.504]	0.121	0.134	0.784	[-0.150, 0.378]	-0.017	0.134	0.984	[-0.252, 0.286]	0.002	0.137	0.984	[-0.242, 0.295]	-0.11	0.164	0.784	[-0.416, 0.233]
Cannabis, W	0.04	0.071	0.800	[-0.099, 0.169]	-0.019	0.07	0.800	[-0.169, 0.107]	0.051	0.074	0.800	[-0.099, 0.181]	-0.011	0.036	0.800	[-0.078, 0.060]	0.045	0.054	0.800	[-0.062, 0.146]	0.076	0.064	0.800	[-0.047, 0.197]	0.074	0.059	0.800	[-0.042, 0.186]
Cannabis, W (lagged)	0.168	0.102	0.140	[-0.042, 0.361]	0.154	0.094	0.126	[-0.023, 0.356]	0.172	0.094	0.126	[-0.011, 0.353]	-0.064	0.069	0.358	[-0.205, 0.075]	0.174	0.092	0.126	[-0.013, 0.341]	0.192	0.111	0.126	[-0.029, 0.040]	**0.261**	**0.099**	**0.070**	**[0.070, 0.443]**
Sex (male) x cannabis, B	0.137	0.173	0.702	[-0.281, 0.431]	-0.131	0.206	0.702	[-0.556, 0.254]	-0.104	0.215	0.702	[-0.514, 0.310]	-0.126	0.222	0.702	[-0.577, 0.312]	0.092	0.233	0.702	[-0.381, 0.553]	0.134	0.246	0.702	[-0.401, 0.604]	-0.12	0.247	0.702	[-0.622, 0.335]
Sex (male) x cannabis, W	**0.48**	**0.141**	**0.019**	**[0.158, 0.698]**	**0.39**	**0.151**	**0.035**	**[0.046, 0.638]**	**0.389**	**0.155**	**0.035**	**[0.041, 0.634]**	**0.828**	**0.225**	**0.035**	**[0.170, 0.983]**	**0.603**	**0.162**	**0.019**	**[0.214, 0.834]**	**0.564**	**0.169**	**0.019**	**[0.166, 0.810]**	0.33	0.21	0.160	[-0.127, 0.670]
Sex (male) x cannabis, W (lagged)	**0.421**	**0.174**	**0.118**	**[0.024, 0.703]**	**0.415**	**0.165**	**0.118**	**[0.048, 0.691]**	0.335	0.184	0.118	[-0.069, 0.647]	0.594	0.287	0.118	[-0.195, 0.966]	0.449	0.234	0.118	[-0.116, 0.807]	0.392	0.209	0.118	[-0.087, 0.729]	0.522	0.242	0.118	[-0.073, 0.881]

Note. When the confidence intervals did not overlap with zero, associations are bolded. B: between-subject level, W: within-subject-level, Pr(>|t|): two-tailed FDR-corrected p-values.

Conclusion

État actuel des connaissances sur les différences sexuelles associées à la consommation d'alcool et de cannabis

Des résultats mitigés sont rapportés dans la littérature sur les DSs structurelles associées aux TUA et aux TUC, car les variations structurelles les plus fréquemment observées, notamment dans l'hippocampe et l'amygdale, ne sont pas systématiquement observées dans les échantillons d'adultes et d'adolescents [29, 156, 157].

Une étude sur un large échantillon d'adulte a observé une association négative entre l'épaisseur du cortex frontal et temporal et le nombre de boissons consommées au cours de la semaine écoulée chez les hommes uniquement [158]. Cette étude est intéressante étant donné la taille importante de l'échantillon et le rapport des termes d'interaction ainsi que l'effet principal du sexe. Une autre étude a rapporté que le volume de l'hippocampe était associé négativement à la consommation d'alcool, avec une réduction volumétrique plus importante chez les hommes qui ont consommé une quantité modérée d'alcool sur un suivi de 30 ans par rapport à leurs homologues féminins [159]. Les résultats de cette étude suggèrent que l'alcool pourrait avoir un impact structurel durable sur les régions sous-corticales du cerveau adulte, mais ces résultats n'ont pas été utilisés puisque la mesure de la consommation de substance n'a pas utilisé une échelle standardisée.

Une autre étude a fait état d'une interaction significative entre le sexe et le TUA pour le volume total du système de récompense qui comprend les régions sous-corticales et corticales. Les hommes alcooliques présentaient un volume plus faible dans le système de récompense par rapport aux femmes alcooliques qui ont été jumelées pour les mesures de consommation d'alcool, et ces différences entre les sexes étaient plus marquées dans le cortex préfrontal et le diencéphale ventral [160]. En revanche, ces résultats n'ont pas été répliqués puisque les chercheurs ont évalué certaines régions choisies a priori plutôt que l'ensemble du cerveau.

Une autre étude a évalué les variations corticales chez les TUA dans le cadre d'une étude cas-témoin et des épaisseurs corticales réduites chez les patients TUA ont été observées dans les hémisphères gauche et droit par rapport aux témoins sains, avec des variations d'épaisseur similaire entre les deux sexes et des variations spécifiques à chacun des deux sexes [161]. Un cortex plus épais a été observé chez les sujets atteints de TUA au niveau du gyrus frontal médian droit, de l'insula droite, du gyrus frontal précentral/inférieur droit et du précuneus droit par rapport à aux témoins sains, avec un effet des années de consommation excessive d'alcool sur l'épaisseur globale du cortex dans l'hémisphère droit des patients TUA uniquement. Alors qu'une diminution de l'épaisseur du cortex a été observée chez les hommes atteints de TUA dans l'insula droite et le gyrus frontal supérieur/médian droit par rapport aux hommes atteints de TUA, une diminution de l'épaisseur a également été observée chez les femmes atteintes de TUA dans le gyrus frontal précentral/moyen droit et le gyrus précentral/postcentral par rapport aux témoins sains. Cependant, aucune analyse interaction d'interaction n'a été réalisée cette étude [161]. Une autre étude a évalué l'impact de l'abus d'alcool sur les structures cérébrales dans un large échantillon d'adultes âgés de 18 à 55 ans et a observé une réduction et une diffusion de l'épaisseur du cortex dans les lobes frontal, temporal, pariétal et occipital. Les femmes semblaient plus affectées par l'alcool que les hommes puisque la réduction de l'épaisseur du cortex orbitofrontal gauche n'a été observée que chez les femmes [162].

Dans l'ensemble, des résultats mitigés sont observés pour les DSs chez les adultes TUA, mais des variations volumétriques plus importantes sont plus fréquemment signalées chez les femmes TUA que chez les hommes TUA. De nombreux facteurs peuvent interférer avec l'évaluation des DSs de manière systématique, tels que le biais du sexe dans la recherche biomédicale et dans le domaine de la toxicomanie, des analyses liées au sexe non effectuées ou non déclarées, ou encore la taille de l'échantillon qui restreint la puissance des analyses.

Des études sur l'impact de l'abus d'alcool chez les adolescents ont fait état de résultats incohérents qui peuvent s'expliquer en partie par les différentes mesures de la consommation d'alcool ou par les divers questionnaires existants utilisés par les chercheurs, comme la consommation excessive d'alcool ou la consommation ponctuelle immodérée. La beuverie a été définie par l'Institut national sur l'abus d'alcool et l'alcoolisme comme étant plus de quatre verres

pour les femmes et plus de cinq verres pour les hommes en deux heures, de sorte que le taux d'alcoolémie est supérieur à 0,8 g/dL[163]. Une étude sur un grand échantillon d'adolescents a observé une réduction volumétrique plus importante du lobe temporal chez les adolescents grands buveurs par rapport à leurs homologues féminins. La consommation importance d'alcool durant l'adolescence semblerait avoir eu un impact sur les trajectoires normales de croissance du cerveau, et ce indépendamment de la consommation de cannabis [65]. Chez les adolescents de sexe masculin, une réduction du volume préfrontal et de l'épaisseur frontale ainsi qu'une hausse de l'épaisseur corticale chez les adolescentes, ont été associées à une consommation excessive d'alcool [164, 165]. Une étude récente a fait état de plusieurs variations structurelles associées à la consommation d'alcool chez les adolescents, mais très peu de différences entre les sexes ont été signalées [6]. Une autre étude sur un petit échantillon d'adolescents a observé une interaction entre le sexe et le TUA puisque des volumes réduits de cortex préfrontal ont été observés chez les adolescentes TUA par rapport aux témoins appariés par sexe, tandis que des volumes accrus dans le cortex préfrontal ont été observés chez les adolescents TUA par rapport aux témoins appariés par sexe en bonne santé [166]. Ces résultats concordent avec l'atrophie de la matière grise dans le cortex préfrontal associée à la consommation excessive d'alcool chez les adolescents, qui est observée chez les femmes par rapport aux hommes [167]. Ces différences entre les sexes ont également été observées au niveau sous-cortical, car un volume réduit dans le thalamus et le putamen a été observé chez les adolescents TUA par rapport aux témoins appariés par sexe, alors que les adolescentes TUA ont présenté des volumes plus importants dans ces deux régions par rapport aux témoins appariés par sexe [168]. Une étude a rapporté que les régions les plus susceptibles d'être associées à la consommation d'alcool chez les adolescents étaient l'hippocampe, le noyau accumbens et le cortex préfrontal et a résumé que le TUA était généralement associé à des tailles d'effet petites à moyennes sur le volume des structures cérébrales lorsque des analyses stratifiées par sexe sont effectuées [157].

Un nombre très limité d'études sur le TUC ont fait état de DSs chez les adultes puisque l'évaluation des différences entre les sexes par des termes d'interaction ou par des analyses stratifiées par sexe qui n'ont pas été systématiquement évaluées [29, 169]. Une étude de morphométrie basée sur le voxel sur un petit échantillon de jeunes adultes a révélé une

augmentation du volume de matière grise dans le cervelet antérieur chez les gros consommateurs de cannabis par rapport aux témoins sains. Les gros consommateurs de cannabis ont également montré des volumes réduits en fonction de la dose dans l'amygdale et le volume cérébelleux de l'hippocampe, mais aucune interaction entre le sexe et les différences de matière grise n'a été observée entre les consommateurs et les non-utilisateurs de cannabis [119]. Si les volumes réduits dans le cortex préfrontal, l'hippocampe et l'amygdale sont parmi les résultats les plus fréquemment rapportés chez les adultes atteints de TUC, plusieurs méta-analyses et études sur de grands échantillons d'adultes n'ont pas observé de telles variations [170-174]. Une autre préoccupation est que ces études n'ont pas évalué les différences entre les sexes et n'ont pas effectué d'analyses stratifiées par sexe. Une récente méta-analyse basée sur 30 études a révélé des volumes réduits dans l'hippocampe et le cortex préfrontal, mais n'a pas évalué les différences entre les sexes [175]. Une autre étude a fait état d'une variation corticale du cortex orbitofrontal spécifique aux femelles atteintes de TUC, les femelles atteintes de TUC présentant une épaisseur réduite par rapport aux femelles non dépendantes et aux témoins appariés par sexe [176].

Si ces résultats nécessitent des études supplémentaires pour confirmer l'existence de différences entre les sexes chez les adultes, des résultats similaires ont également été observés dans des échantillons d'adolescents, ce qui suggère une plus grande sensibilité structurelle du cerveau féminin à la consommation de cannabis [169, 177]. Alors qu'une étude a rapporté une augmentation du volume cortical dans le cortex préfrontal chez les adolescentes par rapport aux adolescents parmi les consommateurs de cannabis dans un petit échantillon d'adolescents [178], une autre étude a observé une augmentation du volume de l'amygdale chez les adolescentes consommatrices de cannabis par rapport à leurs homologues non consommatrices [179]. Bien que des études supplémentaires soient nécessaires sur des échantillons d'adolescents, ces résultats donnent un aperçu des différences sexuelles liées au cannabis qui peuvent se produire tout au long de l'adolescence et des mécanismes neurobiologiques qui pourraient être impliqués dans la plus grande déficience cognitive qui a été associée à la consommation de cannabis chez les adolescentes par rapport à leurs homologues masculins dans une vaste étude de population tout au long de l'adolescence [90]. Il est important de mieux comprendre les mécanismes sous-jacents qui sont à l'origine de ces troubles cognitifs spécifiques au sexe pour réduire au minimum les

troubles cognitifs liés à la consommation de substances chez les adolescents et les jeunes adultes [180]. D'autres études sont encouragées à effectuer des analyses stratifiées par sexe et à évaluer les différences entre les sexes sur des modèles transversaux et longitudinaux afin de combler le vide dans la littérature sur les relations causales potentielles entre la consommation de cannabis et les anomalies structurelles, qui pourraient également être associées au fonctionnement cognitif à l'adolescence et à l'âge adulte [181, 182].

Limites des articles

Comme pour toute autre méta-analyse, les deux premiers articles présentent plusieurs limites. Des résultats faussement négatifs peuvent être signalés dans les deux méta-analyses, qui peuvent avoir été couverts par la correction pour tests multiples, étant donné le grand nombre de régions d'intérêt évaluées dans ces analyses du cerveau entier. Bien que nous n'ayons inclus que les études qui respectaient nos critères d'inclusion, une hétérogénéité substantielle a été observée au sein des études et entre elles dans les deux premiers articles. Cette variation pourrait s'expliquer en partie par les différences dans les changements historiques pour diagnostiquer les troubles liés à la consommation d'alcool et de cannabis au cours des 20 dernières années.

