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AUGUSTO MARTINS LUCAS BITTENCOURT

ALTERAÇÕES CEREBRAIS ESTRUTURAIS ASSOCIADAS AO TRANSTORNO POR USO DE COCAÍNA:
UMA REVISÃO SISTEMÁTICA E METANÁLISE INTEGRATIVA DE ESTUDOS DE NEUROIMAGEM

Porto Alegre 2026

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Pontifícia Universidade Católica
do Rio Grande do Sul

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Orientador: Prof. Dr. Thiago Wendt Viola

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Aprovado em: _____de _____de _____

BANCA EXAMINADORA:

_____
Prof. Dr. Thiago Wendt Viola (orientador)

_____
Prof. Dr. Pedro Eugenio Mazzucchi Santana Ferreira

_____
Profa. Dra. Carla Hervê Moram Bicca

_____
Prof. Dr. Bruno Kluwe Schiavon

Porto Alegre 2026

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RESUMO

Introdução:

O transtorno por uso de cocaína (CUD) tem sido associado a diferenças nas medidas de substância cinzenta (GM); entretanto, metanálises anteriores apresentaram resultados inconsistentes devido à variabilidade metodológica, ao viés de publicação e ao relato seletivo. Para superar essas limitações, esta tese integra, de forma inédita no campo, abordagens multinível frequentistas, modelagem hierárquica bayesiana e metanálise baseada em coordenadas, fornecendo uma síntese abrangente e anatomicamente detalhada dos achados de neuroimagem estrutural no CUD.

Métodos:

Em conformidade com as diretrizes PRISMA (PROSPERO: CRD42024585260), foram incluídos 47 estudos que compararam índices de GM entre indivíduos com CUD e HC. Metanálises multinível de efeitos aleatórios foram conduzidas para quantificar diferenças corticais e subcorticais entre os grupos, considerando moderadores clinicamente relevantes. Modelos hierárquicos bayesianos foram empregados em análises de sensibilidade para abordar o potencial viés de relato, e uma metanálise baseada em coordenadas, por meio do método Activation Likelihood Estimation (ALE), avaliou a convergência espacial entre estudos de morfometria baseada em voxel.

Resultados:

Indivíduos com CUD apresentaram menores medidas de GM nas regiões corticais pré-frontais e temporais, particularmente no giro temporal inferior e no giro frontal médio-rostral. Nas análises subcorticais, observaram-se menores volumes de GM na amígdala, hipocampo, tálamo, globo pálido, núcleo accumbens, tronco encefálico e cerebelo. Maior duração do uso de cocaína e maior gravidade clínica estiveram associadas a estimativas de tamanho de efeito cortical mais negativas e de maior magnitude. A regularização bayesiana produziu estimativas corticais consistentes nas análises de sensibilidade, enquanto a metanálise baseada em coordenadas não identificou clusters que sobrevivessem à correção por erro do tipo família.

Conclusão:

Esta tese identifica padrões consistentes de diferenças estruturais córtico-subcorticais em indivíduos com CUD e estabelece um referencial neuroanatômico integrado que contribui para o refinamento de modelos neurobiológicos do transtorno. Esses achados podem orientar estudos longitudinais futuros e a avaliação de potenciais biomarcadores em neuroimagem.

Palavras-chave:

Transtorno por uso de cocaína; metanálise; ressonância magnética estrutural; inferência bayesiana; substância cinzenta; neurocircuitaria da dependência; biomarcadores candidatos.

ABSTRACT

Background:

Cocaine Use Disorder (CUD) has been associated with alterations in gray matter (GM) measures; however, previous meta-analyses have yielded inconsistent findings due to methodological variability, publication bias, and selective reporting. To address these limitations, this thesis integrates, for the first time in this field, multilevel frequentist approaches, hierarchical Bayesian modeling, and coordinate-based meta-analysis, providing a comprehensive and anatomically resolved synthesis of structural neuroimaging findings in CUD.

Methods:

In accordance with PRISMA guidelines (PROSPERO: CRD42024585260), 47 studies comparing GM indices between individuals with CUD and healthy controls were included. Multilevel random-effects meta-analyses were conducted to quantify cortical and subcortical group differences while accounting for clinically relevant moderators. Hierarchical Bayesian models were implemented as sensitivity analyses to address potential reporting bias, and a coordinate-based meta-analysis using the Activation Likelihood Estimation (ALE) method assessed spatial convergence across voxel-based morphometry studies.

Results:

Individuals with CUD exhibited lower GM measures in prefrontal and temporal cortical regions, particularly in the inferior temporal gyrus and the rostral middle frontal gyrus. Subcortical analyses revealed reduced GM volume in the amygdala, hippocampus, thalamus, pallidum, nucleus accumbens, brainstem, and cerebellum. Longer duration of cocaine use and greater clinical severity were associated with more negative and larger-magnitude cortical effect-size estimates. Bayesian regularization yielded consistent cortical estimates across sensitivity analyses, whereas the coordinate-based meta-analysis identified no clusters surviving family-wise error correction.

Conclusions:

This thesis identifies consistent cortico-subcortical structural differences in individuals with CUD and establishes an integrated neuroanatomical reference framework that contributes to refining neurobiological models of the disorder. These findings may inform future longitudinal studies and the evaluation of candidate neuroimaging biomarkers.

Keywords: Cocaine Use Disorder; Meta-analysis; Structural MRI; Bayesian inference; Gray matter; Addiction neurocircuitry; Candidate Biomarkers.

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LISTA DE ABREVIATURAS E SIGLAS

ACC – Córtex cingulado anterior

ALE – Activation Likelihood Estimation

CT – Espessura cortical

CUD – Transtorno por uso de cocaína

DP – Desvio-padrão

EMTr – Estimulação Magnética Transcraniana repetitiva

EP – Erro padrão

FWE – Family-Wise Error

GM – Substância cinzenta

HC – Controles saudáveis

IC – Intervalo de Confiança

ITG – Giro temporal inferior

MRI – Ressonância Magnética Estrutural

NA – Núcleo Accumbens

OFC – Córtex Orbitofrontal

tDCS – Estimulação transcraniana por corrente contínua

VBM – Voxel-Based Morphometry

VTA – Área tegmentar ventral

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1 INTRODUÇÃO GERAL

1.1 Transtorno por Uso de Cocaína: relevância clínica e epidemiológica

Transtorno por uso de substâncias caracteriza-se como qualquer perturbação que gere alterações fisiológicas, cognitivas e comportamentais devido a um padrão de uso de substâncias definidas, ainda que haja prejuízos significativos ao indivíduo ou a terceiros (Association, 2013). Os transtornos por uso de substâncias são considerados um dos principais problemas de saúde pública mundial, tendo em vista que o número de pessoas que fazem uso de drogas continua em crescimento: estima-se que aproximadamente 292 milhões de pessoas tenham utilizado alguma droga em 2023, o que corresponde a cerca de 5,6% da população mundial entre 15 e 64 anos ("World Drug Report 2025", *[S.d.]*).

O transtorno por uso de cocaína (CUD), por sua vez, caracteriza-se pelo consumo persistente de cocaína, prejuízo na autorregulação e continuidade do uso apesar de consequências adversas (Abuse, 2020; Hasin et al., 2013; Koob; Volkow, 2010; Poisel et al., 2023; Schwartz et al., 2022). Em 2023, aproximadamente 25 milhões de pessoas no mundo (0,47% da população entre 15 e 64 anos) relataram uso de cocaína ("World Drug Report 2025", *[S.d.]*). O seu consumo está disseminado entre todas as classes sociais (Madruga et al., 2017). Os riscos físicos, psicológicos, sociais e legais associados tornam o CUD um problema relevante de saúde pública (Karila et al., 2012; Sanvisens et al., 2021; Schwartz et al., 2022). Estes desfechos parecem ser mediados pelo gênero, com as mulheres mais vulneráveis aos efeitos da dependência química (Heberle et al., 2024; Rebelatto et al., 2022). O esclarecimento e a descrição do perfil dessa população foram indicados como prioridade para a construção de melhores meios de prevenção, tratamento e manutenção dos cuidados existentes (Bastos, 2017).

Dados do Sistema de Informações Hospitalares do SUS ("Produção Hospitalar (SIH/SUS) – DATASUS", *[S.d.]*) indicam que os transtornos mentais e comportamentais decorrentes do uso de substâncias continuam a representar uma parcela significativa das internações psiquiátricas no Brasil, com destaque para os transtornos relacionados ao uso de cocaína e crack ("III Levantamento Nacional sobre o uso de drogas pela população brasileira", 2017; "Produção Hospitalar (SIH/SUS) – DATASUS", *[S.d.]*). Levantamentos nacionais indicam que, após o álcool, a cocaína e seus derivados, incluindo o crack, figuram entre as principais causas de procura por tratamento especializado para transtornos por uso de substâncias no país ("III Levantamento Nacional sobre o uso de drogas pela população brasileira", 2017). Além disso, os custos econômicos associados aos transtornos por uso de substâncias incluem despesas diretas com tratamento e hospitalizações, bem como custos

indiretos relacionados à perda de produtividade e ao impacto social, o que representa um ônus substancial ao sistema de saúde e à economia ("World Drug Report 2025", *[S.d.]*).

Considerando a elevada morbimortalidade e o ônus socioeconômico associados ao CUD, refletidos em internações, perda de produtividade e impactos psicossociais, torna-se imperativo avançar na caracterização neurobiológica do transtorno. A identificação de biomarcadores de neuroimagem e de circuitos-alvo associados a desfechos clínicos pode contribuir para refinar modelos etiopatogênicos, aprimorar a estratificação prognóstica e orientar o desenvolvimento de intervenções mais eficazes.

1.2 Bases neurobiológicas do CUD

As alterações comportamentais e cognitivas que os usuários de cocaína apresentam decorrem, pelo menos em parte, de alterações nos circuitos cerebrais (Volkow; Fowler, 2000). O modelo de três estágios do vício, uso/intoxicação, afeto negativo/abstinência e preocupação/antecipação, organiza o CUD em torno de circuitos específicos: (i) circuito de recompensa (VTA–estriado ventral), responsável por reforço positivo e saliência motivacional; (ii) circuitos de estresse e emoção (amígdala estendida e regiões límbicas), associados a disforia e reforço negativo; e (iii) circuitos fronto-estriatais (córtex pré-frontal, orbitofrontal e cíngulo anterior), relacionados ao controle executivo, tomada de decisão e recaída (Volkow; Koob, 2015; Volkow; Koob; McLellan, 2016).

O aumento da concentração de dopamina na via mesocorticolímbica é uma das alterações funcionais que parecem ter maior relevância para a compreensão das mudanças comportamentais relacionadas ao uso agudo de cocaína, como alterações motivacionais e a consequente manutenção patológica do uso da droga (Pilotte et al., 1996). Sabe-se que a elevada concentração de dopamina na via mesocorticolímbica aumenta a sensação subjetiva de *craving*, caracterizada por desejo intenso pelo uso da droga, em usuários abstinentes (McHugh et al., 2013). A cocaína possui propriedades que estimulam a modulação dopaminérgica em duas das principais vias – a mesocorticolímbica e a nigroestriatal –, e as ativações dessas vias respondem à maior parte dos sintomas decorrentes do uso da droga, como a euforia, o *craving* e alterações de humor (Horvitz, 2000; Pilotte et al., 1996; Salamone; Correa, 2012). Entretanto, sabe-se que, isoladamente, o sistema dopaminérgico é pouco representativo na etiologia e na manutenção do CUD, já que sua ação também depende da circuitaria neuronal disponível.

Quatro circuitos cerebrais inter-relacionados estão envolvidos ou afetados pelo CUD, incluindo o circuito de recompensa - núcleo accumbens (NA) e regiões estriadas adicionais) - o circuito de aprendizagem/memória (amígdala e o hipocampo), o circuito de

motivação/impulso (córtex orbitofrontal – OFC / subcaloso e córtex motor) e o circuito de controle cognitivo (córtex pré-frontal e córtex cingulado) (Volkow; Koob, 2015; Volkow; Koob; McLellan, 2016).

O uso ocasional, limitado e recreativo de uma droga é clinicamente distinto do uso intensivo, visto que é necessária a compilação de sintomas e comportamentos ao longo de pelo menos 12 meses (Association, 2013). A dependência foi conceituada como um ciclo de três estágios: 1) uso/intoxicação; 2) afeto negativo/abstinência; e 3) preocupação/antecipação (Goldstein; Volkow, 2011). Esse ciclo tende a se intensificar ao longo do tempo, pois envolve mudanças alostáticas nos sistemas de recompensa e de estresse do cérebro. O ciclo se desenvolve devido a uma diminuição da sensibilidade aos reforçadores não relacionados aos estímulos principais de adição e à redução da capacidade de inibir comportamentos desadaptativos ou desvantajosos (Asensio et al., 2010). Como resultado desses déficits básicos, a busca e a ingestão de drogas tornam-se o principal impulso motivacional, culminando em comportamentos extremos na busca da "recompensa". Duas fontes primárias de reforço, positivo e negativo, foram descritas para desempenhar um papel neste processo (Koob, 2013). O reforço positivo é definido como o processo pelo qual a apresentação de um estímulo aumenta a probabilidade de uma resposta; o reforço negativo, como o processo pelo qual a remoção de um estímulo aversivo aumenta a probabilidade de uma resposta. No nível celular, a motivação depende da concentração de dopamina no estriado. O uso repetido de drogas leva à *downregulation* das respostas dopaminérgicas a outros incentivos e à perda da capacidade de controle cortical/superior pelo lobo frontal (Asensio et al., 2010; Koob, 2013).

O sistema de recompensa e busca é composto pela área tegmentar ventral (VTA) composta predominantemente de neurônios dopaminérgicos com projeções para o NA (estriado ventral ou putaminal). Nessa região, essas vias têm dois tipos de ativação: ativação tônica, com predomínio de atividade de alta sensibilidade dos receptores D2R, inibitória e que avalia diversos estímulos comportamentais; e ativação fásica, com liberação aguda de dopamina e estimulação (recompensa) dos receptores D1, consolidando memórias prazerosas. Isso pode ser evidenciado por meio de PET, que mede o nível de receptores D2R em patologias relacionadas a comportamentos aditivos. Isso leva à deficiência de resposta dopaminérgica tônica e à avaliação de outras atividades ambientais motivacionais. Além dessas projeções, a VTA projeta para regiões pré-frontais, orbitofrontais, hipocampais e hipotalâmicas, que exercem controle sobre a VTA e otimizam a resposta *go/no-go*, calculando o risco-benefício entre a recompensa e a ação (Asensio et al., 2010; Salamone; Correa, 2012; Volkow; Wise; Baler, 2017).

O que ocorre parcialmente no vício é uma diminuição do controle do córtex pré-frontal sobre o VTA; isso faz com que a pessoa perca o controle e a vontade própria e continue buscando a recompensa da substância, apesar de resultados negativos. Um dos motivos disso é o excesso de glutamato extracelular. Esse *spillover* de glutamato para fora da sinapse, em situações normais, regula a própria excitose glutamatérgica, diminuindo a resposta e facilitando a entrada de outros estímulos relevantes (ex.: pessoa correndo pela vida que pisa sobre um prego e não sente) e a divergência do comportamento. Na adição, o excesso de glutamato impede a ativação do NA, pois todos os receptores glutamatérgicos já estão ocupados. O desequilíbrio glutamatérgico impede o controle do córtex pré-frontal sobre o estriado ventral/dorsal. Em outras palavras, pacientes dependentes têm dificuldade em inibir o uso ou a busca por drogas em presença de estímulos competidores (Kalivas; Kalivas, 2016; Kalivas, 2009).

Adicionalmente, há uma transição da circuitaria límbica, incluindo o estriado ventral e o NA, para uma circuitaria motora ou habitual do estriado dorsal, o que levaria à formação de hábitos mesmo na ausência de estimulação por drogas. Isso explica por que, quanto mais a pessoa usa drogas, mais insensível se torna aos estímulos ambientais que inibem a busca por drogas. Muitos estudos sugerem que a ativação do sistema dopaminérgico mesolímbico impulsiona o desempenho do comportamento direcionado a um objetivo (Salamone et al., 2007), o que sugere que essa seja uma das principais vias envolvidas no CUD (Koob, 2013). A cocaína e as anfetaminas aumentam os níveis de dopamina no NA e na amígdala por meio de ações diretas sobre os terminais dopaminérgicos (Salamone et al., 2007).

Nesse sentido, tem sido consistentemente demonstrado que os usuários de cocaína apresentam amplos prejuízos cognitivos que vão desde funções básicas, como atenção e memória de trabalho, até habilidades mais complexas, como funções executivas, cognição social e tomada de decisão social (Levandowski et al., 2016; Tractenberg et al., 2014, 2012; Viola et al., 2013). O entendimento da apresentação clínica dos transtornos por uso de substâncias considera que as alterações psicobiológicas atuam na manutenção do uso de drogas, explicando, assim, as constantes recaídas, por exemplo. Na busca por uma maior compreensão das possíveis alterações cognitivo-comportamentais, tem havido um interesse crescente por estudos de neuroimagem (Crocker et al., 2017).

A circuitária associada ao prazer/motivação foi demonstrada de forma elegante por pesquisadores alemães. Vollstädt-Klein e colaboradores analisaram as respostas a pistas visuais de álcool em 21 abusadores de álcool e em 10 pessoas que bebiam socialmente. Para tanto, utilizaram a RM funcional para medir a ativação cerebral em figuras relacionadas ao hábito de beber álcool. Entre os indivíduos que bebiam socialmente, a imagem de álcool foi associada à

ativação do estriado ventral/NA, assim como do VTA, sugerindo ativação de vias hedônicas (relacionadas ao prazer; ex.: relaxar com os amigos em um bar). No entanto, os indivíduos que abusam de álcool, surpreendentemente, mostravam ativação do estriado dorsal, relacionada a memórias procedurais ou automáticas, o que demonstra uma transição do prazer associado ao álcool para um hábito comportamental automático, já dissociado das vias de controle pré-frontais. Interessantemente, medidas de pensamento obsessivo-compulsivo e de *craving* correlacionaram-se negativamente com a ativação do VTA/NA e positivamente com a ativação do estriado (Vollstädt-Klein et al., 2010).

Em outro estudo, Small e colaboradores captaram nove pessoas para testar quais regiões cerebrais são responsáveis pelo prazer de comer chocolate e por quando esse prazer se torna aversão. As pessoas pontuavam, a cada vez que comiam, quanto queriam chocolate e quanto estavam satisfeitas. Foram realizadas 7 pausas para comer o chocolate. Após cada vez que as pessoas comiam chocolate, eram submetidas a um PET-scan. Subtraiam os resultados dos primeiros escâneres dos últimos para avaliar as diferenças. O que eles encontraram foi a ativação de áreas relacionadas à recompensa nos primeiros escâneres, quando as pessoas ainda estavam motivadas a comer, como a área subcalosa, a VTA, a ínsula/opérculo e a região orbitofrontal. Isso sugere a ativação do sistema de recompensa-busca logo no início da vontade de comer chocolate. Após atingir a saciedade, entretanto, essas áreas foram progressivamente desativadas, dando lugar à ativação do controle inibitório do córtex pré-frontal e orbitofrontal lateral, assim como do hipocampo posterior e do cíngulo posterior (possível relação com a memória de estarem satisfeitos). Esse estudo elegante mostra a transição normal do ‘querer/vontade’ para a ‘aversão’, evidenciando os mecanismos envolvidos em respostas adaptativas normais que falham nas patologias associadas aos transtornos aditivos. Concluindo, o gostar e o querer estão intrinsecamente ligados. A transição da vontade para a compulsão envolve a passagem de um estímulo motivacional adaptativo a um hábito. Isso envolve a desregulação dos sistemas de recompensa e de aversão, o que leva a um déficit nas vias biológicas do controle comportamental (Small et al., 2001).

Se essas alterações funcionais se consolidam ao longo da progressão do vício, é razoável supor que deixem marcas detectáveis na organização estrutural desses mesmos circuitos. Investigar sistematicamente tais diferenças morfométricas permite avaliar até que ponto os modelos neurocircuitários do CUD se correspondem às evidências anatômicas.

1.3 Neuroimagem estrutural no CUD

Pascual-Leone e colaboradores (1991) foram pioneiros no estudo de neuroimagem em usuários de cocaína (Pascual-Leone; Dhuna; Anderson, 1991). Esse estudo preliminar por tomografia computadorizada demonstrou alterações nos exames desses participantes. O avanço da tecnologia permitiu a aquisição de imagens de maior detalhamento da anatomia do tecido nervoso, como a ressonância magnética estrutural (MRI), que passou a ser amplamente empregada para investigar alterações estruturais no cérebro de usuários de cocaína.

A caracterização morfométrica da substância cinzenta (GM) em estudos de neuroimagem pode ser realizada por meio de diferentes métricas, como o volume, a espessura cortical (CT) e a área de superfície. Embora frequentemente tratadas como equivalentes, essas medidas capturam dimensões neuroanatômicas distintas (Hogstrom et al., 2013; Winkler et al., 2010). O volume cortical resulta, em termos geométricos, da interação entre a espessura e a área de superfície, mas essas componentes apresentam bases neurobiológicas e desenvolvimentais parcialmente independentes (Panizzon et al., 2009; Winkler et al., 2010). Enquanto a CT está mais relacionada à organização laminar e à densidade celular, a área de superfície reflete padrões de expansão cortical associados à hipótese da unidade radial e à morfogênese cortical (Panizzon et al., 2009; Rakic, 1988). Assim, alterações detectadas no volume podem não se reproduzir necessariamente quando analisadas separadamente por CT ou por área de superfície, o que contribui para discrepâncias entre estudos (Fjell et al., 2015; Winkler et al., 2010).

Além das diferenças nas métricas morfométricas, os métodos analíticos empregados também podem influenciar os resultados. A voxel-based morphometry (VBM) opera em um espaço volumétrico padronizado, permitindo comparações voxel a voxel da densidade ou do volume de GM (Ashburner; Friston, 2000, 2005), mas depende fortemente de etapas de segmentação, normalização e suavização, que podem impactar a sensibilidade espacial e a especificidade anatômica (Hutton et al., 2009). Em contraste, abordagens baseadas em superfície, como as implementadas no FreeSurfer, modelam explicitamente a topologia cortical, reconstruindo a superfície e estimando a espessura e a área cortical ao longo dessa geometria (Fischl; Dale, 2000; Fischl et al., 2004). Essas diferenças metodológicas envolvem pressupostos estatísticos e anatômicos distintos, podendo resultar em padrões parcialmente divergentes de alterações regionais, mesmo quando aplicadas a amostras semelhantes (Hutton et al., 2009; Winkler et al., 2010).

Para melhor compreender a base neuroanatômica do CUD, avanços recentes em neuroimagem estrutural têm evidenciado redução do volume de GM em regiões corticais e subcorticais envolvidas nos comportamentos aditivos (Beheshti, 2023; Bittencourt et al., 2021;

Dang et al., 2022; Pando-Naude et al., 2021; Rothmann et al., 2024; Trevisan et al., 2023). Entretanto, estudos prévios têm produzido achados heterogêneos, principalmente devido à variabilidade metodológica, incluindo diferenças nas abordagens analíticas empregadas, diversidade de medidas neuroanatômicas examinadas e considerável heterogeneidade nos fatores clínicos e demográficos das amostras incluídas (Garza-Villarreal et al., 2017; McCurdy et al., 2024; Meade et al., 2020; Narayana et al., 2010; Schinz et al., 2023)(Garza-Villarreal et al., 2017; McCurdy et al., 2024; Meade et al., 2020; Narayana et al., 2010; Schinz et al., 2023).

Bartzokis e colaboradores (2000) compararam usuários de cocaína e anfetamina com controles saudáveis (HC) e encontraram redução do volume da GM na região temporal desses pacientes (Bartzokis et al., 2000). Franklin e colaboradores (2002) obtiveram resultados similares, entretanto, encontraram também uma redução da GM na região orbitofrontal, no córtex cingulado anterior (ACC) e na ínsula (Franklin et al., 2002) Fein e colaboradores (2002) acharam redução apenas no volume de GM na região pré-frontal em usuários de cocaína, sem diferença nas regiões parietal, temporal e frontal entre pacientes e HC (Fein; Di Sclafani; Meyerhoff, 2002). Narayana e colaboradores (2010) empregaram duas técnicas distintas para o processamento de imagens de MRI, com o objetivo de identificar mudanças estruturais no cérebro de dependentes de cocaína. Neste trabalho, os autores não identificaram nenhuma alteração no volume cerebral dos dependentes em comparação com HC (Narayana et al., 2010). Wang e colaboradores (2017) encontraram atrofia na GM do córtex pré-frontal ventromedial e no OFC direito em um grupo de 20 usuários de cocaína (Wang et al., 2017). Em relação às regiões subcorticais, diversos estudos encontraram redução volumétrica em regiões como o NA e o putamen (Barrós-Loscertales et al., 2011; Bittencourt et al., 2021; Garza-Villarreal et al., 2018; Schuch-Goi et al., 2017), ao passo que outros estudos não identificaram a redução dessas regiões (Garza-Villarreal et al., 2017; Narayana et al., 2010). Alguns desses estudos focaram a investigação em regiões de interesse (ROI); outros investigaram o cérebro inteiro, além de terem utilizado diferentes técnicas de processamento das neuroimagens.

Metanálises que tentaram compreender as diferenças cerebrais associadas ao CUD têm reportado diferenças de grupo em GM entre indivíduos com CUD e HC, de forma mais consistente nos córtices pré-frontais e temporais (Ersche et al., 2013; Hall et al., 2015; Pando-Naude et al., 2021), regiões implicadas no controle executivo e na reatividade a estímulos associados à droga (Koob; Volkow, 2016). Algumas relataram menores índices de GM no OFC e no ACC (Ersche et al., 2013; Pando-Naude et al., 2021), enquanto outra enfatizou diferenças em regiões temporais e límbicas, incluindo a ínsula e o hipocampo (Dang et al., 2022). As evidências para o envolvimento subcortical têm sido menos consistentes, com algumas

metanálises relatando diferenças de grupo em medidas estriatais e talâmicas (Hall et al., 2015; Pando-Naude et al., 2021)(Pando-Naude et al., 2021; Hall et al., 2015), enquanto outras não observaram diferenças estatisticamente significativas nessas regiões (Dang et al., 2022; Ersche et al., 2013). Tais inconsistências podem refletir uma heterogeneidade metodológica substancial entre os estudos, incluindo diferenças nas estratégias analíticas, nas características clínicas e epidemiológicas das amostras e na suscetibilidade a vieses estatísticos e de relato (Bartoš et al., 2024; Dang et al., 2022; Ersche et al., 2013; Kunz et al., 2024; Rhodes et al., 2017). Essas variáveis não foram sistematicamente controladas de forma uniforme nas metanálises anteriores.

Para tentar compreender a associação de algumas dessas variáveis clínicas com as alterações cerebrais no CUD, em um estudo transversal publicado pelo nosso grupo, avaliamos métricas de GM cerebral por meio de MRI em usuários de cocaína-crack, em comparação com HC, utilizando duas técnicas diferentes de processamento de neuroimagem (FreeSurfer surface-based e VBM) para investigar alterações de volume, de área de superfície e de CT. Esse estudo apresentou resultados da análise por meio do FreeSurfer compatíveis com alterações significativas na CT em diversas regiões cerebrais, incluindo o córtex pré-frontal, o OFC e o córtex temporal, além de redução volumétrica no hipocampo e no diencéfalo ventral, e de alargamento volumétrico do ventrículo lateral esquerdo. Em contraste, a análise de VBM desse mesmo estudo identificou redução volumétrica do NA e do putamen. Ou seja, nesse nosso estudo, vimos que, numa mesma amostra, os resultados variam conforme a medida morfométrica investigada e a técnica de processamento de neuroimagem empregada (Bittencourt et al., 2021).

Também encontramos correlação entre alterações específicas em regiões cerebrais (córtex pré-frontal e orbitofrontal) e o tempo de uso de crack, compatível com a hipótese de efeito cumulativo do uso de cocaína sobre a estrutura cerebral (Bittencourt et al., 2021). Ademais, identificamos uma associação com anos de uso de cocaína-crack com uma redução da integridade da substância branca cerebral, em especial com fibras que conectam o córtex pré-frontal esquerdo e direito (Tondo et al., 2021), e identificamos um efeito de mediação dos traumas na infância na CT do giro do cíngulo (Bittencourt et al., 2024) de usuários de cocaína-crack em estudo que foi produção científica do meu mestrado e concluído durante o meu doutorado (ANEXO 1). Ainda assim, ao analisarmos dados de ressonância magnética funcional, estimando o funcionamento cerebral em estado de repouso, identificamos que a gravidade dos sintomas de abstinência à cocaína-crack associou-se a menores valores de conectividade cerebral no giro pós-central direito e no giro fusiforme direito, com as mulheres

tendo apresentado menor ativação cerebral em regiões relacionadas à memória, ao reconhecimento de emoções e à percepção sensorial (Sanvicente-Vieira et al., 2022). Há indícios de que, à medida que a abstinência avança, o organismo busca o equilíbrio homeostático existente antes do uso da droga, mas o aumento da atividade funcional em áreas cerebrais relacionadas às recompensas durante a fase de abstinência acaba por se refletir em sintomas de *craving*, potencializando a vulnerabilidade a recaídas, causando quadros clínicos mais graves (Corominas-Roso et al., 2013). Esses achados reforçam a hipótese de que o CUD envolve alterações estruturais e funcionais em circuitos fronto-estriatais e límbicos, potencialmente moduladas por fatores ambientais precoces. Também sinalizam que a variabilidade observada entre estudos pode não se limitar a diferenças metodológicas, mas também à influência de fatores clínicos que modulam a expressão neuroanatômica do CUD. Variáveis como trauma na infância, estágio de abstinência e via de administração da cocaína são candidatas plausíveis a moderar essas alterações estruturais.

Enquanto as mudanças nas estruturas corticais e subcorticais têm sido estudadas em usuários de cocaína inalada e de outros estimulantes, as alterações em usuários de crack ainda são pouco conhecidas. Entre as quatro revisões sistemáticas disponíveis sobre diferenças estruturais cerebrais no CUD, a via de administração da cocaína não foi examinada como moderador em nenhuma análise quantitativa (Dang et al., 2022; Ersche et al., 2013; Hall et al., 2015; Mackey et al., 2019; Pando-Naude et al., 2021), apesar de evidências indicarem que métodos de administração de rápida absorção, como o uso fumado (crack) ou intravenoso, estão associados a maior comprometimento cognitivo, recaída mais precoce e diferenças de GM de maior magnitude em comparação ao uso intranasal (Bittencourt et al., 2021; Poireau et al., 2024; Rothmann et al., 2024). Ademais, estudos fisiológicos têm relatado aumento do risco cerebrovascular em amostras submetidas à administração intravenosa (Kaufman et al., 1998). Essas observações ressaltam a necessidade de avaliar sistematicamente a via de administração da cocaína como variável moderadora em análises estruturais de neuroimagem.

Comorbidades psiquiátricas e médicas, juntamente com o uso de múltiplas substâncias, constituem fontes relevantes, embora frequentemente negligenciadas, de heterogeneidade na pesquisa sobre CUD. Estudos empíricos indicam que transtornos mentais comórbidos e o uso concomitante de outras substâncias intensificam os déficits de GM em regiões pré-frontais, insulares e hipocampais (Alia-Klein et al., 2011; Dang et al., 2022; Kaag et al., 2014; Noyan et al., 2016; Stoychev, 2019). A exclusão dessas variáveis em revisões quantitativas provavelmente contribui para as inconsistências observadas em metanálises anteriores (Dang

et al., 2022; Ersche et al., 2013; Hall et al., 2015; Mackey et al., 2019; Pando-Naude et al., 2021).

A expressão neuroanatômica do CUD provavelmente não é uniforme, e sim modulada por características demográficas e clínicas das amostras. Idade e sexo influenciam as trajetórias de desenvolvimento e declínio cortical (Hogstrom et al., 2013; Ruigrok et al., 2014), enquanto a dose cumulativa, a duração do uso e o estágio de abstinência podem refletir diferentes fases de neuroadaptação associadas ao consumo de cocaína (Ersche et al., 2013; Pando-Naude et al., 2021). A ausência de modelagem sistemática desses moderadores limita a interpretação dos achados disponíveis.

Apesar do volume crescente de estudos de neuroimagem estrutural no CUD, permanece ausente o consenso quanto às alterações neuroanatômicas associadas ao transtorno. As divergências observadas parecem resultar da interação entre heterogeneidade clínica e variabilidade metodológica substancial, como diferenças nas métricas estruturais empregadas (volume, CT e área de superfície), nas estratégias de processamento e análise de imagem (VBM versus abordagens baseadas em superfície), nos parâmetros de aquisição, nos tamanhos amostrais frequentemente reduzidos e na suscetibilidade a vieses estatísticos e de publicação. Ademais, metanálises prévias apresentam limitações importantes, incluindo foco exclusivo em coordenadas reportadas, ausência de integração entre múltiplas métricas morfométricas e exploração limitada de fatores moderadores clínicos. Consequentemente, ainda não está claro se existe um padrão estrutural robusto e reprodutível associado ao CUD, tampouco se as alterações descritas refletem vulnerabilidades pré-existentes, efeitos neurotóxicos cumulativos ou adaptações plásticas decorrentes do uso crônico da substância. Diante dessas lacunas, torna-se necessária uma síntese quantitativa integrativa, metodologicamente rigorosa e orientada por hipóteses neurobiológicas, capaz de examinar, de forma sistemática, a consistência, a magnitude e os possíveis moderadores das alterações estruturais cerebrais associadas ao CUD.

1.4 Abordagem meta-analítica integrativa e modelagem de heterogeneidade

Revisões quantitativas de alta qualidade estabeleceram um padrão regional consistente de redução do volume de GM no CUD, fornecendo suporte relevante aos modelos neurocircuitários da dependência (Ersche et al., 2013; Hall et al., 2015; Pando-Naude et al., 2021). Entretanto, tais sínteses foram limitadas pela heterogeneidade metodológica e clínica substancial, além de práticas de relato na literatura primária que dificultam a integração sistemática de múltiplas métricas morfométricas. Ademais, muitas abordagens tradicionais não modelaram explicitamente a dependência estatística entre múltiplas estimativas extraídas de um

mesmo estudo, o que potencialmente inflaciona a precisão das inferências e restringe a incorporação de moderadores clinicamente relevantes.

O presente estudo avança ao propor um arcabouço quantitativo integrativo que aborda simultaneamente essas limitações. Empregamos modelos meta-analíticos multinível para acomodar a estrutura hierárquica dos dados e preservar a dependência entre efeitos regionais provenientes de um mesmo estudo. Complementarmente, adotamos uma abordagem bayesiana para estimar distribuições posteriores dos efeitos, permitindo uma caracterização probabilística da incerteza, análises de sensibilidade com regularização por priors e maior robustez em contextos de amostras heterogêneas (Cao et al., 2023).

A abordagem bayesiana difere do paradigma frequentista tradicional ao tratar os parâmetros de interesse como distribuições probabilísticas, permitindo a estimação direta da probabilidade de determinados efeitos à luz dos dados observados (Gelman et al., 2013; Wagenmakers et al., 2018). Em vez de dependerem exclusivamente de estimativas pontuais e de valores de p, os modelos bayesianos geram distribuições posteriores que incorporam tanto a informação empírica quanto pressupostos explicitamente definidos por meio de distribuições a priori. Essa estrutura oferece vantagens particulares em contextos caracterizados por heterogeneidade substancial e por tamanhos amostrais variáveis, como ocorre na literatura de neuroimagem estrutural no CUD, especialmente em modelos de efeitos aleatórios (Röver, 2020). Além disso, a possibilidade de regularização por meio de priors contribui para estabilizar estimativas extremas e reduzir a influência desproporcional de estudos individuais (Gelman et al., 2007), promovendo inferências mais robustas e transparentes quanto ao grau de incerteza envolvido. Ao permitir a quantificação explícita da incerteza e a comparação direta entre modelos, a abordagem bayesiana favorece uma interpretação mais gradual e probabilística das evidências, alinhada à natureza cumulativa e heterogênea da pesquisa em neuroimagem psiquiátrica (Van de Schoot et al., 2014).