Aucune variation structurelle liée à la dose n'a pu être évaluée dans les deux premiers articles puisque le statut des sujets a été déterminé en fonction de la présence d'un diagnostic de DCA ou de TUC et ont donc été classés comme cas ou témoins. Bien qu'un diagnostic démontre une gravité considérable du problème clinique, il n'en reste pas moins que tous les sujets ne consommaient pas de la même manière et ne consommaient pas avec la même régularité ou le même schéma. On pourrait alors discuter de l'effet de cette catégorisation dichotomique des sujets que certains pourraient considérer comme réductionnistes. En outre, il existe une grande hétérogénéité au sein des études incluses dans les analyses des articles utilisant la base de données ENIGMA-Addiction. Plusieurs facteurs peuvent expliquer en partie cette variabilité, comme le fait qu'une certaine proportion de sujets témoins peut avoir consommé de l'alcool et du cannabis à des fins récréatives, ou que les hommes et les femmes ont des habitudes de consommation différentes et des produits contenant de l'alcool. Par conséquent, nous n'avons pas pu associer la réduction de la matière grise à des modes de consommation spécifiques en

raison de la classification binaire des sujets. Dans le cadre d'une étude internationale multisites, les cas ont tous été regroupés, indépendamment de l'intensité de la consommation d'alcool et de la période à laquelle ils ont commencé leur consommation excessive. D'autres études ENIMGA sont recommandées pour tenter d'associer des modes de consommation de drogues spécifiques. Pour continuer, cet article s'est uniquement concentré sur les effets spécifiques de l'alcool et du cannabis sur le cerveau adulte. Cependant, les cas de TUA et de TUC sont plus susceptibles de consommer à des fins récréatives d'autres drogues qui n'ont pas été contrôlées dans les analyses. Aucune mesure de la consommation d'alcool ou de tabac n'a été incluse dans les analyses du premier document afin d'être cohérente avec les analyses des autres groupes de travail. Cependant, certains groupes de travail, comme ceux sur la schizophrénie et les troubles bipolaires, ont inclus des médicaments dans les analyses. Une autre limite liée aux deux premiers articles ayant utilisés les données du groupe de travail ENIGMA-Addiction est le manque de systématisme dans l'inclusion des études. Les critères d'inclusion des études dans les deux premiers articles étaient a) la présence de cas TUA ou TUC et des témoins, b) une absence de TUS comorbide ou de toute autre condition psychiatrique ou neurologique (à l'exception des troubles dépressifs et anxieux), c) la complétion des protocoles de neuroimagerie et d'analyses statistiques du consortium ENIGMA et d) une autorisation éthique de l'institution locale de contribuer au groupe de travail ENIGMA-Addiction. Toutes les études qui respectaient ces critères pour les TUA et TUC ont été incluses dans les analyses. Bien que certaines dans la littérature sur les TUA et TUC sont disponibles et auraient pu être incluses dans les méta-analyses, ces dernières auraient pu augmenter l'hétérogénéité entre les études puisqu'elles n'avaient pas complété les protocoles d'imagerie et d'analyses statistiques. Par conséquent, des études disponibles dans la littérature ont été omises des deux méta-analyses afin de minimiser la variabilité entre les études conséquente des différences méthodologiques.

De plus, les protocoles de neuroimagerie du consortium ENIGMA pour les régions sous-corticales ne segmentent pas les sous-territoires de certaines régions d'intérêt. Cette inconsidération des sous-territoires de certaines régions sous-corticales limitent l'interprétation des conséquences liées aux différences structurelles observées chez les sujets TUA et TUC par rapport aux témoins. Bien que les baisses de volumes sous-corticales dans les deux premiers articles observés chez les

sujets TUA et TUC par rapport à leurs témoins convergent avec celles observées dans la littérature, la faible résolution spatiale de la segmentation employée limite les conclusions liées à son volume général. Ainsi, les baisses de volume sous-corticales, notamment dans le thalamus et l'amygdale, dans les sujets TUA par rapport au témoin dans l'article 1 ne peuvent être directement liées aux différences de structure et de fonction observées dans le noyau paraventriculaire thalamique[183] et le noyau basolatéral de l'amygdale dans des études pré-cliniques[184]. De plus, bien que la segmentation du consortium ENIGMA permette d'évaluer les changements au niveau des systèmes de manière globale, ce manque de résolution spatiale dans la segmentation des régions sous-corticales limite également l'interprétation des profils de connectivité spécifiques entre les sous-territoires de ces régions sous-corticales.

L'inclusion de deux études d'adolescents dans les analyses des deux premiers articles était également discutable étant donné le dimorphisme sexuel et les variations volumétriques liées à l'âge au cours de cette période de développement, ce qui peut avoir augmenté le bruit dans les analyses et contribué à la grande variabilité autour des tailles d'effet. La faible puissance statistique a posé un problème dans l'évaluation des différences entre les sexes dans le deuxième article, étant donné le nombre limité d'études qui avaient inclus des femmes ainsi que le nombre de femmes incluses dans les quelques études qui avaient inclus les deux sexes. Ce problème a été observé principalement dans les troubles liés à la consommation de cannabis, mais il a également été constaté dans les troubles liés à la consommation d'alcool.

L'analyse rétrospective de puissance dans le deuxième article a révélé des faibles puissances statistiques pour les termes d'interaction dans le cortex cingulaire antérieur dans le TUA et dans le cortex cingulaire postérieur pour le TUC, ce qui remet en question la validité des résultats obtenus dans cette méta-analyse sur les effets associés au sexe. Des modélisations ont permis d'estimer que plus de 2000 sujets TUA et TUC avec un nombre similaire de contrôles serait requis pour obtenir une puissance de 80%, qui est par convention le seuil de puissance adéquat[97].

Pour le troisième article, la collecte de données a impliqué des mesures de consommation rétrospectives de substances autodéclarées qui peuvent être inexactes ou même biaisées en raison de biais de déclaration ou de mémoire, par exemple des niveaux de consommation de

substances déclarés plus élevés que ceux réellement consommés parmi les sujets ayant déclaré une consommation de substances[185]. Deuxièmement, la taille limitée de l'échantillon restreint notre capacité à déterminer la fiabilité des résultats observés. D'autres cohortes d'adolescents plus importantes sont encouragées à effectuer ce type d'analyse afin d'évaluer la robustesse de nos résultats. Enfin, les trois moments où les participants ont subi des scanneurs d'imagerie ne représentaient pas exactement les stades de développement pubertaire de Tanner, ce qui limite l'interprétation des DSs liées à la puberté dans les mesures cérébrales observées.

Conclusions basées sur les articles neurobiologiques des différences sexuelles sur la dépendance

Les résultats obtenus dans ces trois articles sont généralement cohérents avec les observations rapportées ces dernières années sur l'impact de la consommation d'alcool et de cannabis sur le cerveau des adultes et des adolescents. Dans le premier article, les réductions structurelles sous-corticales observées chez les sujets TUA sont semblables à celles observées dans d'autres conditions psychiatriques majeures telles que les SCZ et les MDD [129, 130, 147]. Ces résultats sont importants car ils contribuent à une meilleure compréhension des variations volumétriques transdiagnostiques observées dans les principales conditions psychiatriques d'ampleur similaire. D'autre part, certaines régions présentent des variations spécifiques aux troubles. De telles observations macroscopiques sont importantes pour mieux comprendre les corrélats neurobiologiques sous-jacents qui semblent être communs à plusieurs affections psychiatriques.

Dans le deuxième article, nous avons observé une réduction des volumes dans le thalamus et le putamen et une réduction de l'épaisseur dans les régions fronto-temporelles chez les mâles TUA ainsi qu'une réduction des volumes dans l'hippocampe, l'amygdale et les accumbens et une réduction de l'épaisseur dans les régions temporelles chez les femelles TUA. Bien que les résultats du deuxième article permettent d'évaluer la pertinence de la réalisation d'analyses d'interaction et de stratification par sexe pour les TUA, l'absence de variations volumétriques significatives après correction pour les comparaisons multiples chez les femmes TUC doit être interprétée avec prudence ; il est très probable que cette absence de résultats soit due à des analyses statistiques sans puissance plutôt qu'à l'absence d'impact de l'abus de cannabis sur le cerveau des femmes

TUC. Cette absence de résultats chez les femmes TUC démontre l'importance de recruter et d'inclure davantage de sujets féminins dans les recherches sur les troubles liés à la consommation de substances afin de mieux évaluer les tailles d'effet avec une puissance statistique adéquate.

Dans le troisième article, une plus grande réduction de l'épaisseur corticale a été associée à la beuverie, mais des changements structurels retardés ont été associés au cannabis. Le sexe a joué un rôle modérateur dans la relation simultanée entre la consommation excessive d'alcool et le volume de l'hippocampe. L'augmentation de la fréquence de la consommation de cannabis a permis de prévoir un volume bilatéral plus faible dans le noyau accumbens deux ans plus tard.

En résumé, la consommation abusive d'alcool est généralement associée à une réduction des volumes sous-corticaux et de l'épaisseur du cortex chez les hommes et chez les femmes, chez les adultes et les adolescents. Des effets structurels plus importants sont observés chez les sujets féminins par rapport à leurs homologues masculins. Alors qu'une altération diffuse des structures cérébrales est observée pour les TUA, une altération plus spécifique des régions frontales a été associée aux TUC chez les adultes. Les adolescents n'ont pas présenté une version atténuée des variations structurelles observées chez les adultes tel que l'on pourrait émettre l'hypothèse. Le résultat le plus fréquemment obtenu dans les trois articles est une baisse de volume bilatérale dans l'hippocampe associée à l'alcool, et plus spécifiquement chez les sujets féminins adultes et adolescents. Cette réduction volumétrique spécifique aux sujets féminins TUA présente des similitudes avec la réduction de la neurogenèse de l'hippocampe induite par l'alcool observée chez les rongeurs femelles[29].

Recommandations

La recherche sur les DSs en psychiatrie est une question qui va au-delà de la sous-représentation des femmes et/ou des hommes dans les échantillons étudiés. Bien que l'augmentation du nombre de sujets féminins soit une décision à encourager afin de disposer d'une puissance statistique suffisante pour détecter les petits effets, d'autres problèmes gravitent autour de cette situation.

La définition des questions de recherche pour lesquelles l'évaluation des DSs et/ou de genre est pertinente serait la première question. Si certaines institutions peuvent recommander une

analyse des DSs et de genre de manière systématique, il est pertinent de se demander s'il vaut mieux effectuer ces analyses indépendamment des questions de recherche et donc faire des constatations fortuites, ou seulement dans le contexte des questions de recherche pour lesquelles les DSs et/ou de genre sont pertinentes. Certains chercheurs pourraient faire valoir que la réalisation de telles analyses sans raisonnement a priori serait contraire à la méthode scientifique, qui repose sur la formulation d'hypothèses. Afin de mieux intégrer les pratiques de recherche biomédicale, y compris la recherche sur les troubles liés à la consommation de substances, nous recommandons l'évaluation systématique des DSs et/ou de genre dans le contexte où les données ont été systématiquement collectées selon les définitions acceptées d'un organisme scientifique ou d'une institution gouvernementale.

Le deuxième point est davantage lié aux analyses statistiques puisqu'il s'agit de considérer le sexe et le genre comme des covariables variant dans le temps lorsque le sexe et le genre ne sont pas les prédicteurs d'intérêt dans les analyses longitudinales. Cette déclaration est particulièrement importante pour les études impliquant des adolescents ou de jeunes adultes en raison des changements possibles d'identité de genre d'un participant qui peuvent se produire pendant ce laps de temps de développement en raison des hormones sexuelles et de l'influence socioculturelle. Une meilleure compréhension du rôle du sexe et du genre est importante dans le domaine de la toxicomanie étant donné l'effet moteur potentiel des hormones sexuelles dans les associations de SDs entre la consommation de substances et le développement cérébral [90].

La troisième question concerne la terminologie utilisée dans le domaine de la toxicomanie. Bien que des progrès considérables aient été réalisés au cours des dernières décennies dans l'utilisation des termes "sexe" et "genre" dans la littérature, la nature interdisciplinaire de la communauté universitaire qui étudie les troubles liés à la consommation de substances a conduit à un abus de langage pour le terme "genre". Ce problème terminologique affecte moins le terme "sexe" car il s'agit d'un concept biologique qui est généralement défini de manière similaire dans toutes les cultures dans les études précliniques et cliniques. Selon les Instituts de recherche en santé du Canada, le sexe fait référence à des caractéristiques physiologiques et physiques mesurables telles que les chromosomes, l'expression des gènes, les niveaux d'hormones et les organes reproducteurs. La mesure du sexe peut être plus difficile car il s'agit d'un concept qui,

contrairement au sexe, n'est pas perçu de manière homogène dans les différentes cultures. Néanmoins, l'évaluation du genre dans les études uni- et multi-sites est possible et recommandée en utilisant des échelles qui peuvent être standardisées, comme le questionnaire à 27 items sur l'identité de genre/la dysphorie de genre pour les adolescents et les adultes (GIDYQ-AA) [186]. L'évaluation de l'identité de genre a également l'avantage de détecter potentiellement tôt un trouble de l'identité de genre chez les adolescents ou chez les patients qui ne seraient pas enclins à prendre les mesures nécessaires pour se référer à une clinique spécialisée en identité de genre par peur d'être ostracisés. Une autre option pourrait être l'élaboration d'un indice de genre qui mesure les rôles des sexes lorsqu'aucune mesure directe du genre n'a été recueillie [187].

Par conséquent, l'inclusion du sexe et du genre comme deux variables indépendantes dans les analyses statistiques des structures cérébrales dans les troubles psychiatriques permettrait d'évaluer l'ampleur des déficiences cérébrales par rapport aux autres identités de sexe et de genre de manière systématique et impartiale. Cette approche inclusive permettrait de mieux comprendre les changements structurels des minorités de genre qui sont sous-étudiées dans le domaine de la toxicomanie et, plus largement, en psychiatrie.

En plus de soutenir l'inclusion d'un plus grand nombre de participantes au niveau des études, nous encourageons les futures études multisites à inclure des mesures harmonisées du sexe et du genre dans leurs analyses afin de saisir ces facteurs sous-étudiés dans le domaine de la dépendance. La collecte d'informations normalisées sur les identités sexuelles et de genre dans toutes les études incluses permettrait d'ajuster les modèles linéaires pour les identités sexuelles et de genre les plus récents des participants, ce qui pourrait donner des estimations plus précises de la taille de l'effet au niveau méta-analytique.

Pour résumer cette section, des politiques standardisées supplémentaires en matière de sexe et de genre sont nécessaires dans les études sur la dépendance afin de mieux comprendre les effets de la dépendance sur le cerveau dans toutes les sous-populations de la société et la manière dont les troubles de santé mentale pourraient a) avoir un impact différent sur le cerveau dans les minorités identitaires et b) évoluer avec l'âge étant donné la fluidité du genre que les sujets inclus peuvent exprimer tout au long d'un essai.

Étapes suivantes

Comme mentionné précédemment, les chercheurs ont souvent négligé d'effectuer des analyses stratifiées par sexe. Il est donc nécessaire de compléter les interactions signalées avec ces analyses stratifiées par sexe par des différences structurelles cas-témoins entre différents troubles psychiatriques. Bien que les études de neuroimagerie aient donné des indications étiopathologiques sur les mécanismes neurobiologiques impliqués dans les principales psychopathologies, peu d'études ont évalué les variations structurelles spécifiques au sexe chez les adultes souffrant d'un trouble psychiatrique tel que le trouble de la consommation d'alcool [36, 88, 188]. Bien qu'une récente méta-analyse ait examiné les différences entre les sexes dans le cerveau d'un adulte sain et ait fait état d'un dimorphisme lié au sexe dans la région sous-corticale et le volume total du cerveau, il n'existe aucun équivalent réalisé sur des adultes souffrant de troubles psychiatriques [189]. Étant donné les variations volumétriques communes aux différents troubles psychiatriques, on ne sait pas encore très bien comment ces variations volumétriques peuvent être spécifiques au sexe, étant donné que certains troubles psychiatriques sont plus fréquents dans un sexe que dans l'autre au cours des périodes de développement [190]. Pour résoudre ce problème, la comparaison des différences entre les sexes et des résultats de méta-analyses spécifiques au sexe dans les troubles psychiatriques peut informer sur les variations structurelles communes et spécifiques aux troubles. En utilisant une approche analytique cohérente, un tel projet pourrait aider à identifier les mécanismes cérébraux et génétiques sous-jacents impliqués dans les biais liés au sexe dans l'ensemble des troubles psychiatriques.

Les analyses effectuées dans les deux premiers articles ont également permis de proposer un réexamen du modèle méta-analytique conventionnel ENIGMA lorsque la puissance statistique peut poser problème, comme dans le cas des analyses des différences entre les sexes pour les troubles liés à la consommation de cannabis. Les récentes avancées méthodologiques du consortium ENIGMA ont permis de développer de nouvelles approches analytiques telles que les méga-analyses à effets mixtes utilisant une méthode d'ajustement par lot pour augmenter la puissance statistique sur de petits échantillons [191]. Une telle approche innovante serait pertinente dans le contexte des analyses stratifiées par sexe des variations volumétriques entre

les différents groupes de travail, puisque ces derniers n'ont fréquemment signalé aucune interaction significative au niveau méta-analytique pour toutes les régions d'intérêt.

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Annexe

Article 1 – Matériel supplémentaire

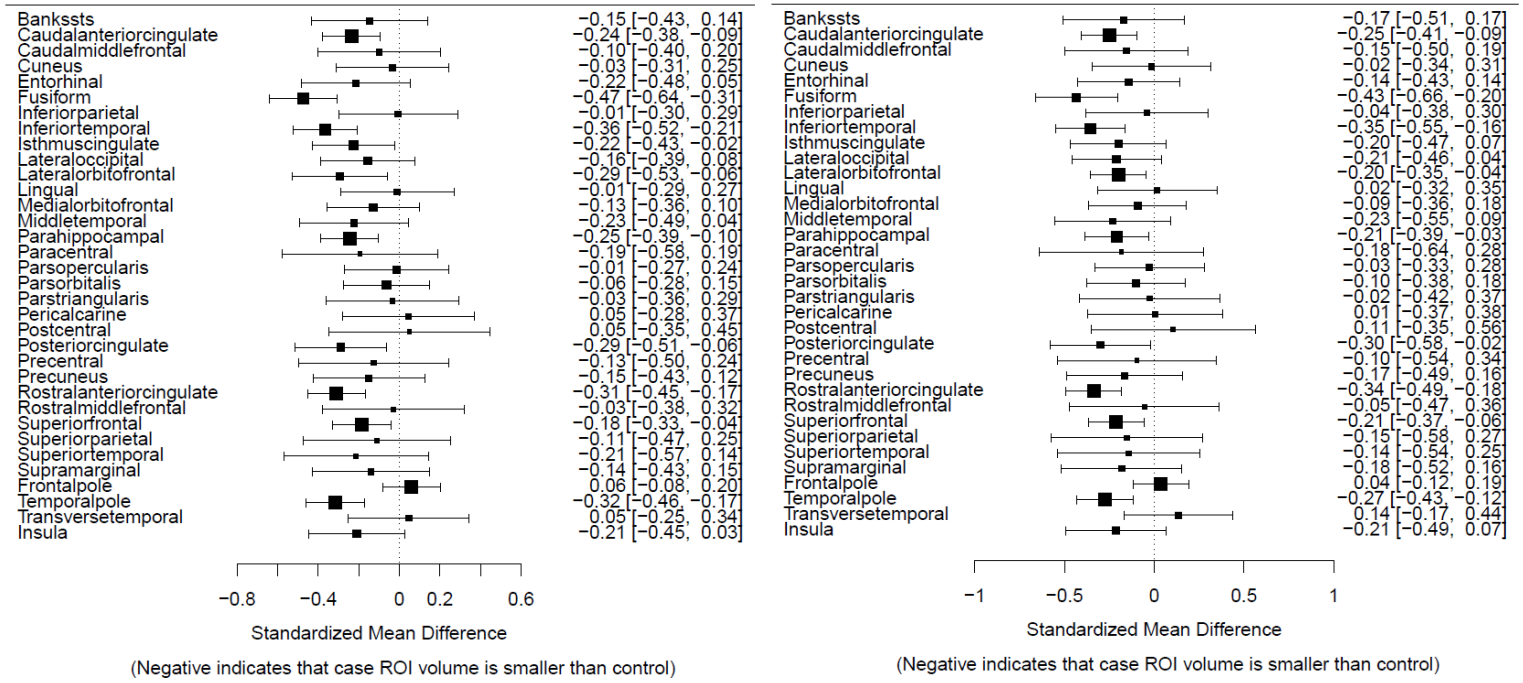

Figure 12. – **Supplementary Figure 1 (Article 1).** Comparison of effect sizes for the bilateral cortical thickness when the study on AUD adolescents (N = 116) is included (Forest plots on the left) and excluded (Forest plots on the right). Bankssts refers to the Banks of the superior temporal sulcus. The effect sizes at the meta-level do not differ significantly when the adolescent study was removed since 95% confidence intervals overlap. When the adolescent study was removed from the AUD analyses, the parahippocampal and posterior cingulate did not remain significant after correcting for multiple comparison. Error bars represent 95% confidence intervals.

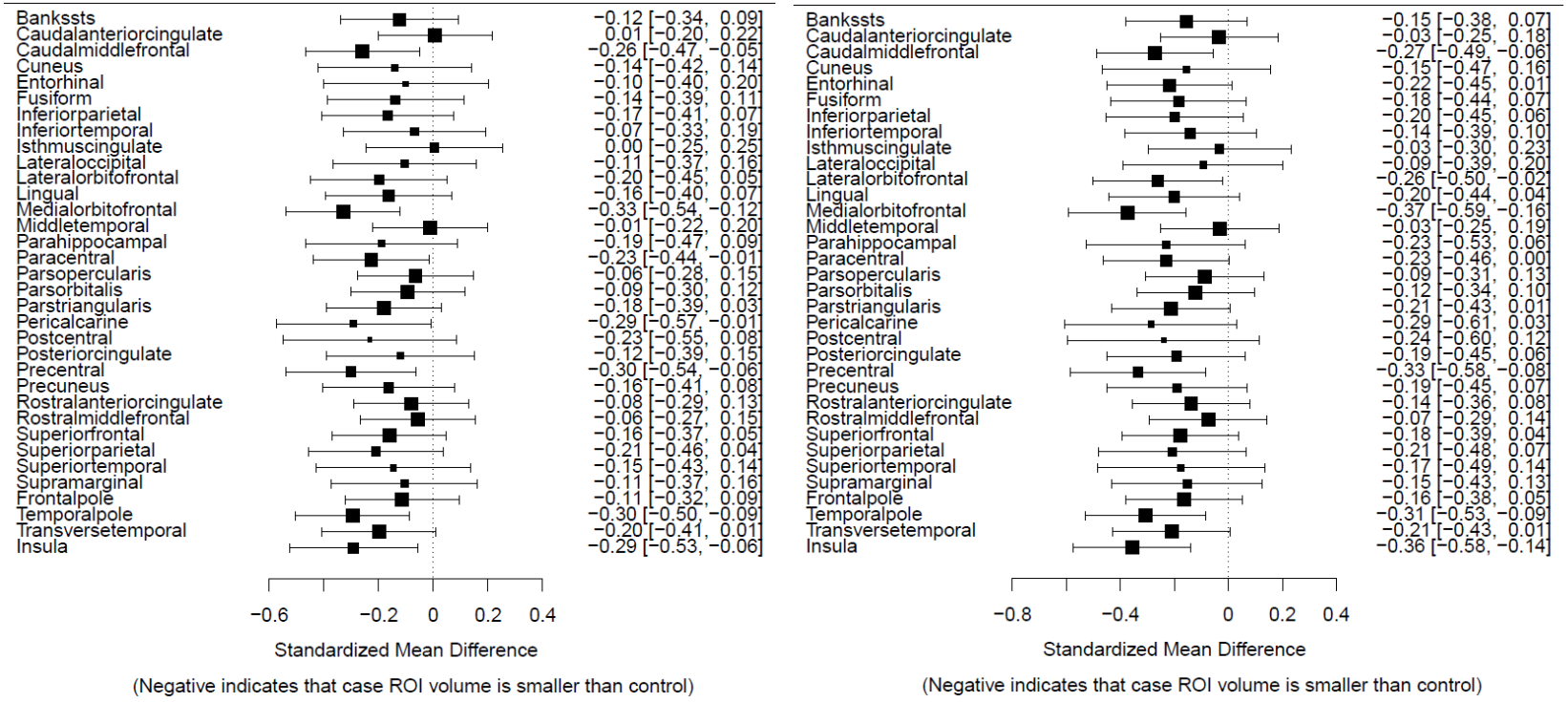

Figure 13. – **Supplementary Figure 2 (Article 1).** Comparison of effect sizes for the bilateral cortical thickness when the study on CUD adolescents (N = 27) is included (Forest plots on the left) and excluded (Forest plots on the right). Bankssts refers to the Banks of the superior temporal sulcus. The effect sizes at the meta-level do not differ significantly when the adolescent study was removed since 95% confidence intervals overlap. However, the medial orbitofrontal cortex and the insula survived FDR correction when the adolescent study was removed from the CUD analyses Error bars represent 95% confidence intervals.