Paralelamente, técnicas baseadas em coordenadas, como o Activation Likelihood Estimation (ALE), foram utilizadas para avaliar a convergência espacial das alterações estruturais entre amostras independentes (Li et al., 2022; Pando-Naude et al., 2021). A integração dessas abordagens permite avaliar não apenas a magnitude média dos efeitos, mas também sua consistência espacial e estabilidade inferencial.

O ALE é uma técnica de metanálise baseada em coordenadas que modela espacialmente a convergência de picos observados em estudos independentes, estimando a probabilidade de ativação ou de alteração estrutural em regiões específicas do cérebro a partir da sobreposição estatística desses focos (Eickhoff et al., 2009; Turkeltaub et al., 2012). Em vez de sintetizar

tamanhos de efeito, o ALE avalia a consistência espacial das evidências reportadas e é particularmente útil em contextos em que os dados completos de mapas estatísticos não estão disponíveis. Entretanto, essa abordagem apresenta limitações conhecidas, incluindo a dependência do relato seletivo de coordenadas significativas, a impossibilidade de incorporar diretamente magnitudes de efeito e as restrições à modelagem de moderadores clínicos e metodológicos. Em metanálises prévias sobre transtornos por uso de substâncias e CUD, tais limitações podem ter contribuído para divergências quanto ao envolvimento subcortical e à extensão das alterações estruturais. Nesse contexto, a integração do ALE com modelos meta-analíticos baseados em tamanhos de efeito permite combinar a avaliação da magnitude média dos efeitos com a análise de sua convergência espacial, promovendo inferências mais abrangentes e robustas acerca da organização neuroanatômica do transtorno.

Adicionalmente, incorporamos moderadores clinicamente relevantes, incluindo a via de administração, comorbidades psiquiátricas e o uso de múltiplas substâncias, com o objetivo de examinar como a variabilidade metodológica e clínica se associa à magnitude e à distribuição das alterações estruturais no CUD. Em vez de testar uma hipótese confirmatória restrita, esta metanálise foi concebida para identificar padrões estruturais que se mantêm consistentes diante de delineamentos heterogêneos e de diferentes apresentações clínicas, contribuindo para o refinamento da caracterização neuroanatômica do CUD e ampliando a robustez e a interpretabilidade translacional dos achados prévios.

Ao integrar modelagem multinível, inferência bayesiana e análise de convergência espacial por ALE, o presente estudo propõe uma abordagem metodológica capaz de enfrentar simultaneamente a heterogeneidade estatística, a variabilidade clínica e as limitações de relato observadas na literatura sobre neuroimagem estrutural no CUD. Essa estratégia permite não apenas estimar a magnitude média das diferenças estruturais, mas também avaliar sua consistência espacial e estabilidade sob diferentes configurações clínicas e metodológicas. A partir desse arcabouço, delineiam-se os objetivos específicos desta investigação, orientados pela necessidade de produzir uma síntese quantitativa mais robusta, integrada e clinicamente informativa das alterações cerebrais associadas ao CUD.

2 OBJETIVOS

2.1 Objetivo geral

2.1.1 Investigar padrões consistentes de alterações estruturais córtico-subcorticais em indivíduos com CUD, integrando abordagens meta-analíticas avançadas para superar as limitações metodológicas da literatura prévia.

2.2 Objetivos específicos

2.2.1 Quantificar diferenças nas medidas de GM cortical e subcortical entre indivíduos com CUD e HC, por meio de metanálises multinível de efeitos aleatórios.

2.2.2 Investigar a influência de variáveis metodológicas e clínicas na heterogeneidade dos tamanhos de efeito observados.

2.2.3 Avaliar o impacto potencial de viés de publicação e de relato seletivo por meio de modelagem hierárquica bayesiana com imputação de regiões não reportadas.

2.2.4 Examinar a convergência espacial dos achados estruturais por meio de uma metanálise baseada em coordenadas (ALE).

2.2.5 Integrar os resultados das diferentes abordagens analíticas, a fim de estabelecer um referencial neuroanatômico consistente para o CUD.

3 MÉTODOS

3.1 Estratégia de busca na literatura

Foi conduzida uma revisão sistemática de acordo com as diretrizes do PRISMA (Page et al., 2021; "PRISMA 2020 statement", *[S.d.]*), com um protocolo definido *a priori* e previamente registrado na plataforma PROSPERO (CRD42024585260). As bases de dados Embase, MEDLINE, Web of Science e PsycINFO foram pesquisadas para identificar estudos publicados até agosto de 2024.

As estratégias de busca foram construídas a partir de três domínios conceituais: (1) CUD, (2) neuroimagem estrutural e (3) neuroanatomia. Os termos relacionados ao CUD incluíram "*cocaine use disorder*", "*cocaine dependence*" e "*cocaine addiction*". Os termos referentes à neuroimagem estrutural incluíram "*structural MRI*", "*voxel-based morphometry*", "*VBM*", "*cortical thickness*", "*surface area*" e "*gray matter*". Os termos neuroanatômicos incluíram "*brain*", "*cortex*", "*subcortical*" e descritores anatômicos relacionados. Dentro de cada domínio, os termos foram combinados pelo operador booleano "*OR*", e os diferentes domínios foram combinados pelo operador "*AND*".

3.2. Critérios de elegibilidade

Foram incluídos estudos que relataram dados originais em artigos completos e utilizaram MRI para comparar a GM (volume, CT ou área de superfície) entre indivíduos com CUD e HC.

Para inclusão, os estudos deveriam apresentar resultados quantitativos de neuroimagem estrutural, incluindo estimativas de tamanho de efeito ou informações estatísticas suficientes para o cálculo dessas estimativas (por exemplo, médias e desvios-padrão ou estatísticas de teste). Para as análises baseadas em coordenadas, os estudos deveriam relatar coordenadas estereotáxicas (x, y, z), definidas em espaços padronizados (MNI ou Talairach), derivadas de análises de cérebro inteiro. Esses critérios garantiram a inclusão de estudos com comparações quantitativas relevantes, baseadas em métodos robustos de neuroimagem, o que aumentou a validade e a comparabilidade das análises. Foram excluídos relatos qualitativos, revisões narrativas, resumos de congresso e estudos que apresentaram apenas descrições qualitativas ou dados quantitativos não extraíveis.

A extração dos dados foi realizada em duplicata por revisores independentes, com a participação de três revisores no processo. Em cada estudo, a extração foi realizada por dois

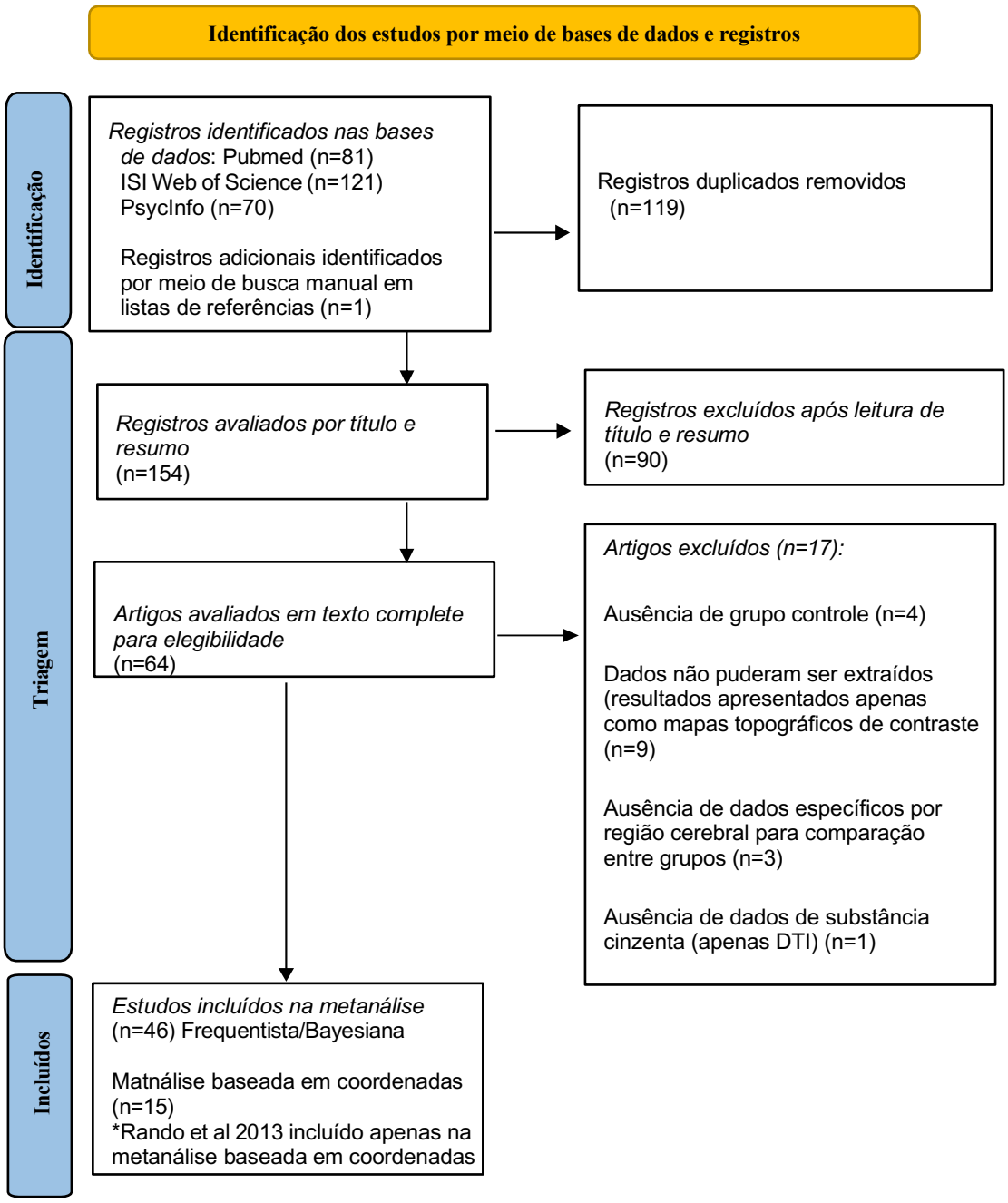
revisores independentes, com um terceiro revisor responsável pela resolução de eventuais discordâncias.

Para maximizar a inclusão de dados e manter a comparabilidade entre as análises, adotou-se uma abordagem em camadas. Estudos com estatísticas completas de comparação entre grupos (por exemplo, valores de t, p ou tamanhos de efeito) foram incluídos tanto nas análises frequentistas quanto nas bayesianas. Estudos que relataram apenas coordenadas estereotáxicas, sem estatísticas resumidas, foram incluídos exclusivamente na metanálise baseada em coordenadas (ALE), permitindo o uso da informação espacial sem introduzir estatísticas incompletas nas análises de tamanho de efeito. Como exemplo, o estudo de Rando et al. forneceu apenas coordenadas, sem estatísticas de teste, e foi incluído apenas na análise ALE (Rando et al., 2013).

A **Figura 1** resume o processo de seleção dos estudos, conforme o PRISMA 2020 (Page et al., 2021; "PRISMA 2020 flow diagram", *[S.d.]*; "PRISMA 2020 statement", *[S.d.]*). Durante a triagem por títulos e resumos, foram excluídos registros que claramente não atendiam aos critérios de elegibilidade, incluindo publicações não originais (revisões ou editoriais), estudos em modelos não humanos, estudos que não envolviam CUD ou que não reportavam desfechos de neuroimagem estrutural.

No total, 273 registros foram identificados (PubMed: 81; ISI Web of Science: 121; PsycINFO: 70; revisão de referências: 1). Após a remoção de 119 duplicatas, 154 registros foram avaliados por título e resumo, dos quais 90 foram excluídos. Sessenta e quatro artigos em texto completo foram analisados, e 17 foram excluídos por motivos como tipo de publicação, indisponibilidade de acesso ou informações amostrais insuficientes. Ao final, 47 estudos foram incluídos nesta revisão, sendo 46 utilizados nas metanálises frequentistas e bayesianas e 15 na metanálise baseada em coordenadas (ALE).

Figura 1. Diagrama de fluxo PRISMA 2020 do processo de seleção de estudos para a metanálise.



Legenda. Fluxograma ilustrando o processo de identificação, triagem, avaliação de elegibilidade e inclusão dos estudos na revisão sistemática e metanálise de achados de neuroimagem estrutural em indivíduos com CUD. O diagrama resume o número de registros identificados nas buscas em bases de dados, a remoção de duplicatas, os artigos avaliados em texto completo e os estudos incluídos nas análises quantitativas e baseadas em coordenadas, seguindo as diretrizes PRISMA 2020.

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3.3. Extração de dados

As variáveis extraídas incluíram informações demográficas, como número de participantes, idade média, média de anos de escolaridade dos grupos CUD e controle e proporção de participantes do sexo masculino no grupo CUD. Para controlar diferenças entre os grupos, foram calculados o delta de idade (idade média do grupo CUD menos a idade média do grupo controle) e o delta de escolaridade (média de anos de escolaridade do grupo CUD menos a média do grupo controle).

Os dados clínicos extraídos incluíram a via de administração da cocaína, o momento da avaliação em estudos longitudinais, distinguindo avaliações na linha de base e de seguimento após períodos de abstinência ou de tratamento, a duração do uso de cocaína e a presença de comorbidades psiquiátricas e médicas. A duração do uso de cocaína foi quantificada em anos, e a via de administração foi categorizada em intranasal, intravenosa ou fumada; estas duas últimas foram agrupadas devido à baixa representatividade amostral e à maior rapidez de absorção em comparação à via intranasal (Hatsukami; Fischman, 1996).

Dada a elevada heterogeneidade na descrição das comorbidades entre os estudos e o número limitado de delineamentos longitudinais, essas variáveis foram integradas por meio da criação de um indicador amostral de gravidade clínica das manifestações de CUD. Apresentações clínicas menos graves foram definidas como aquelas provenientes de amostras sem comorbidades psiquiátricas ou médicas relevantes ou, no caso de estudos longitudinais, de avaliações de seguimento nas quais os participantes apresentaram sintomas de abstinência mais leves e abstinência sustentada. Em contraste, apresentações clínicas mais graves foram caracterizadas pela presença de comorbidades psiquiátricas (por exemplo, transtorno de déficit de atenção e hiperatividade, depressão maior, dependência de álcool ou de cannabis) ou médicas (por exemplo, HIV+) em pelo menos 50% da amostra ou, em estudos longitudinais, por avaliações de linha de base associadas a sintomas de abstinência mais intensos e a períodos de abstinência mais curtos. O uso de nicotina não foi considerado moderador nas análises quantitativas. Embora seja altamente prevalente em indivíduos com CUD, a exposição à nicotina foi definida e reportada de forma inconsistente entre os estudos incluídos, sendo frequentemente tratada como uma característica basal da amostra, e não como um transtorno por uso de substância comórbido. Além disso, a limitada variabilidade entre os estudos e a elevada heterogeneidade na mensuração do uso de nicotina inviabilizaram sua integração confiável como variável moderadora. Em contraste, o uso de álcool e de cannabis apresentou

maior variabilidade e relatos mais consistentes entre os estudos, o que permitiu sua inclusão nas análises de moderação.

Essa estratificação é sustentada pela literatura empírica, que demonstra que usuários de cocaína com comorbidades psiquiátricas, como transtornos de humor ou transtornos de ansiedade, apresentam consistentemente maiores taxas de recaída e menores durações de abstinência quando comparados a usuários sem essas comorbidades (Palazón-Llecha et al., 2024). Estudos de coorte de grande porte reforçam essa associação, evidenciando que a presença de comorbidades psiquiátricas e condições médicas está relacionada com menor tempo até à recaída e maiores taxas de abandono do tratamento para o CUD (Andersson; Wenaas; Nordfjærn, 2019; Gómez Pérez et al., 2025). Além disso, transtornos afetivos comórbidos e o uso concomitante de outras substâncias, como benzodiazepínicos ou álcool, têm sido associados a maior vulnerabilidade à recaída (Wang et al., 2021). Por fim, indivíduos que apresentam sintomas de abstinência mais intensos na linha de base, avaliados por meio de instrumentos padronizados (por exemplo, a Cocaine Selective Severity Assessment – CSSA), demonstram probabilidade significativamente menor de manter abstinência contínua ao longo do tempo (Palazón-Llecha et al., 2024). Em conjunto, esses achados validam o uso da carga de comorbidades e da gravidade dos sintomas de abstinência como marcadores clinicamente relevantes para distinguir apresentações de menor e maior gravidade na presente metanálise.

Os descritores de neuroimagem incluíram a estratégia analítica empregada (análises de cérebro inteiro ou baseadas em regiões de interesse), o desfecho morfométrico derivado da MRI (volume de GM, CT ou área de superfície), o hemisfério cerebral e o rótulo anatômico reportado pelos autores. O mesmo estudo foi elegível para contribuir com mais de uma entrada de tamanho de efeito ao apresentar resultados de múltiplas regiões cerebrais, quando os participantes foram estratificados por características clínicas (por exemplo, presença ou ausência de comorbidades) ou por sexo, ou ao incluir avaliações longitudinais por MRI. Nos delineamentos longitudinais, cada ponto temporal foi tratado como uma entrada independente no conjunto de dados. Diferentes métricas morfométricas (volume, espessura cortical e área de superfície) foram incluídas e modeladas como moderadoras nas análises meta-analíticas.

Foram incluídos nesta metanálise tanto estudos baseados em análises de cérebro inteiro quanto em regiões de interesse (ROI). A inclusão de delineamentos ROI justifica-se pelo fato de que esses estudos frequentemente investigam regiões cerebrais diretamente implicadas nos mecanismos da dependência, como o córtex pré-frontal, o estriado e áreas límbicas, e a integração de ambos os tipos de abordagens amplia a base de evidências disponível, permitindo uma avaliação mais abrangente das alterações estruturais associadas ao uso de cocaína. Para

garantir transparência metodológica e reduzir potenciais vieses, a estratégia analítica empregada (cérebro inteiro ou ROI) foi registrada como um descritor para cada tamanho de efeito e considerada nas análises de heterogeneidade. Essa abordagem é consistente com metanálises prévias de neuroimagem em transtornos por uso de substâncias, que demonstram que a incorporação de dados provenientes de ROI contribui para maior cobertura anatômica e para o controle de diferenças metodológicas entre os estudos (Dang et al., 2022; Ersche et al., 2013; Hall et al., 2015, p. 20)(Dang et al., 2022; Ersche et al., 2013; Hall et al., 2015). As características de delineamento e os dados de neuroimagem dos estudos incluídos estão resumidos no **APÊNDICE A**.

3.4. Desfechos

Para cada comparação incluída, foram extraídos, quando disponíveis, a média e o desvio-padrão (DP) das métricas de neuroimagem para os grupos com CUD e HC. Quando apenas erros-padrão foram reportados, estes foram convertidos em desvios-padrão por meio da multiplicação pelo tamanho da amostra ao quadrado. Nos casos em que médias e desvios-padrão, ou estimativas de erro, estavam disponíveis apenas em formato gráfico (por exemplo, gráficos de barras), os valores foram extraídos com o software GetData Graph Digitizer (versão 2.26.0.20, © S. Fedorov) (Fedorov, *[S.d.]*). Quando estatísticas descritivas não estavam disponíveis, foram coletadas estatísticas de teste do tipo t ou z, assumindo-se distribuição normal. Nos casos em que apenas valores de p foram reportados, estes foram registrados para posterior estimativa dos tamanhos de efeito. Além disso, quando disponíveis em estudos baseados em análises voxel-wise de cérebro inteiro, foram extraídas as coordenadas estereotáxicas dos picos significativos (x, y, z). Todos os rótulos anatômicos foram posteriormente mapeados para regiões do atlas cortical de Desikan–Killiany (aparc) (Desikan et al., 2006) ou para o atlas de segmentação subcortical automática (aseg) (Fischl et al., 2002), conforme implementado no pacote ggseg (versão 1.6.6) (Mowinckel; Vidal-Piñeiro, 2020).

Esses procedimentos garantiram a padronização dos desfechos e a maximização da informação disponível para análises quantitativas e baseadas em coordenadas.

3.5. Análise dos dados

Os tamanhos de efeito (d de Cohen) e suas respectivas variâncias amostrais foram calculados por meio da função escalc() do pacote metafor (versão 0.5-7) (Viechtbauer, 2010), no ambiente R versão 4.2.0 (“R Core Team (2022) R A Language and Environment for

Statistical Computing. R Foundation for Statistical Computing, Vienna. - References - Scientific Research Publishing", *[S.d.]*). Considerando que os estudos incluídos puderam contribuir com múltiplas entradas de tamanho de efeito, empregou-se um modelo de metanálise multinível de efeitos aleatórios, utilizando a função rma.mv() (Viechtbauer, 2010). Esse modelo incorporou dois níveis hierárquicos, com entradas de tamanho de efeito aninhadas aos respectivos estudos, permitindo o tratamento simultâneo da variabilidade intraestudo e interestudo. A ponderação das estimativas foi realizada com base no método de variância inversa, incorporando a variância amostral e a variância entre estudos estimada (τ^2). Todas as análises foram conduzidas separadamente para os conjuntos de dados corticais e subcorticais.

Inicialmente, foram conduzidas meta-regressões univariadas para investigar a influência de fatores metodológicos e demográficos na heterogeneidade observada. As variáveis avaliadas incluíram o desfecho morfométrico, o método analítico (cérebro inteiro ou ROI), o hemisfério cerebral, o delta de idade, o delta de escolaridade e a proporção de participantes do sexo masculino, com a heterogeneidade avaliada por meio da estatística Q e de seus respectivos valores de p. Em seguida, foram examinadas características clínicas das amostras com CUD, incluindo a duração do uso, a principal via de administração e a classificação da apresentação clínica em menor ou maior gravidade, como potenciais moderadores. Por fim, os modelos multivariados incluíram a região cerebral (ggseg_region) (Mowinckel; Vidal-Piñeiro, 2020) e os moderadores que se mostraram estatisticamente significativos nas análises univariadas. A proporção de heterogeneidade explicada foi estimada pelo pseudo-R^2.

Diante do viés inerente à literatura de neuroimagem, particularmente em estudos baseados em análises de cérebro inteiro que tendem a reportar apenas regiões com diferenças estatisticamente significativas entre grupos, foi conduzida uma metanálise bayesiana multinível como análise de sensibilidade, utilizando o pacote brms (Bürkner, 2017, 2018). Para esse fim, estudos que empregaram estratégias de análise de cérebro inteiro, mas não reportaram achados nulos, tiveram entradas imputadas para todas as regiões anatômicas não explicitamente documentadas. Essas regiões foram incorporadas ao conjunto de dados com tamanhos de efeito e variâncias ausentes. O modelo bayesiano espelhou a estrutura do modelo frequentista, adotando priors fracamente informativos para os efeitos regionais padronizados do CUD e priors exponenciais para os componentes de variância. Foram utilizados priors centrados em zero (0, 0,3 ou 0, 1,0), refletindo uma suposição conservadora de que a maioria dos efeitos verdadeiros em estudos de neuroimagem, especialmente nas comparações não reportadas, tende a ser de pequena magnitude. Embora evidências biológicas prévias sugiram reduções de volume, CT e área de superfície associadas ao CUD, optou-se deliberadamente por priors

neutros, a fim de evitar a introdução de viés direcional na estimação de dados ausentes. O modelo incluiu efeitos fixos para a região anatômica (ggseg_region), bem como para moderadores metodológicos e amostrais previamente identificados como significativos, e interceptos aleatórios nos níveis de estudo (Study_ID) e de entrada (Entry_ID), de modo a refletir a estrutura hierárquica dos dados. O código completo das análises está descrito no **APÊNDICE E**.

Na etapa final, foi conduzida uma metanálise baseada em coordenadas, restrita a estudos que reportaram coordenadas estereotáxicas (x, y, z) provenientes de comparações voxel-wise de cérebro inteiro. Para estudos que forneceram focos derivados de morfometria baseada em voxel (VBM), utilizou-se o software GingerALE (versão 3.0.1) (Frahm et al., 2023; Turkeltaub et al., 2002). Quando necessário, as coordenadas originalmente reportadas no espaço Talairach foram convertidas para o espaço MNI por meio da transformação de Lancaster (icbm2tal) (Lancaster et al., 2007). Considerou-se um número mínimo de 14 experimentos para a realização da análise, conforme recomendado, a fim de garantir limiares de significância corrigidos pelo erro familiar (FWE) e reduzir a probabilidade de que clusters significativos sejam impulsionados por estudos isolados. Quando múltiplos contrastes ou focos sobrepostos foram reportados a partir da mesma amostra, o contraste principal de cérebro inteiro foi mantido, comparando indivíduos com CUD e HC, geralmente correspondente à comparação de maior tamanho amostral.

A metanálise ALE foi conduzida por meio de um algoritmo de efeitos aleatórios, que considera a incerteza associada ao tamanho amostral de cada experimento (Eickhoff et al., 2009). Para cada conjunto de focos, foram gerados mapas de ativação modelada (Modeled Activation – MA), utilizando uma máscara anatômica, as coordenadas dos focos e uma suavização gaussiana com largura à meia-altura (Full-Width at Half Maximum – FWHM) empiricamente derivada do tamanho amostral. A imagem final de ALE foi obtida como a união de todos os mapas de MA. A distribuição nula da estatística ALE foi determinada por meio de um método analítico (Eickhoff et al., 2012), e a significância estatística foi avaliada com um limiar corrigido por erro familiar (FWE) de $p < 0,05$, com base em 5.000 permutações. Aplicou-se um volume mínimo de cluster de 1 mm^3 ao mapa ALE final.

3.6. Avaliação da qualidade metodológica e risco de viés

Para assegurar uma avaliação sistemática e transparente da qualidade metodológica dos estudos incluídos, adotou-se um instrumento composto por 10 itens, inspirado em recomendações previamente estabelecidas para metanálises de neuroimagem (Müller et al.,

2018), conforme detalhado no **APÊNDICE B**. Esse instrumento abrangeu domínios metodológicos centrais, incluindo a acurácia do diagnóstico do CUD (por meio de avaliação clínica ou instrumentos validados), a caracterização rigorosa dos grupos controle (com rastreio de outros transtornos psiquiátricos ou neurológicos), o relato explícito da principal via de administração da cocaína, a documentação clara do status de tratamento ou de abstinência no momento da aquisição das imagens de neuroimagem e o relato de comorbidades psiquiátricas, com estimativas de prevalência ou análises por subgrupos.

Adicionalmente, o instrumento contemplou a descrição adequada dos dados demográficos (idade, sexo, escolaridade e lateralidade), o controle estatístico dessas variáveis e de outros potenciais fatores de confusão clínica nas análises de neuroimagem, o uso de delineamentos longitudinais, quando disponíveis, e a divulgação completa dos achados de neuroimagem, incluindo resultados não significativos. Cada estudo foi avaliado conforme esses critérios, permitindo quantificar o rigor metodológico, identificar potenciais fontes de viés e fortalecer a interpretação dos achados da presente metanálise. Os escores de qualidade foram utilizados para caracterização metodológica dos estudos e para apoiar a interpretação dos resultados, não sendo empregados como pesos adicionais nas análises quantitativas.

4 RESULTADOS

4.1 Associações de variáveis metodológicas e clínicas com achados estruturais de neuroimagem

A **Tabela 1** resume as associações entre variáveis metodológicas e clínicas e a heterogeneidade dos tamanhos de efeito dos achados de neuroimagem nas comparações entre indivíduos com CUD e HC. Para os dados corticais, o delta de idade ($p = 0,02$) e a proporção de participantes do sexo masculino ($p = 0,03$) explicaram significativamente a heterogeneidade observada nas metanálises. Esses resultados indicam que estimativas de tamanho de efeito mais negativas foram observadas quando o grupo CUD era, em média, mais velho do que o grupo controle. Em contraste, amostras com maior proporção de participantes do sexo masculino no grupo CUD apresentaram diferenças de menor magnitude entre os grupos quanto à CT, à área de superfície e ao volume.

Tabela 1. Teste dos efeitos de variáveis metodológicas e clínicas sobre os tamanhos de efeito.

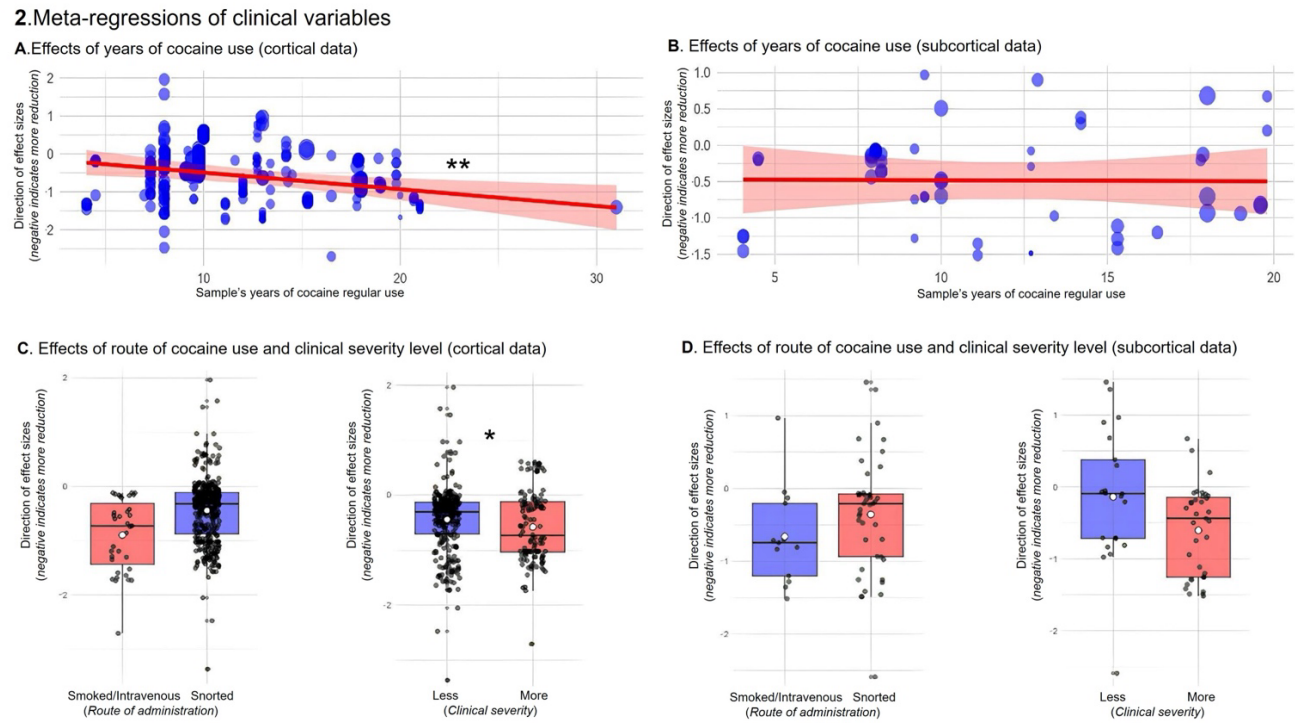
Conjunto de dados corticais							Conjunto de dados subcorticais					
	K (amostras)	Estimativas	EP	95% IC	Q-test *p*-val	pR^2	*K* (amostras)	Estimativas	EP	95% IC	Q-test *p*-val	pR^2
Desfecho morfométrico	419				0.138	-	56				-	-
Volume (referência)	230				-		56				-	
Área	21	+0.113	0.09	-0.08 to 0.30	0.256							
Espessura	168	-0.052	0.04	-0.14 to 0.03	0.242							
Tipo de análise	419				0.182	-	56				0.226	-
ROI (referência)	175				-		38				-	
Whole brain	244	-0.267	0.20	-0.66 to 0.12	0.182		18	-0.366	0.30	-0.96 to 0.22	0.226	
Hemisfério	419				0.122	-	56				0244	-
Bilateral (referência)	96				-		18				-	
Esquerdo	145	-0.225	0.14	-0.49 to 0.04	0.108		18	-0.492	0.29	-1.06 to 0.08	0.094	
Direito	178	-0.263	0.13	-0.53 to 0.01	0.059		20	-0.436	0.28	-0.99 to 0.12	0.127	
Delta de idade[ca]	408	**-0.057**	**0.02**	**-0.10 to 0.01**	**0.027**	4.1%	53	+0.021	0.03	-0.05 to 0.09	0.568	-
Delta de escolaridade[cb]	399	+0.059	0.07	-0.07 to 0.19	0.399	-	47	-0.048	0.01	-0.26 to 0.16	0.661	-
Sexo masculino (%)[cd]	414	**+0.005**	**0.01**	**0.00 to 0.01**	**0.032**	4.0%	54	-0.001	0.01	-0.03 to 0.01	0.349	-
Anos de uso de cocaína	410	**-0.0371**	**0.01**	**-0.07 to -0.01**	**0.020**	9.8%	53	-0.001	0.02	-0.05 to 0.04	0.904	-
Via de uso de cocaína	419				0.291	-	56				0.458	-
Intranasal (referência)	384				-		43				-	
Fumada or Intravenosa	35	-0.1406	0.26	-0.66 to 0.37	0.291		13	-0.1294	0.34	-0.80 to 0.54	0.458	
Nível de gravidade clínica	419				0.046	1.5%	56				0.288	-
Menor	294				-		21				-	
Maior	125	**-0.1861**	**0.13**	**-0.58 to -0.07**	**0.046**		35	-0.3012	0.25	-0.80 to 0.20	0.458	

Legenda. Meta-regressões e comparações entre subgrupos. Estimativas negativas do coeficiente indicam diferenças entre grupos (isto é, maior redução associada ao CUD. c = variável contínua. a (delta de idade) = média de idade do grupo CUD menos a média de idade do grupo controle (valores positivos indicam que o grupo CUD é mais velho; negativos, que o grupo controle é mais velho). b (delta de escolaridade) = média de anos de escolaridade do grupo CUD menos a média do grupo controle (valores positivos indicam maior escolaridade no grupo CUD). d = porcentagem de homens no grupo CUD. pR^2 = pseudo-R^2 indicando a proporção de heterogeneidade explicada para cada modelo significativo.

Não foram observadas associações estatisticamente significativas entre o tipo de desfecho morfométrico (espessura, área de superfície ou volume), o tipo de análise (regiões de interesse versus cérebro inteiro), o hemisfério cerebral (bilateral, esquerdo ou direito) e o nível de escolaridade, nem heterogeneidade nas metanálises corticais e subcorticais. No entanto, observou-se uma tendência a diferenças de maior magnitude entre os grupos no hemisfério direito na metanálise de CT ($p = 0,059$). Dessa forma, o hemisfério cerebral foi mantido nas análises subsequentes de metarregressão, juntamente com o delta de idade e a proporção de participantes do sexo masculino.