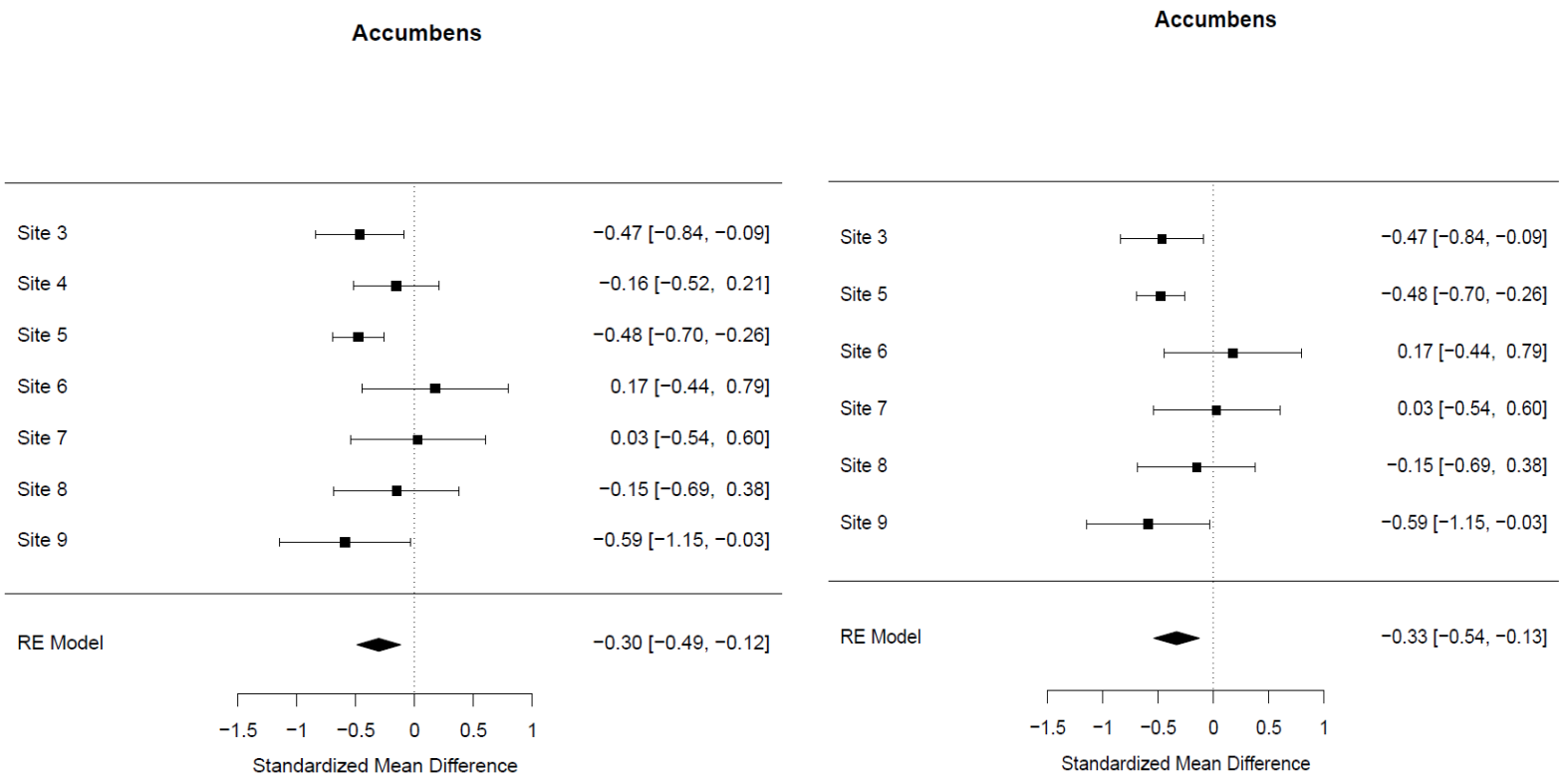

Figure 14. – **Supplementary Figure 3 (Article 1)**. Comparison of effect sizes for the accumbens when the study on AUD adolescents (Study 4, N = 116) is included (Forest plot on the left) and excluded (Forest plot on the right). The effect size at the study -level does not differ significantly from the other studies since 95% confidence intervals overlap. The impact on the meta-analytic estimate is marginal since the estimated effect size across studies varies of 0.03 unit and is significant in both samples after correcting for multiple comparisons. Studies 3-9 refer to the studies presented in Table 1, respectively. Error bars represent 95% confidence intervals.

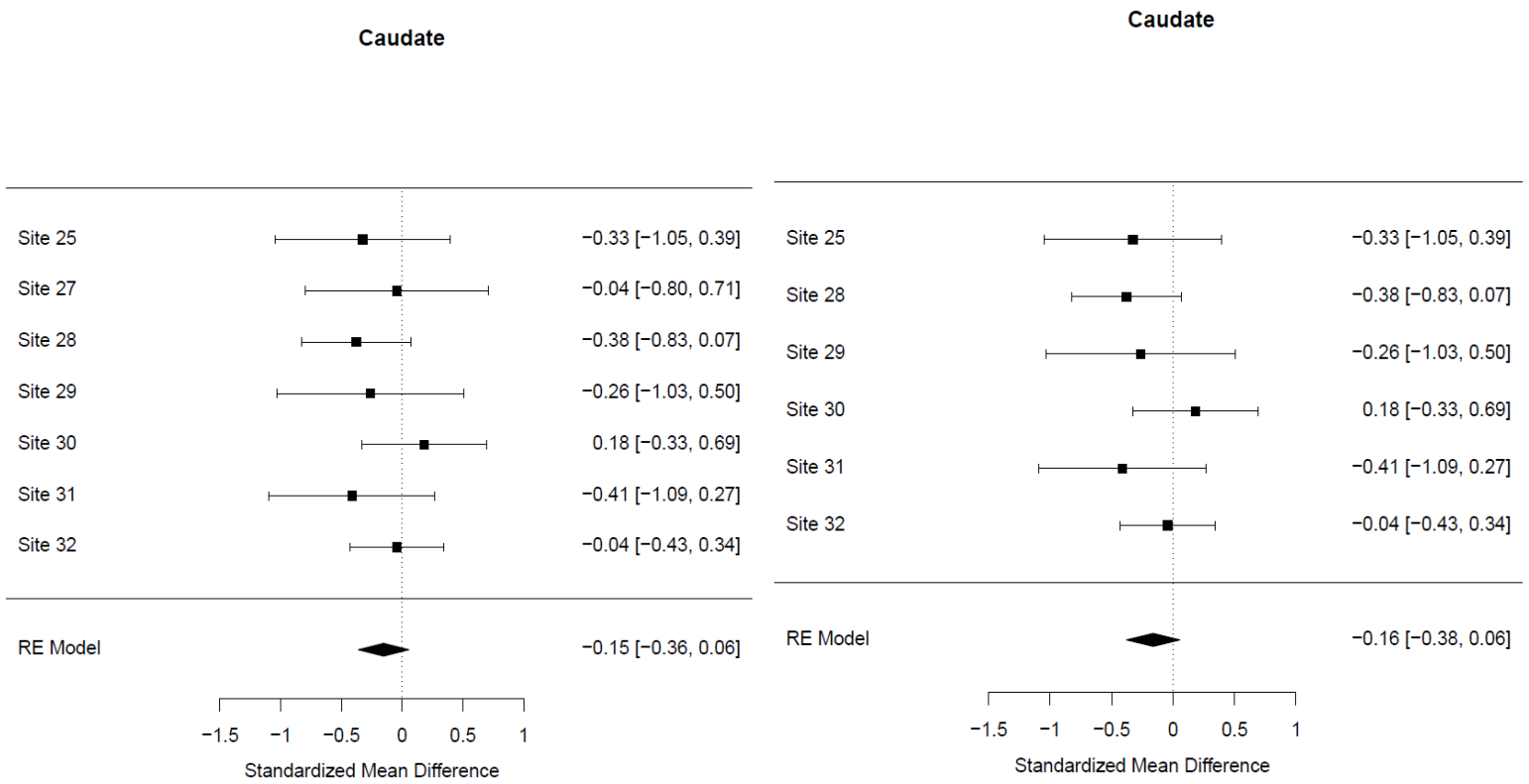

Figure 15. – **Supplementary Figure 4 (Article 1).** Comparison of effect sizes for the caudate when the study on CUD adolescents (Study 27, N = 27) is included (Forest plot on the left) and excluded (Forest plot on the right). The effect size at the study -level does not differ significantly from the other studies since 95% confidence intervals overlap. The impact on the meta-analytic estimate is marginal since the estimated effect size across studies varies of 0.03 unit and is significant in both samples after correcting for multiple comparisons. Studies 3-9 refer to the studies presented in Table 1, respectively. Error bars represent 95% confidence intervals.

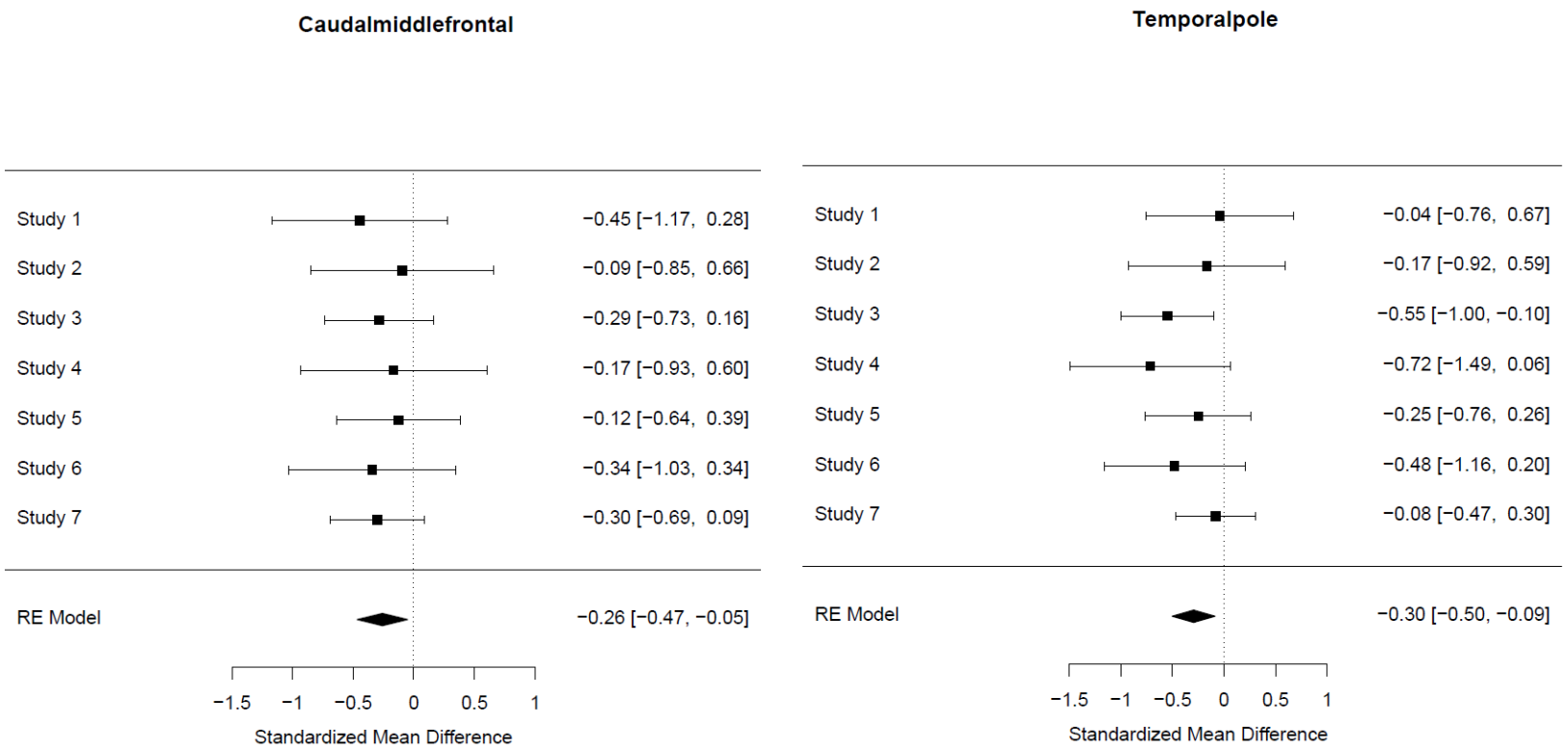

Figure 16. – **Supplementary Figure 5 (Article 1).** Cortical thickness in cannabis use disorder participants in two regions of interest. These reduced cortical thicknesses were significant before but not after correcting for multiple comparisons. These panels support the idea that the variability around the effect within a study is much larger than the variability around the effect across studies. Error bars represent 95% confidence intervals.

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Article 2 – Matériel supplémentaire

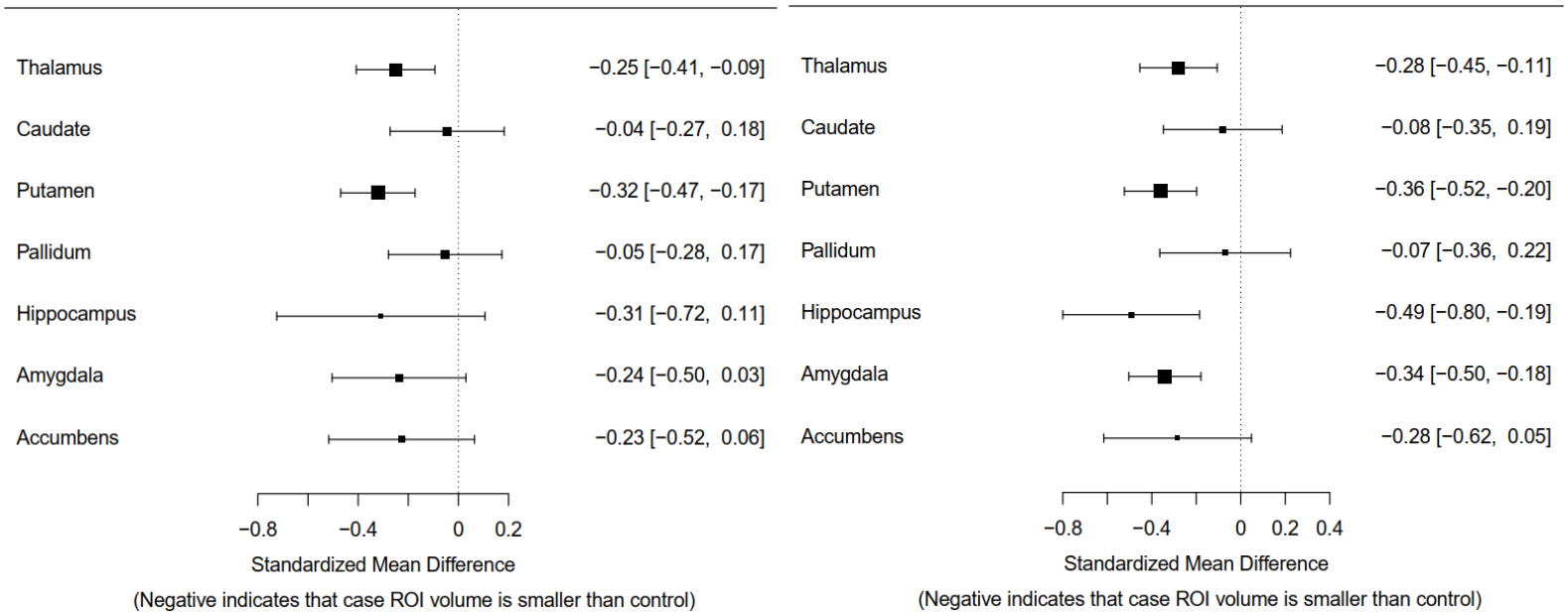

Figure 17. – **Supplementary Figure 1 (Article 2)**. Bilateral subcortical volumetric variations observed in AUD males when compared to their male counterparts when an adolescent study (N = 116) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and intracranial volume and error bars represent 95% confidence intervals. The thalamus and putamen survived FDR correction when the adolescent study was included, and the thalamus, putamen, hippocampus and amygdala survived FDR correction when the adolescent study was excluded form the analyses.

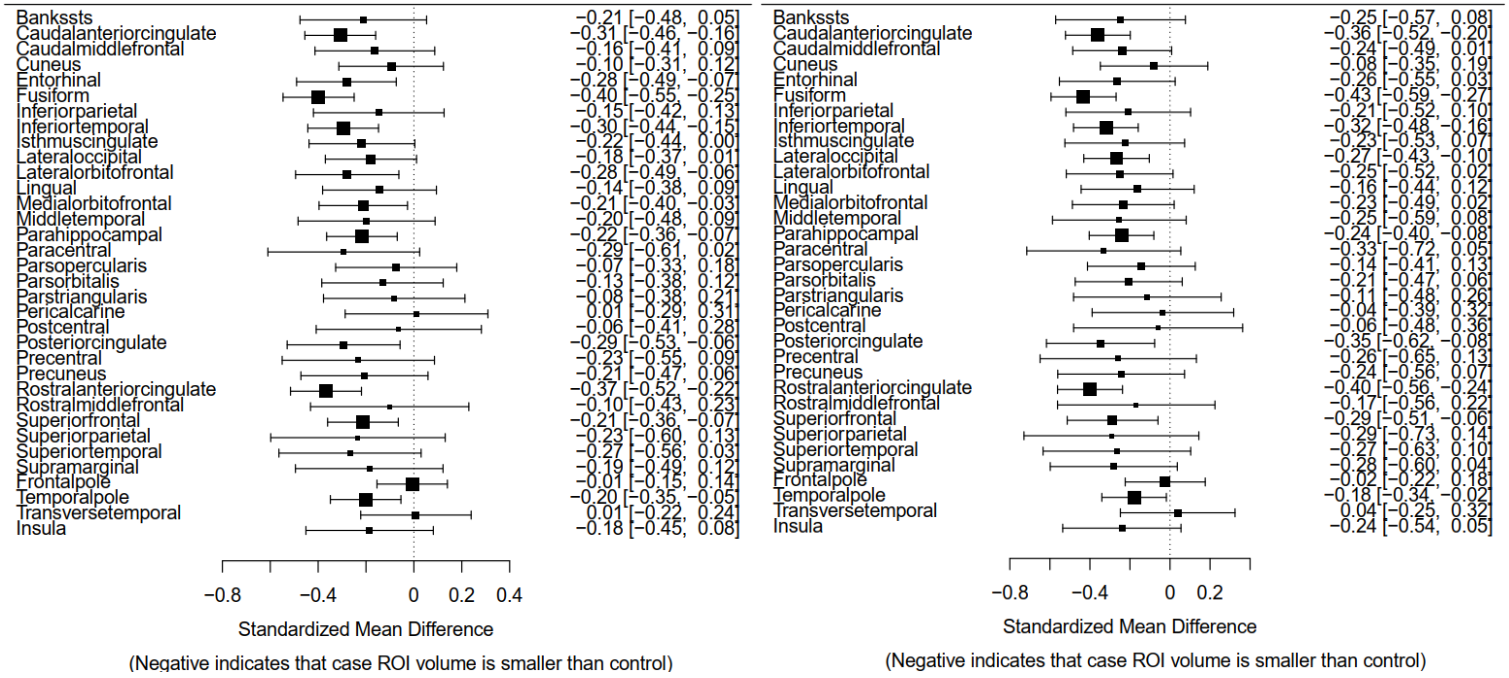

Figure 18. – **Supplementary Figure 2 (Article 2)**. Bilateral cortical thickness variations observed in AUD males when compared to their male counterparts when an adolescent study (N = 116) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and error bars represent 95% confidence intervals. The caudal anterior cingulate, entorhinal, fusiform, inferior temporal, lateral orbitofrontal, parahippocampal, posterior cingulate, rostral anterior cingulate, superior frontal and temporal pole survived FDR correction when the adolescent study was included.

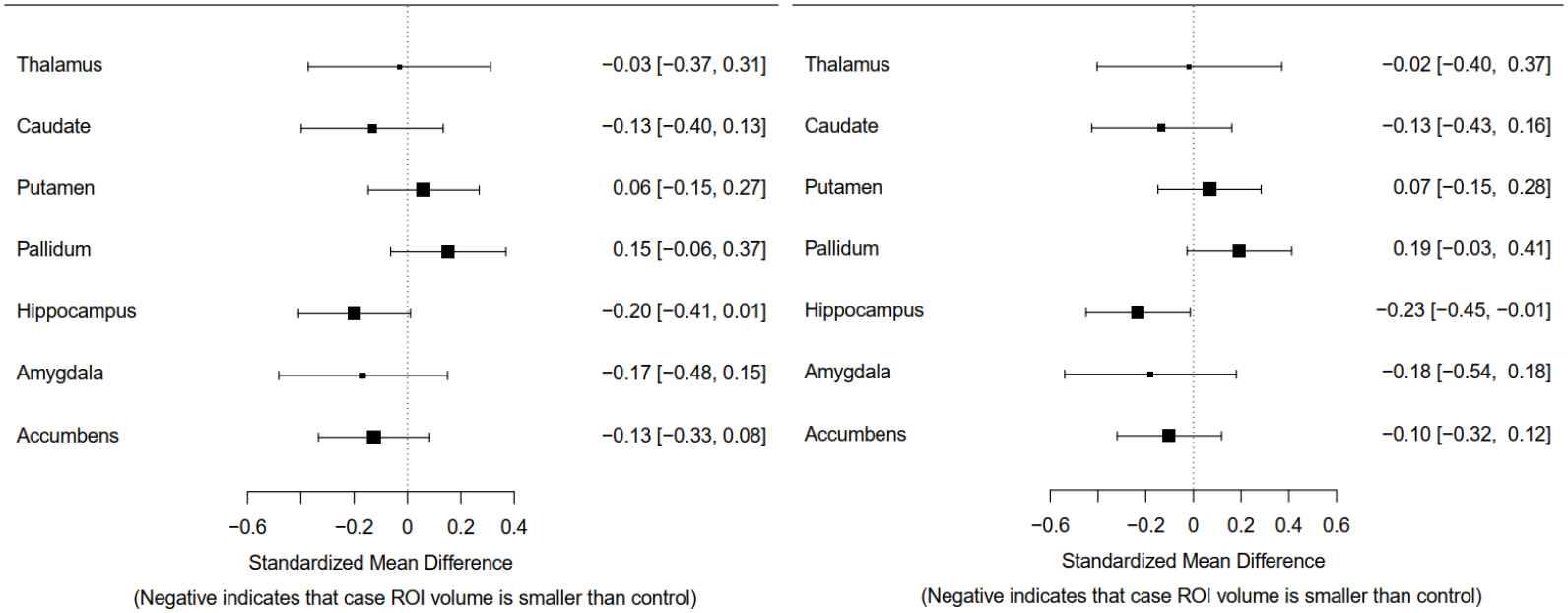

Figure 19. – **Supplementary Figure 3 (Article 2)**. Bilateral subcortical volumetric variations observed in CUD males when compared to their male counterparts when an adolescent study (N = 27) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and intracranial volume and error bars represent 95% confidence intervals. No effect survived FDR correction in both plots.

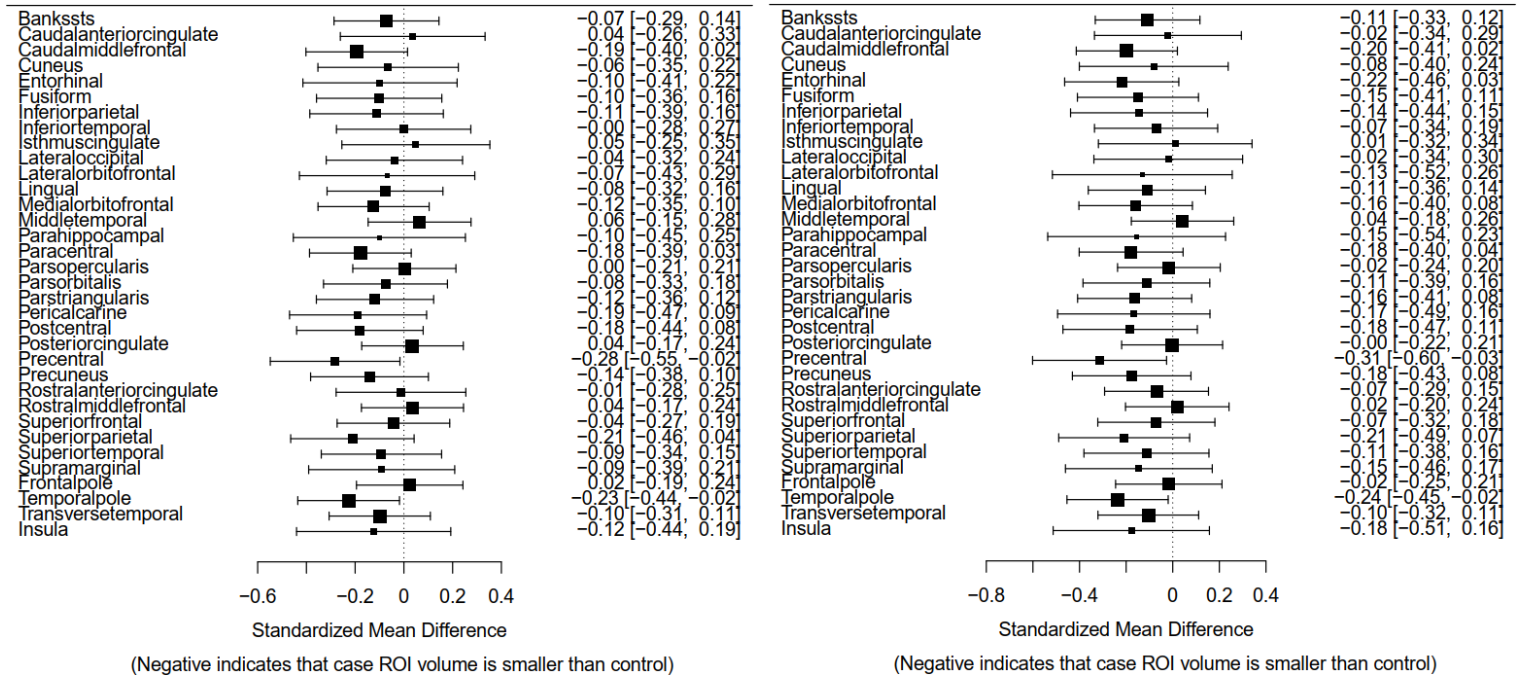

Figure 20. – **Supplementary Figure 4 (Article 2)**. Bilateral cortical thickness variations observed in CUD males when compared to their male counterparts when an adolescent study (N = 27) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and error bars represent 95% confidence intervals. No effect survived FDR comparison in both plots.

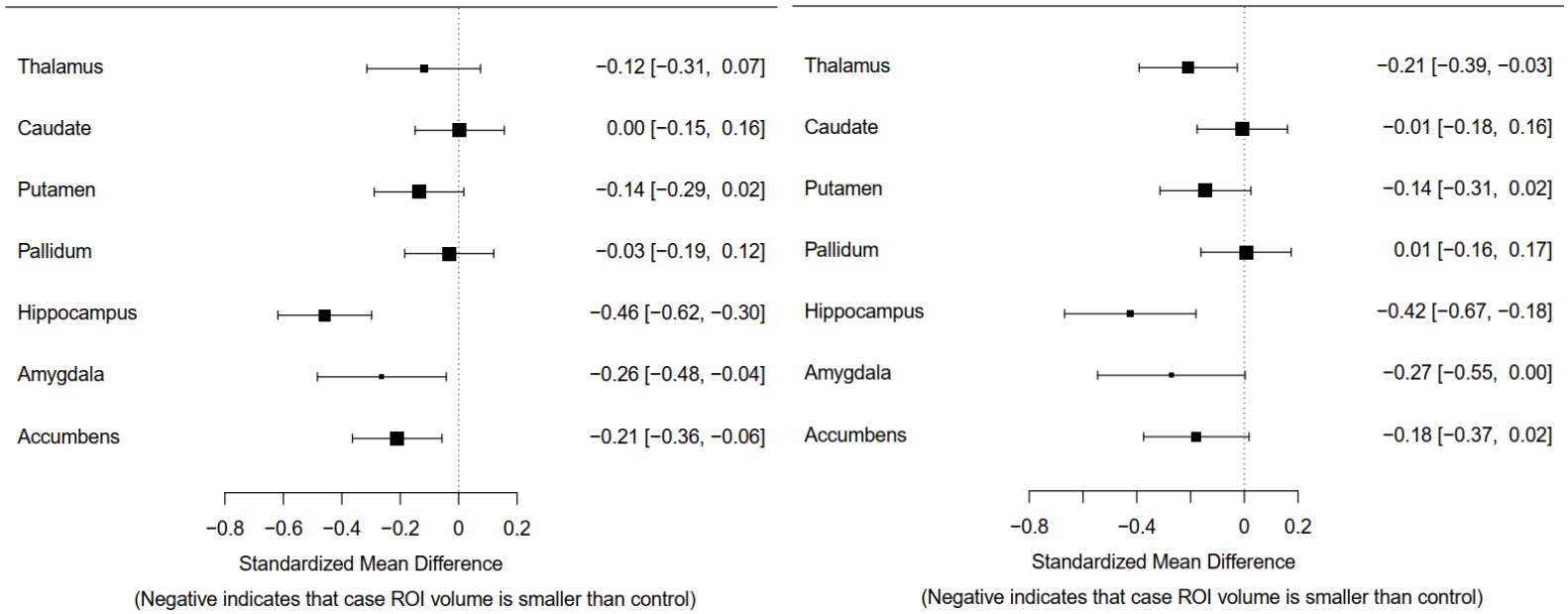

Figure 21. – **Supplementary Figure 5 (Article 2)**. Bilateral subcortical volumetric variations observed in AUD females when compared to their female counterparts when an adolescent study (N = 116) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and intracranial volume and error bars represent 95% confidence intervals. The hippocampus, amygdala and accumbens survived FDR correction when the adolescent was included.