No que se refere às variáveis clínicas, a **Figura 2** resume essas análises, e as estimativas completas das metarregressões estão apresentadas na **Tabela 1**. O número de anos de uso de cocaína explicou significativamente a heterogeneidade na metanálise cortical ($Q = 7,44$; $p = 0,02$; Fig. 2A), mas não na metanálise subcortical ($Q = 0,01$; $p = 0,90$; Fig. 2B). Esse resultado indica que maior duração do uso de cocaína esteve associada a estimativas de tamanho de efeito cortical mais negativas e de maior magnitude (coeficiente = -0,037; erro = 0,017; pseudo-R^2 = 9,84%). O fator nível clínico também se associou significativamente à heterogeneidade na análise cortical ($Q = 3,96$; $p = 0,046$; Fig. 2C), mas não na metanálise subcortical ($Q = 1,12$; $p = 0,288$; Fig. 2D). Amostras caracterizadas por maior gravidade clínica, incluindo níveis mais elevados de sintomas relacionados à abstinência e maior prevalência de comorbidades psiquiátricas (por exemplo, transtorno de déficit de atenção e hiperatividade, depressão maior, dependência de álcool ou de cannabis) ou médicas (por exemplo, HIV+), apresentaram estimativas de tamanho de efeito cortical mais negativas e de maior magnitude (coeficiente = -0,186; erro = 0,093; pseudo-R^2 = 1,53%). Em análise post hoc restrita às amostras com apresentações clínicas mais graves, não foram observadas diferenças significativas entre características relacionadas a outros transtornos por uso de substâncias, principalmente as referidas como transtorno por uso de álcool e transtorno por uso de cannabis, e outras comorbidades psiquiátricas ou médicas quanto aos tamanhos de efeito corticais ($Q = 0,12$; $p = 0,727$). Adicionalmente, embora a principal via de administração da cocaína (isto é, intranasal versus fumada ou intravenosa) não tenha explicado significativamente a heterogeneidade (dados corticais: $Q = 1,11$; $p = 0,291$; dados subcorticais: $Q = 0,55$; $p = 0,458$), ambas as análises indicaram tendência a estimativas de tamanho de efeito mais negativas e de maior magnitude quando o uso intranasal não foi a via predominante de administração.

Figura 2. Meta-regressões de variáveis clínicas



4.2 Diferenças de GM entre grupos nas regiões cerebrais no CUD

A **Figura 3** resume as metanálises das segmentações regionais corticais e subcorticais. Essas metanálises incluíram a variável moderadora correspondente às regiões mapeadas pelo ggseg, além do hemisfério cerebral, do delta de idade e da proporção de participantes do sexo masculino. Volume, CT e área de superfície foram agrupados na análise primária do subconjunto cortical (k = 419). As estimativas meta-analíticas para cada região mapeada, juntamente com o número correspondente de observações, estão apresentadas no **APÊNDICE C**. Os tamanhos de efeito disponíveis variaram de 5 (por exemplo, bankssts, polo frontal, paracentral, pericalcarino e giro temporal transverso) a 37 (pars triangularis). A **Figura 3A** destaca as regiões corticais com diferenças estatisticamente significativas ($p < 0,05$) em comparação com a região de referência, o polo temporal, que foi a única a apresentar um coeficiente positivo. Esse resultado indica que o giro temporal superior, o giro frontal médio-rostral, o giro occipital-lateral, o giro frontal superior, o giro temporal inferior (ITG), o giro fusiforme, o OFC lateral e o giro temporal médio apresentaram diferenças entre os grupos, mais negativas e de maior magnitude, nas medidas corticais. Destaca-se que o ITG e o giro frontal médio-rostral apresentaram estimativas de tamanho de efeito negativo de maior magnitude ($p < 0,001$). Esse modelo explicou 10,6% da heterogeneidade total ($p < 0,0001$).

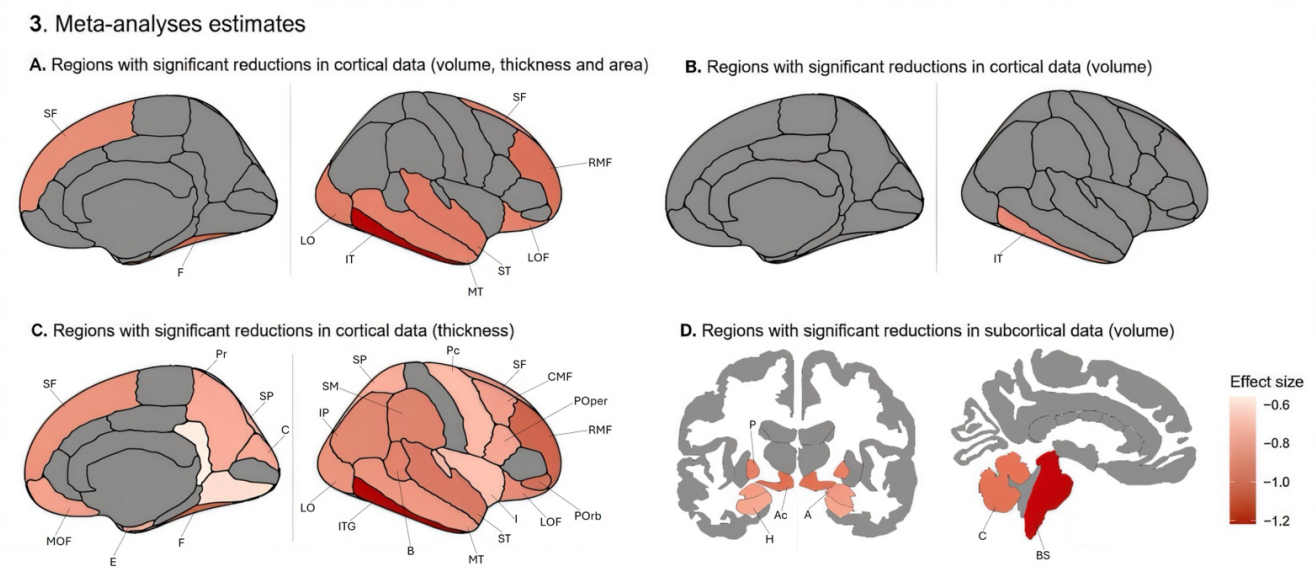
Embora o desfecho morfométrico cortical não tenha explicado significativamente a heterogeneidade (**Tabela 1**), foram realizadas duas análises estratificadas, separadamente, para o volume (k = 230) e a CT (k = 168). Após ajuste para hemisfério cerebral, diferença de idade e proporção de participantes do sexo masculino, foram observadas associações negativas entre os participantes do grupo CUD e as medidas do ITG tanto nas análises volumétricas (estimativa = −0,293; EP = 0,119; p = 0,014) quanto nas análises de CT (estimativa = −1,111; EP = 0,240; $p < 0,001$). Notavelmente, o ITG foi a única região cerebral com diferenças estatisticamente significativas na análise volumétrica (**Fig. 3B**), enquanto diversas outras áreas apresentaram redução da CT (por exemplo, giro frontal médio rostral, pars triangularis, giro temporal médio, OFC lateral, giro frontal médio caudal, entre outras; **Fig. 3C**) em comparação com a região de referência, o polo temporal (dados completos no **APÊNDICE C**).

De modo semelhante, embora a variável tipo de análise não tenha explicado significativamente a heterogeneidade (Tabela 1), foram realizadas duas análises estratificadas, separadamente, para dados baseados em regiões de interesse (ROI; k = 175) e para dados de cérebro inteiro (whole-brain; k = 244) no conjunto cortical. Após ajuste para hemisfério cerebral, diferença de idade e proporção de participantes do sexo masculino, ambos os modelos

indicaram que o ITG apresentou estimativas de tamanho de efeito negativo de maior magnitude nas comparações entre indivíduos com CUD e HC (modelo ROI: estimativa = −1,284; EP = 0,233; $p < 0,001$; modelo cérebro inteiro: estimativa = −0,484; EP = 0,111; $p < 0,001$).

As estimativas subcorticais (k = 56) são apresentadas na **Figura 3D**. Os tamanhos de efeito disponíveis variaram de 2 (isto é, ventrículo lateral e tronco encefálico) a 15 (isto é, núcleo caudado) nas análises volumétricas (**APÊNDICE C**). A **Figura 3D** destaca as regiões subcorticais com diferenças estatisticamente significativas ($p < 0,05$) em comparação com a região de referência, o ventrículo lateral, que apresentou coeficiente positivo. Isso indica que a amígdala, o tronco encefálico, o cerebelo, o hipocampo, o globo pálido, o tálamo e o NA apresentaram estimativas de tamanho de efeito negativo de maior magnitude entre as regiões subcorticais, sendo que o tronco encefálico, o cerebelo e o NA exibiram as maiores diferenças entre os grupos ($p < 0,01$). Esse modelo explicou 3,1% da heterogeneidade total ($p = 0,024$). Para os dados subcorticais, não foram realizadas análises estratificadas por tipo de estudo (cérebro inteiro versus ROI) devido ao número reduzido de estudos na categoria de cérebro inteiro.

Figura 3. Estimativas das metanálises



4.3. Análise de sensibilidade utilizando abordagem bayesiana

Para avaliar a influência do relato seletivo e de dados escassamente observados em estudos baseados em análises de cérebro inteiro, o conjunto de dados corticais foi expandido de 419 tamanhos de efeito reportados para 1.769, por meio da imputação de tamanhos de efeito para regiões cerebrais não reportadas. No conjunto de dados subcortical, o número de tamanhos de efeito aumentou de 56 para 262. Essas entradas adicionais corresponderam a estudos que empregaram uma estratégia analítica de cérebro inteiro, mas não relataram todos os desfechos regionais. Os tamanhos de efeito ausentes e suas respectivas variâncias foram tratados como parâmetros desconhecidos e estimados em um arcabouço bayesiano.

O primeiro modelo bayesiano utilizou um prior Normal(0, 0,3), fracamente informativo, aplicado aos tamanhos de efeito padronizados, incorporando a expectativa de que a maioria dos efeitos verdadeiros seja de pequena magnitude e centrada em torno de zero, embora permita que efeitos moderados permaneçam plausíveis. Esse prior foi escolhido com o objetivo de promover uma regularização conservadora, parcialmente compensando potenciais vieses decorrentes do relato seletivo de efeitos estatisticamente significativos na literatura. Em regiões com dados limitados, esse prior tende a contrair as estimativas em direção a zero; por outro lado, em regiões com maior volume de dados, sua influência é comparativamente menor, conforme evidenciado pela similaridade com o modelo que utilizou um prior mais amplo. Para avaliar a robustez das conclusões em relação à escolha do prior, foi ajustado um segundo modelo empregando um prior Normal(0, 1,0) mais amplo para os tamanhos de efeito, o qual atribui probabilidade a priori substancial a efeitos positivos e negativos de maior magnitude, mantendo-se, contudo, centrado em zero.

A **Tabela 2** demonstra que, no primeiro modelo bayesiano, apenas duas regiões corticais — o ITG e o giro frontal médio-rostral — apresentaram forte evidência posterior de diferenças negativas entre os grupos, uma vez que seus intervalos de credibilidade se situaram inteiramente abaixo de zero. Os diagnósticos de convergência foram satisfatórios, com valores de $\hat{R}$ para todos os parâmetros amostrados variando entre 0,9997 e 1,0038 (mediana ≈ 1,0004), e tamanhos efetivos de amostra entre 2.084 e 3.789 para os efeitos aleatórios no nível de Study_ID e entre 3.310 e 5.398 para os efeitos aleatórios no nível de Entry_ID. Nenhuma região subcortical apresentou evidência semelhante sob essa especificação do modelo. Para o modelo subcortical, os diagnósticos de convergência também foram satisfatórios, com valores de $\hat{R}$ variando entre 0,9998 e 1,0022 (mediana ≈ 1,0003) e tamanhos efetivos de amostra entre 2.926

e 3.321 para Study_ID e entre 2.347 e 3.964 para Entry_ID. As estimativas posteriores completas encontram-se apresentadas no **APÊNDICE D**.

No modelo que utilizou o prior Normal(0, 1,0) mais amplo, o ITG e o giro frontal médio rostral voltaram a apresentar forte evidência posterior de diferenças negativas entre os grupos. Além disso, outras regiões corticais, incluindo o giro fusiforme, o giro orbitofrontal lateral e o giro temporal superior, também exibiram estimativas de tamanho de efeito negativas, com intervalos de credibilidade inteiramente abaixo de zero, associadas ao CUD. Em contrapartida, as regiões subcorticais não apresentaram, novamente, evidência clara de diferenças entre os grupos.

Tabela 2. Resultados da metanálise Bayesiana

Região cerebral	Narrow Prior (0, 0.3)				Wider Prior (0, 1.0)			
	Estimativa	EP	-95% CrI	+95% CrI	Estimativa	SE	-95% CrI	+95% CrI
Conjunto de dados corticais								
Giro fusiforme	-0,21	0,13	-0,47	0,04	**-0,46**	**0,19**	**-0,83**	**-0,07**
Giro temporal inferior	**-0,45**	**0,12**	**-0,63**	**-0,26**	**-0,69**	**0,17**	**-1,02**	**-0,36**
Giro occipital lateral	-0,13	0,12	-0,37	0,10	-0,36	0,18	-0,71	0,01
Córtex orbitofrontal lateral	-0,11	0,09	-0,29	0,06	**-0,33**	**0,16**	**-0,64**	**-0,01**
Giro temporal médio	-0,11	0,1	-0,32	0,08	-0,34	0,17	-0,67	0,01
Giro frontal médio rostral	**-0,22**	**0,09**	**-0,39**	**-0,05**	**-0,43**	**0,16**	**-0,74**	**-0,11**
Giro frontal superior	-0,08	0,08	-0,24	0,09	-0,29	0,16	-0,60	0,02
Giro temporal superior	-0,14	0,1	-0,34	0,06	**-0,37**	**0,17**	**-0,69**	**-0,03**
Conjunto de dados subcorticais								
Amígdala	-0,1	0,21	-0,51	0,30	-0,13	0,41	-0,92	0,66
Tronco encefálico	-0,23	0,25	-0,71	0,27	-0,58	0,45	-1,44	0,31
Cerebelo	-0,16	0,19	-0,52	0,21	-0,25	0,35	-0,36	1,02
Hipocampo	-0,05	0,21	-0,46	0,37	-0,05	0,41	-0,85	0,76
Pálido	-0,03	0,22	-0,46	0,40	-0,12	0,39	-0,89	0,64
Tálamo	0,03	0,22	-0,40	0,46	0,04	0,39	-0,73	0,83
Núcleo accumbens	-0,18	0,25	-0,66	0,30	-0,24	0,47	-1,16	0,69

Legenda: Metanálises bayesianas que incorporam tanto os tamanhos de efeito observados quanto os tamanhos de efeito ausentes imputados. Os valores apresentados correspondem às médias posteriores (Estimativa) e aos desvios-padrão posteriores (EP), acompanhados de intervalos de credibilidade de 95% (CrI). Coeficientes negativos indicam volumes cerebrais menores em indivíduos com CUD em comparação com controles. O painel esquerdo apresenta os resultados de um modelo com prior Normal(0, 0.3), fracamente informativo sobre os efeitos populacionais (“prior estreito”), enquanto o painel direito apresenta os resultados de um modelo com prior Normal(0, 1.0), mais amplo.

4.4. Análises complementares baseadas em coordenadas

Para examinar a convergência espacial entre estudos independentes, foi conduzida uma metanálise baseada em coordenadas, restrita aos 15 experimentos que reportaram coordenadas estereotáxicas de pico provenientes de comparações de morfometria baseada em voxel (VBM) de cérebro inteiro entre indivíduos com CUD e HC. Ao todo, 101 focos foram analisados por meio do algoritmo ALE implementado no software GingerALE (versão 3.0.1) (Eickhoff et al., 2009; Wang et al., 2021). A análise aplicou a correção por erro do tipo família (Family-Wise Error – FWE) com limiar de $p < 0,05$, utilizando 5.000 permutações e volume mínimo de cluster de 1 mm^3, em consonância com as recomendações estabelecidas para metanálises baseadas em coordenadas (Lancaster et al., 2007). O valor máximo de ALE obtido (0,017257173) não ultrapassou o limiar de significância corrigido pelo FWE (0,019126007); portanto, nenhum cluster sobreviveu à correção para múltiplas comparações. Assim, nenhuma região apresentou convergência espacial estatisticamente significativa das diferenças na GM entre as amostras com CUD.

5 DISCUSSÃO INTEGRATIVA

5.1 Integração entre achados corticais e subcorticais

Esta metanálise identificou diferenças negativas consistentes nas medidas de GM entre indivíduos com CUD e HC, particularmente nos córtices pré-frontais e temporais, regiões centrais para o controle executivo, a tomada de decisão, a regulação emocional e a reatividade a pistas associadas à droga (Pando-Naude et al., 2021; Volkow; Koob; McLellan, 2016; Volkow; Michaelides; Baler, 2019). Esses achados são congruentes com modelos que postulam comprometimento da regulação top-down e aumento da reatividade às pistas no contexto da dependência (Goldstein et al., 2009, 2010; Volkow; Koob, 2015), além de ampliarem as evidências de metanálises prévias que enfatizaram diferenças de grupo em regiões pré-frontais, temporais e límbicas (Dang et al., 2022; Ersche et al., 2013; Pando-Naude et al., 2021). Ao integrar a síntese tradicional de tamanhos de efeito, a inferência bayesiana e os métodos baseados em coordenadas (ALE), aumentamos a precisão espacial das estimativas, reduzimos o impacto do relato seletivo e fornecemos validação complementar entre abordagens analíticas distintas. Essa combinação fortalece a confiança na reprodutibilidade das diferenças de grupo observadas e ressalta sua potencial relevância para a geração de hipóteses e para futuras investigações de marcadores candidatos em neuroimagem e de circuitos com implicações para intervenções.

Um achado central desta metanálise foi que o ITG emergiu como a região cortical que apresentou as maiores e mais consistentes diferenças entre grupos entre indivíduos com CUD e HC. Após o ajuste por covariáveis metodológicas e características amostrais, o ITG permaneceu como a região com as estimativas de tamanho de efeito mais negativas e foi a única área cortical a demonstrar diferenças estatisticamente significativas entre os grupos tanto nas análises volumétricas quanto nas de CT. As estimativas negativas consistentes, também observadas nas análises bayesianas, reforçam a reprodutibilidade desse achado e indicam que o ITG constitui um correlato anatômico robusto na literatura de neuroimagem estrutural sobre CUD. Em termos conceituais, o ITG pode ser interpretado como um nó perceptivo-associativo relevante para o processamento de pistas e significados aprendidos, que tende a ser recrutado em estados de saliência motivacional (Goldstein et al., 2009; Miyashita, 1993); por isso, sua robustez sugere que é um alvo prioritário para hipóteses mecanísticas e estudos longitudinais.

Sob uma perspectiva neurobiológica, estudos experimentais e clínicos prévios sugerem que processos como desregulação glutamatérgica, estresse oxidativo e alterações na sinalização dopaminérgica podem ser particularmente relevantes para alterações em regiões corticais

caracterizadas por elevada plasticidade e alta demanda metabólica, como é o caso do ITG (Cunha-Oliveira; Rego; Oliveira, 2008; Dietrich et al., 2005; Goyal et al., 2014; Herculano-Houzel, 2011; Kalivas, 2004; Volkow; Koob; McLellan, 2016). Entretanto, considerando a natureza transversal dos dados disponíveis, tais mecanismos devem ser interpretados como modelos explicativos plausíveis, e não como vias causais diretas.

Nossas análises, baseadas no tamanho de efeito, identificaram índices reduzidos de substância GM nas regiões frontais e temporais. Entretanto, a metanálise baseada em coordenadas não identificou clusters que sobrevivessem à correção por erro familiar (FWE; $p < 0,05$; 5.000 permutações). O maior valor de ALE observado (0,017) foi inferior ao limiar corrigido (0,019), indicando uma sobreposição espacial insuficiente entre os estudos incluídos. Esse resultado provavelmente decorre do número limitado de estudos com dados baseados em coordenadas disponíveis (n = 15; 101 focos) e da inconsistência nos padrões de relato. Simulações indicam que pelo menos 14 experimentos são necessários para obter resultados de ALE confiáveis (Eickhoff et al., 2016); embora nossa amostra tenha ligeiramente ultrapassado esse número, a sensibilidade permaneceu limitada (Frahm et al., 2023). Metanálises anteriores com menos de 14 estudos também não identificaram resultados consistentes por meio de ALE em conjuntos de dados reduzidos (Dang et al., 2022; Ersche et al., 2013; Mackey et al., 2019; Pando-Naude et al., 2021). Além disso, muitos estudos de VBM relatam apenas clusters estatisticamente significativos e omitem resultados nulos, o que resulta em bases de dados menos abrangentes (Button et al., 2013; Eickhoff et al., 2017; Müller et al., 2018). Assim, a ausência de clusters convergentes provavelmente reflete o tamanho amostral limitado e o viés de relato, e não a inexistência de convergência espacial consistente (Nichols et al., 2017; Poldrack et al., 2017; Salimi-Khorshidi et al., 2009).

Esse achado é consistente com evidências de que o método ALE é sensível a amostras pequenas, à flexibilidade dos limiares estatísticos e à ausência de relatos completos de resultados nulos (Eklund; Nichols; Knutsson, 2016; Salimi-Khorshidi et al., 2009; Woo; Krishnan; Wager, 2014). Estudos futuros devem padronizar o relato de análises de cérebro inteiro, incluindo resultados não significativos, a fim de esclarecer os padrões espaciais das diferenças associadas ao CUD (Müller et al., 2018; Nichols et al., 2017; Poldrack et al., 2017; Turkeltaub et al., 2012)(Müller et al., 2018; Nichols et al., 2017; Poldrack et al., 2017; Turkeltaub et al., 2012).

5.2 Associação entre alterações estruturais e variáveis clínicas

Nas análises de moderação, a principal via de administração da cocaína não explicou a heterogeneidade entre os estudos, nem nos dados corticais (Q = 1,11; p = 0,291) nem nos subcorticais (Q = 0,55; p = 0,458). Ainda assim, as estimativas pontuais foram mais negativas na categoria não intranasal em ambos os conjuntos de dados, embora a incerteza associada tenha sido substancial. A interpretação desses achados é limitada pelo relato escasso e inconsistente: apenas 12 estudos do conjunto de dados relataram claramente a via de uso predominante entre os participantes **(APÊNDICE B)**, e poucos compararam diretamente diferentes vias em coortes equivalentes. Assim, as evidências atuais não sustentam diferenças consistentes específicas da via de administração no nível meta-analítico; entretanto, ressaltam a importância do relato padronizado da via de administração como variável-chave para estudos futuros com poder estatístico adequado.

Tentativas de examinar, de forma mais granular, diferenças por via de administração enfrentam limitações práticas relevantes no contexto do CUD, como a alta instabilidade social, a evasão do seguimento e a dificuldade de recontato, o que reduz a viabilidade de coortes comparativas com caracterização homogênea. Esses obstáculos, aliados ao relato incompleto nas amostras publicadas, contribuem para a baixa precisão das estimativas meta-analíticas desse moderador.

A utilização de diferentes métricas morfométricas, como volume, CT e área de superfície, pode ser interpretada tanto como uma limitação quanto como uma força do presente estudo. Por um lado, trata-se de uma fonte de heterogeneidade metodológica, uma vez que essas medidas capturam propriedades neuroanatômicas distintas e não são diretamente equivalentes entre si, o que pode introduzir variabilidade nos resultados e dificultar comparações diretas entre estudos. Por outro lado, essa mesma heterogeneidade representa uma força analítica, pois permite uma avaliação mais abrangente das alterações estruturais associadas ao CUD. Ao incorporar diferentes métricas e modelá-las como moderadores nas análises, o presente estudo buscou capturar múltiplas dimensões da morfologia cerebral, contribuindo para uma compreensão mais integrada e ecologicamente válida das alterações neuroanatômicas.

A gravidade clínica foi operacionalizada de forma ampla neste estudo, incorporando variáveis como padrão de uso, via de administração, presença de comorbidades e características clínicas reportadas nos estudos primários. Essa abordagem reflete uma limitação importante da literatura existente, na qual não há padronização na definição ou na mensuração da gravidade do transtorno por uso de cocaína. A decisão de adotar uma definição mais abrangente foi intencional e baseada em dois fatores principais. Primeiro, a heterogeneidade dos estudos incluídos inviabiliza a aplicação de um único critério uniforme de gravidade sem perda

substancial de dados. Segundo, o transtorno por uso de substâncias é um fenômeno multidimensional, no qual a gravidade não se limita à frequência ou à quantidade de uso, mas também envolve aspectos comportamentais, clínicos e contextuais. Dessa forma, optou-se por uma abordagem mais inclusiva, permitindo explorar a gravidade como um construto contínuo e multifacetado, ainda que isso introduza maior variabilidade nas análises.

Uma contribuição central desta metanálise foi a avaliação explícita de moderadores clinicamente relevantes. Os resultados indicam que maior gravidade clínica e maior duração do uso de cocaína estão associadas a estimativas de tamanho de efeito mais negativas para medidas corticais de GM, mas não para estruturas subcorticais. Esse padrão é consistente com estudos longitudinais e transversais prévios que reportaram associações entre uso prolongado de cocaína e menor CT ou volume, particularmente em regiões frontais e temporais, bem como evidências de normalização parcial após reduções sustentadas no consumo (Bittencourt et al., 2021; Crunelle et al., 2014; Hirsiger et al., 2019; Ide et al., 2014; McCurdy et al., 2024; Parvaz et al., 2017; Rothmann et al., 2024; Schinz et al., 2023).

O envolvimento preferencial de regiões corticais pode refletir diferenças na demanda metabólica e na plasticidade estrutural em comparação às regiões subcorticais, embora mecanismos causais não possam ser estabelecidos devido às limitações das evidências disponíveis (Clare et al., 2024; Du et al., 2021; Serra et al., 2023; Wang et al., 2025). Perfis clínicos mais graves, incluindo comorbidades psiquiátricas (por exemplo, depressão, transtorno de déficit de atenção e hiperatividade, transtornos por uso de álcool ou cannabis) e condições médicas, como infecção pelo HIV, estiveram associados a diferenças corticais de maior magnitude entre os grupos. Essa observação é consistente com estudos prévios que indicam que patologia dual e uso de múltiplas substâncias estão associados a piores desfechos clínicos e a diferenças estruturais mais pronunciadas em diferentes transtornos por uso de substâncias (Bachi et al., 2018; Haorah et al., 2025; Kroll et al., 2020; Meade et al., 2020; Stoychev, 2019; Tesselaar et al., 2025; Wakim et al., 2021).

Em conjunto, esses achados sugerem que diferenças estruturais cerebrais, gravidade clínica, comorbidades e uso de múltiplas substâncias coexistem como marcadores de um fenótipo clínico mais grave no CUD, em vez de refletirem efeitos isolados ou específicos do transtorno (Meyerhoff, 2017; Pando-Naude et al., 2021; Unterrainer et al., 2019). Notavelmente, análises post hoc não identificaram diferenças significativas entre comorbidades relacionadas ao uso de substâncias e outras comorbidades psiquiátricas ou médicas, indicando que a carga cumulativa de multimorbidade, e não categorias diagnósticas específicas, está associada a maior envolvimento cortical. Esses resultados ressaltam a necessidade de

delineamentos longitudinais para elucidar as trajetórias temporais e de ensaios clínicos que avaliem intervenções personalizadas ou multimodais para subgrupos de maior gravidade.

5.3 Implicações clínicas e translacionais

Entre as regiões identificadas, o ITG destacou-se como o achado cortical mais robusto desta metanálise, apresentando estimativas de tamanho de efeito negativas consistentes tanto nas análises volumétricas quanto nas de CT, além de evidência posterior forte e estável nos modelos bayesianos sob diferentes especificações de prior. Esse padrão é coerente com metanálises prévias que identificaram envolvimento consistente de regiões temporais e fronto-temporais no CUD (Dang et al., 2022; Mackey et al., 2019; Pando-Naude et al., 2021). Em nível hierárquico semelhante, o giro frontal médio rostral também demonstrou diferenças estruturais significativas e evidência convergente entre as abordagens frequentistas e bayesianas, reforçando o envolvimento de circuitos pré-frontais associados ao controle executivo e à regulação comportamental, conforme amplamente descrito em modelos neurobiológicos da dependência (Ersche et al., 2013; Goldstein et al., 2010; Koob; Volkow, 2016). Outras regiões corticais, incluindo o OFC lateral, o giro temporal superior e o giro fusiforme, apresentaram diferenças negativas consistentes nas análises frequentistas e mantiveram evidência posterior sob o prior bayesiano mais amplo, embora com menor estabilidade sob uma regularização conservadora. No conjunto subcortical, amígdala, hipocampo, NA, globo pálido, tálamo, tronco encefálico e cerebelo exibiram diferenças negativas significativas nas análises frequentistas, em consonância com sínteses anteriores que relataram envolvimento subcortical em usuários de cocaína (Hall et al., 2015; Pando-Naude et al., 2021); contudo, tais achados não se mantiveram robustos nos modelos bayesianos, sugerindo maior sensibilidade à heterogeneidade e menor estabilidade inferencial. Essa organização hierárquica indica que, embora múltiplos nós dos circuitos córtico-subcorticais estejam envolvidos no CUD, o ITG e o giro frontal médio rostral emergem como os correlatos anatômicos mais consistentes e estatisticamente robustos no conjunto das análises realizadas.

Medidas reduzidas de GM no OFC e no giro frontal médio-rostral são consistentes com modelos neurocognitivos que implicam essas regiões no controle inibitório e nos processos de tomada de decisão relevantes para o CUD (Goldstein et al., 2010; Koob; Volkow, 2016). Diferenças entre grupos nessas áreas têm sido repetidamente observadas em estudos prévios de neuroimagem e podem estar relacionadas a padrões comportamentais caracterizados por uso compulsivo de drogas e por prejuízo da autorregulação (Goldstein et al., 2009; Koob; Volkow, 2016; Volkow; Fowler; Wang, 2003).

De modo semelhante, diferenças entre grupos envolvendo o hipocampo e os córtices temporais podem estar associadas à variabilidade em processos relacionados à memória, incluindo a codificação e a evocação de pistas relacionadas à droga, os quais são centrais aos modelos de aprendizagem mal adaptativa na dependência (Avchalumov; Mandyam, 2021; Kober et al., 2016). Volumes reduzidos de GM na ínsula também têm sido relacionados ao processamento interoceptivo e à atribuição de saliência, funções frequentemente implicadas no craving e na reatividade a pistas (Droutman; Read; Bechara, 2015; Naqvi et al., 2014). Em conjunto, esses padrões de diferenças entre grupos estão alinhados a arcabouços teóricos que enfatizam o controle executivo, a compulsividade e a saliência de pistas como dimensões centrais do CUD, reforçando a relevância de intervenções que mobilizem esses sistemas neurais (Dang et al., 2022; Ersche et al., 2013; Koob; Volkow, 2016; Zilverstand et al., 2018).

O ITG, frequentemente implicado em paradigmas de reatividade a pistas, desempenha um papel no processamento perceptivo e semântico ao integrar informações visuais a conteúdos associativos e emocionais por meio de projeções para a amígdala e o hipocampo, contribuindo, assim, para a atribuição de saliência motivacional a pistas relacionadas à droga (Hanlon et al., 2014; Hill-Bowen et al., 2021; Miyashita, 1993). Nesse sentido, alterações no ITG podem refletir marcadores estruturais associados à reorganização funcional dos circuitos fronto-temporo-límbicos, sem implicar necessariamente um papel causal primário (Garavan et al., 2000; Jasinska et al., 2014; Kosten et al., 2006).

Diferenças estruturais nessa região podem, portanto, auxiliar na identificação de indivíduos com maior risco de recaída induzida por pistas e contribuir para o delineamento de estratégias de neuromodulação baseadas em redes, direcionadas a nós de controle pré-frontais ou parietais funcionalmente conectados aos córtices temporais (Balderston et al., 2022; Dejoie et al., 2024; Madeo et al., 2020; Pettorruso et al., 2019; To et al., 2018; Vasileiadi et al., 2023).

Do ponto de vista translacional, regiões pré-frontais, como o giro frontal médio rostral e o OFC lateral, têm sido alvos de protocolos de neuromodulação não invasiva no CUD. A estimulação magnética transcraniana repetitiva (EMTr), particularmente quando aplicada ao córtex pré-frontal dorsolateral, utiliza pulsos magnéticos repetitivos para modular a excitabilidade cortical e a conectividade funcional de redes fronto-estriatais implicadas no controle inibitório e no craving, com evidências preliminares de redução de consumo e de reatividade a pistas (Ekhtiari et al., 2019; Terraneo et al., 2016). De modo semelhante, a estimulação transcraniana por corrente contínua (tDCS) emprega correntes elétricas de baixa intensidade para promover modulação subpolarizante ou despolarizante da atividade cortical, geralmente com montagem ânodo-cátodo sobre regiões pré-frontais, visando restaurar o

equilíbrio entre os sistemas de controle executivo e os circuitos de saliência (Batista et al., 2015; Ekhtiari et al., 2019). Considerando que o ITG integra redes fronto-temporo-límbicas envolvidas na atribuição de significado a pistas associadas à droga, alterações estruturais nessa região podem representar um marcador potencial de reorganização de rede e um candidato a ser investigado em estudos que avaliem resposta a intervenções direcionadas a circuitos pré-frontais no CUD.

O ITG, que emergiu como o achado cortical mais robusto desta metanálise, ocupa posição estratégica em redes fronto-temporo-límbicas envolvidas na integração perceptivo-associativa de pistas relacionadas à droga (Hanlon et al., 2014; Jasinska et al., 2014). Alterações estruturais nessa região podem refletir reorganizações funcionais que ampliam a saliência motivacional dos estímulos associados ao consumo. Embora não constitua um alvo clássico de neuromodulação direta, o ITG integra circuitos conectados a regiões pré-frontais frequentemente estimuladas em protocolos de EMTr e tDCS, sugerindo que intervenções baseadas em redes podem modular indiretamente sua atividade (Ekhtiari et al., 2019; Madeo et al., 2020; Terraneo et al., 2016).

De forma análoga à utilização do córtex cingulado subgenual como marcador funcional em protocolos acelerados de EMTr na depressão, como no protocolo SAINT (Cole et al., 2020). futuras investigações poderiam explorar se padrões estruturais ou funcionais envolvendo o ITG se associam à resposta terapêutica a intervenções direcionadas a circuitos frontais no CUD. Tal abordagem exigiria delineamentos longitudinais e integração multimodal, mas ofereceria uma via promissora para a identificação de marcadores de estratificação e para o monitoramento da resposta terapêutica.

5.4 Síntese integrativa dos achados.

Em conjunto, os achados desta metanálise indicam que o CUD está associado a um padrão distribuído de diferenças estruturais predominantemente corticais, com maior consistência nos córtices pré-frontais e temporais, particularmente no ITG, enquanto as alterações subcorticais apresentam maior variabilidade entre os estudos. A magnitude dessas diferenças mostrou-se sensível a moderadores clínicos, como a gravidade e a duração do uso, sugerindo que parte da heterogeneidade observada na literatura reflete variações fenotípicas reais, e não apenas ruído metodológico. A ausência de convergência espacial significativa no nível voxel-wise, por sua vez, não invalida os padrões identificados em modelos multinível, mas evidencia limitações estruturais do campo quanto à padronização de relato e à disponibilidade de dados completos. Assim, os resultados apontam para um modelo no qual as

alterações corticais associadas ao CUD emergem de forma probabilística e modulada pelo contexto clínico, reforçando a necessidade de abordagens integrativas que considerem simultaneamente a magnitude do efeito, a consistência espacial e a heterogeneidade fenotípica na interpretação das evidências neuroanatômicas.