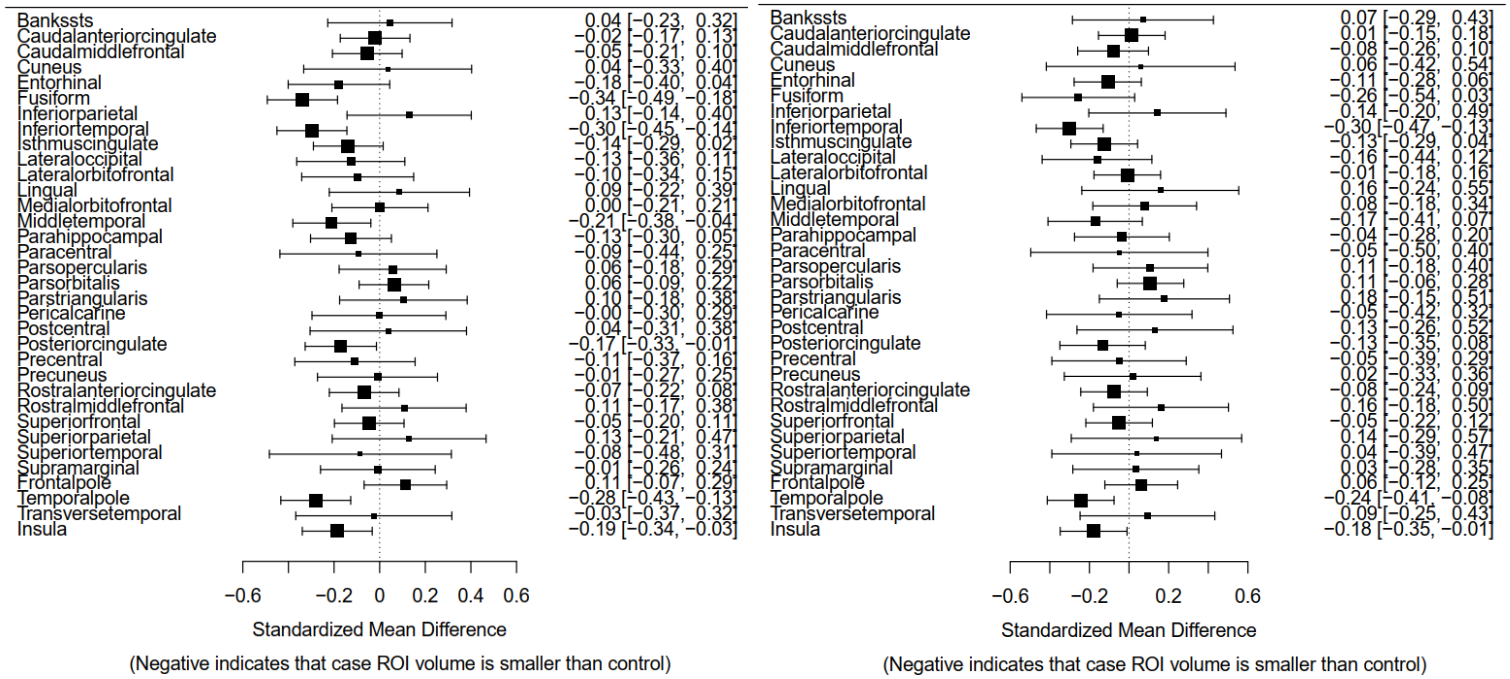

Figure 22. – **Supplementary Figure 6 (Article 2)**. Bilateral cortical thickness variations observed in AUD females when compared to their female counterparts when an adolescent study (N = 116) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and error bars represent 95% confidence intervals. The fusiform, inferior temporal and temporal pole survived FDR correction when the adolescent study was included whereas only the inferior temporal and temporal pole survived FDR correction when the adolescent study was removed from the analyses.

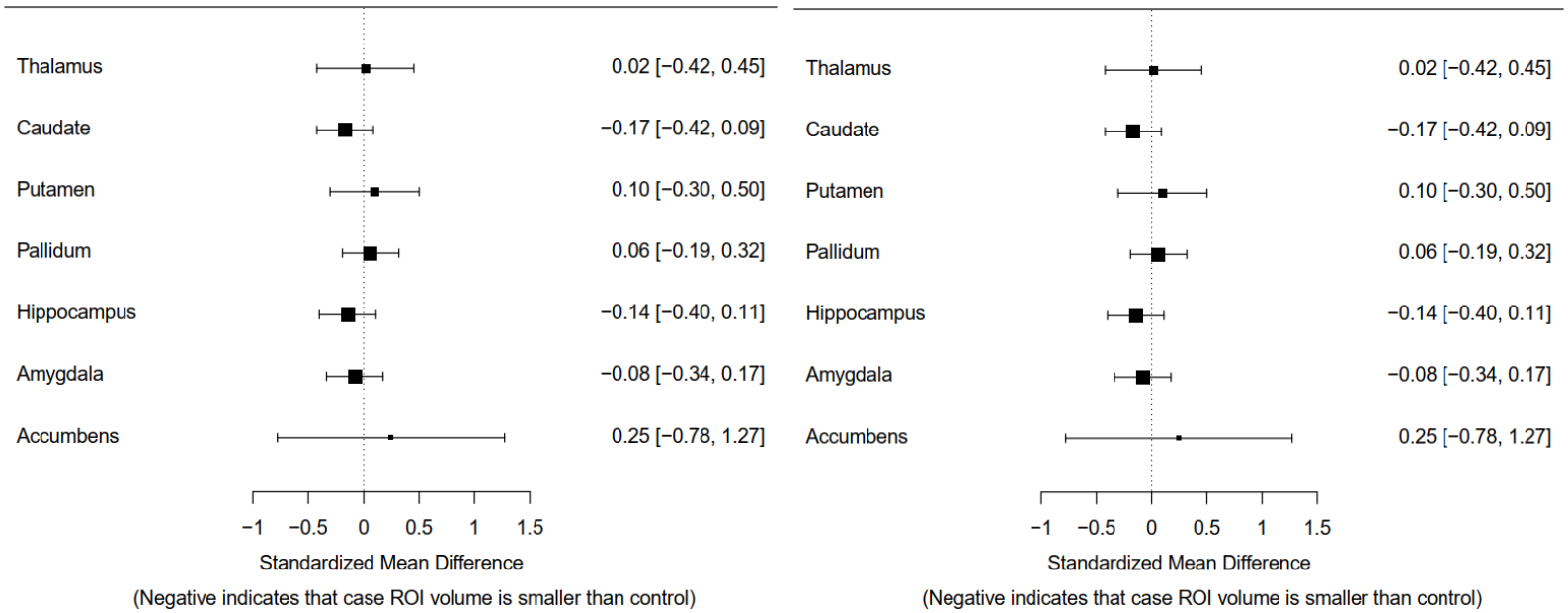

Figure 23. – **Supplementary Figure 7 (Article 2)**. Bilateral subcortical volumetric variations observed in CUD females when compared to their female counterparts when an adolescent study (N = 27) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and intracranial volume and error bars represent 95% confidence intervals. The effect sizes and confidence intervals are the same between the two plots since one study as well as the adolescent study were removed from the analyses in both plots due to a lack of included females. The substantial heterogeneity in the accumbens is related to the effect size calculated for the Trinity-THC study.

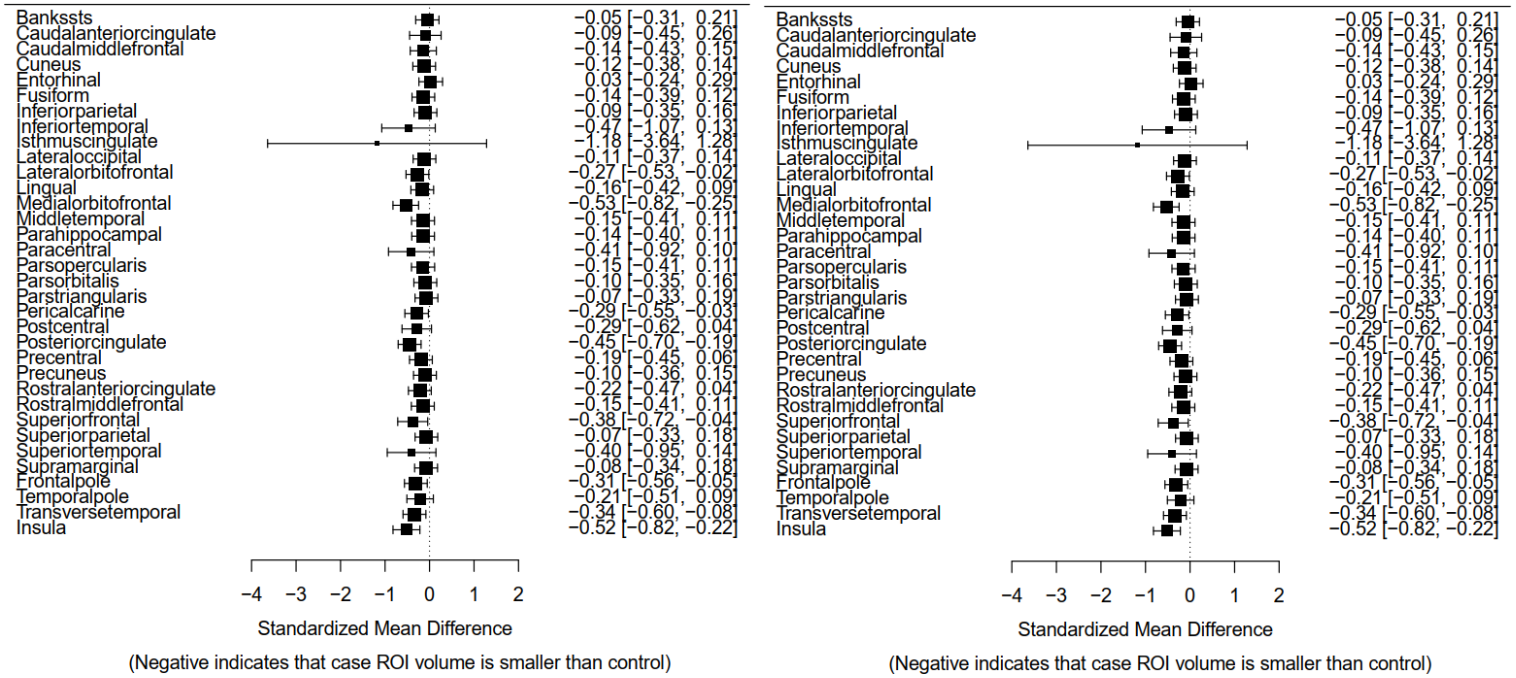

Figure 24. – **Supplementary Figure 8 (Article 2)**. Bilateral cortical thickness variations observed in CUD females when compared to their female counterparts when an adolescent study (N = 27) is included (plot on the left) and excluded (panel on the right) in the sex-stratified analysis. We covaried for age and error bars represent 95% confidence intervals. The medial orbitofrontal, posterior cingulate and insula survived FDR correction. The substantial heterogeneity in the isthmus cingulate is related to the effect size calculated for the Trinity-THC study, which is much larger (d = −5.18, CI [−6.71, −3.65]) than the other included studies (none was significant since they all crossed the non-effect line set at 0).

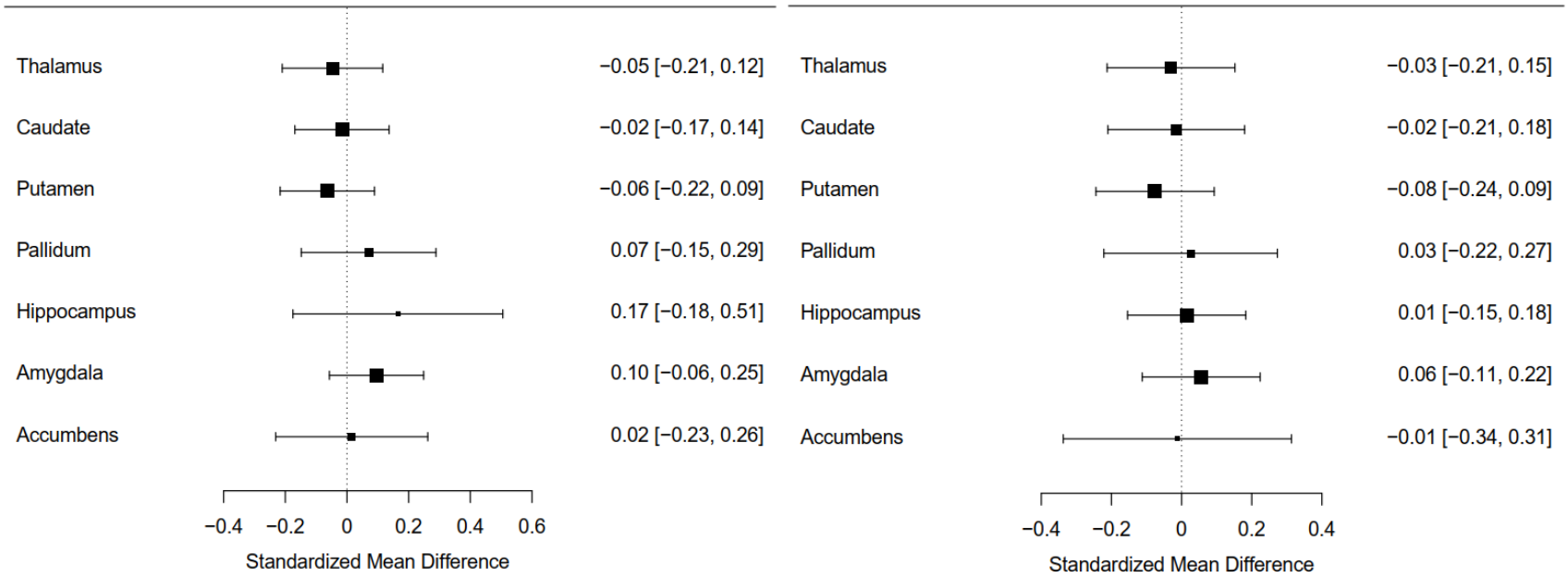

Figure 25. – **Supplementary Figure 9 (Article 2)**. Meta-analytic sex-by-diagnosis interactions for bilateral subcortical volumetric variations in AUD subjects when an adolescent study (N = 116) is included (plot on the left) and excluded (panel on the right). We covaried for age and intracranial volume, and error bars represent 95% confidence intervals.

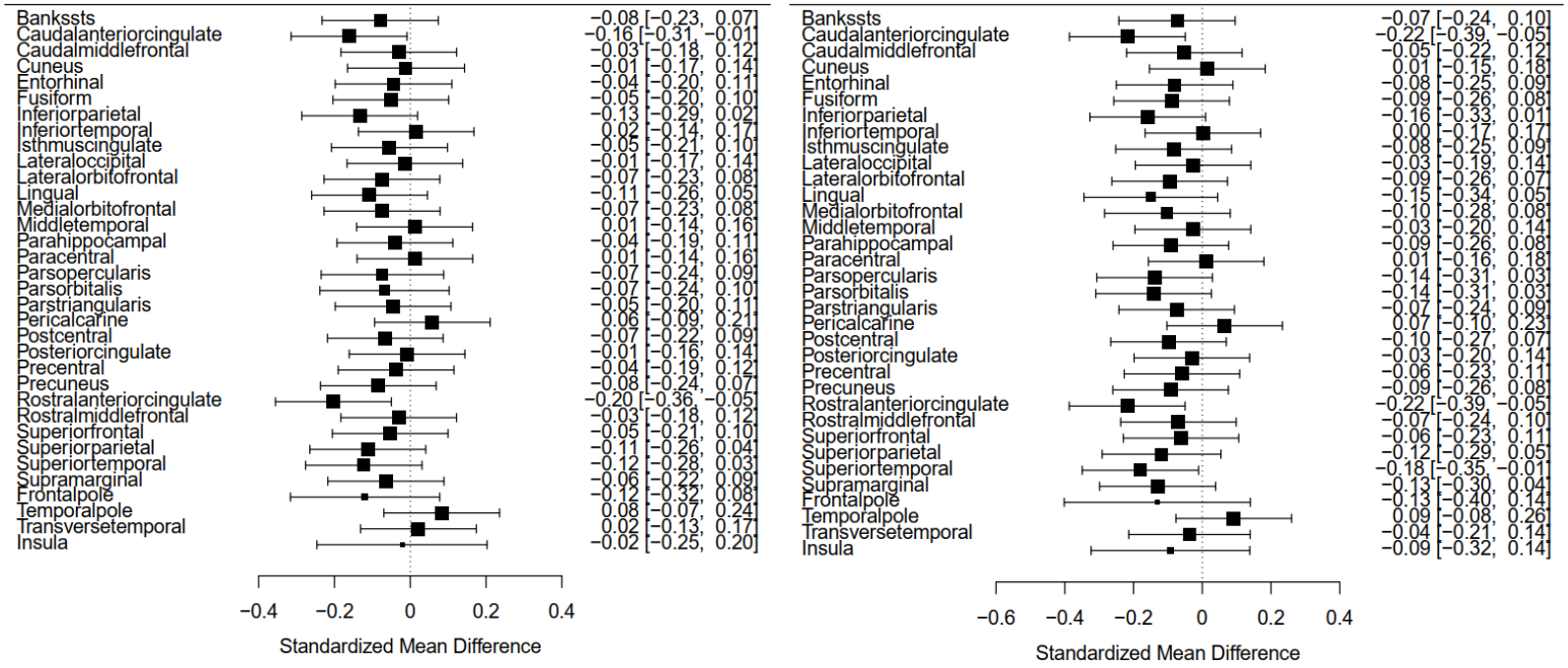

Figure 26. – **Supplementary Figure 10 (Article 2)**. Meta-analytic sex-by-diagnosis interactions for bilateral subcortical volumetric variations observed in AUD subjects when an adolescent sit study e (N = 116) is included (plot on the left) and excluded (panel on the right). We covaried for age, and error bars represent 95% confidence intervals. No effect survived FDR correction.

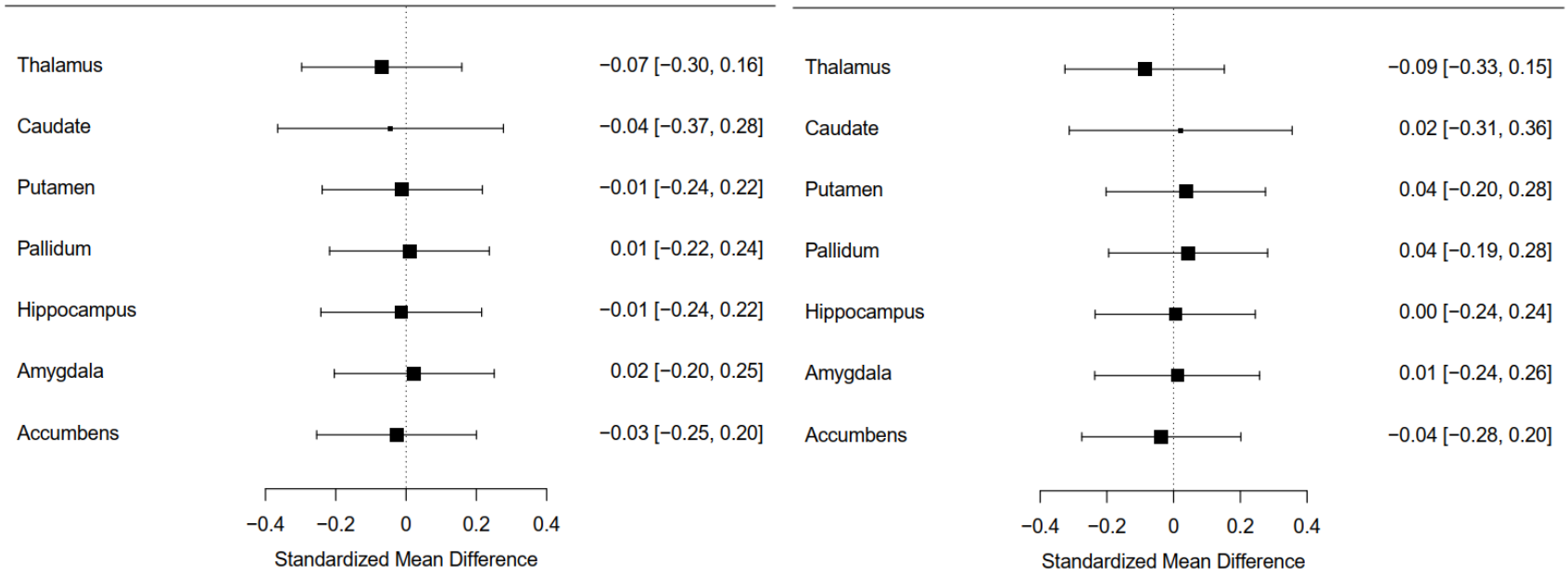

Figure 27. – **Supplementary Figure 11 (Article 2)**. Meta-analytic sex-by-diagnosis interaction effects for bilateral subcortical volumetric variations observed in CUD subjects when an adolescent study (N = 27) is included (plot on the left) and excluded (panel on the right). We covaried for age, and error bars represent 95% confidence intervals.

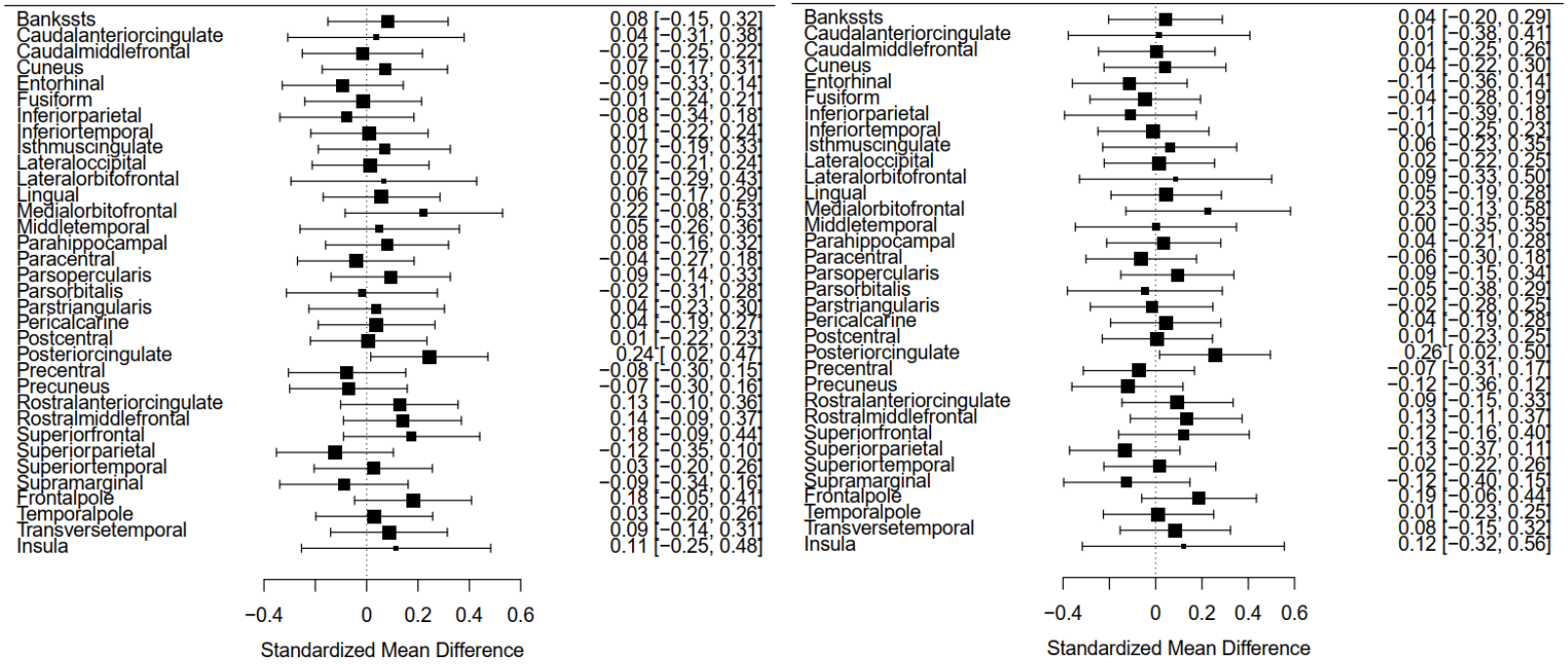

Figure 28. – **Supplementary Figure 12 (Article 2)**. Meta-analytic sex-by-diagnosis interaction effects for bilateral subcortical volumetric variations observed in CUD subjects when an adolescent study (N = 27) is included (plot on the left) and excluded (panel on the right). We covaried for age, and error bars represent 95% confidence intervals.