6 LIMITAÇÕES E PERSPECTIVAS FUTURAS

Diversas limitações devem ser consideradas na interpretação destes achados. Observa-se heterogeneidade metodológica substancial entre os estudos incluídos, abrangendo diferenças nas técnicas de avaliação neuroanatômica, nos critérios diagnósticos, nas vias de administração da cocaína e nas características clínicas das amostras, o que pode comprometer a consistência e a generalização dos resultados. Além disso, viés de publicação e relato seletivo de achados positivos permanecem possíveis, apesar do uso de análises de sensibilidade bayesianas destinadas a mitigá-los. Não foram contatados os autores dos estudos primários para solicitação de dados adicionais não publicados, o que pode ter limitado a disponibilidade de informações clínicas ou regionais específicas. Contudo, essa limitação foi parcialmente mitigada por meio de estratégias analíticas conservadoras, desenvolvidas para atenuar os efeitos do relato seletivo e de dados ausentes. A maioria dos estudos incluídos adotou delineamento transversal, o que impede inferências causais sobre a relação temporal entre o uso de cocaína e as diferenças estruturais cerebrais. Embora tenham sido adotadas medidas para minimizar a inclusão de amostras sobrepostas entre publicações, não é possível excluir completamente eventual dependência residual entre estudos.

Adicionalmente, a variabilidade nas comorbidades psiquiátricas e médicas entre os participantes pode contribuir substancialmente para a heterogeneidade dos resultados. Poucos estudos controlaram rigorosamente o uso concomitante de outras substâncias, como álcool, nicotina e cannabis, o que pode ter influenciado as diferenças observadas entre os grupos. A operacionalização da gravidade clínica adotada também constitui uma limitação. Em virtude da elevada heterogeneidade e da escassez de relatos específicos de comorbidades entre os estudos (por exemplo, diversidade de diagnósticos psiquiátricos, uso de múltiplas substâncias e condições médicas, como infecção pelo HIV), essas variáveis foram agregadas em um único indicador de gravidade ao nível da amostra, em vez de modelar separadamente comorbidades psiquiátricas, comorbidades médicas e uso de múltiplas substâncias como moderadores distintos.

Outra limitação refere-se à análise dicotômica da via principal de administração da cocaína (intranasal versus não intranasal), em vez de uma comparação separada entre os usos intranasal, por via fumada e por via intravenosa. Essa decisão refletiu a baixa e heterogênea representação das vias fumada e intravenosa nos estudos incluídos, o que inviabilizou a realização de modelos estáveis de metarregressão em três níveis. Consequentemente, possíveis

padrões estruturais específicos associados ao uso fumado ou intravenoso não puderam ser plenamente diferenciados na presente metanálise.

Existem também limitações adicionais inerentes às abordagens baseadas em coordenadas, como o método ALE, que dependem exclusivamente de estudos que reportam coordenadas estereotáxicas precisas, o que pode introduzir viés de seleção. Por fim, a escassez de dados longitudinais limita a compreensão da evolução temporal e da potencial reversibilidade das diferenças estruturais cerebrais. Pequenas imprecisões nas transformações de coordenadas ou nas conversões anatômicas também podem afetar a precisão espacial, especialmente em regiões cerebrais menos frequentemente examinadas.

Além das limitações mencionadas, é importante reconhecer que as metanálises dependem intrinsecamente da qualidade metodológica e da consistência dos estudos primários incluídos. Assim, eventuais vieses sistemáticos, erros de mensuração ou limitações não reportadas nesses estudos podem ser incorporados às estimativas agregadas, ainda que estratégias analíticas robustas tenham sido empregadas para mitigar tais efeitos. Ademais, o CUD constitui uma condição clinicamente e neurobiologicamente heterogênea, possivelmente composta por subtipos distintos com trajetórias e perfis estruturais específicos. Essa diversidade pode limitar a identificação de um padrão estrutural único e contribuir para a variabilidade observada entre os estudos.

Futuras pesquisas deverão priorizar delineamentos longitudinais, amostras clinicamente bem caracterizadas e estratégias analíticas que permitam modelar potenciais subtipos neurobiológicos do CUD. Além disso, torna-se fundamental aprimorar a padronização no relato de dados primários. Tendo em vista que observamos que uma parcela significativa dos estudos não reportou, de forma padronizada, informações essenciais para sínteses quantitativas, incluindo a descrição detalhada da via principal de administração da cocaína, a proporção de comorbidades psiquiátricas e médicas nas amostras e a disponibilização de resultados não significativos, com estatísticas passíveis de metanálise (por exemplo, médias, desvios-padrão, estimativas de efeito ou coordenadas estereotáxicas completas). A adoção de práticas de relato mais transparentes e sistemáticas poderá reduzir a heterogeneidade metodológica, minimizar o impacto do relato seletivo e favorecer maior convergência espacial e estatística entre estudos independentes.

7 CONCLUSÃO

A presente tese teve como objetivo realizar uma síntese quantitativa e anatomicamente detalhada das alterações estruturais de GM associadas ao CUD, integrando modelagem multinível, inferência bayesiana e metanálise baseada em coordenadas. Ao combinar essas estratégias complementares, buscou-se enfrentar limitações recorrentes na literatura, incluindo a heterogeneidade clínica, a dependência estatística entre estimativas regionais e os potenciais vieses de relato.

Os resultados indicam um padrão consistente de diferenças estruturais predominantemente corticais, envolvendo regiões pré-frontais e temporais, com destaque para o ITG e o giro frontal médio-rostral, além de alterações subcorticais distribuídas ao longo de circuitos límbicos e estriatais. A duração do uso e a maior gravidade clínica associaram-se a diferenças corticais de maior magnitude, evidenciando que a variabilidade observada na literatura reflete, ao menos em parte, uma modulação fenotípica real.

Embora a convergência espacial ao nível voxel-wise tenha sido limitada, os modelos baseados em tamanhos de efeito revelaram padrões regionais robustos, sugerindo que a inconsistência espacial na literatura decorre mais de limitações estruturais do campo do que da ausência de alterações.

Em conjunto, os achados indicam que o CUD está associado a alterações distribuídas em circuitos córtico-subcorticais envolvidos no controle executivo, na saliência motivacional e no processamento emocional. Tais alterações não constituem marcadores diagnósticos isolados, mas sim padrões probabilísticos que emergem em contextos clínicos heterogêneos.

Os achados desta meta-análise têm implicações relevantes tanto para a compreensão neurobiológica quanto para a aplicação clínica no CUD, ao abrir caminho para o desenvolvimento de biomarcadores estruturais potencialmente úteis na predição da resposta ao tratamento e na estratificação de pacientes. Além disso, os resultados têm valor significativo para a psicoeducação, permitindo traduzir achados neurobiológicos em linguagem acessível a pacientes e familiares. A compreensão de que o transtorno envolve alterações cerebrais mensuráveis pode contribuir para reduzir o estigma, aumentar a adesão ao tratamento e promover uma visão mais integrada e baseada em evidências sobre a condição.

Ao integrar diferentes tradições meta-analíticas e incorporar moderadores clínicos frequentemente negligenciados, esta tese contribui para uma caracterização mais precisa, estratificada e translacional do CUD. Mais do que identificar regiões isoladas, o presente trabalho explicita que compreender o CUD exige reconhecer a heterogeneidade como dimensão

constitutiva do fenômeno, o que orienta futuras investigações rumo a modelos neurobiológicos mais refinados e clinicamente informativos.

8 ASPECTOS ÉTICOS E FINANCIAMENTO

8.1 Financiamento

Este estudo foi financiado, em parte, pela Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – código de financiamento 001. O estudo também contou com apoio do Programa de Bolsas Pro-Stricto – PUCRS.

8.2 Declaração de Conflito de Interesses

Os autores declaram não haver conflitos de interesse potenciais.

8.3 Aspectos Éticos

Esta pesquisa consistiu em uma revisão sistemática e uma metanálise baseadas exclusivamente em dados previamente publicados na literatura científica, sem coleta direta de dados com seres humanos nem acesso a informações identificáveis. Portanto, não foi necessária submissão ao Comitê de Ética em Pesquisa, conforme as diretrizes vigentes para pesquisas secundárias baseadas em dados de domínio público.

O estudo foi conduzido de acordo com as recomendações metodológicas internacionais para revisões sistemáticas e metanálises, incluindo as diretrizes PRISMA, garantindo rigor científico, transparência e reprodutibilidade.

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APÊNDICES

APÊNDICE A – MATERIAL SUPLEMENTAR 1 DO ARTIGO PUBLICADO

Supplementary Material 1 – Search Strategy and Study Selection Details

Este apêndice corresponde ao Material Suplementar 1 do artigo:

Bittencourt AML et al.
Patterns of Structural Brain Differences in Cocaine Use Disorder: Integrating Multilevel Frequentist, Bayesian, and Coordinate-Based Meta-Analyses.
Drug and Alcohol Dependence, 2026.

Supplementary Table S1. Design and neuroimaging data from the included studies

Study	Sample	Substance patterns of use	Measures	Neuroimaging Data	Main neuroimaging findings	Clinical data findings	Dual psychopathology	Outcome	Analysis
1. X. Geng et al. 2017 (1)	**Study design -** cross-sectional **Participants -** 64 non-treatment-seeking cocaine users (NTSCUs) (59 meeting DSM-IV-TR criteria for cocaine dependence; three cocaine abuse; and two users with past abuse or dependence), 67 healthy controls and an independent treatment-completed cohort (n = 45) of cocaine-dependent individuals scanned at the end of a 30-day residential treatment programme. **Male/female -** NTSCUs 49/15 Healthy control 46/21 treatment-completed cohort 39/6	**Cocaine users** (n=64) Cocaine dependence 4.24 +-1.66 Years of cocaine use 13.0+-6.6 Composition of current nicotine use (non-/low-level/high-level smokers) 16/35/13 **Healthy controls:** No use Composition of current nicotine use (non-/low-level/high-level smokers) 41/10/16 **Cocaine-dependent users (n = 45) Treatment-completed cocaine cohort** Years of cocaine use 8.3+- 5.4 Days used cocaine (past 90 days) 70.6 +-23.0	SCID-I WTAR FSIQ WASI Inventory of Drug Use Consequences (InDUC) Comprehensive physical examination DSM-IV-TR	**MRI Scanner** - 3T **Whole Brain or Regions of interest (ROIs) analysis** – Whole brain. **MRI techniques –** Freesurfer **Cortical thickness –** Yes **Brain Volumes -** No **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - Preprocessing of resting-state functional MRI, which was conducted in AFNI and SPM8. SPSS 20.0	Compared with healthy control subjects, the NTSCU group showed thinner bilateral insula and thicker bilateral temporal poles (TPs) (P corrected < 0.05; There was no significant difference in the mean cortical thickness between the groups. By combining structural and functional imaging data from a matched cohort of NTSCUs and healthy control subjects, we identified cortical thickness differences that are in turn, associated with altered functional circuits whose nodes include key components of the salience network and DMN.	All participants were subjected to a urine toxicology screen to detect the potential use of a wide range of therapeutic and recreational substances. Positive findings likely to interfere with the study (e.g.psychiatric medications or illicit drugs not disclosed by the participant) were exclusionary. Participants with a positive breathalyser test for alcohol on the scanning day were rescheduled. The treatment cohort included 45 TCDs who had completed a Minnesota Model psychosocial residential treatment programme. >50% of patients relapsed to drug	No evidence	Right insula Left insula Right temporal pole Left temporal pole	Frequentist Bayesian

		Days since last cocaine use prior to the MRI scan 22.7 +- 3.9 Nicotine use (Cigarettes per day) 12.0 +-10.6				use in the first month and only 18% of patients remained abstinent at 168 days follow-up.			

2. L. Moreno López et al. 2012 (2)	**Study design -** cross-sectional **Participants -** 38 cocaine-dependent individuals, mean age = 29.58, SD = 6.53, and 38 non-drug using controls, mean age = 31.08, SD = 5.14 All participants were male. Cocaine users were recruited in an inpatient therapeutic community ("Proyecto Hombre"), in the city of Granada, Spain. They also had regular use of tobacco, alcohol, cannabis and MDMA. To enter the study, cocaine users had to be abstinent for at least 30 days (for any drug but tobacco), as confirmed by weekly urine tests, in this way, they could rule out acute and residual effects of previously used drugs on brain structure,	**Healthy controls (n=38)** Tobacco (current smokers %): 44.7% **Cocaine-dependent individuals (n=38)** (during of use in years) Cocaine 100% (4.05 ± 3.07) Cannabis 76,31% (2.35 ± 3.17) MDMA 50% (2.27 ± 1.90) Alcohol 100% (7.38 ± 5.77) Tobacco 86,8% (9.19 ± 7)	The Hamilton Rating Scales for Depression and Anxiety (HAM-D and HAM-A) UPPS-P Impulsive Behavior Scale. DSM-IV	**MRI Scanner** - 3T whole body MRI scanner (Phillips Achieva). **Whole Brain or Regions of interest (ROIs) analysis** – whole-brain voxel-based morphometry analyses (VBM) **MRI techniques –** T1-weighted 3D imaging **Cortical thickness –** No **Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - Data was processed and analyzed using SPM8 and VBM8 toolbox.	The cocaine group had significantly lower GM and WM volumes than controls. Cocaine dependent individuals showed lower GM volumes in a number of sections of the OFC (left superior and medial frontal gyrus), right inferior frontal gyrus, right insula, left amygdala and parahippocampal gyrus, left inferior and middle temporal gyrus, and bilateral caudate. Likewise, cocaine dependent individuals showed lower WM volumes in the left inferior and medial frontal gyrus, superior temporal gyrus, right anterior cingulate cortex, insula and caudate. Not find significant associations between the main patterns of drug use (amount, duration and age of onset of cocaine abuse) and GM and WM volumes	Cocaine patients had elevated levels of trait impulsivity, and these scores were differentially associated with GM volumes in the left inferior frontal gyrus, insula and putamen (lack of premeditation), and left middle frontal gyrus (negative urgency). Inferior and medial superior frontal clusters positively correlated with impulsivity in cocaine users, and negatively in controls; conversely, insula and putamen correlated negatively with impulsivity in cocaine patients and showed no correlations in controls.	SUD-Alcohol in >50%	Left amygdala Left caudate Right caudate Right insula Left middle temporal Right pars triangularis Left rostral middle frontal	Frequentist Bayesian Coordinates

3. Meade CS et al. 2020 (3)	**Study design -** cross-sectional **Participants -** 39 cocaine-dependent individuals. Primarily male (61.5%) and predominantly African American (82.1%), with an average age of 45.44 years. COC+ 40 non-drug using controls, primarily male (60%) and mostly African American (72.5%), with an average age of 43.45 years. COC-	COC+ 17.87 years (SD = 8.20 In the 30 days prior to screening: 10.69 days (SD = 7.66) Number of days since last use was 4.31 (SD = 5.67 * 69% reporting use within the past 3 days. Cocaine-dependent individuals: In addition to cocaine, many participants also used substances: Alcohol (87%) Cannabis (46%) and Cigarettes (64%) regularly Some participants non-drug used alcohol (55%) and cannabis (25%).	Barratt Impulsiveness Scale (BSI-11) Monetary Choice Questionnaire (MCQ) Substance Use Measures. DSM-IV-TR	**MRI Scanner** - 3.0T **Whole Brain or Regions of interest (ROIs) analysis** – whole-brain voxel-based morphometry (VBM). **MRI techniques –** T1-weighted structural imaging **Cortical thickness –** No **Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - No	COC+ had broad reductions in GMV compared to COC- in bilateral frontal, parietal, occipital, and cerebellar regions. Lower GMV correlated with trait impulsivity in lateral prefrontal regions and with delayed reward discounting in medial prefrontal regions, while lower GMV correlated with both measures in the posterior parietal cortex. COC+ demonstrated significantly higher impulsivity than COC- on all measures, but the nature of the correlation with GMV was similar in both groups.	Participants also completed another urine toxicology screen for cocaine, cannabis, methamphetamine, opioids, and benzodiazepines. Reflecting the multi-faceted nature of impulsivity, these results show that trait and behavioral measures of impulsivity map differentially onto altered brain morphology. While the brain-behavior patterns were similar in COC+ and COC-, suggesting that impulsivity varies on a continuous spectrum, cocaine-related abnormalities in frontal-parietal brain systems may contribute to heightened impulsivity.	No evidence	Bilateral Cerebellum cortex Left Insula Right Pericalcarine Bilateral Rostral middle frontal Left Superior parietal Right Superior parietal Right Temporal pole	Frequentist Bayesian Coordinates

4. Rando et al. 2013 (4)	**Study design -** cross-sectional Participants: 36 voluntary treatment-seeking individuals (18 men/ 18 women; ages 25–46) with cocaine dependence. 50 healthy comparison subjects (28 men/ 22 women; ages 18–50) were also recruited from the community through local advertisements.	Recent cocaine use Days cocaine use last 90 days: Male: 46.78 (SD 23.50) Female: 45.72 (SD 25.12) Total cocaine use last 90 days: Male: 47.50 (SD 42.71) Female: 48.55 (SD 55.28) Mean cocaine use per use last 90 days: Male: 1.22 (SD 1.50) Female: 1.11 (SD 0.76)	Structured Clinical Interview for DSM-IV	**MRI Scanner** - high-resolution T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scan. **Whole Brain or Regions of interest (ROIs) analysis** – whole brain VBM **MRI techniques –** T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scan. **Cortical thickness –** No	There were no differences between the CD and the healthy control groups on sex and race. However, the CD patients were older, with a lower IQ, and included more smokers than the control group. The amount of alcohol used in the 30 days prior to treatment and the number of days of alcohol use during the same 30 days was significantly greater in abstinent CD subjects than healthy controls In this study, compared with healthy controls, abstinent CD subjects were found to have smaller GMV in a number of cortical	Individuals using opiates and with a history of opiate dependence were excluded. Comparison subjects consumed up to 25 alcoholic drinks or less per month (less than 7 drinks/week), had negative urine toxicology screens on admission into the study, and did not meet criteria for current or lifetime abuse or dependence criteria for	No evidence	Left medial orbitofrontal cortex Precuneus and cuneus (regions surrounding the parietal-occipital sulcus)	Coordinates

		Years of cocaine use: Male: 11.53 (SD 6.47) Female: 8.89 (SD 6.52) Alcohol, marijuana and nicotine use prior to admission was included but those requiring medical detoxification from alcohol were excluded.		**Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - Image segmentation and registration were performed using, respectively, the New Segment and DARTEL registration algorithms incorporated in Statistical Parametric Mapping (SPM8; Wellcome Department of CognitiveNeurology). New Segment is an extension of the default 'Unified Segmentation' algorithm retained from SPM5. The whole-brain statistical analysis was conducted in SPM8 using random field-	regions and larger GMV in the left cerebellum.We found lower GMV in the left inferior frontal gyrus, insula, superior temporal gyrus, and hippocampus in female CD subjects, as well as in temporal, parietal, and occipital cortices, compared to female controls. Male CD subjects were found to have lower GMV in a large area of the superior frontal cortex compared with male controls.We found sex-specific differences in limbic and paralimbic regions, with only CD women showing lower GMV in the left hippocampus and insula.	alcohol or any illicit drug. Individuals taking medications for medical conditions and those on medications for comorbid psychiatric disorders and those requiring acute medical attention were also excluded.			

				based cluster-size testing and family-wise error rate (FWE) correction for multiple comparisons.					

5. Songli Mei, et al. 2015 (5)	Study design - cross-sectional **Participants:** 34 cocaine-dependent patients meeting DSM-IV criteria and having used cocaine within the past 28 days. 9 female/ 25 male. Age 39.3 (+-7.7) 41 healthy control participants without recent substance use. 17 female/ 24 male. Age 29.7 (+-10.1)	Lifetime cocaine use: years (SD) 7.9 (5.7) Cocaine-dependent individuals: Cocaine 15.2 (6.9) Cigarettes 22.0 (11.3) Heroin 0.35 (1.7) Alcohol 7.1 (8.9) Marijuana 2.1 (4.9)	Barratt Impulsiveness Scale (BIS-11) Structured Clinical Interview (SCID) Demographic and Clinical Assessments DSM-IV	**MRI Scanner** - 3-T **Whole Brain or Regions of interest (ROIs) analysis** – specific ROIs such as the amygdala and hippocampus **MRI techniques – FreeSurfer** **Cortical thickness – no** **Brain Volumes -** yes **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data** - Intracranial volume (ICV) was generated during this processing.	In cocaine-dependent participants, smaller amygdala volumes were significantly associated with higher impulsivity scores, particularly in attentional impulsivity. This correlation was not observed in healthy controls. Although there was no significant overall group difference in amygdala volume between cocaine users and controls, cocaine-dependent individuals with higher impulsivity showed a tendency for smaller left amygdala volumes.	Participants were excluded if they had not used cocaine within the past 28 days, less than a 3rd grade reading level, metal in their body, or any acute or unstable illness including untreated psychotic disorders or current use of prescribed psychotropic medications or were pregnant, breast feeding, color-blind,or left-handed. Cocaine-dependent individuals scored higher on all subscales of the Barratt Impulsiveness Scale (BIS-11) compared to controls. A limitation of this study is that it assessed only amygdalar and hippocampal volumes.	SUD-Alcohol in >50%	Left Amygdala Right Amygdala Left Hippocampus Right Hippocampus	Frequentist Bayesian

6. ME Sim et al. 2007 (6)	Study design - cross-sectional Participants: 40 cocaine-dependent subjects (41.47 +- 6.9 years, 27 male/13 female 41 healthy age- and sex-matched comparison subjects (38.7 +-8.8 years, 26 male/15 female.	**Cocaine use (years):** **15.3 (SD 6.3)** **Cocaine use in prior month (days)** **17.8 (SD 8.4)** **Nicotine use in past 30 days:** CD 16.8 Control Group 0.87 **Alcohol abuse/ dependence** CD 20 (52,6%) Control group 0%	Trail Making Test: Trails A Trails B Stroop Color-Word Test The Grooved Pegboard Test Structured Clinical Interview for DSM-IV Axis I Disorders	**MRI Scanner** - voxel-based morphometry (VBM) **Whole Brain or Regions of interest (ROIs) analysis** – 1.5 whole-body imaging system (Horizon Echo-Speed, General Electric Medical Systems, Milwaukee, WI, USA) **MRI techniques –** VBM **Cortical thickness – No** **Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - Additional analysis included correlations of gray and white matter volumes with neuropsychological performance, such as executive function and	Cocaine-dependent individuals had significantly lower gray matter volumes in several brain areas, including bilateral premotor cortex, right orbitofrontal cortex, bilateral temporal cortex, left thalamus, bilateral cerebellum. Additionally, there was a reduction in the right cerebellar white matter volume. The duration of cocaine use negatively correlated with the gray matter volumes of the right and left cerebellum, indicating that prolonged cocaine use was associated with greater reductions in cerebellar gray matter. Reduced cerebellar gray matter volumes were associated with poorer performance on executive function tasks, such as the Stroop and Trail Making Tests, and motor performance on the Grooved Pegboard Test.	Potential cocaine-dependent subjects were excluded if they had a current dependence on any psychoactive drugs other than cocaine, alcohol, or nicotine, neurological or psychiatric disorders requiring immediate treatment, schizophrenia or bipolar illness, serious medical illness, prescribed psychoactive medications, asthma, amenorrhea due to pregnancy, abnormal laboratory results during screening, or contraindications to scanning. Cocaine-dependent subjects with a current history of alcohol dependence not requiring	SUD-Alcohol in >50%	Left cerebellum cortex Right cerebellum cortex Left inferior temporal Right inferior temporal Right lateral orbitofrontal Left superior frontal Right superior frontal Right superior temporal Left thalamus proper	Frequentist Bayesian Coordinates

				motor skills, suggesting structural deficits impact cognitive and motor abilities in cocaine-dependent individuals.		medical detoxification was accepted.			

7. J.S. Ide et al. 2013 (7)	Study design - cross-sectional Participants: 84 dependent (CD): 29 female/ 55 male 39.8 ± 7.6 age 86 healthy control (HC) subjects: 39 female/ 47 male. 38.1 ± 11.0	Cigarette smokers CD: 66 (79%) HC: 27 (31%) Years of cocaine use 18.0 ± 8.2 Years of alcohol use: CD: 16.5 ± 9.1 HC: 15.6 ± 13.0 Years of cannabis use CD 9.3 ± 7.3 HC 0.06 ± 0.28	Structured Clinical Interview for DSM-IV Beck Depression Inventory (BDI) State-Trait Anxiety Inventory (STAI)	**MRI Scanner** - 3T MRI scanner (Siemens Trio) **Whole Brain or Regions of interest (ROIs) analysis** – Voxel-based morphometry (VBM) and fractional amplitude of low-frequency fluctuations (fALFF) for whole-brain and specific ROIs. **MRI techniques –** Structural MRI for gray matter volume and functional MRI (fMRI) for resting-state BOLD signal fluctuation analysis **Cortical thickness – no** **Brain Volumes -** yes **Cortical Surface Area** – no **fMRI** – yes **DTI** – no **Another neuroimaging data** - fALFF of BOLD signals, specifically assessing	Compared to HC, CD individuals showed decreased gray matter (GM) volumes in frontal and temporal cortices, middle/posterior cingulate cortex, and the cerebellum, at $p < 0.05$, corrected for multiple comparisons. The GM volume of the bilateral superior frontal gyri (SFG) and cingulate cortices were negatively correlated with years of cocaine use, with women showing a steeper loss in the right SFG in association with duration of use. In contrast, the right ventral putamen showed increased GM volume in CD as compared to HC individuals. Compared to HC, CD individuals showed increased fractional amplitude of LFF (fALFF) in the thalamus, with no significant overlap with regions showing GM volume loss.	CD: Lifetime depression (n, %) 22 (26%) The results showed reduced gray matter volume in certain cortical and subcortical regions among cocaine-dependent individuals, with differences in spontaneous activity levels, especially in the thalamus.	No evidence	Left cerebellum cortex Right cerebellum cortex Left cuneus Right inferior temporal Right insula Left lateral orbitofrontal Right lingual Right middle temporal Left postcentral Right postcentral Left postcentral Left posterior cingulate Left precentral Right precuneus Right putamen Left superior frontal Left superior frontal Right superior frontal Right superior frontal Left temporal pole	Frequentist Bayesian Coordinates

				spontaneous neural activity in regions like the thalamus and frontal gyri.					

8. Hanlon CA et al. 2011 (8)	**Study design -** cross-sectional A total of 73 participants: 24 active cocaine users Age 38.9±0.9 Male/female: 17/7 Days per week using 3.5±0.4 Years of use 11.1±1.2 24 abstainers (abstinent for at least 1 month) Age 37.0±1.5 Male/female: 15/9 Days per week using 4.6±0.5 Years of use 10.2±1.5 25 nondrug-abusing controls rigorously matched for age, gender, and IQ. Age 36.2±1.0 Male/female: 12/13	**Cocaine** Age at first use (years) Cocaine users: 23.8±1.4 Cocaine abstainers 20.5±1.0 Days per week using Cocaine users: 3.5±0.4 Cocaine abstainers 4.6±0.5 Years of use Cocaine users: 11.1±1.2 Cocaine abstainers: 10.2±1.5 Days since last use* Cocaine users: 1.9±0.4 Cocaine abstainers 243.8±56.5 Alcohol risk (AUDIT) Cocaine users: 12.3±2.6 Abstainers: 9.2±3.4 Nondrug: 3.3±1.5 Cigarette use: Cocaine users:	DSM-IV Axis I Disorders [SCID] IQ test (Wechsler Abbreviated Scale of Intelligence). Cambridge Neuropsychological Test Automated Battery (CANTAB). Beck Depression Inventory Spielberger State-Trait Anxiety Inventory	**MRI Scanner** - 1.5T GE magnetic resonance imaging scanner, using 3-D SPGR for structural imaging. **Whole Brain or Regions of interest (ROIs) analysis** – Whole-brain **MRI techniques –** Voxel-Based Morphometry (VBM) **Cortical thickness – no** **Brain Volumes -** no **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data** - Cognitive performance was assessed through neuropsychological tests, and statistical parametric mapping was used to correlate cognitive performance with brain tissue	The abstainers had significantly higher gray matter density than the current cocaine users in neocortical areas including the frontal and temporal cortex. In contrast to the users, there was no difference in white matter density in the abstainers relative to the controls. The abstainers performed better than current users on several behavioural tasks. Within users and abstainers, cortical density was correlated with performance on memory and reaction time tasks. Subcortical gray matter density was lower in both the users and abstainers relative to the controls. Within abstainers, subcortical tissue density was correlated with the ability to set-shift.	These data suggest that individuals able to remain abstinent from cocaine for at least 1 month have elevated neocortical tissue density and perform better on multiple cognitive tests, relative to current cocaine users. Larger, longitudinal studies are needed to address this interaction between abstinence, cognition, and cortical tissue density directly. The current cocaine users reported that cocaine was their primary drug of choice using crack or both crack and powdered cocaine.	MIld depression >50%	Right caudate Bilateral cerebellum cortex Right medial orbitofrontal Left medial orbitofrontal Left rostral middle frontal Right rostral middle frontal Left superior temporal	Frequentist Bayesian

		92 Abstainers: 68 Nondrug: 40 Marijuana use: Cocaine users: 35 Abstainers: 9 Nondrug: 0		density across groups.					

9. Moeller SJ et al. 2014 (9)	**Study design -** cross-sectional. This multimodal imaging study 33 Cocaine Use Disorder (CUD): uCUD group (unimpaired Cocaine Use Disorder) (n = 18); 15 male / 3 female iCUD group (impaired Cocaine Use Disorder) (n = 15). 13 male / 2 female 20 Healthy Controls 18 male / 2 female	**Cocaine users:** Age at onset (years): uCUD 24.7 (7.3) iCUD 29.1 (7.3) Duration of use, y: uCUD 16.5 (8.2) iCUD 11.6 (6.8) Past month use, d/wk: uCUD 0.8 (1.4) iCUD 1.9 (1.9) Past month use, $ uCUD 28.0 (43.3) iCUD 42.3 (53.1) Current abstinence, median (range) uCUD 31 (0-1825) iCUD 4 (0-548) Longest abstinence, median (range) uCUD 1003.5 (21-3650) iCUD 210 (18-2920) Other drugs: Cigarette smokers (current or past/nonsmokers)	Beck Depression Inventory II (BDI-II) Cocaine Selective Severity Assessment Scale (CSSA) Severity of Dependence Scale (SDS) Cocaine Craving Questionnaire Wide Range Achievement Test III (WRAT-III) Wechsler Abbreviated Scale of Intelligence (WASI) Levels of Emotional Awareness Scale (LEAS) DSM-IV	**MRI Scanner** - 4-T whole-body Varian/Siemens MRI scanner **Whole Brain or Regions of interest (ROIs) analysis** – The primary analysis focused on specific ROIs, particularly the rostral anterior cingulate cortex (rACC) and insula. Additional whole-brain voxel-based analyses were conducted. **MRI techniques –** fMRI and VBM **Cortical thickness – no** **Brain Volumes -** yes **Cortical Surface Area** – no **fMRI** – yes **DTI** – no **Another neuroimaging data** - The study also included measures like the Levels of Emotional Awareness	Compared with the other 2 study groups, the impaired insight CUD group had lower error-induced rostral anterior cingulate cortex (rACC) activity as associated with more frequent cocaine use, less gray matter within the rACC, and lower Levels of Emotional Awareness Scale scores.	The study also included measures like the Levels of Emotional Awareness Scale (LEAS) to correlate with neuroimaging data, bridging cognitive and emotional self-awareness with structural and functional brain imaging findings. The results linked reduced LEAS scores to lower gray matter volume and hypoactivation in the rACC, pointing to diminished emotional awareness in individuals with impaired insight in cocaine addiction. Urine test results positive for drugs other than cocaine in CUD cases and positive urine screen results for	High withdrawal	Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate	Frequentist Bayesian

		uCUD16/2 iCUD 11/4 HC 4/16 Daily cigarettes (current smokers: n = 9/13/2) uCUD 7.3 (5.7) iCUD 7.4 (2.5) HC 7.0 (4.2)		Scale (LEAS) to correlate with neuroimaging data,		any drugs in controls were exclusionary.			

10. Bittencourt et al. 2022 (10)	**Study design -** cross-sectional **Participants -** 78 participants with Crack-cocaine chronic use (CK) and 53 healthy controls (HC). **Male/female -** Healthy controls – 18/35 Crack-cocaine-users - 40/38	**CK Group** Crack-cocaine – 9.46 years of regular use Alcohol – 6.30 years of regular use Cannabis - 15.50 years of regular use Tobacco - 13.77 years of regular use **HC Group** Alcohol – 0.26 years of regular use Tobacco – 17.46 years of regular use	CTQ ASI-6 Sociodemographic interview SCID-IV	**MRI Scanner** - 3.0T **Whole Brain or Regions of interest (ROIs) analysis** – only cingulate cortical thickness regions were evaluated **MRI techniques –** Freesurfer **Cortical thickness –** Yes **Brain Volumes -** No **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - No	Group comparisons revealed significant differences in six out of eight cingulate cortices, showing lower thickness in the CK group. Furthermore, years of regular cocaine use was the variable most associated with cingulate thickness. Negative correlations were found between CTQ scores and the isthmus cingulate (right hemisphere), as well as with the rostral anterior cingulate (left hemisphere). In the mediation analysis, a significant negative direct effect of lifetime cocaine use on the isthmus cingulate and an indirect effect of cocaine use mediated by CTQ score.	The CK group was older, had fewer years of education, had higher rates of unemployment, and had fewer participants self-declared as white. Furthermore, the CK group had more severe exposure to early life stress experiences than the control group, with higher CTQ scores among CK participants than HC.	No evidence	Leftcaudal anterior cingulate Right caudal anterior cingulate Right isthmus cingulate Left isthmus cingulate Right posterior cingulate Left posterior cingulate Leftrostral anterior cingulate Rightrostral anterior cingulate	Frequentist Bayesian

11. Barrós - Loscertales et al. 2011 (11)	**Study design** - cross-sectional **Participants -** 20 male cocaine-dependent (recruited from Addiction Treatment Service of San Agustín in Castellón, Spain) 16 healthy age-, education- and intelligence matched control men and no diagnosis of substance abuse or dependence	Cocaine-dependent group: daily consumption (40%), 1-2 days/week (20%), 3-5 days/week (30%), weekends (10%). In addition to cocaine, cigarettes (65%), alcohol (50%), cannabis (20%), amphetamines (5%), heroin (0%), other psychoactive substances (5%). The control and patient groups did not differ in terms of the distribution of smokers (56% controls vs 65% patients, $p > 0.1$)	DSM-IV Matrix Reasoning Test from WAISIII Edinburgh Handedness Inventory	**MRI Scanner** - **1.5T Siemens Avanto** with a standard quadrature head coil **Whole Brain or Regions of interest (ROIs) analysis** – whole-brain voxel-based morphometry (VBM). **MRI techniques –** 3D High resolution T1-weigh; VBM **Cortical thickness –** No **Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** -	Whole brain voxel-wise analyses with an age-adjusted ANCOVA showed significantly reduced GM in the left striatum and the right supramarginal gyrus for the cocaine group. Charts voxel means for these clusters revealing that the percentage of volume change between controls and patients was 14.8% for the striatum and 12.1% for the supramarginal gyrus. The age of the first cocaine use variable showed no positive or negative association with brain volume in any region. On the other hand, the years of cocaine use variable inversely related to local GM volumes in bilateral middle frontal gyri, left superior frontal gyrus, parahippocampus, posterior cingulate cortex, bilateral amygdala, parietal operculum (insula), right middle temporal gyrus and cerebellum (culmen).	Global brain volume effects were removed from the data to allow inferences on local GM volume changes. The screening for alcohol and cannabis consumption habits was not considered in the control group, and may involve structural effects on the cohorts. In the case of cannabis and amphetamine, as they involved a small group of participants of our already small cocaine group, we excluded them from the control group and repeated the analyses. In the cocaine-dependent group, background of depressive symptoms (n=3), and anxiety symptoms (n=3), but never	No evidence	Right caudate Right supramarginal Coordinates: yes	Frequentist Bayesian Coordinates

						a DSM-IV Axis I disorder, and these symptoms were absent at the time			

12. Bittencourt et al. 2020 (12)	**Study design -** case-control observational study **Participants -** 18 male crack-cocaine dependents (CD) enrolled in long-term rehab program 17 male healthy controls (HC) matched for age, ethnicity, and education, with no history of drug and alcohol dependence/abuse and no psychiatric or neurological disorder	**CD Group (n=18)** Crack-cocaine mean time use - 9.5 ± 5.8 years Age of crack-cocaine use onset (mean)- 19.6 ± 5.9 years Alcohol – 7.9 ± 6.4 years of regular use and 5.7 ± 5.4 years in life that drank at least 5 drinks a day, 3 or more days a week Tobacco - 10.4 ± 7.6 years of regular use **HC Group (n=17)** had no history of alcohol and nicotine regular use All subjects presented alcohol abuse and had no history of another illicit drug dependence	Handedness Inventory Non-patient version of Structured Clinical Interview for DSM- 5 (SCID) Addiction Severity Index – 6th version (ASI-6) Cocaine Selective Scale Assessment (CSSA)	**MRI Scanner** - 3.0T Signa (GE) whole body scanner **Whole Brain or Regions of interest (ROIs) analysis** – only Regions of Interest (Desikan–Killiany Atlas32) **MRI techniques –** 3D T1-weighted images; Freesurfer and VBM **Cortical thickness –** Yes **Brain Volumes -** No **Cortical Surface Area** – No **fMRI** - No **DTI** – No **Another neuroimaging data** - FreeSurfer''s QDEC tool version 5.0 cross-sectional pipeline - brain analysis with FMRIB Software Library v5.0	FreeSurfer analyses of cortical volumes and the same analyses with VBM showed no significant differences between the two groups (p>0.05). FreeSurfer analyses of subcortical regions showed a significant lower volume in right hippocampus (p=0.049) and right ventral diencephalon* (p=0.048) of CD when compared to HC. The CD group showed enlargement of the left inferior lateral ventricle (p=0.012). VBM analyses of subcortical regions showed a significantly lower volume in left Putamen and left nucleus accumbens (NAcc) of CD when compared to HC (p=0.015). FreeSurfer analyses revealed brain regions with significant reductions of CT in CD relative to controls (left inferior temporal cortex (ITC), left orbitofrontal cortex (lOFC) and left rostro frontal cortex (lRFC)), while there were no brain regions with higher CT in the CD group	ITC CT was negatively correlated with crack-cocaine years of use, while there was no significant association in lRFC. Furthermore, there was no significant correlation between crack-cocaine years of use and GM volumes in VBM significant clusters (i.e. putamen and nucleus accumbens). There was no significant correlation between alcohol and cigarettes years of use, age of crack-cocaine use onset, CSSA score, drug use severity, ASI-6 alcohol composite score and GM alterations. Although we used the same dataset in our FreeSurfer and VBM analyses, there was	No evidence	Right hippocampus Left inferior temporal Left lateral orbitofrontal Left lateral ventricle Left pars triangularis Right ventral DC	Frequentist Bayesian

					*Ventral diencephalon= hypothalamus with mammillary body, subthalamic, lateral geniculate, medial geniculate and red nuclei, substantia nigra and surrounding white matter	surprisingly no overlap between the results in the areas in which we found significant effects.			