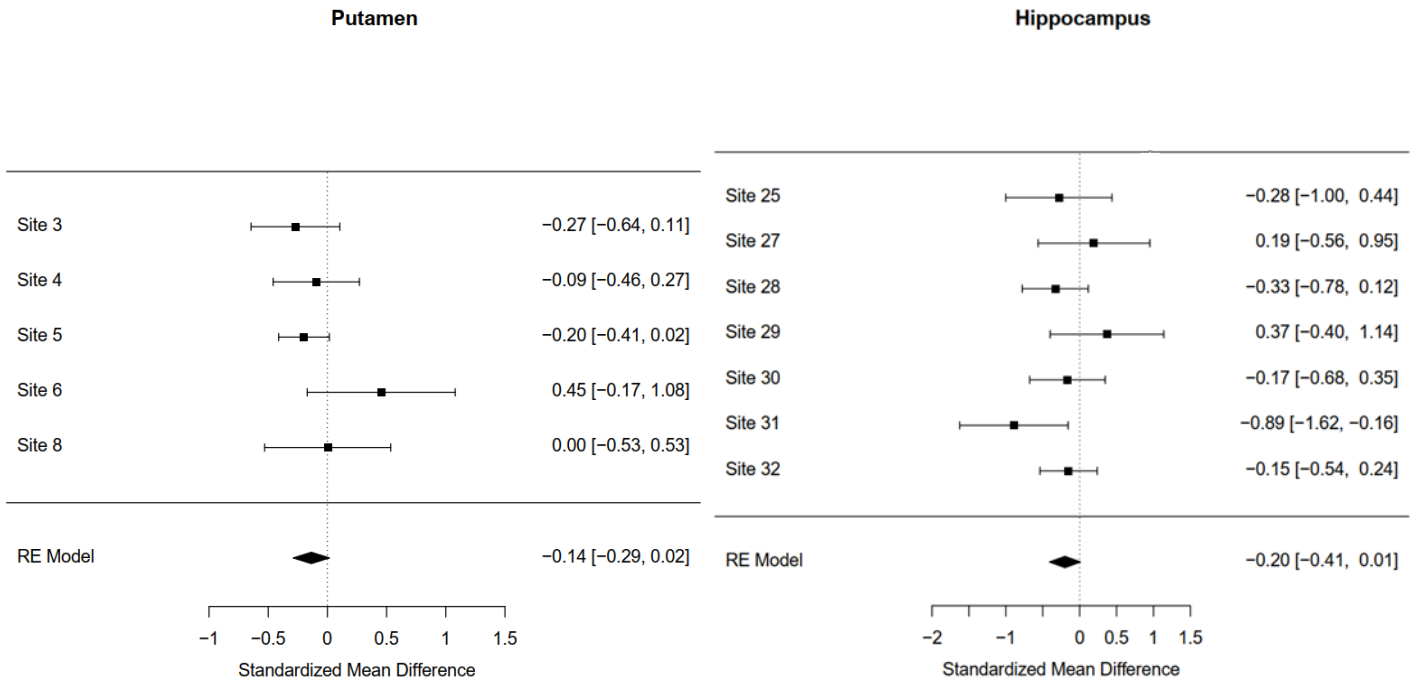

Figure 29. – **Supplementary Figure 13 (Article 2)**. Heterogeneity within the studies is larger than the heterogeneity across included studies is included for AUD females for the putamen (plot on the left) and for the CUD males for the hippocampus (plot on the right) with adolescent studies included.

Supplementary References

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Article 3 – Matériel supplémentaire

Supplementary materials

Supplementary analysis: Exploratory relationships between substance use and temporal, parietal and occipital lobe structure, and sex differences

Binge-drinking frequency

At the between-person level there was no significant association between binge-drinking and brain structure in temporal, parietal and occipital lobes. This secondary analysis revealed additional negative associations between binge-drinking frequency and cortical thickness. Significant concurrent associations between binge-drinking and bilateral cortical thickness were observed, with reduced cortical thickness in the banks of the superior temporal (Estimate =-0.087, 95% CI=[-0.185, -0.005], p_{FDR}=0.160), inferior parietal (Estimate =-0.119, 95% CI=[-0.200,-0.047], p_{FDR}=0.014), postcentral (Estimate =-0.130, 95% CI=[-0.253,-0.017], p_{FDR}=0.136), superior parietal (Estimate =-0.136, 95% CI=[-0.224,-0.056], p_{FDR}=<0.001), supramarginal (Estimate -0.129, 95% CI=[-0.216, -0.053], p_{FDR}<0.001) and lateral occipital (Estimate =-0.143, 95% CI=[-0.251,-0.053], p_{FDR}=0.013). The secondary analysis did not reveal any associations between within-subject lagged binge drinking frequency and the parietal, temporal and occipital lobes. No associations between sex and binge-drinking, or the interaction between these two variables were observed.

Cannabis use frequency

At the between-person level there was no significant association between cannabis use frequency and brain structure in temporal, parietal and occipital lobes. No FDR-corrected significant sex-by-cannabis interactions use frequency were observed. Significant

concurrent time-varying associations were revealed for cannabis use and the lateral occipital (Estimate=-0.100, 95% CI=[-0.157,-0.04], p_{FDR}=0.013), superior parietal (Estimate=-0.102, 95% CI=[-0.160,-0.045], p_{FDR}<0.001) and supramarginal (Estimate=-0.064, 95% CI= [-0.125,-0.012], p_{FDR}=0.098). No lagged associations were observed.

Tableau 10. – **Supplementary Table 1 (Article 3)**. Estimated Parameters for the Alcohol Model in Significant Parietal, Temporal and Occipital Cortical Regions in a Sample of Adolescents (N = 130) Assessed Three Times Over 4 years

	Banks of the superior temporal				**Inferior parietal**				**Postcentral**				**Superior parietal**				**Supramarginal**				**Lateral occipital**			
Predictor	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**
Intercept	31.963	71.586	0.933	[-113.1, 179.4]	32.574	65.494	0.933	[-94.1, 183.1]	26.923	77.661	0.933	[-119.4, 187.2]	30.206	73.189	0.933	[-120.4, 176.2]	35.794	69.547	0.933	[-89.9, 184.3]	36.035	82.246	0.933	[-151.6, 185.7]
Time	**-0.986**	**0.033**	**<0.001**	**[-1.062,-0.927]**	**-1.001**	**0.035**	**<0.001**	**[-1.086, -0.946]**	**-0.945**	**0.047**	<0.001	**[-1.047, 0.864]**	**-0.998**	**0.044**	**<0.001**	**[-1.108, -0.936]**	**-0.993**	**0.033**	**<0.001**	**[-1.072, -0.939]**	**-0.990**	**0.040**	**<0.001**	**[-1.086, -0.928]**
Age	-0.218	0.406	0.950	[-0.949, 0.571]	-0.208	0.34	0.950	[-0.762, 0.475]	-0.164	0.422	0.950	[-0.906, 0.641]	-0.18	0.395	0.950	[-0.824, 0.590]	-0.255	0.399	0.950	[-0.928, 0.539]	-0.214	0.404	0.950	[-0.815, 0.619]
Sex (male)	-0.081	0.117	0.889	[-0.288, 0.167]	-0.012	0.12	0.920	[-0.240, 0.227]	-0.081	0.107	0.889	[-0.282, 0.128]	0.046	0.12	0.889	[-0.190, 0.279]	-0.056	0.119	0.889	[-0.279, 0.183]	0.059	0.112	0.920	[-0.160, 0.273]
Binge-drinking, B	0.107	0.390	0.999	[-0.644, 0.870]	-0.166	0.326	0.999	[-0.757, 0.508]	-0.116	0.389	0.999	[-0.844, 0.625]	-0.018	0.414	0.999	[-0.738, 0.767]	-0.039	0.372	0.999	[-0.734, 0.694]	-0.208	0.365	0.999	[-0.799, .657]
Binge-drinking, W	**-0.087**	**0.046**	**0.160**	**[-0.185. -0.005]**	**-0.119**	**0.039**	**0.014**	**[-0.200, -0.047]**	**-0.130**	**0.061**	0.136	**[-0.253, -0.017]**	**-0.136**	**0.043**	**<0.001**	**[-0.224, -0.056]**	**-0.129**	**0.042**	**<0.001**	**[-0.216, -0.053]**	**-0.143**	**0.051**	**0.013**	**[-0.251, -0.053]**
Binge-drinking, W (lagged)	-0.057	0.084	0.910	[-0.233, 0.090]	-0.106	0.08	0.910	[-0.278, 0.0460]	-0.057	0.139	0.910	[-0.33, 0.209]	-0.044	0.125	0.910	[-0.332, 0.183]	-0.103	0.08	0.910	[-0.263, 0.054]	-0.109	0.110	0.910	[-0.350, 0.083]
Sex (male) x binge-drinking, B	0.523	0.273	0.504	[-0.148, 0.857]	0.633	0.237	0.504	[-0.052, 0.909]	0.364	0.333	0.626	[-0.445, 0.823]	0.554	0.265	0.504	[-0.183, 0.879]	0.551	0.257	0.504	[-0.094, 0.886]	0.493	0.305	0.504	[-0.360, 0.870]
Sex (male) x binge-drinking, W	-0.180	0.217	0.980	[-0.581, 0.238]	-0.172	0.209	0.980	[-0.564, 0.233]	0.041	0.224	0.980	[-0.398, 0.440]	-0.041	0.212	0.980	[-0.445, 0.358]	-0.168	0.21	0.980	[-0.551, 0.241]	-0.224	0.202	0.980	[-0.601, 0.169]
Sex (male) x binge-drinking, W (lagged)	-0.114	0.388	0.948	[-0.809, 0.598]	-0.257	0.385	0.948	[-0.799, 0.622]	-0.082	0.374	0.948	[-0.773, 0.630]	-0.045	0.392	0.948	[-0.730, 0.730]	-0.312	0.378	0.948	[-0.827, 0.563]	-0.159	0.370	0.948	[-0.789, 0.657]

Note. When the confidence intervals did not overlap with zero, associations are bolded. B: between-subject level, W: within-subject-level, Pr(>|t|): two-tailed FDR-corrected p-values.

Tableau 11. – **Supplementary Table 2 (Article 3)**. Estimated Parameters for the Cannabis Model in Significant Parietal, Temporal and Occipital Cortical Regions in a Sample of Adolescents (N = 130) Assessed Three Times Over 4 years

	Inferior parietal				Lateral occipital				Superior parietal				Supramarginal				Entorhinal			
Predictor	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**	**Estimate**	**Std. Er**	**Pr(>|t|)**	**95% CI**
Intercept	32.618	77.784	0.971	[-109.7, 205.0]	34.844	83.942	0.933	[-132.7, 200.5]	36.291	81.102	0.971	[-117.4, 209.9]	45.332	83.498	0.971	[-116.9, 219.1]	-1.210	79.966	0.986	[-171.5, 165.3]
Time	**-0.959**	**0.024**	**<0.001**	**[-1.018, -0.918]**	**-0.907**	**0.020**	**<0.001**	**[-0.951, -0.871]**	**-0.918**	**0.018**	**<0.001**	**[-0.956, -0.883]**	**-0.945**	**0.022**	**<0.001**	**[-1.000, -0.910]**	0.280	0.192	0.265	[-0.219, 0.549]
Age	-0.203	0.373	0.983	[-0.778, 0.601]	-0.218	0.412	0.950	[-0.826, 0.630]	-0.220	0.400	0.983	[-0.792, 0.649]	-0.285	0.407	0.983	[-0.836, 0.631]	0.008	0.405	0.986	[-0.753, 0.742]
Sex (male)	-0.025	0.117	0.989	[-0.238, 0.219]	-0.020	0.108	0.920	[-0.225, 0.199]	-0.033	0.110	0.989	[-0.243, 0.191]	-0.057	0.115	0.989	[-0.268, 0.175]	**0.278**	**0.112**	**0.546**	**[0.037, 0.479]**
Cannabis, B	-0.266	0.176	0.773	[-0.547, 0.128]	-0.197	0.167	0.999	[-0.501, 0.166]	-0.142	0.171	0.773	[-0.432, 0.237]	-0.150	0.185	0.773	[-0.449, 0.272]	-0.124	0.190	0.773	[-0.511, 0.236]
Cannabis, W	**-0.058**	**0.028**	**0.136**	**[-0.117, -0.006]**	**-0.100**	**0.030**	**0.013**	**[-0.157, -0.040]**	**-0.102**	**0.028**	**<0.001**	**[-0.160, -0.045]**	**-0.064**	**0.029**	**0.098**	**[-0.125, -0.012]**	0.074	0.074	0.821	[-0.07, 0.214]
Cannabis, W (lagged)	-0.016	0.055	0.968	[-0.129, 0.084]	-0.085	0.054	0.910	[-0.196, 0.009]	-0.044	0.056	0.968	[-0.164, 0.059]	-0.010	0.052	0.968	[-0.113, 0.090]	0.142	0.117	0.968	[-0.099, 0.362]
Sex (male) x cannabis, B	**0.591**	**0.212**	**0.224**	**[0.045, 0.881]**	**0.535**	**0.197**	**0.504**	**[0.080, 0.857]**	**0.614**	**0.199**	**0.224**	**[0.133, 0.883]**	0.507	0.227	0.288	[-0.040, 0.881]	-0.174	0.266	0.569	[-0.650, 0.393]
Sex (male) x cannabis, W	0.115	0.237	0.767	[-0.345, 0.539]	-0.535	0.261	0.980	[-0.895, 0.066]	0.287	0.323	0.652	[-0.392, 0.833]	0.191	0.243	0.652	[-0.298, 0.609]	0.314	0.201	0.652	[-0.120, 0.646]
Sex (male) x cannabis, W (lagged)	0.166	0.238	0.753	[-0.321, 0.605]	-0.295	0.440	0.948	[-0.941, 0.706]	0.165	0.487	0.891	[-0.858, 0.918]	0.209	0.270	0.753	[-0.343, 0.710]	0.184	0.212	0.753	[-0.260, 0.533]

Note. When the confidence intervals did not overlap with zero, associations are bolded. B: between-subject level, W: within-subject-level, Pr(>|t|): two-tailed FDR-corrected p-values.