13. Xu et al. 2023 (13)	**Study design -** Cross-sectional study OpenNEURO database **Participants -** 68 CUD individuals, cocaine dependency with active consumption (at least 2x/week in last month) excluded: current dependence for other substances (alcohol or nicotine) Gender (F/M): 8/60 52 matched HC Gender (F/M): 9/43	**CD Group (n= 68)** onset of cocaine use: 20.66 (5.21) years of cocaine use: 9.75 (6.46) week dose of cocaine use: 2.77 (1.22) years of tobacco use: 12.29 (7.54) **HC Group (n= 52)** onset of cocaine use: 0.64 (3.21) years of cocaine use: 0.46 (2.62) week dose of cocaine use: 0.12 (0.83) years of tobacco use: 5.64 (7.64) **Kg**	All participants were asked to respond to an array of questionnaires administered by trained psychologists who were blinded to this study to obtain CUD severity measures and tobacco use.	**MRI Scanner** - 3.0 T (Phillips Healthcare) **Whole Brain or Regions of interest (ROIs) analysis** – **MRI techniques –** Freesurfer v7.3.2; 3D T1 weighted images; SBM **Cortical thickness –** Yes **Brain Volumes -** only cortical volume **Cortical Surface Area** – Yes **fMRI** – No **DTI** – **Another neuroimaging data** -The average value of **CT, CV, CMC** and **SA** within 34 automatically cortical parcellations were defined by the Desikan atlas in each hemisphere.	Abnormal neuroanatomical patterns in CUD: for CMC pattern, patients showed increased CMC in widespread cortical regions with almost positive effect size. For CT pattern, patients showed decreased CT in widespread cortical regions, especially in left lateral occipital gyrus, right lingual gyrus, right entorhinal cortex, right fusiform gyrus and right insula with medium effect size. For CV pattern, patients showed decreased CV in widespread cortical regions, especially in right fusiform gyrus with medium effect size. For the SA pattern, patients showed both increased and decreased SA in different cortical regions. In CUD individuals, the abnormal anatomical patterns showed significant differences between each other.	The decreased CT of the right insula was significantly associated with the years of cocaine use in CUD individuals. However, no other significant correlations were found between anatomical indices and clinical characteristics in CUD individuals ($p > 0.05$).	No evidence	Left bankssts Left bankssts Right bankssts Right bankssts Left caudal anterior cingulate Left caudal anterior cingulate Right caudal anterior cingulate Right caudal anterior cingulate Left caudal middle frontal Left caudal middle frontal Right caudal middle frontal Right caudal middle frontal Left cuneus Left cuneus Right cuneus Right cuneus Left entorhinal Left entorhinal Right entorhinal Right entorhinal Left frontal pole Left frontal pole Right frontal pole Right frontal pole Left fusiform Left fusiform Right fusiform Right fusiform Left inferior parietal	Frequentist Bayesian Coordinates

								Left inferior parietal Right inferior parietal Right inferior parietal Left inferior temporal Left inferior temporal Right inferior temporal Right inferior temporal Right insula Left insula Left insula Right insula Right insula Left isthmus cingulate Left isthmus cingulate Right isthmus cingulate Right isthmus cingulate Left lateral occipital Left lateral occipital Right lateral occipital Right lateral occipital Left lateral orbitofrontal Left lateral orbitofrontal Right lateral orbitofrontal Right lateral orbitofrontal	

								Left lingual Left lingual Right lingual Right lingual Left medial orbitofrontal Left medial orbitofrontal Right medial orbitofrontal Right medial orbitofrontal Left middle temporal Left middle temporal Right middle temporal Right middle temporal Left paracentral Left paracentral Right paracentral Right paracentral Left parahippocampal Left parahippocampal Right parahippocampal	

								Right parahippocampal Left pars opercularis Left pars opercularis Right pars opercularis Right pars opercularis Left pars orbitalis Left pars orbitalis Right pars orbitalis Right pars orbitalis Left pars triangularis Left pars triangularis Right pars triangularis Right pars triangularis Left pericalcarine Left pericalcarine Right pericalcarine Right pericalcarine Left postcentral	

								Left postcentral Right postcentral Right postcentral Left posterior cingulate Left posterior cingulate Right posterior cingulate Right posterior cingulate Left precentral Left precentral Right precentral Right precentral Left precuneus Left precuneus Right precuneus Right precuneus Left rostral anterior cingulate Left rostral anterior cingulate Right rostral anterior cingulate Right rostral anterior cingulate Left rostral middle frontal Left rostral middle frontal Right rostral middle frontal Right rostral middle frontal Left superior frontal	

								Left superior frontal Right superior frontal Right superior frontal Left superior parietal Left superior parietal Right superior parietal Right superior parietal Left superior temporal Left superior temporal Right superior temporal Right superior temporal Left supramarginal Left supramarginal Right supramarginal Right supramarginal Left temporal pole Left temporal pole Right temporal pole Right temporal pole	

								Left transverse temporal Left transverse temporal Right transverse temporal Right transverse temporal	

14. Matuskey et al. 2014 (14)	**Study design -** cross-sectional **Participants -** 14 medically healthy, non–treatment seeking subjects with CD Gender (F/M): 4/10 14 HC subjects reported age-matched: compared with previously reported age-matched Gender (F/M): 5/9	**CD Group (n= 14)** Race (Caucasian/African American/Hispanic/Other): 3/9/1/1 Years of cocaine use: 21(7) weekly cocaine use (US dollars): 652(617) weekly cocaine use (g): 4.6(4.4) weekly alcohol use (drinks): 16(13) daily nicotine use (cigarettes): 10(7) cannabis use in the last week (joints): 3(7) **HC Group (n=14)** Race (Caucasian/African American/Hispanic/Other): 10/3/0/1 significant nicotine (except for one subject), alcohol, or illicit substance use was not present in HC subjects.	Mini-International Neuropsychiatric Interview or Structured Clinical Interview for DSM-IV, Axis I disorders Hamilton Depression Rating Scale Barratt Impulsiveness Scale State Trait Anxiety Inventory Childhood Trauma Questionnaire	**MRI Scanner** - Siemens 3T MAGNETOM Trio system **Whole Brain or Regions of interest (ROIs) analysis** – Whole brain and Regions of interest (ROI) **MRI techniques –** VBM **Cortical thickness –** No **Brain Volumes -** Yes (VBM?) **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - GMM FAST (FMRIB's Automated Segmentation Tool, v3.1; FMRIB) Dynamic PET scan data (5-HT1B positron emission tomography (PET) radioligand [11C] P943 to image receptor availability), using the	Results of the initial multilinear reference tissue model analysis in nine ROI showed an overall group-by-region effect, with BPND reductions in CD subjects in the anterior cingulate, hypothalamus, and frontal cortex. Shows the decreases in gray matter in CD subjects found with VBM (all differences found in frontal regions). Similar group-by-region effects and emergence of statistically significant findings in the frontal cortex; as well as confirmation of a significant difference in the anterior cingulate and hypothalamus.	Within CD subjects, positive associations were observed between years of cocaine use and BPND in the amygdala, putamen, and thalamus. Weekly cocaine use (in dollars spent) showed a statistical trend in the anterior cingulate. Daily nicotine use was significant in the frontal cortex and ventral striatum with the anterior cingulate close to significance. There was a correlation with the physical abuse subscale of the Childhood Trauma Questionnaire in the pallidum and the state subscale of the State Trait Anxiety Inventory in the thalamus, but no other factors examined in measures of past trauma,	No evidence	Bilateral lateral orbitofrontal Bilateral posterior cingulate Bilateral rostral anterior cingulate Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral temporal pole Coordinates: yes	Frequentist Bayesian Coordinates

				PETtrace cyclotron and a TRACERlab FX C automated synthesizer (GE Healthcare) MRI template (Montreal Neurological Institute coordinates) PET-to-MRI and the MRI-to-template transforms		anxiety, impulsivity, or depression were significant.			

15. Lim et al. 2008 (15)	**Study design -** cross-sectional **Participants -** 21 men and women (mean age 42.5 and mean 18.9 years of cocaine use) Gender (F/M): 10/11 -abstinence ≥ 4 days (self-report) -minimum of 6 months of self-reported cocaine use (including intravenous, nasal, smoking or combinations of methods of use) -must have used ≥ 6 days in the last month Cocaine use was confirmed by urine drug screen 21 age/gender-matched controls were included Gender (F/M): 10/11	**CD Group (n=21)** Handedness (% right): 85.7% Age (years): 42.5 (6.1) Lifetime cocaine use (years): 18.9 (8.4) Alcohol use (days per prior month): 6.9 (6.7) Education (years): 13.1 (1.7) **HC Group (n=21)** Handedness (% right): 90% Age (years): 40.9 (7.4) Lifetime cocaine use (years): 0 Alcohol use (days per prior month): 3.9 (7.2) Education (years): 15.5 (1.3)	Structured clinical interview for DSM-IV axis I conditions (SCID) SCID I/P (patient version) - CD group SCID I/NP (non-patient version) - HC group Barratt impulsiveness scale (BIS-11)	**MRI Scanner** - 3T scanner Trio, Siemens **Whole Brain or Regions of interest (ROIs) analysis** – Regions of interest (ROI) **MRI techniques –** T1 weighted images (coronally); Proton density (PD) and T2-weighted images (axially); 3D Flash sequence; VBM **Cortical thickness –** No **Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – Yes **Another neuroimaging data** - FMRIB Software Library brain extraction tool (BET) PD acquisition was aligned to the T1 brain using linear regis- tration (FLIRT)	**DTI findings**: for group differences (CD and HC) in all three ROIs revealed a significant group difference. Univariate tests for the three ROIS revealed a significant difference in the inferior frontal region but not in the superior frontal or occipital regions. CD subjects had significantly lower FA than HC subjects in inferior frontal WM. **Volumetric findings:** no evidence of group differences in the superior frontal region: WM. In contrast, the CD group had smaller inferior frontal GM volumes than controls and there was a trend toward a smaller inferior frontal WM volume in the CD group. age was not significantly associated with inferior frontal GM volume, but duration of cocaine use may be associated **DTI and volumetric measures relation:** FA was significantly correlated with GM volume in the inferior frontal region, but FA was not significantly correlated with WM volume in that same region.	Results from the voxel-wise correlational analysis examining the relationship between BIS-11 score and FA for the CD group only. These data indicate that low FA in the internal capsule and the genus and body of the corpus callosum is associated with increased impulsivity as measured by the BIS-11. Voxel-wise correlation results for cocaine users only, showing regions in which low fractional anisotropy was related to high impulsivity.	No evidence	Bilateral Medial Orbitofrontal Bilateral Superior Frontal	Frequentist Bayesian

				Masks for three regions (whole cerebrum, inferior frontal, and superior frontal)					

16. Schuch-Goi et al. 2017 (16)	**Study design -** cross-sectional **Participants -** 15 crack-cocaine (male) patients recently discharged from the Addiction Unit of the Hospital de Clínicas de Porto Alegre 15 healthy controls matched for gender, age, education and handedness. All participants were male	**CD Group (n=15)** None of the subjects fulfilled criteria for abuse or dependence of other drugs. Positive urine tests for cocaine at hospital admission and at least 15 days of inpatient detoxification. All patients were on chlorpromazine treatment, at a maximum dose of 300mg per day. All subjects presented alcohol abuse. **HC Group (n=15)** None of the subjects fulfilled criteria for abuse or dependence of other drugs.	Structured Clinical Interview for DSM-IV (SCID) Addiction Severity Index - 6th Version (ASI-6)	**MRI Scanner** - 1.5T Philips Achieva **Whole Brain or Regions of interest (ROIs) analysis** – Regions of interest **MRI techniques –** Freesurfer v5.1 / T1 high resolution sagittal 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) **Cortical thickness –** No **Brain Volumes -** Yes(cortical volume) **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data** - -Kolmogorov-Smirnov test -Intracranial volumes were regressed out from Accumbens volumes, and residuals were	Controls had greater volumes in the left accumbens compared to patients. Right accumbens volumes were also greater in controls, and had near-significant differences between groups. Groups did not differ regarding intracranial volumes. The same was found for the left and right globus pallidus.	NAcc volumes were decreased in patients with crack-cocaine addiction, right and left sides. Groups did not differ regarding age, gender (all subjects were males), education, marital status and occupation. Patients had at least 15 days of detoxification. Patients that fulfilled criteria for dependence of any other substances were excluded. But, episodes of alcohol abuse are extremely prevalent in the population of crack-cocaine dependents, probably to reduce stimulant effects of the substance. In order to maintain the generalization of our results, we chose not to exclude alcohol	SUD-Alcohol in >50%	Left ventral DC Right ventral DC	Frequentist Bayesian

				analysed, in order to control for differences in intracranial volumes.		abuse in the sample.			

17. Schinz et al. 2023 (17)	**Study design -** cross-sectional **Participants -** 74 CUD patients 65 male/ 9 female 62 matched healthy controls: 51 male/ 11 female between 18 and 50 years of age	**Cocaine dependence Group (n=74)** Sex (F/M): 9/65 Age (years): 31.0 ± 7.3 BCST (total errors): 52.6 ± 19.2 CCQ (n=71): 142.1 ±44.2 BIS: 61.2 ±15.4 Years consuming cocaine (n=68): 9.1±6.8 Average weekly cocaine dose (n=69): 1–4 grams **Alcohol Tobacco Cannabis** **HD Group (n=62)** Sex (F/M):11/51 Age (years): 30.6 ± 8.3 BCST (total errors): 40.7 ± 19.9 CCQ: N/A BIS: 45 ±14.9	Cocaine Craving Questionnaire (CCQ) Barratt Impulsiveness Scale (BIS-11) Berg's Card Sorting Test (BCST) MINI International Neuropsychiatric Interview - Plus Spanish version 5.0.0	**MRI Scanner - Philips Ingenia 3 Tesla MRI scanner** with a 32-channel head coil to acquire high-resolution structural images. **Whole Brain or Regions of interest (ROIs) analysis** – focused on **Regions of Interest (ROIs)**: Regions of interest and whole brain. **MRI techniques –** T1-weighted **Surface-Based Morphometry** was used to assess cortical thickness by measuring the brain's surface structure. **Relevance Vector Regression** was employed for the BrainAGE model to estimate biological brain age, comparing brain measures	We found significantly lower cortical thickness in bilateral prefrontal cortices, posterior cingulate cortices, and the temporoparietal junction and significantly increased BrainAGE in patients with CUD [mean (SD) = 1.97 (±3.53)] compared to healthy controls ($p < 0.001$, Cohen's $d = 0.58$). Increased BrainAGE was associated with longer cocaine abuse duration. This dose-dependent effect suggests that longer exposure to cocaine may accelerate age-related structural changes in the brain.	Results demonstrate structural brain abnormalities in CUD, particularly lower cortical thickness in association cortices and dose-dependent, increased brain age. The structural brain changes, including reduced cortical thickness and increased BrainAGE, suggest that cocaine use has a lasting impact on brain health, potentially contributing to cognitive deficits and accelerating the brain aging process.	No evidence	Right bankssts Left caudal middle frontal Right cuneus Left inferior parietal Right inferior parietal Left lateral occipital Right lingual Left pars triangularis Right precentral Left precuneus Right precuneus Left rostral middle frontal Right rostral middle frontal Left superior frontal Right superior frontal	Frequentist Bayesian

				with normal population aging patterns. **Cortical thickness – yes** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data -** Brain Age Gap Estimate (BrainAGE) was used as an additional measure, a neuroimaging biomarker of brain aging based on deviations from normative aging data. This was central to the study's aim to evaluate accelerated brain aging associated with prolonged cocaine use.				

18. Rabin et al. 2020 (18)	**Study design -** cross sectional study ENIGMA Addiction Consortium **Participants -** 210 cocaine dependent male and female (were excluded if they met criteria for current dependence for another substance (excluding nicotine, caffeine, and alcohol) or had a lifetime diagnosis of a psychotic illness) 210 control group gender and age matched participants	**Cocaine Group (n=210)** **-Male (CDM) n=140** Age: 37.79 (6.7) Education: 12.48 (1.4) Race (AA/white/Asian/ other): 76/24/13/27 TIV (mL): 1,519.67 (129.90) Duration of cocaine use (years): 15.24 (8.8) Current cigarette smoker (Y/N): 54/86 Presence of an alcohol use disorder (Y/N): 14/126 **-Female (CDW) n= 70** Age: 39.56 (7.6) Education: 12.24 (1.6) Race (AA/white/Asian/ other): 36/11/9/14 TIV (mL): 1,368.52 (135.35) Duration of cocaine use (years): 17.82 (9.0)	DSM-IV diagnoses using the Structured Clinical Interview or Mini International Neuropsychiatric Interview Axis I disorder	**MRI Scanner** - not specified **Whole Brain or Regions of interest (ROIs) analysis** – Whole brain **MRI techniques –** VBM (SPM12); T1-weighted, **Cortical thickness –** no **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** following six post hoc comparisons were tested: (a) CTLW versus CDW; (b) CTLM versus CDM; (c) CDM versus CDW; (d) CTLM versus CTLW; (e) CTLW versus CDM; and (f) CTLM versus CDW	Controls had greater GMV compared to the group of individuals with CD in several frontal brain regions including the bilateral superior frontal gyrus, left frontal pole, right orbitofrontal cortex, left anterior cingulate gyrus, right supplementary motor cortex, and the left inferior temporal gyrus. Significant differences in GMV between the genders were also found, such that men demonstrated greater GMV in the cerebellar vermis, while women demonstrated greater GMV in several cortical and subcortical regions including the frontal gyrus, thalamus, parahippocampal gyrus, caudate, and lateral cerebellum as compared to men.	The diagnosis × gender interaction revealed significant results in two regions, the left anterior insula and the left lingual gyrus, with the former driven by a diagnosis difference within the women (CDW < CTLW). Whole-brain regression analysis did not show any significant effects for an association between duration of cocaine use and GMV. However, separate whole-brain regression analyses within CDM and CDW revealed a negative relationship between duration of cocaine use and GMV in the right hippocampus in CDM but not CDW	No evidence	Left insula Left insula Left lingual Left lingual	Frequentist Bayesian Coordinates

		Current cigarette smoker (Y/N): 31/39 Presence of an alcohol use disorder (Y/N): 6/64 **Control Group (n=210)** **-Male (CTLM) n=140** Age: 37.02 (8.5) Education: 14.71 (2.6) Race (AA/white/Asian/ other): 70/38/5/27 TIV (mL): 1,506.44 (129.82) Duration of cocaine use (years): n/a Current cigarette smoker (Y/N): 10/130 Presence of an alcohol use disorder (Y/N): n/a **-Female (CTLW) n=70** Age: 37.15 (9.8) Education: 14.51 (2.1) Race (AA/white/Asian/ other): 40/22/0/8				Adding current cigarette smoking and alcohol use disorder as covariates did not change these results.			

		TIV (mL): 1,391.68 (121.53) Duration of cocaine use (years): n/a Current cigarette smoker (Y/N): 5/65 Presence of an alcohol use disorder (Y/N): n/a *TIV, total intracranial volume							
19. Hirsiger et al. 2019 (19)	**Study design –** longitudinal observational cohort study **Participants -** 29 cocaine users (CU) Based on changes in hair cocaine concentration, CU were classified as Decreasers (n=15) or Sustained Users (n=14); cocaine as primary drug with level consumption >0.5mg/month and abstinence duration < 6 months (to ensure regular use) 38 matched controls for age, gender, and time between the two measurements;	**Cocaine Group (n=29)** **-Decreasers (n=15)** Age (years): 31.5 (5.5) Sex (F/M): 7/8 Education (year): 10.7 (1.7) Verbal IQ (MWT-B): 104.5 (11.8) ADHD-SR score: 13.8 (8.6) BDI score: 8.2 (8.2) **Cocaine**: (**n=14**) Times per week: 2.4 (2.0) Grams per week: 1.9 (1.4) Years of use: 7.5 (5.6) Cumulative dose (g): 811 (929)	DSM-IV Axis I (MINI/SCID-I) Interview for Psychotropic Drug Consumption Cocaine Craving Questionnaire (CCQ) Beck Depression Inventory (BDI) Fagerström Test of Nicotine	**MRI Scanner** - 3T Philips Achieva **Whole Brain or Regions of interest (ROIs) analysis** – Regions of interest **MRI techniques –** T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE); Freesurfer (v5.3.0) **Cortical thickness –** Yes **Brain Volumes - Yes**	Specifically, the larger the amount of cocaine used, and the longer cocaine had been used, the thinner the lateral frontal regions were. Group differences were additionally found in the ACC where CU showed a significantly smaller CSA than controls. Moreover, the two CU groups did not differ in any measured GM variables (CT, CSA, subcortical volumes) at baseline. The amount of cigarettes smoked a day was not significantly correlated with alterations seen in CT, and CSA supporting earlier findings that show that frontal GM alterations found in CU	Exclusion criteria for CU were the presence of DSM-IV Axis I adult psychiatric dis- orders—except for cocaine, cannabis, nicotine, alcohol abuse/depen-dence, attention deficit hyperactivity disorder (ADHD), and a previous depressive episode. <u>Supplementary</u>: due to technical problems 3 participants had no value for	High withdrawal (Longitudinal)	Bilateral caudate Bilateral caudate Bilateral lateral orbitofrontal Bilateral lateral orbitofrontal Bilateral lateral orbitofrontal Bilateral lateral orbitofrontal Bilateral medial orbitofrontal Bilateral medial orbitofrontal Bilateral medial orbitofrontal Bilateral medial orbitofrontal Bilateral medial orbitofrontal Bilateral pallidum Bilateral pallidum Bilateral pars triangularis Bilateral pars triangularis	Frequentist Bayesian

	excluded: displayed a current or previous DSM-IV Axis I psychiatric disorders (except for nicotine dependence), and illegal drug use of >15 lifetime occasions or during the past 6 months except for cannabis.	Maximum dose (g/d): 4.5 (3.0) Last consumption (d): 10 (15) Cocaine craving: 30.1 (15.7) **Alcohol** Grams per week: 265.0 (598.4) Years of use: 12.3 (7.7) **Nicotine** Smoking (yes/no): 12/3 Cigarettes per day: 9.9 (11.3) Years of use:9.1 (8.4) **Cannabis** Grams per week: 2.3 (7.2) Years of use: 7.9 (8.7) **Amphetamine (n=14)** Grams per week: 0.3 (0.5) Years of use: 4.0 (4.2) Cumulative dose (g): 75 (128) **-Sustained users (n=14)** Age (years): 32.9 (7.1) Sex (F/M): 2//12 Education (year): 9.4 (0.7) Verbal IQ (MWT-B): 98.2 (9.0)	Dependence standard German vocabulary test to estimate verbal intelligence (IQ) ADHD self-rating scale (ADHD-SR) Rapid Visual Processing (RVP) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) Letter Number Sequencing Task (LNST)	**Cortical Surface Area** – Yes **fMRI** – **DTI** – No **Another neuroimaging data -**	are not associated with smoking severity. There was a significant association between CT and sustained attention but the correlation with working memory was not significant. Correlations with other substances did not reach significance. Follow-up: Change in sustained attention performance from baseline to follow-up. The analysis was corrected for verbal IQ, ADHD-SR score, the amount of alcohol consumed between baseline and follow-up, and the time interval between the two measurements. Our main results showed CT recovery in lateral frontal regions after decreasing or ceasing cocaine intake. In contrast–albeit not significantly–CT further declined in Sustained Users in the same regions over the study period.	ADHD, IQ, and BDI (of each group: control, decreased and sustained user). For those participants, missing values were replaced with their group mean. Cognitive data for sustained attention (n=51) and working memory (n=63) performance was available for a subset of the included participants. For the RVP task, 28 controls, 12 Decreasers, and 11 Sustained Users had available data at both measurement points. The LNST, a test commonly used to test the verbal working memory, was completed by a subset of 63 participants (37 controls, 14 Decreasers, and 12 Sustained Users).		Bilateral pars triangularis Bilateral pars triangularis Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral superior frontal Bilateral superior frontal Bilateral superior frontal Bilateral superior frontal Bilateral thalamus proper Bilateral thalamus proper	

		ADHD-SR score: 18.8 (9.0) BDI score: 10.2 (9.5) **Cocaine**: Times per week: 2.7 (1.9) Grams per week: 5.9 (13.5) Years of use: 8.6 (5.2) Cumulative dose (g): 1966 (2125) Maximum dose (g/d): 3.9 (3.5) Last consumption (d): 10 (11) Cocaine craving: 26.1 (11.8) **Alcohol** Grams per week: 306.2 (607.0) Years of use: 13.4 (6.9) **Nicotine** Smoking (yes/no): 14/0 Cigarettes per day: 12.5 (8.1) Years of use: 14.5 (6.1) **Cannabis** Grams per week: 2.4 (5.0) Years of use: 12.9 (6.6) **Amphetamine** Grams per week: 0.0 (0.1) Years of use: 0.0 (0.1)				Sustained Users had a significantly lower verbal IQ than the controls and Decreasers.			

		Cumulative dose (g): 154 (307) **Control Group (n=38)** Age (years):30.0 (6.8) Sex (F/M):15/23 Education (year): 10.5 (1.5) Verbal IQ (MWT-B): 107.2 (9.8) ADHD-SR score: 6.7 (5.7) BDI score: 2.6 (3.0) **Cocaine**: Times per week: - Grams per week: - Years of use: - Cumulative dose (g): - Maximum dose (g/d): - Last consumption (d): - Cocaine craving: - **Alcohol (n=35)** Grams per week: 77.9 (110.7) Years of use: 11.0 (6.2) **Nicotine** Smoking (yes/no): 27/11 Cigarettes per day: 5.0 (6.2)							

		Years of use: 7.1 (6.9) **Cannabis (n=37)** Grams per week: 0.0 (0.2) Years of use: 3.7 (5.6) **Amphetamine (n=0)** Grams per week: 0.0 (0.0) Years of use: 0.0 (0.0) Cumulative dose (g): 0.0 (0.0)							
20. Crunelle et al. 2014 (20)	**Study design -** cross sectional **Participants -** 30 non-treatment-seeking cocaine-dependent individuals (males) if using cocaine regularly, i.e., using at least 1 g of cocaine per week during at least 12 consecutive months prior to inclusion 33 non-drug using controls (males) have never used cocaine	**CD Group (n=30)** Age: 32 ±9 years IQ: 103 ±8 BDI scores: 11 ±6 BIS scores: -total: 73.8 ±7.8 -attentional impulsiveness: 17.7 ±5.1 -motor impulsiveness: 24.5 ±6.5 -non-planning impulsiveness:28.5 ±4.4 FTND nicotine dependency scores: 5 ±2 Smokers: 80% smokers Alcohol: 87% alcohol consumers	DSM-IV criteria Mini International Neuropsychiatric Interview (MINI) Barratt Impulsivity Scale (BIS) Fagerström Test for Nicotine Dependence (FTND) Beck Depression Inventory (BDI)	**MRI Scanner** - 3.0-T Philips Achieva **Whole Brain or Regions of interest (ROIs) analysis** – regions of interest **MRI techniques –** T1-weighted images; VBM **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -**	Voxel-wise group comparisons revealed smaller GM volumes in cocaine users compared to controls only in the left middle frontal gyrus). No larger regional GM volumes were observed in COC compared to HC. Also, there were no WM volume differences between non-treatment-seeking cocaine-dependent individuals and non-drug using controls.	Voxel-wise correlations with GM volume showed that attentional impulsiveness was significantly negatively associated with the right OFC (encompassing the superior, middle, and inferior gyri) and the left precentral gyrus, whereas a positive correlation was observed between motor impulsiveness and volume of the right superior frontal gyrus coordinates.	SUD-Alcohol in >50%	Right inferior parietal Right medial orbitofrontal Left precentral Right superior frontal	Frequentist Bayesian Coordinates

		Alcohol weekly: 163 ±131 g recreational cannabis: (40%) ecstasy: (33%) amphetamine: (20%) sedative-users (7%) Regular cocaine use (days/week): 2 ±1 Cocaine per session (g): 2.6 ±1.9 g **HD Group (n=30)** Age: 33 ±9 years IQ: 106 ±9; BDI scores: 3 ±5 BIS scores: -total: 59.4 ±6.9 -attentional impulsiveness: 11.9 ±3.6 -motor impulsiveness: 20.5 ±4.1 -non-planning impulsiveness: 15.5 ±5.4 FTND nicotine dependency scores: 4 ±2 Smokers: 15% smokers Alcohol: 83% alcohol consumers Alcohol weekly: 82 ±80 g	Dutch variant of the National Adult Reading Test (DART) => IQ	SPM8 (Statistical Parametric Mapping)		Measures of non-planning impulsiveness were positively associated with volume in the right inferior parietal gyrus. The positive correlation between motor impulsiveness and volume in the right superior frontal gyrus also remained significant. For non-planning impulsiveness, a trend remained with GM volume correlation in the right inferior parietal gyrus. No significant associations between duration of cocaine use and frontal GM volume were observed. BIS attentional impulsiveness and GM volume remained significantly correlated after controlling for BDI and FTND			

		no use of illegal substances in the HC group				scores in the right OFC (inferior and superior gyri) and in the left precentral gyrus			
21. Vaquero et al. 2017 (21)	**Study design -** cross-sectional **Participants -** 30 detoxified CD inpatients Gender (F/M): 6/24 30 drug-naive controls Gender (F/M): 6/24 -Usable functional images from four controls had to be removed from the analysis because of an excessive movement artifact-> 26 HC Excluded: patients with history of opiate abuse or dependence or currently under treatments with opioid agonist or antagonist	**Cocaine group (n= 30)** Gender (F/M): 6/24 Age (y): 32.9 (5.9) Years of education: 10.6 (2.4) WAIS matrices score: 15.5 (4.1) TAP score: 22.3 (4.4) Dickmann impulsivity score total (DII): 8.3 (3.4) Sensitivity to Punishment (SP) and Sensitivity of Reward (SR) Questionnaire: SP: 10.4 (5.8) SR: 14.8 (5.4) Average duration of cocaine use: 12.9 years (range: 4-27) Average age at first use: 19.9 years (range: 14–29) The estimated weekly use of cocaine in the	DSM-IV-R axis-I (psychiatric disorders and alcohol and opiate use disorders) Gehring's task Dickmann impulsivity inventory (DII) NASH (Spanish version) = TAP ("Teste de Acentuación de Palabras") Sensitivity to Punishment and Sensitivity of Reward Questionnaire	**MRI Scanner** - 3 T (TRIO Tim syngo MR B17, Siemens) **Whole Brain or Regions of interest (ROIs) analysis** – ROI **MRI techniques –** VBM; T1-weighted images **Cortical thickness – no** **Brain Volumes - Yes** **Cortical Surface Area** – **fMRI** – Yes **DTI** – Yes **Another neuroimaging data -** Four functional main regions of interest (ROIs) were derived from the whole sample analysis by drawing a 10 mm sphere around the peak coordinate: right ventral striatum (RVstr), left	The contrast 'over- all gain' (win5 + win25 + boost10 + boost50) versus 'overall loss' (lose5+lose25) for the entire 56-subject sample led to areas of increased BOLD response in the right and left ventral striatum (RVstr and LVstr, respectively), the medial prefrontal cortex (mPFC), including areas in the anterior cingulate and orbitofrontal cortices and the posterior cingulate cortex (PCC).in the anterior cingulate and orbitofrontal cortices and the posterior cingulate cortex (PCC). The between-subject analysis showed that patients had greater gray matter volume in the right caudate nucleus and in the right inferior and middle orbitofrontal gyri than controls. No decreases in gray matter volume were found in the patient group.	The behavioral measures obtained from the gambling task included reaction times and the probability (between 0 and 1) of choosing 25 over 5. Both patients and controls showed similar behavioral patterns. significant positive correlation was found between the weekly cocaine consumption in grams in the month prior to admission and GM volume in the OFC; significant negative correlation was found between the aforementioned weekly cocaine consumption, and the	No evidence	Bilateral caudate Bilateral lateral orbitofrontal Bilateral medial orbitofrontal Coordinates: yes	Frequentist Bayesian Coordinates

		month prior to treatment admission: 17 g (range:1-75) **HC group (n= 30)** Gender (F/M): 6/24 Age (y): 32.3 (6.6) Years of education:11.5 (1.8) WAIS matrices score: 15.3 (3.6) TAP score: 22.8 (3.5) Dickmann impulsivity score total (DII): 5.5 (2.9) Sensitivity to Punishment (SP) and Sensitivity of Reward (SR) Questionnaire: SP: 9.0 (5.7) SR: 9.6 (5.2)	Matrix Reasoning . From the WAIS-III	ventral striatum (LVstr), medial prefrontal cortex (mPFC) including areas in the anterior cingulate and orbitofrontal cortices, and posterior cingulate cortex (PCC); Functional images were collected using T2 weighted		parameter estimate (β-value) of the loss condition in the mPFC. Duration of the abstinence period was inversely correlated with the parameter estimates of the boost condition in the clusters of the left and right ventral striata.			
22. Xu et al. 2014 (22)	**Study design -** Longitudinal observational cohort study **Participants -** 23 cocaine patients Gender (F/M): 6/23 54 healthy controls gender (F/M): 22/54	**Cocaine group (n=23)** Age: 39.7 (8.1) Education (years): 12.0 (1.9) Cigarette smokers: 19 (82.6%) Race/ethnicity -Caucasian: 7 (30.4%)	DSM-IV Structured clinical interview (SCID) Substance Abuse Calendar	**MRI Scanner** - 3-T scanner (Siemens Trio) **Whole Brain or Regions of interest (ROIs) analysis** – **MRI techniques –** T1 weighted ; FreeSurfer	Healthy participants and cocaine-dependent patients did not show significant differences in volumes of the amygdala and hippocampus, after controlling for age, gender, and ICV. Volumes of the amygdala and	All cocaine-dependent participants received weekly individual cognitive-behavioral therapy (CBT). Within the cocaine-dependent	SUD-Alcohol in >50%	Left amygdala Right amygdala Left hippocampus Right hippocampus	Frequentist Bayesian

	excluded if urine samples were positive for any substance; pregnancy, left-handedness, current psychiatric diagnoses, or unstable medical conditions	-African-american: 12 (52.2%) -Hispanic: 2 (8.7%) -Multiracial/Other: 2 (8.7%) Never married/Living alone, N (%): 16 (60.5) Unemployed, N (%): 19 (82.6) Total number of months incarcerated, lifetime: 32.8 (48.8) Lifetime psychiatric diagnoses, N (%): -Alcohol-use disorder: 15 (65.2) -Major depression 6 (21.1) -Anxiety disorder 0 (0) History of substance use: -Days cocaine use in 28 days prior to treatment: 14.6 (7.2) -Days of alcohol use in 28 days prior to treatment: 7.1 (9.0)	Timeline-Follow-Back method Addiction Severity Index (ASI)	**Cortical thickness – No** **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** Intracranial volume (ICV) was generated during this processing	hippocampus in mm3 (Mean (SD)). Cocaine-dependent: Amygdala: - left: 1627.5 (223.2) - right: 1745.6 (226.9) Hippocampus: - left: 3986.6 (402.5) - right: 4087.4 (399.6) Healthy controls: Amygdala - left: 1725.9 (274.2) - right: 1832.6 (257.3) Hippocampus: - left: 4048.4 (527.3) - right: 4188.5 (466.9)	patients, we found significant positive correlations between hippocampal volumes and cocaine- use measures, consistent with hypothesis 3. Specifically, more days self-reported cocaine use within the 28 days before enrollment into the clinical trial were associated with greater hippocampal volumes after controlling for ICV, age, and gender. The main findings were that: (1) pre-treatment cocaine use negatively correlated with cocaine abstinence during treatment; and (2) pre-treatment hippocampal volume positively			

		-Years of regular cocaine use, lifetime: 8.2 (5.5) Cocaine use days before treatment: 14.6 (7.2) Longest abstinence during treatment: 43.8 (27.4) % Negative urines during treatment: 47.6 (41.4) **HC group (n=54)** Age: 29.6 (10.1) Education (years): 14.9 (1.7) Cigarette smokers: 5 (9.3%) Race/ethnicity -Caucasian: 34 (63%) -African-american: 14 (25.9%) -Hispanic: 1 (1.9%) -Multiracial/Other: 5 (9.2%)				correlated with cocaine use before and during treatment and mediated the positive correlation between the two measures. Relative to the group receiving CBT only, the patient sub-group receiving CBT plus CM had a significantly longer duration of abstinence and greater percentage of cocaine-negative urine samples. However, the two patient subgroups showed similar correlations between their pre-treatment and within-treatment indices of cocaine use, and between these indices and volumes of the amygdala and hippocampus			

23. Alia-Klein et al. 2011 (23)	**Study design -** cross-sectional **Participants -** 40 male CUD (they reported use a mean (SD) of 2.1 (1.5) days before the study) After MAOA genotyping: CUD low: n=22 CUD high: n =18 42 male controls (CON) After MAOA genotyping: low: n=20 high: n=22 Current use or dependence on other drugs was denied and corroborated by preimaging urine tests in all participants (urine was negative for all other drugs in all participants).	**CUD group (n=40)** - **Low (n=22)** Age (years): 45 (1) Race, No. black/white: 18/4 Education, y: 13 (0.3) SES: 32 (2) Verbal IQ: 93 (3) Nonverbal IQ: 9 (1.0) BDI symptoms score: 9 (2) Age at CUD onset, y: 24 (1.3) Cocaine intake, g/occasion: 1.9 (1.0) Cocaine use, y: 19 (1.4) Cigarette smokers, No. (%): 17 (77) Cigarettes, No./d: 8 (1) Age at smoking onset, y: 15 (2) Years of smoking: 21 (2) Alcohol abuse, No. (%): 15 (68) Alcohol consumption, oz: 62 (10) Age at alcohol abuse onset, y: 15 (1) Years of drinking: 19 (2.0)	Structured Clinical Interview for DSM-IV Axis I Disorders (research version) Wide-Range Achievement Test 3 reading Matrix Reasoning subset of the Wechsler Abbreviated Scale of Intelligence Beck Depression Inventory (BDI) Addiction Severity Index	**MRI Scanner** - 4-T imager (Variant/Siemens) **Whole Brain or Regions of interest (ROIs) analysis** – ROI **MRI techniques –** T1-weighted **Cortical thickness –** NO **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -**	Controlling for age and total brain tissue, individuals with CUD had GMV reductions in the left OFC, right DLPFC, right DLPFC, temporal cortex, temporal cortex, and hippocampus and parahippocampal gyrus compared with CON a similar pattern of results were obtained in the CUD group with lifetime alcohol and with cigarette smoking At this SPM threshold, there were no regions of increased GMV in CU compared with CON and no main effects of genotype as assessed with MAOA*L or MAOA*H contrasts. However, there was a significant CUD MAOA interaction effect exclusively in the OFC. the whole-brain correlation results of all 3 drugs were overlaid, showing a visible overlap of the detrimental effects of all drugs on the hippocampus.	Additional differences included race (fewer whites in the CUD group than the CON group) and higher depression symptom score in CUD (9 [2]) than CON (3 [1]), with no genotype effects and lower verbal intelligence (CUD, 90 [2]; CON, 97 [2]) and an interaction with the CUD-H group having lower scores than the CON-H group. The participants with CUD reported use of a mean (SEM) of 1.7 (0.8) g of cocaine per occa-sion with no genotype effects CUD-H x CON-H: demonstrated a diagnosis effect of GMV reductions in the hippocampus; however, this	SUD-Alcohol in >50%	Bilateral hippocampus Bilateral lateral orbitofrontal Bilateral parahippocampal Bilateral rostral middle frontal Bilateral temporal pole	Frequentist Bayesian Coordinates

		-High (n=18): Age (years): 45 (1) Race, No. black/white: 17/1 Education, y: 13 (0.4) SES: 26 (2) Verbal IQ: 86 (2) Nonverbal IQ: 9 (1.0) BDI symptoms score: 9 (2) Age at CUD onset, y: 28 (2.0) Cocaine intake, g/occasion: 1.6 (0.4) Cocaine use, y: 19 (1.3) Cigarette smokers, No. (%): 13 (72) Cigarettes, No./d: 9 (1) Age at smoking onset, y: 17 (1) Years of smoking: 22 (2) Alcohol abuse, No. (%): Alcohol consumption, oz: 59 (6) Age at alcohol abuse onset, y: 16 (1) Years of drinking: 17 (3.0) **CON group (n=42)**				contrast did not produce significant results in any of the other main effect regions, including the OFC, even at a reduced threshold. In terms of drug exposure factors, all participants with CUD used cocaine (smoked crack) in the past 0 to 7 days before imaging and met DSM-I criteria for current cocaine dependence. In the CUD group (n=40), with increasing years of cocaine exposure, there were more volume reductions in the OFC, DLPFC and hippocampus; a similar pattern results in the CUD group with lifetime alcohol and with cigarette smoking.			

		- **Low (n=20)** Age (years): 40 (1) Race, No. black/white: 14/6 Education, y: 13 (0.3) SES: 34 (3) Verbal IQ: 92 (3) Non verbal IQ: 10 (0.5) BDI symptoms score: 2 (1) Age at CUD onset, y: NA Cocaine intake, g/occasion: NA Cocaine use, y: NA Cigarette smokers, No. (%): 5 (25) Cigarettes, No./d: 6 (1) Age at smoking onset, y: 17 (2) Years of smoking: 4 (5) Alcohol abuse, No. (%): NA Alcohol consumption, oz: 34 (1) Age at alcohol abuse onset, y: NA Years of drinking: 5 (1.0) - **High (n=22)** Age (years): 38 (1)							

		Race, No. black/white: 12/10 Education, y: 14 (0.5) SES: 34 (3) Verbal IQ: 101 (3) Nonverbal IQ: 11 (1.0) BDI symptoms score: 5 (1) Age at CUD onset, y: NA Cocaine intake, g/occasion: NA Cocaine use, y: NA Cigarette smokers, No. (%): 4 (18) Cigarettes, No./d: 4 (2) Age at smoking onset, y: 19 (1) Years of smoking: 2 (2) Alcohol abuse, No. (%): NA Alcohol consumption, oz: 30 (3) Age at alcohol abuse onset, y: NA Years of drinking: 2 (0.5)							
24. Rasgado-Toledo et al.	**Study design -** cross-sectional observational **Participants -**	**CUD group (n=60)** Age: 31.23 (18-50) Sex: 6/54	DSM-IV criteria Cocaine Craving Questionn	**MRI Scanner** - 3T system (Philips Healthcare) **Whole Brain or Regions of**	Viso-NODDI values were significantly higher in CUD in some of the Regions of Interests (ROI) compared to HC. Specifically, in cingulate	CUD participants showed a significantly higher tobacco dependency,	SUD-Alcohol in >50%	Left brain stem Right brain stem Right cerebellum cortex	Frequentist Bayesian

2022 (24)	as part of the Mexican MRI dataset of patients with cocaine use disorder (SUDMEX CONN) 60 cocaine use disorder patients (CUD) Gender (F/M): 6/54 43 non-CUD controls (HC) were matched by age (± 2y), sex, education and handedness Gender (F/M): 8/35	Education completed: Middle School Handedness (right/left): 53/4 Ambidextrous: 3 Onset age of consumption (n=59): 20 (12-41) Years consuming (n=59): 10 (1-28) Average consumption per intake: <0.8g: 5 1.6-2.4g: 13 3.2-5.6g: 26 8-9 g: 6 9-10 g: 3 >10 g: 3 Monthly expense in cocaine (USD) (n=56): $127.5 (±$205.59) Tobacco dependency (n=52): 34 Alcohol dependence lifetime (n=57): 26 Years of tobacco use (n=52): 13.71 (±8.03) **HC group (n=)** Age: 30.86 (18–48)	aire—Now (CCQ) Addiction Severity Index (ASI) Barratt Impulsiveness Scale (BIS-11)	**interest (ROIs) analysis** – Whole brain and ROI **MRI techniques –** rsfMRI, T1 weighted, HARDI, fDKI ; FreeSurfer 6.0 **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – **fMRI** – resting state fMRI? **DTI** – HARDI +NODDI? **Another neuroimaging data -** The order of the sequences was: rsfMRI, T1w, HARDI, fDKI, and was maintained across participants.	and hippocampal gyrus, forceps minor, medial lemniscus, superior longitudinal and uncinate fasciculus. In GM, higher Viso-NODDI values were found in superior temporal sulcus, orbitofrontal, inferior and middle temporal gyrus, inferior and middle frontal gyrus, inferior parietal gyrus, lateral occipital, postcentral gyrus, posterior cingulate, supramarginal gyrus, pallidum and cerebellum	years of tobacco use and a lower education when compared to controls. Positive correlations were found with impulsiveness index (BIS-11) in cognitive and motor, cocaine age onset of consumption and cocaine dose per week. On the other hand, Tobacco total years use, CCQ-Now and Addiction severity index was negatively correlated with WM structures and other GM regions. The multiple regression results were an overall effect of age and cocaine dosage per week, tobacco and alcohol use, and impulsivity on Viso-NODDI values in left Uncinate, left Superior Longitudinal Fasciculus,		Right inferior parietal Right inferior temporal Right lateral occipital Left lateral orbitofrontal Left middle temporal Left pallidum Left parahippocampal Left pars opercularis Left pars triangularis Right pars triangularis Right postcentral Right posterior cingulate Right posterior cingulate Left rostral anterior cingulate Left rostral middle frontal Right rostral middle frontal Left superior temporal Right supramarginal	

		Sex (F/M): 8/35 Education completed: High School Handedness (right/left): 36/4 Ambidextrous: 3 Onset age of consumption: NA Years consuming: NA Average consumption per intake: NA Monthly expense in cocaine (USD): NA Tobacco dependency (n=41): 18 Alcohol dependence lifetime (n=36): 0 Years of tobacco use (n=41): 6.39 (±8.145)				left Inferior Frontal gyrus pars triangularis and opercularis, left rostral Middle Frontal gyrus, lateral orbitofrontal, right Lateral Occipital, right posterior Cingulate gyrus and right postcentral.			
25. Parvaz et al. 2016 (25)	**Study design -** longitudinal cohort **Participants -** 19 right-handed treatment-seeking iCUD (current cocaine dependence (N = 14), or cocaine depen-	**CD group (n=19 -baseline** Age (years): 42.58 ± 7.63 Gender (male/female): 13/6 Race (African American/Hispanic/Other): 12/3/4	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)	**MRI Scanner** - 4 T Varian/Siemens **Whole Brain or Regions of interest (ROIs) analysis** – Whole brain and ROI **MRI techniques –**	The whole-brain 2 × 2 flexible factorial design yielded a significant Group main effect, such that HC showed greater GMV in the left cuneus and the right precuneus compared to iCUD, and iCUD showed greater GMV in the right	Toxicology screens were performed on both study days, and all were negative for psychoactive drugs and their metabolites (cocaine, methamphetami	High withdrawal (Longitudinal) No evidence	Left medial orbitofrontal Right medial orbitofrontal Left pars triangularis Left medial orbitofrontal Right medial orbitofrontal	Frequentist Bayesian

	dence in partial (N = 4) or sustained (N = 1) remission) Gender (male/female): 13/6 - were referred from three addiction treatment facilities and were free of sustained/maintenance medication for >30 days prior to and throughout the study. 12 healthy controls Gender (male/female): 11/1	Education (years): 12.68 ± 2.75 Non-Verbal IQ (WASI-II MRS): 9 ± 3.65 State Depression (BDI-II): 6.84 ± 7.69 <u>Drug use:</u> Cigarette use (current/past/none): 13/3/3 Current cigarette use (number of cigarettes/day): 3.58 ± 5.18 Quantity of alcohol use in last year (oz./week): 57.58 ± 77.45 Lifetime duration of cocaine use (years): 12.74 ± 7.42 Abstinence from cocaine (days): 149.32 ± 189.46 Self-reported craving (CCQ):8.95 ± 8.55 **6-month follow-up** State Depression (BDI-II): 5.68 ± 8.21 Drug use	Addiction Severity Index Beck Depression Inventory (BDI-II) 18-item Cocaine Selective Severity Assessment Scale Wechsler Abbreviated Scale of Intelligence (Wechsler 1999) 3-item Severity of Dependence Scale 5-item Cocaine Craving Questionnaire Timeline Follow-back Calendar (CL-90) Wisconsin	T1-weighted modified T2-weighted; VBM **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** **Baseline (T1)**: Initial scans and assessments. **Follow-up (T2)**: After six months of sustained reduced or no drug use (for iCUD) or a matched interval (for HC).	supplementary motor, the left medial superior frontal and the right parietal/occipital cortices. At a lower threshold, the right middle occipital cortex, the right IFG and the right dorsal ACC as well as bilateral vmPFC showed a trend for Group-by-Time interaction. Planned comparisons revealed that the longitudinal comparison in the iCUD (6-month follow-up > baseline) yielded increased GMV in the left IFG and in the bilateral vmPFC	ne/amphetamines, phencyclidine, benzodiazepines, cannabis, opiates and barbiturates), except for one participant (N = 1) whose urine was positive for cocaine and who reported using cocaine three days prior to the follow-up scan day. Included mild marijuana and ecstasy abuse (N = 1), alcohol use disorder (N = 3), opiate use disorder (N = 1), unipolar depression (N = 1), antisocial personality disorder (N = 4) and post-traumatic stress disorder (N = 1)-> length of abstinence prior to beginning the study. The iCUD showed increased task		Left pars triangularis	

		Current cigarette use (number of cigarettes/day): 4.89 ± 6.014.89 ± 6.01 Quantity of alcohol use in last year (oz./week): 47.63 ± 55.37 Abstinence from cocaine (days): 271.95 ± 202.56 Self-reported craving (CCQ): 5.42 ± 6.15 **HC group (n=12)** Age (years): 39.33 ± 8.66 Gender (male/female): 11/1 Race (African American/Hispanic/Other): 6/1/5 Education (years): 12.71 ± 1.60 Non-Verbal IQ (WASI-II MRS): 10.92 ± 3.34 State Depression (BDI-II): 1.50 ± 2.47 Drug use: Cigarette use (current/past/none): 3/1/8 Current cigarette use (number of	Card Sorting Test (WCST) Modified color–word Stroop task Attention Network Test Iowa Gambling Task (IGT)			accuracy on the WCST from baseline to follow-up. the iCUD showed a sign can't increase in net IGT score from baseline to follow-up			

		cigarettes/day): 2 ± 5.78 Quantity of alcohol use in last year (oz./week): 32.44 ± 26.11 Lifetime duration of cocaine use (years): —- Abstinence from cocaine (days): — Self-reported craving (CCQ): —							
26. Bachi et al. 2018 (26)	**Study design -** cross sectional **Participants -** 47 cocaine users (23 iCUD with low childhood trauma (CUD-L), and 24 iCUD with high childhood trauma (CUD-H)) Gender (F/M): 9/38 29 healthy controls (CON) Gender (F/M): 9/20	**CD group (n=47)** **- CUD-L (n=23)** Age: 47.0 ± 7.9 Education: 13.1 ± 1.8 Gender (F/M): 3/20 Race: 19 African American (82.6%) Nicotine: 21.8 ± 11.2/ 15.4± 4.1/NA Alcohol: 14.8 ± 12.1/15.3 ± 3.6/3.9 ± 2.9 Cocaine:18.5 ± 8.8/20.9 ± 5.5/3.8 ± 3.8 Cannabis: 5.9 ± 7.5/17.2 ± 1.4/1.2 ± 0.5 Severity of cocaine	DSM-IV Axis I Disorders Addiction Severity Index Cocaine Selective Severity Assessment Scale Severity of Dependence Scale Cocaine Craving Questionnaire CTQ total score	**MRI Scanner** - 3T Skyra (Siemens) **Whole Brain or Regions of interest (ROIs) analysis** – whole brain and regions of interest (Orbitofrontal cortex) **MRI techniques –** VBM; T1-weighted **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No	The whole-brain SPM analysis showed a significant group main effect in the right lateral OFC, the bilateral middle temporal gyri, and the dorsal anterior cingulate gyrus. Follow-up pairwise whole-brain comparison showed significantly reduced GMC in the right lateral OF in the CUD-H as compared to CON and even as compared to CUD-L, but CUD-L and CON groups did not differ Reduced GMC in the bilateral middle temporal gyri were observed in CUD-H as compared to CON. Lifetime years, age initiation and years of	iCUD with increased childhood trauma severity reported reduced constraint and a trend for increased depression symptoms Across all CUD, the post hoc analysis using hierarchical regression demonstrated that the continuous measure of childhood trauma accounted for 37.7% of variance in GMC in the right	SUD-Alcohol in >50%	Right lateral orbitofrontal Right middle temporal Left middle temporal	Frequentist Bayesian Coordinates

		dependence: 4.0 ± 5.1 Cocaine craving: 13.3 ± 10.7 Cocaine withdrawal: 15.9 ± 13.0 Cocaine: days since last use: 4.0 ± 4.6 Current alcohol: 2 abuse Childhood trauma: 33.2 ± 5.4 Constraint: 82.6 ± 9.4 Depression: 5.6 ± 6.6 **- CUD-H (n=24)** Age: 45.8 ± 7.8 Education: 12.7 ± 1.6 Gender: 6/24 Race: 16 African American (66.7%) Nicotine: 22.3 ± 11.9/17.4 ± 6.7/NA Alcohol: 17.3 ± 10.1/13.9 ± 2.8/4.1 ± 3.6 Cocaine: 16.8 ± 9.5/20.7 ± 6.3/6.9 ± 7.8 Cannabis: 10.3 ± 12.2/20.1 ± 5.3/1.5 ± 1.7 Severity of cocaine dependence: 4.8 ± 5.2	Beck Depression Inventory-II (BDI) Multidimensional Personality Questionnaire (MPQ)	**Another neuroimaging data -** HCP PreFreeSurfer pipeline, FLIRT, FNIRT, and statistical tools (SPM12 and VBM8)	heavy use with GMC in our main effect regions reached significance.	lateral OFC, while constraint and depression explained 10.2%, above and beyond the effects of age, education, TIV and lifetime drug use variables. Thus, beyond demographics and drug use, and beyond constraint and depression, the experience of childhood trauma-related to OFC GMC reduction. Decreased GMC in the right lateral OFC was also significantly associated with increased depression and decreased constraint.			

		Cocaine craving: 12.8 ± 14.0 Cocaine withdrawal: 16.1 ± 12.8 Cocaine: days since last use: 1.7 ± 1.2 Current alcohol: 11 dependence Childhood trauma: 57.9 ± 11.1 Constraint: 71.7 ± 14.1 Depression: 10.1 ± 8.5 **HC (CON) group (n=29)** Age: 41.9 ± 7.9 Education: 14.6 ± 1.9 Gender (F/M): 9/20 Race: 22 African American (75.9%) Nicotine: 16.7 ± 15.5/ 16.3 ± 2.2/NA Alcohol: 9.3 ± 10.1/17.3 ± 5.8/1.6 ± 1.2 Cocaine: NA Cannabis: NA Severity of cocaine dependence: NA Cocaine craving: NA Cocaine withdrawal: NA							

		Cocaine: days since last use: NA Current alcohol: 0 Childhood trauma: 34.2 ± 5.1 Constraint: 82.3 ± 8.2 Depression: 2.9 ± 4.2							
27. Rabin et al. 2021 (27)	**Study design -** cross-sectional **Participants -** 71 individuals with CUD (CUD+ / CUD-ST / CUD-LT) - cocaine primary drug of choice: smoking (n=51), nasally (n=17), a combination (n=2), or IV (n=1) 45 healthy controls (CTL)	**CD group (n= 71)** **- CUD + (n=28)** active users urine positive for cocaine (recent use <72h) Sex (M/F): 20/8 Race (Caucasian/AA/ other): 0/26/2 Age: 49.6 ± 6.0 Education: 12.7 ± 2.5 Verbal IQ (WRAT): 95.5 ± 9.4 Non-verbal IQ (matrix reasoning): 9.5 ± 3.4 Depression (BDI): 5.3 ± 3.9 Duration of cocaine abstinence (in days): 2.0 ± 1.4 (range 0-5 days) Cocaine age of onset: 23.1 ± 7.2	Structural Clinical Interview for DSM-IV/DSM-5 Addiction Severity Index (ASI) Cocaine Selective Severity Assess-ment Scale Cocaine Craving Questionn aire Beck Depressio n Inventory II Wide Range Achieveme	**MRI Scanner** - 3 T Skyra (Siemens) **Whole Brain or Regions of interest (ROIs) analysis** – whole brain and ROI (cerebellum and amygdala) **MRI techniques –** VBM; T1 weighted; HCP PreFreeSurfer structural pipeline **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -**	Significant group differences in the bilateral cerebellum -and bilateral amygdala. Revealed that compared to CTL and CUD-LT, CUD + had smaller bilateral GMV in the cerebellum -. Compared to CUD-LT, CUD + demonstrated lower GMV in the bilateral amygdala. Whole-brain analyses revealed significant positive associations between duration of cocaine abstinence and GMV in the bilateral cerebellum and right amygdala.	Whole-brain analyses revealed a significant positive association between ERT percent correct for happiness (but not sadness and fear) and GMV in the right cerebellum and a similar trend for left cerebellum.	No evidence	Left cerebellu m cortex Right cerebellu m cortex	Frequentist Bayesian

		Lifetime cocaine use (years): 22.4 ± 7.6 Days of cocaine use in past 30 days: 13.6 ± 7.8 Withdrawal (CSSA): 20.4 ± 11.1 Craving (CCQ): 26.7 ± 11.3 Cigarette smokers (current/past/never): 26/0/2 CPD of current smokers: 7.1 ± 5.6 Lifetime alcohol (years): 21.3 ± 9.7 Lifetime alcohol use to Intoxication (years): 3.9 ± 6.7 Days of alcohol use in past 30 days: 6.7 ± 5.5 Alcohol to intoxication in past 30 days: 0.8 ± 2.61 Current AUD (n): 2 Past SUD (n): 15 **- CUD-ST (n=23)** short-term abstinence defined by	nt Test III: Reading Scale Emotion Recognition Task (ERT) - from Cambridge Neuropsychological Test Automated Battery	HCP PreFreeSurfer structural pipeline (based on FSL 5.0.6 and FreeSurfer 5.3.0-HCP) MRI scans were conducted within one month of the Emotion Recognition Task (ERT) administration					

		negative urine for cocaine and self-reported abstinence of less than 6 months Sex (M/F): 22/1 Race (Caucasian/AA/ other): 2/20/1 Age: 47.7 ± 8.0 Education: 12.6 ± 1.7 Verbal IQ (WRAT): 93.7 ± 10.9 Non-verbal IQ (matrix reasoning): 10.3 ± 3.2 Depression (BDI): 6.2 ± 8.3 Duration of cocaine abstinence (in days): 35.9 ± 40.6 (range 23-120 days) Cocaine age of onset: 23.1 ± 5.0 Lifetime cocaine use (years): 19.5 ± 8.2 Days of cocaine use in past 30 days: 2.70 ± 4.4 Withdrawal (CSSA): 10.8 ± 9.4 Craving (CCQ): 13.6 ± 10.1							

		Cigarette smokers (current/past/never): 17/6/0 CPD of current smokers: 6.8 ± 5.5 Lifetime alcohol (years): 17.4 ± 10.4 Lifetime alcohol use to Intoxication (years): 5.0 ± 7.9 Days of alcohol use in past 30 days: 1.4 ± 2.3 Alcohol to intoxication in past 30 days: 0.4 ± 1.3 Current AUD (n): 3 Past SUD (n):14 **- CUD-LT (n=20)** long-term abstinence defined by negative urine for cocaine and self-reported abstinence for 6 months or longer Sex (M/F): 18/2 Race (Caucasian/AA/other): 2/13/5 Age: 45.8 ± 7.4							

		Education: 12.7 ± 1.5 Verbal IQ (WRAT): 98.5 ± 10.5 Non-verbal IQ (matrix reasoning): 9.5 ± 2.9 Depression (BDI): 6.8 ± 7.6 Duration of cocaine abstinence (in days): 1603.6 ± 1487.8 (range 182–5840 days) Cocaine age of onset: 23.2 ± 5.8 Lifetime cocaine use (years): 15.8 ± 6.7 Days of cocaine use in past 30 days: 0.0 Withdrawal (CSSA): 13.0 ± 14.8 Craving (CCQ): 4.5 ± 7.3 Cigarette smokers (current/past/never): 11/7/2 CPD of current smokers: 8.3 ± 5.9 Lifetime alcohol (years): 20.6 ± 10.7 Lifetime alcohol use to Intoxication							

		(years): 9.8 ± 10.0 Days of alcohol use in past 30 days: 1.3 ± 3.6 Alcohol to intoxication in past 30 days: 0.0 ± 0.0 Current AUD (n): 1 Past SUD (n): 17 **HC group (n=45)** Sex (M/F): 30/15 Race (Caucasian/AA/ other): 7/32/6 Age: 39.4 ± 9.2 Education: 13.6±2.9 Verbal IQ (WRAT): 100.9±9.5 Non-verbal IQ (matrix reasoning): 10.7±2.8 Depression (BDI): 4.1±5.9 Cigarette smokers (current/past/never): 11/5/29 CPD of current smokers: 4.2±2.5 Lifetime alcohol (years): 11.1±11.3							

		Lifetime alcohol use to Intoxication (years): 1.5±3.7 Days of alcohol use in past 30 days: 1.3±2.5 Alcohol to intoxication in past 30 days: 0.1±0.6							
28. Konova et al. 2012 (28)	**Study design -** case control **Participants -** 21 CUD used crack ⁄ cocaine in the past 14 days (n=19) 21 healthy controls matched on all demo-graphic variables except for cigarette smoking history	**CD group (n= 21)** Age (years): 43.1±1.6 Gender (M/F): 17/4 Race (African American⁄ Caucasian⁄ Hispanic⁄ Asian): 16/4/0/1 education (y): 13.6±0.4 Verbal IQ (WRAT III: Reading Scale): 94.9±2.8 Non-verbal IQ (WASI - Matrix Reasoning Scale): 10.2 ±0.8 Depression (BDI-II): 5.0±1.0 Socioeconomic status (HI): 35.0±2.9 Cigarette smokers (current or past⁄	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Wide Range Achievement Test III – Reading Scale Wechsler Abbreviated Scale of Intelligence – Matrix Reasoning Scale Beck Depression Inventory II	**MRI Scanner** - 4T (Varian/Siemens) **Whole Brain or Regions of interest (ROIs) analysis** – whole brain and ROI (striatum and ventromedial prefrontal cortex) **MRI techniques –** T1 and T2 weighted; VBM **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – Yes **DTI** – **Another neuroimaging data -**	Compared with controls, CUD had reduced gray matter volume of the medial orbitofrontal cortex extending to the gyrus rectus. No group differences were observed for the striatum. Parametric deactivations with increasing money value were observed in the left pre-⁄subgenual anterior cingulate cortex and bilateral middle⁄ posterior cingulate, consistent with these regions' roles within the default mode network.	In CUD, accuracy was negatively correlated with BOLD response in the putamen (50¢ > 0¢), such that higher activity was associated with lower differential accuracy (50¢ > 0¢). Cocaine use (days ⁄ week in the past year) correlated positively with. activation in the putamen (50¢ > 0¢). For the VMPFC (cluster from the group effect), there was a negative correlation with cocaine craving. Across subjects, the linear	No evidence	Bilateral caudate Bilateral medial orbitofrontal	Frequentist Bayesian Coordinates

		non-smokers): 16/5 Daily cigarettes (current smokers): 12.3±1.8 Time since last cigarette (within 4 h / > 4 h / overnight or more): 7/3/3 Alcohol use lifetime (years): 15.1±2.8 Cocaine use lifetime (years): 17.8±1.5 Duration of current abstinence/time since last cocaine use (days): 100.6±86.8 (median= 3) Days / week of cocaine use during the past 12 months:3.1±0.5 Withdrawal symptoms: 18-item CSSA (0–126): 12.7±1.9 Cocaine craving: five-item questionnaire (0–45): 15.2±2.3 **HC group (n=21)** Age (years): 38.9 ± 1.3	Wide Range Achievement Test III: Reading Scale Hollingshead index monetary reward paradigm (also described in Goldstein et al., 2007, 2009a, 2010)			contrast for money revealed increased activation in several brain regions that have been reported in previous reward studies (Liu et al., 2011), including the right cerebellum and left inferior frontal gyrus (a cluster encompassing the left anterior insula).			

		Gender (M/F): 18/3 Race (African–American / Caucasian / Hispanic / Asian): 12/6/2/1 education (y): 14.1±0.4 Verbal IQ (WRAT III: Reading Scale): 101±2.5 Non-verbal IQ (WASI - Matrix Reasoning Scale): 10.8±0.6 Depression (BDI-II): 2.7±0.8 Socioeconomic status (HI): 34.6±2.6 Cigarette smokers (current or past/non-smokers): 5/16 Daily cigarettes (current smokers): 8.3±2.3 Time since last cigarette (within 4 h/> 4 h/ overnight or more): 1/3/0 Alcohol use lifetime (years): 10.6±3.5							
29.	**Study design -** cross-sectional	**SDI group (n= 19)**	DSM-IV criteria	**MRI Scanner** - 3-T MR scanner	There was significantly	A small, significant	SUD-Alcohol in >50%	Right medial orbitofrontal	Frequentist Bayesian

Tanabe et al. 2009 (29)	**Participants -** 19 SDI (9 women/10 men) 20 control subjects (14 women/6 men)	Age: 35±7 (21-47) Gender: 10M/9F IQ: 103±12 (80-121) Education: 12±3 (6-16) Dependence/abuse and last use (yrs): Cocaine 14/3 and 4.7 ± 4.8 (0.2–18) Alcohol: 13/2 and 3.2 ± 8.3 (0.8–9) Amphetamine 12/2 and 2.4 ± 2.1 (1–8) Cannabis 11/4 and 4.4±4.6 (0.2-16) Opiate 5/2 and 6.4 ±7.4 (0.2-22) Club drugs 1/2 and 5.3±5.9 (1-18) Hallucinogens 1/9 and 8.0±6.3 (0.3-22) Sedative 1/4 and 5.7±6.5 (0.3-22) **HC group (n=20)** Age: 33±11 (23-50) Gender: 6M/14F IQ: 112±8 (91-130) Education: 14±2 (12-19)	Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM) Wechsler Abbreviated Scale of Intelligence in which Vocabulary Matrix Reasoning subtests	**Whole Brain or Regions of interest (ROIs) analysis** – whole brain and ROI (right and left medial OFC) **MRI techniques –** VBM; T1 and T2 weighted **Cortical thickness –** **Brain Volumes -** **Cortical Surface Area** – **fMRI** – **DTI** – **Another neuroimaging data -** We used a modification of the IGT adapted for a functional magnetic resonance imaging (MRI) experiment.	more GM specifically in bilateral medial OFC in control subjects compared with SDI; The most significant difference was right medial OFC. Left and right medial orbitofrontal regions confirmed the results from the whole brain analyses (control > SDI)	negative correlation between medial OFC GM volume and avoidance of bad decks was observed across groups. Among SDI there was no correlation between medial OFC GM volume and abuse and dependence symptom count (11 total, from 7 dependence and 4 abuse symptoms).		Left medial orbitofrontal	

30. Schlaepfer et al. 2005 (30)	**Study design -** cross sectional **Participants -** 16 male substance abusers, included cocaine IV (n=14), methamphetamine (n=9), heroin IV (n=15) and cannabis (n=16) 16 male healthy controls matched in age, sex and race	**CD group (n= 16)** Mean age 38.8±6.2 yr History of substance abuse of 7–12 yr (9.2 ± 3.2 yr) Educational level: -Completed high school (n=13) -Completed college or professional school (n=3) **HC group (n= 16)** Age (38.4 ± 7.4 yr) Educational level: -Completed high school (n=12) -Completed college or professional school (n=4)	DSM-IV SCID interview	**MRI Scanner** - 1.5 T Signa **Whole Brain or Regions of interest (ROIs) analysis** – whole brain and ROI **MRI techniques –** Proton density and T2-weighted images **Cortical thickness – No** **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** Cavalieri principle of stereological volume measurements	Total brain volume / Grey-matter volume / White-matter volume / Volume of lateral ventricles / Frontal grey-matter volume / Frontal grey-matter volume Substance abusers had significantly less frontal white-matter volume percentage than controls as determined either by the segmentation method or by the stereological method. Volumes for total grey matter, total white matter, frontal grey matter, and lateral ventricles were not significantly different in the two groups.	The two methods of analysis of brain volume (segmentation and stereology) were used to cross-validate observed differences between substance abusers and controls.	No evidence	Bilateral lateral ventricle	Frequentist Bayesian
31. Franklin et al. 2002 (31)	**Study design -** Cross sectional **Participants -** 13 male COC patients ("crack" smoking was the primary mode of cocaine administration) 16 male control subjects	**CD group (n= 13)** Mean age: 42 (SD 6.3) Mean years of cocaine use approximately: 13 (SD 6.5) Average number of days of	DSM-IV DSM-IV Axis-I or Axis-II disorders Cocaine Selective Severity	**MRI Scanner** - 1.5 T **Whole Brain or Regions of interest (ROIs) analysis** – Whole brain **MRI techniques –** T1-weighted	significant gray matter concentration decreases in the Ventromedial orbitofrontal cortex (VMOF), Anterior cingulate (AC), Anteroventral insular cortex (AVI), and superior temporal cortices of the COC	There still were no significant correlations between density decreases in the COC group and dollar amount spent during a cocaine binge, years of cocaine use, or number	No evidence	Left insula Left lateral orbitofrontal Right lateral orbitofrontal Right rostral anterior cingulate Left superior temporal	Frequentist Bayesian Coordinates

		cocaine used during the last 30: 15 (SD 7.3) Spending roughly $106.00 (SD $154.40) Years of education: 12 (SD=1.1) Race: -Black American (n=13) **HC group (n= 16)** Mean age: 32 (SD= 6.9) Years of education: 17 (SD= 2.6) Race: -Black American (n=6) -White American (n=9) -Asian American (n=1)	Assessment (CSSA) Beck Depression Inventory (BDI) Addiction Severity Index (ASI) Schedule of Affective Disorders and Schizophrenia – Lifetime (SADS-L) interview Global Assessment of Functioning (GAF) ratings	**Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -**	group in comparison with the control group	of days used out of the last 30. The COC group was 100% black American and the control group was 38% black American, 56% white American, and 6% Asian American.		Right superior temporal + coordinates	
32. G. Fein et al. 2002 (32)	**Study design -** comparative cross-sectional neuroimaging study with correlational analysis **Participants -** 46 substance dependent male subjects at 6-week abstinence:	**CD group (n= 46)** **—Cr (n=17)** Age: 39±7 Years of education: 13.4 ±1.3 Ethnicity: 16 AA, 1 C Mean lifetime alcohol use (drinks/month): 22±31	DSM-IV MicroCog Assessment of Cognitive Functioning	**MRI Scanner** - 1.5 T **Whole Brain or Regions of interest (ROIs) analysis** – Whole Brain **MRI techniques –** T1-weighted, T2-weighted and a proton-density (PD) weighted image,	Normal controls, CrA and Cr did not differ on IC (1453+- 148 cm3 versus 1429+-132 cm3 versus 1369+-87 cm3, ns).	There were no differences among the groups in volumes of total cortical gray matter, white matter, ventricular or sulcal CSF.	SUD-Alcohol in >50% No evidence	Bilateral caudal middle frontal Bilateral caudal middle frontal	Frequentist Bayesian

	-17 Crack-cocaine dependent subjects (Cr) - 29 crack-cocaine and alcohol dependent subjects (CrA) 20 Health controls (HC) *Subjects were monitored via urine screens that tested for the presence of alcohol, cocaine, amphetamines, benzodiazepines, and opiates. ** exclusion criteria: other substances dependence	Duration of mean lifetime alcohol use (months): N/A Peak alcohol use (months): N/A Duration of peak alcohol use (months): N/A Mean lifetime crack use. (Dollars/months) : 977 ±1178 Duration of mean lifetime crack use (months):174±75 Peak crack use (dollars/month): 2739±2935 Duration of peak crack use (months): 26±25 —**CrA group (n=29)** Age: 42±6 Years of education: 12.8±2.0 Ethnicity: 16 AA, 6 C, 7 H Mean lifetime alcohol use (drinks/month): 286±232 Duration of mean lifetime alcohol use		**Cortical thickness – No** **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -**					

		(months): 288±89 Peak alcohol use (months): 544 ±289 Duration of peak alcohol use (months):67±66 Mean lifetime crack use. (Dollars/months) : Duration of mean lifetime crack use (months): Peak crack use (dollars/month): Duration of peak crack use (months) Age: Years of education: Ethnicity: Mean lifetime alcohol use (drinks/month): Duration of mean lifetime alcohol use (months): Peak alcohol use (months): Duration of peak alcohol use (months) Mean lifetime crack use.							

		(Dollars/months): Duration of mean lifetime crack use (months): Peak crack use (dollars/month): Duration of peak crack use (months) **HC group (n= 20)** Age: Years of education: Ethnicity: Mean lifetime alcohol use (drinks/month): Duration of mean lifetime alcohol use (months): Peak alcohol use (months): Duration of peak alcohol use (months) Mean lifetime crack use. (Dollars/months): Duration of mean lifetime crack use (months): Peak crack use (dollars/month):							

		Duration of peak crack use (months)							
33. J. A. Matochik et al. 2003 (33)	**Study design -** cross-sectional **Participants -** 14 individuals with history of cocaine disorder 11 healthy control individuals Exclusion criteria: a past or current history of neurological problems, abnormal findings on the neurological examination, pregnancy, or left-handedness *matched for age and level of education	**CD group (n= 14)** Age(y): 36.3±4.7 (range 28-43) Education (y): 13.1±1.6 Mother's education (y): 12.0±2.9 Shipley IQ: 96.4±11.6 Cocaine use/week (g): 3.4±2.8 Cocaine use duration (y): 8.1±5.0 Gender (M/F): 11/3 Ethnicity -African america n: 10 -Asian: 1 -Caucasian: 3 -Hispanic: - **HC group (n= 11)** Age(y): 33.8±4.5 (range 28-42) Education(y): 14.5±3.0 Mother's education (y): 13.9±3.1 Shipley IQ: 100.3±10.0 Gender (M/F): 7/4	Diagnostic and Statistical Manual of Mental Disorders–IV Drug Use Survey Questionn aire Addiction Severity Index Diagnostic Interview Schedule Shipley Institute of Living Scale (Shipley IQ)	**MRI Scanner** - 1.5-T **Whole Brain or Regions of interest (ROIs) analysis** – Regions of interest **MRI techniques –** T1-weighted; VBM **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** software SPM99 gray matter and white matter	Subjects in the comparison group had a greater density of gray matter in the cingulate gyrus, lateral prefrontal cortex, and medial and lateral aspects of the orbitofrontal cortex, primarily in the right hemisphere. Analysis of white matter in the frontal cortex found no regions where there were differences in tissue density between subjects.	The duration of cocaine use (in years) was negatively correlated with tissue density in the white matter contained within the small volume template for the frontal cortex. There was no correlation (positive or negative) of gray matter tissue density in the frontal cortex with duration of cocaine use.	No evidence	Right caudal middle frontal Bilateral caudal middle frontal Bilateral caudal middle frontal Right lateral orbitofrontal Left medial orbitofrontal Right medial orbitofrontal Left rostral anterior cingulate Left rostral anterior cingulate Right rostral anterior cingulate Right rostral anterior cingulate Right rostral anterior cingulate + Coordinates	Frequentist Bayesian Coordinates

		Ethnicity -African americaⁿ: 6 -Asian: - -Caucasian: 4 - Hispanic: 1							
34. K.-M. Wakim et al. 2022 (34)	**Study design** - cross-sectional **Participants:** Initial Sample: The study initially enrolled 93 participants. Exclusions for MRI Data Analysis: After quality control, 86 participants were included in the final MRI dataset, as some scans were excluded due to cocaine-positive urine samples or low-quality imaging. Neurocognitive Testing: For neurocognitive testing analysis, 90 participants were retained after similar exclusions for quality control and drug-positive tests on the testing day. Four groups of participants were recruited: Participants: 90 HIV- CD (n = 34) (M/F: 13: 21) Age in years: M (SD): 42.7 (12.2)	KMSK, M (SD) [range] **Cocaine** HIV-/CD- 0.55 (2.02) [0, 10%] HIV-/CD+ 14.30 (2.00) [10, 16] HIV+/CD- 0.50 (1.10) [0, 4] HIV+/CD+ 13.20 (3.26) [7, 16] **Opiates** HIV-/CD- 0.09 (0.514) [0, 3] HIV-/CD+ 7.95 (5.45) [0, 13] HIV+/CD- 0 (0) [0, 0] HIV+/CD+ 1.20 (2.40) [0, 7] **Tobacco** HIV-/CD- 3.16 (3.96) [0, 11]	Kreek-McHugh-Schluger-Kellogg Scale (KMSK) Barratt Impulsivity assessment (BIS) DSM-5 Wechsler Adult Intelligence Scale (WAIS) Trail Making Test (Trails A and B) Hopkins Verbal Learning Test – Revised (HVLT-R) International HIV Dementia	**MRI Scanner** - 3 Tesla (3T) Siemens Prisma whole-body scanner was used, equipped with a 64-channel head coil. **Whole Brain or Regions of interest (ROIs) analysis** – Both whole-brain and ROI analyses were conducted. Regions specifically examined included the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula, caudate, and putamen. **MRI techniques –** Structural T1-weighted imaging using MPRAGE sequence.	The study did not find significant interaction effects between HIV and CD on brain structure or neurocognitive performance. Primary findings indicated that HIV status was the main driver of neurocognitive impairment, with CD as a secondary contributor. Higher caudate volume was observed in participants with a history of cocaine dependence. HIV+ participants exhibited cortical thinning in the left precentral gyrus, showing some impact on brain structure.	HIV individuals - Unlike some studies suggesting compounded effects of comorbid conditions, this study's finding of no synergistic effect between HIV and CD is intriguing. It suggests that while both conditions impact brain health, their combined presence may not exacerbate neurocognitive or structural decline as initially hypothesized.	HIV+	Bilateral caudate Bilateral insula Bilateral insula Bilateral medial orbitofrontal Bilateral medial orbitofrontal Bilateral putamen Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate Bilateral caudate Bilateral insula Bilateral insula Bilateral medial orbitofrontal Bilateral medial orbitofrontal Bilateral putamen Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate	Frequentist Bayesian

	CD+ (n = 21) (M/F: 12: 9) Age in years: M (SD): 42.6 (10.3) HIV+ CD (n = 20) (M/F: 13: 7) Age in years: M (SD): 44.7 (13.1) CD+ (n = 15) (M/F: 8: 7) Age in years: M (SD): 49.1 (7.4)	HIV-/CD+ 9.81 (3.23) [0, 13] HIV+/CD- 5.55 (5.35) [0, 13] HIV+/CD+ 8.36 (3.15) [0, 12] **Alcohol** HIV-/CD- 6.97 (3.12) [0, 12] HIV-/CD+ 10.86 (2.49) [4, 13] HIV+/CD- 7.45 (3.42) [0, 13] HIV+/CD+ 9.60 (3.54) [0, 13]	Scale (IHDS)	High-resolution structural MRI images were processed for cortical thickness and brain volume assessments. **Cortical thickness – yes** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data -** Vertex-wise analysis identified lower cortical thickness in the left precentral gyrus among HIV+ individuals, controlled for multiple comparisons.					
35. Rothmann et al. 2023 (35)	Study design: cross-sectional **Participants: 80** **CUD,** n1= 30, 16 females/14 male) age 31.50 (±6.15)	Cocaine use disorder: CUD: Years of regular use: 7.3 (±4.20) Age of onset (years): 20.5 (±5.92)	The Structured Clinical Interview for DSM-V Addiction Severity Index (ASI-	**MRI Scanner** - GE HDxt 3T scanner with an eight--channel radiofrequency head coil to measure the CT. A high-resolution T1-	Significant differences in CT were found between the groups in both hemispheres. Cocaine Use Disorder (CUD) participants showed intermediate CT values: - Lower than young	CUD participants exhibited brain aging patterns resembling those of elderly controls in certain regions, despite being	SUD-Cannabis in >50%	Right fusiform Right inferior parietal Left inferior temporal Right inferior temporal	Frequentist Bayesian

	Health Control Group (YC, n1= 30, 16 females/14 male) young participants; age 30.33 (±5.01) **Elderly Control Group** (EC, n1= 20, 14 females/6 male) adults who participated in the Brazilian SuperAgers study (Borelli et al., 2021), investigating protective factors against dementia and Alzheimer's disease (AD). age 80 years old or above; 82.37 (±2.39)	Lifetime Use ratio: 0.23 (±.12) Past 30 days use: 15.1 (±12.74) Cannabis use disorder **Age--paired control group:** Cannabis use disorder:0 Years of regular use:0.4 (±.55) Age of onset (years): 19.3 (±4.52) Lifetime use ratio:0.002 (±.11) Past 30 days use:0 (±.0) **Cocaine use disorder group:** Cannabis use disorder: 20 Years of regular use: 4.2 (±4.17) Age of onset (years): 15.8 (±3.60) Lifetime use ratio: 0.12 (±.13) Past 30 days use: 4.2 (±10.49) Tobacco use disorder Age--paired control group:	-6) Mini-Mental State Examination (MMSE)	weighted anatomical image was collected. **Whole Brain or Regions of interest (ROIs) analysis** – whole-brain **MRI techniques –** FreeSurfer 6.0 **Cortical thickness – yes** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data -** Statistical analyses were performed using Statistical Package for the Social Sciences.	controls (YC) ($p = 0.016$). - Higher than elderly controls (EC) ($p < 0.001$) - The YC group had higher CT values than the EC group ($p < 0.001$). The right fusiform gyrus in the CUD group displayed CT values similar to the EC group, significantly thinner than YC. In regions such as the right inferior temporal gyrus, inferior parietal cortex, and left superior parietal cortex, CUD values fell between YC and EC. Certain areas (e.g., right pars triangularis, superior temporal gyrus, precentral gyrus) showed reduced CT in the CUD group compared to YC but were not related to EC values.	approximately 50 years younger. Findings support the hypothesis of **accelerated brain aging** in CUD, emphasizing the impact of substance use on cortical thinning and neurodegeneration.		Right paracentral Right pars triangularis Left precentral Right precentral Right precentral Right precuneus Right rostral middle frontal Left superior frontal Right superior frontal Left superior parietal Left superior temporal Right superior temporal Left supramarginal Right supramarginal Right transverse temporal	

		Tobacco use disorder: 4 Years of regular use: 1.60 (±2.50) Age of onset (years): 16.7 (±3.93) Lifetime use ratio: 0.03 (±.06) Past 30 days use: - **Cocaine use disorder group:** Tobacco use disorder:12 Years of regular use: 4.96 (±5.62) Age of onset (years): 14.1 (±3.32) Lifetime use ratio: 0.15 (±.19) Past 30 days use: 18.5 (±14.05) **Elderly control group:** Tobacco use disorder: 5 Years of regular use: 18.4 (±12.4) Age of onset (years): - Lifetime use ratio: 0.69 (±.13) Past 30 days use: - **Alcohol use disorder Age--paired**							

		control group: Alcohol use disorder: 0 Years of regular use: 0.7 (±1.17) Age of onset (years): 17.0 (±3.14) Lifetime use ratio: 0.02 (±.03) Past 30 days use: 0.8 (±2.85) **Cocaine use disorder group:** Alcohol use disorder: 15 Years of regular use: 5.4 (±7.29) Age of onset (years): 14.4 (±2.72) Lifetime use ratio: 0.16 (±.19) Past 30 days use: 4.0 (±6.83) **Elderly control group:** Alcohol use disorder:0 Years of regular use: 0.3 (±1.25) Age of onset (years): - Lifetime use ratio: 0.003 (±.01) Past 30 days use:-							

36. S.Gardini, A. Venneri 2011 (36)	Study design: cross-sectional **Participants: 62** 24 healthy controls mean age = 33.21, SD = 7.06; mean education = 12.75, SD = 2.47 14 cocaine abuse mean age = 31.07, SD = 5.86; mean education = 11.21, SD = 3.33 24 individuals had opiate abuse mean age = 31.33, SD = 5.23; mean education = 9.62, SD = 2.81	Heroin patients: mean years of abuse 11.29, SD 5.61 Cocaine patients: mean years of abuse 13.41, SD 4.94 Some individuals were polydrug users, but the study does not provide detailed information about the specific additional drugs used.	Structured Clinical Interview for DSM–SCID I	**MRI Scanner** - 3T Philips Intera MRI system with a Turbo Field Echo sequence. **Whole Brain or Regions of interest (ROIs) analysis** – Gray matter volumes in the whole brain were analyzed. Focused comparisons in areas such as the posterior insula, middle occipital gyrus, putamen, posterior cingulate, cerebellum, and parahippocampal gyrus. **MRI techniques –** Voxel-Based Morphometry (VBM). **Cortical thickness – no** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no	Cocaine abusers had **lower gray matter volumes** in the following regions: 1. Left Middle Occipital Gyrus 2. Right Lentiform Nucleus 3. Right Posterior Insula	Cocaine abuse impacted limbic and medial-temporal regions (e.g., posterior cingulate, parahippocampal gyrus, cerebellum), which are associated with emotion regulation and memory. Heroin abusers had lower gray matter volumes in Right Posterior Insula. Heroin abuse predominantly affected parietal and frontal regions (e.g., precentral gyrus, postcentral gyrus, inferior parietal lobule), which are linked to pain perception, motor control, and somatosensory processing. No significant differences were found in white matter volumes	No evidence	Left cuneus Right insula Right putamen	Frequentist Bayesian Coordinates

				Another neuroimaging data -					
37. Parvaz et al. 2011 (37)	Study design: cross-sectional **Participants: 39 17 HC** (10 male/7 female) **Age 40.3 ± 6.7** **22 CUD** (18 male/4 female) Age 42.9 ± 6.2	Cigarette smokers (current or past/nonsmokers) HC 4/13 CUD 17/5 Cigarette use (lifetime, years; current or past smokers) HC 17.2 ± 11.3 CUD 20.6 ± 9.0	Clinical interview for DSM-IV Axis I Disorders Wide Range Achievement Test WRAT-3 Wechsler Abbreviated Scale of	**MRI Scanner** - 4-T Varian/Siemens scanner. T1-weighted anatomical scan. **Whole Brain or Regions of interest (ROIs) analysis** – whole-brain and regions of interest (ROIs):	**MRI Results (Gray Matter Volume and P300 Correlations)** **Healthy Controls**: A significant positive correlation was found between **P300 reward modulation** (45¢ – 0¢) and **regional gray matter (GM) volume** in:	**Healthy Controls**: Showed robust reward sensitivity in both P300 amplitude and GM volume in PFC subregions. Greater PFC GM volume was associated with stronger reward-modulated P300	No evidence	Right lateral orbitofrontal Left pars opercularis Right rostral anterior cingulate Right rostral middle frontal	Frequentist Bayesian Coordinates

		Daily cigarettes (current smokers: n = 3/16) HC 10.0 ± 7.0 CUD 10.7 ± 6.1 **Age of onset of cocaine use (years)** **24.1 ± 6.5** **Duration of current abstinence (days)** **4.5 ± 4.9** **Severity of Dependence Scale** **6.1 ± 3.9** **Cocaine use (past 30 days)15.1 ± 8.3** **Cocaine use (lifetime, years)17.8 ± 6.9** Alcohol use (past 30 days; n = 7/22) HC 1.9 ± 2.0 CUD 5.9 ± 6.9 Alcohol use (lifetime, years; n = 7/22) HC 9.9 ± 10.8 CUD 15.0 ± 12.0	Intelligence (WASI) Beck Depression Inventory II Hollingshead Index Cocaine Selective Severity Assessment Scale (CSSA)	Dorsolateral prefrontal cortex (DLPFC) Ventrolateral prefrontal cortex (VLPFC) Anterior cingulate cortex (ACC) Lateral orbitofrontal cortex (OFC) **MRI techniques –** Voxel-Based Morphometry (VBM) **Cortical thickness – no** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data -** The study combined EEG data (P300 amplitude responses) with MRI-derived structural information to investigate correlations between electrophysiological sensitivity to	Right dorsolateral prefrontal cortex (DLPFC; BA 46). Right anterior cingulate cortex (ACC; BA 32). Left ventrolateral prefrontal cortex (VLPFC; BA 44). Right lateral orbitofrontal cortex (OFC; BA 47). No correlations were found for absolute P300 amplitudes. **Cocaine Use Disorder (CUD)**: No significant correlations were observed between P300 responses and GM volume. This indicates a lack of reward-related structural-functional coupling in CUD participants. **Group Comparisons (Gray Matter Volume Differences)** Healthy controls showed **significantly greater GM volume** in: Left VLPFC (BA 44). Left OFC (BA 11, including the rectal gyri). No regions had greater GM volume in the CUD group compared to controls.	amplitudes. **Cocaine Use Disorder (CUD)**: Demonstrated reduced P300 reward sensitivity and diminished PFC GM volume. No significant correlation between GM volume and reward-related P300 modulation. These findings highlight the **critical role of PFC structural integrity** in modulating reward-related neural responses, which is disrupted in individuals with CUD.			

				reward and gray matter volume in the PFC.					
38. A. O. Ceceli et al. 2022 (38)	Study design: cross-sectional **Participants: 96** 32 individuals with HUD Heroin Use Disorder [aged 40.2 (standard deviation=7) years, 7 females/ 25 male] 32 individuals with CUD [aged 43.4 (standard deviation=7) years, 6 females/ 26 male] 32 HC [aged 41.1 (standard deviation =9) years, 6 females/ 26 male],	Cigarette smoker (Current/Past/Never) HC 9/7/16 CUD 25/6/1 HUD 32/0/0 Days since last use: HC - CUD 241 (545) HUD 199 (258) Past month use, days: HC - CUD 5.62 (8.2) HUD 0.22 (0.7) Lifetime use, years: HC - CUD 16.5 (8.4) HUD 11.0 (7.7) included alcohol use disorder	Mini International Neuropsychiatric Interview Statistical Manual of Mental Disorders (DSM)-5 disorders Addiction Severity Index Short Opiate Withdrawal Scale Cocaine Selective Severity Assessment	**MRI Scanner** - Siemens 3.0 T Skyra (Siemens Healthcare) with a 32-channel head coil. **Whole Brain or Regions of interest (ROIs) analysis** – Whole brain and ROIs, **fronto-striatal regions**, including: Ventromedial prefrontal cortex (vmPFC). Inferior frontal gyrus (IFG). Striatum (nucleus accumbens, caudate, and putamen). **MRI techniques –**	Overall, individuals with heroin use disorder had smaller vmPFC and NAcc/putamen volumes than healthy controls. Bilateral lower IFG grey matter volume patterns were specifically evident in cocaine versus heroin use disorders. Correlations between addiction severity measures and putamen grey matter volume did not reach nominal significance level in this sample. These results indicate alterations in dopamine-innervated regions (in the vmPFC and NAcc) in heroin addiction. For the first time we demonstrate lower IFG grey matter volume specifically in cocaine compared with heroin	Unlike heroin addiction, **no significant differences in GMV** were found between the CUD group and healthy controls for most brain regions. This finding contradicts previous studies showing structural impairments in **prefrontal and striatal regions** in cocaine users. It raises questions about whether these null results reflect **methodological differences**, smaller sample	SUD-Cannabis/Alcohol in >50%	Bilateral medial orbitofrontal Right pars triangularis Left ventral DC	Frequentist Bayesian

		(HUD n=3; CUD n=11) Marijuana use disorder (HUD n=1; CUD n=7) Sedative use disorder (HUD n=4; CUD n=1) Phencyclidine use disorder (CUD n=1) Meth/amphetamine use disorder (HUD n=2; CUD n=1) Major depressive disorder (HUD n=3) Post-traumatic stress disorder (CUD n=1) and specific phobias (CUD n=2).	Heroin Craving Questionnaire Cocaine Craving Questionnaire	Voxel-Based Morphometry (VBM) **Cortical thickness – no** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data -** Associations between GMV and measures such as craving, dependence severity, and drug use patterns were analyzed. Specific trends (e.g., posterior putamen GMV linked to cocaine craving) were identified but did not survive correction for multiple comparisons.	use disorder, suggesting a signature of reduced inhibitory control, which remains to be tested directly using select behavioural measures. Overall, results suggest substance-specific volumetric changes in human psychostimulant or opiate addiction, with implications for fine-tuning biomarker and treatment identification by primary drug of abuse.	sizes, or the unique neurobiology of chronic cocaine users.			

39. Q. He et al. 2018 (39)	Study design: cross-sectional 39 male military veterans with different stages of cocaine addiction and long-term abstinence (from 1 year up to 30 years) **Participants: 39** Age 56.5 ± 5.4 years. **CUD 32** **HC 7**	**USERS:** Participants who had used cocaine within the last year (n = 12). Reported **continuous cocaine use** within the past year. However, the study does not specify the cumulative duration of cocaine use. **ABSTINENCE:** Participants in abstinence from cocaine for varying periods (n = 20). Subdivided into three subgroups: **ABS1:** 1-5 years of abstinence (n = 5). **ABS2:** 6-10 years of abstinence (n = 5). **ABS3:** More than 10 years of abstinence (n = 10). Não diz o tempo	Beck Depression, Inventory (BDI) Drug Use and Addiction History Symptom Checklist-58 (SCL-58) SF-36 Health Survey	**MRI Scanner** - 3T Siemens MAGNETOM Tim/Trio scanner, 12-channel head coil. **Whole Brain or Regions of interest (ROIs) analysis** – Whole Brain and ROIs: Striatum: Associated with reward processing. Insula: Linked to craving. Lateral Prefrontal Cortex (LPFC): Involved in inhibitory control. Medial Orbitofrontal Cortex (mOFC) and Ventromedial Prefrontal Cortex (vmPFC): Key regions for decision-making. **MRI techniques:** voxel-based morphometry (VBM). T1-weighted 3D	The results suggest that there are significant differences in brain structure (GMV) between cocaine USERS and CONTROLS, with USERS showing higher volumes in the neural systems for processing reward and craving (striatum and insula), and lower volumes in neural systems involved in both inhibitory control (lateral aspects of prefrontal cortex) and decision-making (medial aspects of OFC/VMPFC region). These differences can reflect the imbalance USERS typically have, as hypo-activity in prefrontal regions is often linked to reduced GMV and insular abnormality can be associated with increased GMV. These results further show that after a period of cocaine abstinence, there are observed differences in GMV that may reflect neural recovery compared with the USERS group. These possibly recovered regions stretch over three neural systems (reward,	Cocaine-dependent patients were screened and recruited from the original 321 male military veterans who met dependence criteria for cocaine and were admitted to cocaine treatment in 1988–1989. Follow-up interviews were conducted in 1990–1991, 1991–1992, and 2002–2003.	No evidence	Right caudate Left caudate Right frontal pole Left insula Left medial orbitofrontal Right medial orbitofrontal Left rostral middle frontal Bilateral superior frontal	Frequentist Bayesian

		de uso, apenas abstinência.		Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence. Blood Oxygen Level Dependent (BOLD) imaging during a **cue-reactivity task** **Cortical thickness – no** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – yes **DTI** – no **Another neuroimaging data -** Connectivity changes were correlated with years of abstinence.	craving, and inhibitory control), but do not include the neural system linked to decision-making. Specifically, the ABSTINENCE group showed higher GMV (relative to USERS) in the lateral frontal pole bilaterally, and the DLPFC bilaterally, whereas USERS showed higher GMV (relative to the ABSTINENCE group) in the right striatum.				
40. D. G. Smith et al. 2013 (40)	Study design: cross-sectional (brief report) Participants: 58 healthy control volunteers with body mass indexes (BMI) ranging from normal weight to obese. 60 cocaine-dependent individuals with similar	**Healthy controls (n=58)** BMI: 17.8–33.5, mean = 25.5 **Cocaine-dependent individuals (n=60)** BMI: 16.6–32.7, mean= 24.2	Not informed	**MRI Scanner** - 3T **Whole Brain or Regions of interest (ROIs) analysis** – Regions of interest **MRI techniques –** T1 structural	In control participants, four significant clusters negatively correlated with BMI bilaterally throughout the OFC ($P < 0.001$), whereas in cocaine users, two regions in the right OFC negatively correlated with BMI ($P < 0.001$).	A significant positive correlation suggests there is a relationship between the effect these two variables (years of cocaine use and BMI) have on the OFC, and also	No evidence	Bilateral lateral orbitofrontal	Frequentist Bayesian

	BMIs (16.6–32.7, mean= 24.2) and a span of 31 years of cocaine use (mean= 9.8 years)			**Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** FSLVBM 1.1	These areas overlapped in the right middle orbitofrontal gyrus, superior orbitofrontal gyrus and gyrus rectus. OFC volume negatively correlated with years of cocaine use in two bilateral clusters ($P < 0.001$)	confirms that there is a stable relationship in OFC volume within an individual in relation to these two separate variables.			

41. G.A. van Winge n et al. 2013 (41)	Study design: cross-sectional Participants:39 **10 non-medicated male ADHD patients with comorbid cocaine dependence** Age (mean years, SD) 37 ± 7 **14 non-medicated male ADHD patients without cocaine dependence** Age (mean years, SD) 32 ± 7 **15 healthy control participants:** Age (mean years, SD) 37 ± 6	**10 non-medicated male ADHD patients with comorbid cocaine dependence:** Cocaine use Years of cocaine use (mean, SD) 12.7 ± 6.5 Days since last cocaine use (mean, SD) 562 ± 484 Number of relapses (mean, SD) 0.4 ± 0.5 Nicotine use (Amount of smokers N; (%)) 7/10 (70%) FTND score for smokers 6.9 ± 1.6 **14 non-medicated male ADHD patients without cocaine dependence:** Nicotine use (Amount of smokers N; (%)) 6/14 (43%) FTND score for smokers 3.0 ± 0.6	Adult ADHD Diagnostic Interview DSM IV the Mini International Neuropsychiatric Interview (MINI) Dutch version of the National Adult Reading Test (DART) ADHD Symptom Rating Scale (ASRS) The Barratt Impulsivity Scale (BIS-11) Beck Depression Inventory (BDI) The Fagerström Test for Nicotine	**MRI Scanner** - 3T Intera full-body scanner (Philips Healthcare).T1-weighted whole-brain high-resolution imaging. **Whole Brain or Regions of interest (ROIs) analysis** – Whole Brain and ROIs: putamen, caudate nucleus, anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC). **MRI techniques –** Voxel-Based Morphometry (VBM) **Cortical thickness – no** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – no **DTI** – no **Another neuroimaging data** - Correlations	In a whole brain analysis, ADHD patients with and without cocaine dependence showed smaller volumes in the right putamen and cerebellum compared to healthy controls. In addition, ADHD patients without cocaine dependence showed larger volumes in the midbrain and in the precentral gyrus compared to healthy control participants and larger volumes in the occipital cortex compared to ADHD patients with comorbid cocaine dependence. A direct comparison using the a priori defined ROI approach showed that ADHD patients with cocaine dependence had smaller putamen volumes than ADHD patients without cocaine dependence.	ADHD patients with cocaine dependence show more profound grey matter volume reductions in the striatum compared to ADHD patients without cocaine dependence. Possible implications for treatment are discussed.	ADHD	Left caudate Right caudate Right medial orbitofrontal Left medial orbitofrontal Right putamen Left putamen Right rostral anterior cingulate Left rostral anterior cingulate + coordinates	Frequentist Bayesian Coordinates

		15 healthy control participants: Nicotine use (Amount of smokers N; (%)) 6/15 (40%) FTND score for smokers 4.8 ± 1.5	Dependence (FTND)	between GMV and: Cocaine use duration (negative association with right putamen volume).					

42. Meade et al. 2021 (42)	Study design: cross-sectional Participants: 72 COC+group 35 Age in years, M (SD) 45.40 (6.45) Male 21/ Female 14 COC-group 37 Age in years, M (SD) 43.03 (7.50) Male 21/ Female 16	Participants in both groups reported past month use of nicotine (50%), alcohol (69%), and marijuana (36%), but COC+ were significantly more likely to have used nicotine and alcohol. **COC +** Daily nicotine, n (%) 21 (60%) Any alcohol, n (%) 30 (86%) Any marijuana, n (%) 16 (46%) **COC -** Daily nicotine, n (%) 12 (32%) Any alcohol, n (%) 20 (54%) Any marijuana, n (%) 10 (27%)	Structured Clinical Interview for DSM-IV Mini International Neuropsychiatric Interview assessed DSM-IV Monetary Choice Questionnaire (MCQ) Addiction Severity Index-Lite (ASI-Lite) Cocaine Craving	**MRI Scanner** - GE Discovery MR750 3T scanner. 8-channel head coil. **Whole Brain or Regions of interest (ROIs) analysis** – Both **MRI techniques –** Combined structural, functional, and diffusion MRI modalities using MCCAR + jICA (multi-site canonical correlation analysis with joint independent component analysis). **Cortical thickness – no** **Brain Volumes - yes** **Cortical Surface Area** – no **fMRI** – yes **DTI** – yes **Another neuroimaging data -** Multimodal Fusion Outputs:	The sample was 58% male and 78% African American. As expected, participants with CUD had higher delay discounting compared to those without CUD. One joint component was identified that correlated with delay discounting across all modalities, involving regions in the thalamus, dorsal striatum, frontopolar cortex, occipital lobe, and corpus callosum. The components were negatively correlated with delay discounting, such that weaker loadings were associated with higher discounting. The component loadings were lower in persons with CUD, meaning the component was expressed less strongly.	Our findings reveal structural and functional co-alterations linked to delay discounting, particularly in brain regions involved in reward salience, executive control, and visual attention and connecting white matter tracts. Importantly, these multimodal networks were weaker in persons with CUD, indicating less cognitive control that may contribute to impulsive behaviors.	No evidence	Bilateral fusiform Right precuneus Left precuneus Bilateral precuneus Left rostral middle front	Frequentist Bayesian Coordinates

				Combined GMV, FA, and ReHo to identify joint components linked to delay discounting. Joint independent components revealed co-altered brain regions, including: Thalamus. Dorsal striatum. Fronto-polar cortex. Occipital lobe. Corpus callosum.					
43. A.M. Kaag et al. 2014 (43)	Study design: cross-sectional Participants: 88 **HC (n = 35)** Age 33 ± 19 **CU (n = 53)** Age 31 ± 12 Cocaine dependence 89% Years of cocaine use 8 ± 6 Onset age of cocaine use 19 ± 4	**HC (n = 35)** Alcohol use (units per week) 5 ± 9 Nicotine use (amount of smokers) 5.7% FTND score for smokers 2.5 ± 0.7 **CU (n = 53)** Alcohol use (units per week) 24 ± 21 Nicotine use (amount of	MINI Neuropsychiatric Interview DSM IV Fagerström Test for Nicotine Dependence (FTND) Barratt Impulsiveness Scale (BIS-11)	**MRI Scanner** - acquired on a 3.0-T whole body MR scanner (Philips Achieva) with a 32 channel SENSE head coil. **Whole Brain or Regions of interest (ROIs) analysis** – Whole Brain and ROIs: Prefrontal Cortex (PFC):	Compared to HC, CU had a smaller SA of the superior temporal cortex but a larger SA of the insula. There were divergent relations between trait impulsivity and SA of the superior temporal cortex and insula (positive in HC, negative in CU) and CT of the anterior cingulate cortex (negative in HC, positive in CU). Within CU, there was a negative association between monthly cocaine use and CT of	The distinct relation between trait impulsivity and cortical morphometry in CU and HC might underlie inefficient control over behavior resulting in maladaptive impulsive behavior such as cocaine abuse.	No evidence	Bilateral inferior temporal Bilateral inferior temporal Bilateral inferior temporal Bilateral insula Bilateral insula Bilateral insula Bilateral lateral orbitofrontal Bilateral lateral orbitofrontal Bilateral lateral orbitofrontal Bilateral middle temporal	Frequentist Bayesian

	Grams of cocaine use per month 7.6 ± 8	smokers) 76% FTND score for smokers 5 ± 4 Secondary cannabis use (>once a week) 28%		Linked to impulsivity and decision-making. Parietal Cortex: Associated with attentional control. Temporal Cortex: Involved in emotional regulation. **MRI techniques –** T1-weighted high-resolution anatomical imaging. Freesurfer software. **Cortical thickness – yes** **Brain Volumes - yes** **Cortical Surface Area** – yes **fMRI** – no **DTI** – no **Another neuroimaging data -** Morphometric Correlations: Associations between cortical metrics (volume, thickness,	the insula and superior temporal cortex.			Bilateral middle temporal Bilateral middle temporal Bilateral pars triangularis Bilateral pars triangularis Bilateral pars triangularis Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate Bilateral rostral anterior cingulate Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral rostral middle frontal Bilateral superior frontal Bilateral superior frontal Bilateral superior frontal Bilateral superior temporal Bilateral superior temporal Bilateral superior temporal	

				surface area) and impulsivity (BIS-11 scores). Higher impulsivity correlated with: Thinner cortices in prefrontal regions. Smaller GM volumes in temporal areas.					
44. Moreno-Lopez et al. 2017 (44)	**Study design:** Cross-sectional **Participants:** 65 CDI 21 Healthy controls	Interview for Research on Addictive Behavior and the FrSBe	Frontal Systems Behavior Scale (FrSBe) – self and informant versions (apathy, disinhibition, executive dysfunction, global). Interview for Research on Addictive Behavior. Structured Clinical Interview	**MRI Scanner** - 3T **Whole Brain or Regions of interest (ROIs) analysis** – Whole Brian and ROIs (ACC, OFC, DLPFC, insula and striatum) **MRI techniques –** T1-weighted 3D-TFE **Cortical thickness – Brain Volumes - Cortical Surface Area** – **fMRI** – **DTI** –	Cocaine-dependent individuals showed reduced gray matter volume in the left DLPFC when compared with HC (pFWE < 0.05) Poorer awareness of apathy deficits → greater dorsal striatum volume. Poorer awareness of disinhibition deficits → greater left OFC volume. Underestimation and overestimation of executive deficits → both	CDI systematically underestimated apathy, executive dysfunction, and global deficits compared with informants. Impaired self-awareness of motivational and cognitive deficits associated with higher relapse risk and poorer treatment outcomes.	SUD-Alcohol in >50%	Bilateral caudate Bilateral insula Bilateral medial orbitofrontal Bilateral rostral anterior cingulate Right rostral middle frontal Left rostral middle frontal	Frequentist Bayesian

			for DSM-IV (SCID).	**Another neuroimaging data -** MNI space	linked to lower DLPFC volume. Whole-brain analysis: apathy/global discrepancy scores correlated with inferior temporal and posterior parietal cortex volumes.				
45. Moeller et al. 2016 (45)	Study design: Cross-sectional case control Participants: 13 healthy controls M/F: 7/6 22 individuals with CUD M/F: 15/7 - CUD- (urine negative cocaine): 14 individuals with remitted CUD - CUD+ (urine positive cocaine): 8 individuals with active CUD	**HC (n=13)** Gender (M/F): 7/6 Race (African-American/Caucasian/other): 9/2/2 Age (y): 42.4 ±6.9 Education (y): 14.4 ±1.9 Verbal IQ (WRAT III): 99.7 ±7.8 **CUD - (n=14)** Gender (M/F): 11/3 Race (African-American/Caucasian/other): 7/4/3 Age (y): 44.9 ±8.5 Education (y): 13.6 ±1.5 Verbal IQ (WRAT III): 99.9 ±9.8 Cocaine age onset (y): 24.2 ±6.9	Structured Clinical Interview for DSM-IV Axis I Disorders Addiction Severity Index Cocaine Selective Severity Assessment Scale Severity of Dependence Scale Cocaine Craving Questionnaire Verbal IQ: WRAT III –	**MRI Scanner** - 3T **Whole Brain or Regions of interest (ROIs) analysis** – Regions of Interest and whole brain **MRI techniques –** T1-weighted **Cortical thickness –** No **Brain Volumes - Yes** **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** 3D MPRAGE sequence MNI space	Controlling for age, GMV group differences emerged in the left rACC (p=0.05) and right rACC (p=0.003). Follow-up pairwise comparisons showed that CUD+ had lower rACC GMV than controls (left ROI: p=0.02; right ROI: p=0.001) and CUD- (right ROI only: p=0.02). On these same measures, CUD- did not differ from control (left ROI: p=0.50; right ROI: p=0.14).	Bilateral rACC GMV was positively correlated with metacognitive accuracy: the lower the left and right rACC volumes (controlling for age), the lower the metacognitive accuracy. Correlations between metacognitive accuracy and GMV remained significant after controlling for depression (left ROI: p=0.005; right ROI: p=0.02) and cigarette smoking (left ROI: p=0.005;	Mild depression > 50% No evidence	Right rostral anterior cingulate Left rostral anterior cingulate Right rostral anterior cingulate Left rostral anterior cingulate	Frequentis Bayesian

		Cocaine duration of use (y): 13.4 ±6.0 Cocaine past month use (days/week): 0.6 ±1.6 Cocaine current abstinence (min - max days, median): 4 - 5840, 365 Marijuana Status (current/past/none): 1/4/9 Alcohol Status (current/past/none): 3/6/5 Opioid Status (current/past/none): 2/2/10 **CUD + (n=8)** Gender (M/F): 4/4 Race (African-American/Caucasian/other): 7/0/1 Age (y): 46.3 ±9.1 Education (y): 12.5 ±1.4 Verbal IQ (WRAT III): 90.9 ±9.1	Scaled Score Non-Verbal IQ: WASI – Matrix Reasoning Scale Beck Depression Inventory II			right ROI: p=0.02).			

		Cocaine age onset (y): 25.3 ±9.8 Cocaine duration of use (y): 20.0 ±7.7 Cocaine past month use (days/week): 3.1 ±2.7 Cocaine current abstinence (min - max days, median): 1-180, 12 Marijuana Status (current/past/none): 0/1/7 Alcohol Status (current/past/none): 2/2/4 Opioid Status (current/past/none): 0/2/6							
46. Moreno-Lopez et al. 2014 (46)	Study design: Cross-sectional case control Participants: 21 healthy controls (HCs) with no history of any substance-related disorder (except nicotine) 20 cocaine dependent individuals (CDIs)	**HC (n=21)** Age: 31 (4.6) Years of education: 10.38 (1.96) Verbal IQ: 105.76 Alcohol (n=4) Tobacco (n=8) Cannabis (n=4) **CDI (n=20)** Age: 34.6 (6.81)	Kaufman Brief Intelligence test Structured Clinical Interview DSM-IV Conners Adult ADHD Diagnostic	**MRI Scanner** - 3T **Whole Brain or Regions of interest (ROIs) analysis** – Region of interest **MRI techniques –** T1 weighted turbo-gradient-echo sequence	Four ROIs (ventromedial prefrontal cortex, IFG, insula and cerebellum) Severity of cocaine use is also a similarly strong predictor of gray matter abnormalities in the cerebellum.	There were no significant group effects on gray matter volumes in the targeted ROIs (at pFWE-SVC < .05). However, within-group analyses for the CDI group showed that severity of cocaine use	SUD-Alcohol in >50%	Bilateral cerebellum cortex Bilateral insula Bilateral medial orbitofrontal	Frequentist Bayesian

		Years of education: 9.7 (1.62) Verbal IQ: 101.75 Patterns of drug use: -Cocaine: grams/month: 7.5 duration of use (month): 34.5 Duration of abstinence (months): 1 Other drugs: MDMA (n=4) Hallucinogens (n=2) Alcohol (n=18) Tobacco (n=15) Cannabis (n=6)	Interview for DSM-IV Interview for Research on Addictive Behavior	(3D-TFE) **Cortical thickness –** No **Brain Volumes -** Yes **Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** VBM8 toolbox DARTEL normalization MNI space		significantly correlated with regional gray matter volume within the cerebellum. Specifically, we observed a cluster of significant negative correlation located in the left lobe of the cerebellar cortex			
47. Makris et al. 2008 (47)	Study design: Cross-sectional case control Participants: 20 matched controls (CON) 20 cocaine-dependent patients (COC) -All users rated cocaine as their predominant substance, although 18 of 20 subjects also used nicotine, and 16 of 20 used alcohol	**CON (n= 20)** Age: 34.1 ±9.4 Years of education: 15.5 ±1.4 Gender (%male): 45% Race (% Caucasian): 70% Handedness (% Right): 80% **COC (n= 20)** Age: 34.3 ±10.8 Years of education: 13.6 ±2.4	Anger Attacks Questionnaire Edinburgh Handedness Questionnaire Hamilton Rating Scale for Depression (HAM-D) Inventory of	**MRI Scanner** - **Whole Brain or Regions of interest (ROIs) analysis** – Regions of interest **MRI techniques –** T1-weighted **Cortical thickness –** Yes **Brain Volumes - Yes**	ROI: orbitofrontal cortex (FOC), anterior cingulate gyrus and paracingulate cortex (CGa/PAC), insular cortices (INS), and dorsolateral prefrontal cortex (DLPFC) Subregions composed of sets of elementary parcellation units or regions of interest (PUs)were then assessed for cortical thickness.	Total cortical volume was significantly less ($p = 0.047$) in COC subjects relative to CON subjects. Mean thickness across anatomically linked PUs was significantly thinner in COC subjects for right RWR subregions by	SUD-Alcohol in >50%	Right inferior parietal Right insula Right medial orbitofrontal Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis	Frequentist Bayesian

		Gender (%male): 45% Race (% Caucasian): 70% Handedness (% Right): 80% Years of cocaine use: 12.0 ±9.8 Years of alcohol use: 14.6 ±11.9	Depressive Symptomatology (IDDRS) MGH Cognitive and Physical Functioning Questionnaire Health Survey (SF-36) Temperament and Character Inventory (TCI) Wechsler Abbreviated Scale of Intelligence (WASI) American Society of Addiction Medicine Patient Placement Criteria 2-Revised	**Cortical Surface Area** – No **fMRI** – No **DTI** – No **Another neuroimaging data -** Cardviews-FreeSurfer (CV-FS) and Freesurfer (FS) methods		multivariate GLM. After correcting for multiple comparisons, the right inferior precentral gyrus (PRG) contained a cluster that was significantly thinner, whereas the dorsolateral aspect of the left occipital lobe (OLs) and angular gyrus (AG) contained clusters that were significantly thicker in the COC subjects.		Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right pars triangularis Right rostral anterior cingulate Right rostral middle frontal Right superior frontal	

			(ASAM-PPC2R)						

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APÊNDICE B – MATERIAL SUPLEMENTAR 2 DO ARTIGO PUBLICADO

Dataset of Included Neuroimaging Studies

Este apêndice corresponde ao **Material Suplementar 2** do artigo publicado em *Drug and Alcohol Dependence*.
Ele contém a base de dados completa dos estudos de neuroimagem incluídos na revisão sistemática e metanálise.

Bittencourt AML et al.
Patterns of Structural Brain Differences in Cocaine Use Disorder: Integrating Multilevel Frequentist, Bayesian, and Coordinate-Based Meta-Analyses.
Drug and Alcohol Dependence, 2026.

Study ID	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8	Criterion 9	Criterion 10
1	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
2	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
3	Yes	Yes	No/NR	Yes	Yes	No/NR	Yes	Yes	No/NR	No/NR
4	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
5	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
6	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
7	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
8	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
9	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	Yes
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/NR	Yes
11	No/NR	Yes	No/NR	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
12	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	Yes	No/NR	No/NR
13	Yes	Yes	No/NR	No/NR	Yes	Yes	Yes	Yes	No/NR	Yes
14	Yes	Yes	No/NR	Yes	Yes	No/NR	Yes	Yes	Yes	No/NR
15	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/NR	Yes
16	Yes	Yes	Yes	Yes	Yes	Yes	No/NR	No/NR	No/NR	Yes
17	Yes	Yes	No/NR	No/NR	No/NR	No/NR	Yes	Yes	No/NR	Yes
18	Yes	Yes	No/NR	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
19	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	Yes	Yes
20	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
21	No/NR	Yes	Yes	No/NR	Yes	No/NR	No/NR	Yes	No/NR	No/NR
22	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	Yes
23	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	Yes	No/NR	Yes
24	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	Yes
25	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	Yes	No/NR
26	Yes	Yes	No/NR	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
27	Yes	Yes	Yes	Yes	Yes	No/NR	Yes	Yes	No/NR	No/NR
28	No/NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/NR	No/NR

29	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
30	Yes	Yes	No/NR	Yes	Yes	No/NR	No/NR	No/NR	No/NR	No/NR
31	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	Yes	No/NR	No/NR
32	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
33	Yes	Yes	Yes	No/NR	No/NR	Yes	No/NR	Yes	No/NR	No/NR
34	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
35	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	Yes
36	Yes	Yes	No/NR	No/NR	No/NR	No/NR	Yes	No/NR	No/NR	No/NR
37	Yes	Yes	Yes	No/NR	Yes	Yes	Yes	Yes	No/NR	No/NR
38	Yes	Yes	Yes	Yes	Yes	No/NR	Yes	Yes	No/NR	Yes
39	No/NR	Yes	Yes	No/NR	No/NR	No/NR	No/NR	Yes	No/NR	No/NR
40	No/NR	No/NR	No/NR	No/NR	No/NR	No/NR	No/NR	Yes	No/NR	No/NR
41	Yes	Yes	Yes	No/NR	Yes	No/NR	No/NR	No/NR	No/NR	Yes
42	Yes	Yes	No/NR	Yes	Yes	No/NR	Yes	Yes	No/NR	No/NR
43	Yes	Yes	No/NR	No/NR	Yes	No/NR	Yes	Yes	No/NR	Yes
44	Yes	Yes	Yes	No/NR	Yes	No/NR	No/NR	Yes	No/NR	No/NR
45	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
46	Yes	Yes	Yes	No/NR	Yes	No/NR	Yes	Yes	No/NR	No/NR
47	Yes	Yes	No/NR	No/NR	Yes	Yes	Yes	Yes	No/NR	Yes

Criteria
1. Were patients diagnosed with cocaine use disorder by clinicians using reliable criteria or validated instruments?
2. Were control participants clinically assessed for the presence of substance use disorders and other mental or neurological disorders?
3. Did the authors report whether patients were seeking treatment, currently in treatment, or abstinent at the time of assessment, and, if abstinent, for how long?
4. Did the authors report the primary route of cocaine administration?
5. Did the authors report psychiatric comorbidities, including other substance use disorders, either by detailing their prevalence in the clinical sample or by creating subgroups based on comorbidities?
6. Did the authors report key sample characteristics, such as age, sex, education, and handedness?
7. Did the authors control the neuroimaging analyses for at least one of the above variables (age, sex, education, or handedness)?

8. Were clinically relevant variables (e.g., years of substance use or presence of comorbidities) examined in relation to neuroimaging findings?
9. Was the study longitudinal?
10. Were summary statistics reported for all neuroimaging findings analyzed? Including those with no significant group differences

APÊNDICE C - MATERIAL SUPLEMENTAR 3 DO ARTIGO PUBLICADO

Additional Data and Analytical Outputs

Este apêndice corresponde ao **Material Suplementar 3** do artigo publicado em *Drug and Alcohol Dependence* e contém dados adicionais utilizados nas análises da revisão sistemática e da metanálise.

Bittencourt AML et al.
Patterns of Structural Brain Differences in Cocaine Use Disorder: Integrating Multilevel Frequentist, Bayesian, and Coordinate-Based Meta-Analyses.
Drug and Alcohol Dependence, 2026.

Brain Region	K - Samples	Estimate	SE	Z-value	P-value	CI Lower	CI Upper
bankssts	5	-0,3041	0,1606	-1,8938	0,0583	-0,6188	0,0106
caudal anterior cingulate	6	-0,1117	0,156	-0,7157	0,4742	-0,4175	0,1941
caudal middle frontal	10	-0,2424	0,1535	-1,5793	0,1143	-0,5431	0,0584
cuneus	7	-0,2274	0,1488	-1,5283	0,1264	-0,519	0,0642
entorhinal	4	-0,2433	0,1722	-1,4136	0,1576	-0,5807	0,0941
frontal pole	5	-0,273	0,1683	-1,6218	0,1048	-0,6028	0,0569
fusiform	6	-0,4521	0,1591	-2,841	**0,0045**	-0,764	-0,1402
inferior parietal	10	-0,2598	0,1396	-1,8607	0,0628	-0,5396	-0,0139
inferior temporal	14	-0,6749	0,1325	-5,0905	**<.0001**	-0,9347	-0,4152
insula	25	-0,1596	0,1175	-1,359	0,1741	-0,3898	0,0706
isthmus cingulate	6	-0,2053	0,156	-0,8412	0,4002	-0,4371	0,1764
lateral occipital	6	-0,3437	0,1531	-2,2448	**0,0248**	-0,6437	-0,0436
lateral orbitofrontal	24	-0,2979	0,1237	-2,4082	**0,016**	-0,5404	-0,0555
lingual	8	-0,1863	0,1432	-1,3011	0,1932	-0,4668	0,0943
medial orbitofrontal	34	-0,1936	0,1262	-1,5336	0,1251	-0,4409	0,0538
middle temporal	12	-0,3161	0,1358	-2,3283	**0,0199**	-0,5822	-0,05
paracentral	5	-0,0497	0,1636	-0,304	0,7611	-0,3704	0,2709
parahippocampal	6	-0,0847	0,1535	-0,5519	0,581	-0,3855	0,2161
pars opercularis	6	-0,2099	0,1615	-1,2997	0,1937	-0,5264	0,1066
pars orbitalis	4	-0,3224	0,1722	-1,8723	0,0612	-0,6599	0,0151
pars triangularis	37	-0,1771	0,1227	-1,4432	0,149	-0,4177	0,0634
pericalcarine	5	-0,0318	0,1614	-0,1969	0,8439	-0,3481	0,2846
postcentral	8	-0,1454	0,1404	-1,0361	0,3001	-0,4206	0,1297
posterior cingulate	10	-0,2002	0,1381	-1,45	0,1471	-0,4708	0,0704
precentral	10	-0,1378	0,139	-0,9911	0,3216	-0,4102	0,1347
precuneus	11	-0,158	0,1384	-1,3678	0,1714	-0,4606	0,0963
rostral anterior cingulate	36	-0,1487	0,1227	-1,2122	0,2254	-0,3892	0,0918
rostral middle frontal	30	-0,3948	0,1183	-3,3366	**0,0008**	-0,6267	-0,1629
superior frontal	25	-0,2931	0,1396	-2,0987	**0,0244**	-0,5093	-0,1369
superior parietal	7	-0,1617	0,1504	-1,0754	0,2822	-0,4565	0,133
superior temporal	14	-0,3489	0,1342	-2,5987	**0,0094**	-0,6126	-0,0857

supramarginal	8	-0,262	0,1503	-1,7431	0,0813	-0,5566	0,032
temporal pole	10	Intercept (Reference)					
transverse temporal	5	-0,1837	0,1641	-1,1194	0,263	-0,5055	0,138

APÊNDICE D - MATERIAL SUPLEMENTAR 4 DO ARTIGO PUBLICADO

Additional Meta-analytic Results

Este apêndice corresponde ao **Material Suplementar 4** do artigo publicado em *Drug and Alcohol Dependence* e apresenta resultados adicionais das análises meta-analíticas realizadas neste estudo.

Bittencourt AML et al.
Patterns of Structural Brain Differences in Cocaine Use Disorder: Integrating Multilevel Frequentist, Bayesian, and Coordinate-Based Meta-Analyses.
Drug and Alcohol Dependence, 2026.

Region	Estimate	Est. Error	Lower 95% CI	Upper 95% CI
bankssts	-0.1	0.12	-0.33	0.15
caudalanteriorcingulate	0.07	0.12	-0.17	0.3
caudalmiddlefrontal	-0.05	0.12	-0.28	0.18
cuneus	-0.03	0.11	-0.26	0.19
entorhinal	-0.04	0.13	-0.3	0.22
frontalpole	-0.07	0.13	-0.33	0.2
fusiform	-0.23	0.12	-0.47	0.01
inferiorparietal	-0.06	0.1	-0.26	0.15
inferiortemporal	**-0.45**	**0.12**	**-0.63**	**-0.26**
insula	0.02	0.09	-0.15	0.19
isthmuscingulate	0.05	0.12	-0.18	0.28
lateraloccipital	-0.13	0.12	-0.37	0.1
lateralorbitofrontal	-0.1	0.09	-0.27	0.07
lingual	-0.0	0.11	-0.22	0.21
medialorbitofrontal	-0.02	0.09	-0.19	0.15
middletemporal	-0.11	0.1	-0.31	0.08
paracentral	0.12	0.13	-0.13	0.37
parahippocampal	0.09	0.12	-0.14	0.33
parsopercularis	-0.02	0.12	-0.26	0.22
parsorbitalis	-0.11	0.14	-0.37	0.16
parstriangularis	0.01	0.08	-0.15	0.18
pericalcarine	0.13	0.13	-0.11	0.38
postcentral	0.04	0.11	-0.17	0.25
posteriorcingulate	-0.01	0.1	-0.21	0.19
precentral	0.05	0.1	-0.16	0.25
precuneus	-0.1	0.1	-0.3	0.1
rostralanteriorcingulate	0.03	0.08	-0.13	0.2
rostralmiddlefrontal	**-0.2**	**0.08**	**-0.36**	**-0.04**
superiorfrontal	0.01	0.09	-0.18	0.24

superiorparietal	-0.02	0.1	-0.21	0.16
superiortemporal	-0.14	0.1	-0.33	0.06
supramarginal	0.06	0.12	-0.29	0.17
temporalpole	0.17	0.11	-0.05	0.38
transversetemporal	0.01	0.13	-0.25	0.26

APÊNDICE E - MATERIAL SUPLEMENTAR 7 DO ARTIGO PUBLICADO

CÓDIGO DE ANÁLISE ESTATÍSTICA UTILIZADO NA METANÁLISE

R Script for the Meta-analytic Statistical Analyses

Este apêndice apresenta o script em linguagem **R** utilizado para a preparação dos dados, o cálculo dos tamanhos de efeito e a execução das análises meta-analíticas frequentistas e bayesianas descritas neste estudo.

Bittencourt AML et al.
Patterns of Structural Brain Differences in Cocaine Use Disorder: Integrating Multilevel Frequentist, Bayesian, and Coordinate-Based Meta-Analyses.
Drug and Alcohol Dependence, 2026.

```
library(dplyr)
library(tidyr)
library(purrr)
library(metafor)
library(readxl)
library(brms)
library(ggseg)

setwd("G:/Meu Drive/OneDrive PUCRS/Documentos/Augusto Bittencourt/Meta-Análise/Paper")

data <- read_excel("Data_analysis.xlsx")
data <- data[!apply(data, 1, function(row) all(is.na(row) | row == "")), ]

# Start conversions and effect sizes calculations
# https://www.metafor-project.org/doku.php/tips:assembling_data_smd

data <- data |>
  mutate(
    # Convert SE to SD only when Dispersion_Index == "SE"
    Control_Dispersion_SD = case_when(
      Dispersion_Index == "SE" ~ Control_Dispersion * sqrt(Control_Sample_Size),
      TRUE ~ NA_real_
    ),
    Coca_Dispersion_SD = case_when(
      Dispersion_Index == "SE" ~ Coca_Dispersion * sqrt(Coca_Sample_Size),
      TRUE ~ NA_real_
    ),

    # Replace SE with SD only for SE rows; keep original otherwise
    Control_Dispersion = case_when(
      Dispersion_Index == "SE" ~ Control_Dispersion_SD,
      TRUE ~ Control_Dispersion
```

```
    ),
    Coca_Dispersion = case_when(
      Dispersion_Index == "SE" ~ Coca_Dispersion_SD,
      TRUE ~ Coca_Dispersion
    )
  )


data <- data |>
  mutate(
    Coca_Dispersion = round(Coca_Dispersion, 3),
    Control_Dispersion = round(Control_Dispersion, 3)
  )

# Assuming Z-score is an approximation of t-val
data <- data%>%
  mutate(
    t_val = coalesce(t_val, z_val_with_direction)
  )

# Escalc considering regular mean/SD, t-val, and p-val (considering the direction by the sign)
# If non-significant p-values were not reported, they were assumed as 0.50
dat2 <- escalc(
  measure="SMD", m1i=Coca_Centrality, sd1i=Coca_Dispersion,
  n1i=Coca_Sample_Size, m2i=Control_Centrality, sd2i=Control_Dispersion,
  n2i=Control_Sample_Size, ti = t_val, pi=sign*p_val, data = data
)

data <-NULL

# Generating additional clinical variables
dat2 <- dat2 |>
```

```
  mutate(
    coca_years_more10 = if_else(
      is.na(Coca_Years_Use) | Coca_Years_Use < 10,
      0,
      1
    )
  )

dat2 <- dat2 |>
  mutate(
    coca_years_more15 = if_else(
      is.na(Coca_Years_Use) | Coca_Years_Use < 15,
      0,
      1
    )
  )

dat2$Mean_Sample_Age <- (dat2$Control_Age + dat2$Coca_Age)/2
dat2$Mean_Sample_Education <- (dat2$Control_Education_Years + dat2$Coca_Education_Years)/2
dat2$Mean_Sample_White_Ethnicity <- (dat2$Control_White_Ethnicity + dat2$Coca_White_Ethnicity)/2


# Stratify based on cortical versus subcortical
Cortical_data <- dat2 %>% filter(Main_Category == "Cortical")
Subcortical_data <- dat2 %>% filter(Main_Category == "Subcortical")
cortical_subcortic <- c("Cortical", "Subcortical")
cortical_subcortical <- dat2 %>%
  filter(Main_Category %in% cortical_subcortic)

# Stratify based on ROI vs whole-brain
Cortical_data_ROI <- Cortical_data %>% filter(Analysis_Method == "ROI")
Cortical_data_WB <- Cortical_data %>% filter(Analysis_Method == "Whole_Brain")
```

```
################## CORTICAL DATA
# 1. Run your meta-analysis - GGSEG Regions - CORTICAL REGIONS
table(Cortical_data$ggseg_region) # Temporal pole has the more positive coefficient
Cortical_data$ggseg_region <- relevel(factor(Cortical_data$ggseg_region), ref = "temporal pole")
res_mv <- rma.mv(
  yi, vi,
  mods = ~ factor(ggseg_region) + factor(Hemisphere) + Age_Delta + Coca_Men_Perc,
  random = list(~1 | Entry_ID, ~1 | Study_ID),
  method = "REML",
  data = Cortical_data
)
res_mv


Cortical_data_ROI$ggseg_region <- relevel(factor(Cortical_data_ROI$ggseg_region), ref = "insula")
res_mv <- rma.mv(
  yi, vi,
  mods = ~ factor(ggseg_region) + factor(Hemisphere) + Age_Delta + Coca_Men_Perc,
  random = list(~1 | Entry_ID, ~1 | Study_ID),
  method = "REML",
  data = Cortical_data_ROI
)
res_mv

Cortical_data_WB$ggseg_region <- relevel(factor(Cortical_data_WB$ggseg_region), ref = "temporal pole")
res_mv <- rma.mv(
  yi, vi,
  mods = ~ factor(ggseg_region) + factor(Hemisphere) + Age_Delta + Coca_Men_Perc,
  random = list(~1 | Entry_ID, ~1 | Study_ID),
  method = "REML",
  data = Cortical_data_WB
```

```
)
res_mv



# 2. Run your meta-analysis - GGSEG Regions - SUBCORTICAL REGIONS
Subcortical_data$ggseg_region <- relevel(factor(Subcortical_data$ggseg_region), ref = "lateral ventricle")
res_mv <- rma.mv(
  yi, vi,
  mods = ~ factor(ggseg_region),
  random = list(~1 | Entry_ID, ~1 | Study_ID),
  method = "REML",
  data = Subcortical_data
)
res_mv

ggseg(atlas = dk, mapping = aes(fill = value), data = df) +
  scale_fill_gradient(low = "white", high = "red") +
  theme_void()

# 3. Meta-regressions
res_mv <- rma.mv(
  yi, vi,
  mods = ~ factor(Severity_level),
  random = list(~1 | Entry_ID, ~1 | Study_ID),
  method = "REML",
  data = Subcortical_data
)
res_mv
```

```
library(ggplot2)

ggplot(Cortical_data, aes(x = factor(coca_aspirated), y = yi, fill = factor(coca_aspirated))) +
  geom_violin(trim = FALSE, alpha = 0.5) +
  geom_jitter(width = 0.15, alpha = 0.6, size = 2) +
  stat_summary(fun = mean, geom = "point", shape = 21, size = 3, fill = "white") +
  scale_fill_manual(values = c("0" = "red", "1" = "blue")) +
  labs(
    title = "Distribution of Observed Effect Sizes by Coca Aspirated Status",
    x = "Coca Aspirated",
    y = "Observed Effect Size (yi)"
  ) +
  theme_minimal() +
  theme(legend.position = "none")



######### BAYESIAN MODEL

# 1. Get all unique cortical regions
all_regions <- unique(Cortical_data$ggseg_region)

# 2. Get whole-brain studies
whole_brain_studies <- Cortical_data %>%
  filter(Analysis_Method == "Whole_Brain") %>%
  distinct(Study_ID)

# 3. Define two hemispheres manually
hemispheres <- tibble(Hemisphere = c("Left", "Right"))

# 4. Create combinations: Study_ID × Hemisphere × Region
expanded_rows <- crossing(whole_brain_studies, hemispheres, ggseg_region = all_regions)
```

```
# 5. Identify which Study_ID + Hemisphere + Region are already present
existing_combinations <- Cortical_data %>%
  filter(Analysis_Method == "Whole_Brain") %>%
  select(Study_ID, Hemisphere, ggseg_region)

# 6. Keep only combinations that are **missing**
missing_combinations <- anti_join(expanded_rows, existing_combinations,
                                  by = c("Study_ID", "Hemisphere", "ggseg_region"))

# 7. Get study-level covariates (averaged if multiple rows exist)
study_covariates <- Cortical_data %>%
  group_by(Study_ID) %>%
  summarise(
    Age_Delta = mean(Age_Delta, na.rm = TRUE),
    Coca_Men_Perc = mean(Coca_Men_Perc, na.rm = TRUE),
    Analysis_Method = first(Analysis_Method),
    .groups = "drop"
  )

# 8. Merge missing rows with covariates
missing_data <- missing_combinations %>%
  left_join(study_covariates, by = "Study_ID") %>%
  mutate(
    yi = NA_real_,
    vi = NA_real_,
    Entry_ID = NA_real_,
    reported = 0
  )

# 9. Mark original data as reported
Cortical_data <- Cortical_data %>%
```

```
  mutate(reported = 1)

# 10. Combine full dataset
Cortical_data_complete <- bind_rows(Cortical_data, missing_data)

Cortical_data_complete <- Cortical_data_complete %>%
  mutate(
    Original_Entry_ID = Entry_ID,
    Entry_ID = row_number()
  )



fit_bayes <- brm(
  yi | se(sqrt(vi)) ~ 0 + ggseg_region + Hemisphere + Age_Delta + Coca_Men_Perc +
    (1 | Entry_ID) + (1 | Study_ID),
  data = Cortical_data_complete,
  prior = c(
    prior(normal(0, 0.3), class = "b"),
    prior(exponential(1), class = "sd")
  ),
  family = gaussian(),
  chains = 4,
  cores = 4,
  iter = 4000,
  control = list(adapt_delta = 0.95)
)

summary(fit_bayes, prob = 0.95)
summary(fit_bayes, prob = 0.89)

rh <- rhat(fit_bayes)
```

```
range(rh)          # min / max Rhat
summary(rh)
bulk_ess <- fit_bayes$ess_bulk
tail_ess <- fit_bayes$ess_tail
summary(bulk_ess)
summary(tail_ess)



fit_bayes <- brm(
  yi | se(sqrt(vi)) ~ 0 + ggseg_region + Hemisphere + Age_Delta + Coca_Men_Perc +
    (1 | Entry_ID) + (1 | Study_ID),
  data = Cortical_data_complete,
  prior = c(
    prior(normal(0, 1), class = "b"),
    prior(exponential(1), class = "sd")
  ),
  family = gaussian(),
  chains = 4,
  cores = 4,
  iter = 4000,
  control = list(adapt_delta = 0.95)
)

summary(fit_bayes, prob = 0.95)
summary(fit_bayes, prob = 0.89)
```

```
# 1. Get all unique subcortical regions
all_regions <- unique(Subcortical_data$ggseg_region)

# 2. Get whole-brain studies
whole_brain_studies <- Subcortical_data %>%
  filter(Analysis_Method == "Whole_Brain") %>%
  distinct(Study_ID)

# 3. Define two hemispheres manually
hemispheres <- tibble(Hemisphere = c("Left", "Right"))

# 4. Create combinations: Study_ID × Hemisphere × Region
expanded_rows <- crossing(whole_brain_studies, hemispheres, ggseg_region = all_regions)

# 5. Identify which Study_ID + Hemisphere + Region are already present
existing_combinations <- Subcortical_data %>%
  filter(Analysis_Method == "Whole_Brain") %>%
  select(Study_ID, Hemisphere, ggseg_region)

# 6. Keep only combinations that are **missing**
missing_combinations <- anti_join(expanded_rows, existing_combinations,
                                  by = c("Study_ID", "Hemisphere", "ggseg_region"))

# 7. Get study-level covariates (averaged if multiple rows exist)
study_covariates <- Subcortical_data %>%
  group_by(Study_ID) %>%
  summarise(
    Age_Delta = mean(Age_Delta, na.rm = TRUE),
    Coca_Men_Perc = mean(Coca_Men_Perc, na.rm = TRUE),
    Analysis_Method = first(Analysis_Method),
    .groups = "drop"
  )
```

```
# 8. Merge missing rows with covariates
missing_data <- missing_combinations %>%
  left_join(study_covariates, by = "Study_ID") %>%
  mutate(
    yi = NA_real_,
    vi = NA_real_,
    Entry_ID = NA_real_,
    reported = 0
  )

# 9. Mark original data as reported
Subcortical_data <- Subcortical_data %>%
  mutate(reported = 1)

# 10. Combine full dataset
Subcortical_data_complete <- bind_rows(Subcortical_data, missing_data)

Subcortical_data_complete <- Subcortical_data_complete %>%
  mutate(
    Original_Entry_ID = Entry_ID,
    Entry_ID = row_number()
  )



fit_bayes <- brm(
  yi | se(sqrt(vi)) ~ 0 + ggseg_region + Hemisphere + Age_Delta + Coca_Men_Perc +
    (1 | Entry_ID) + (1 | Study_ID),
  data = Subcortical_data_complete,
  prior = c(
    prior(normal(0, 0.3), class = "b"),
```

```
    prior(exponential(1), class = "sd")
  ),
  family = gaussian(),
  chains = 4,
  cores = 4,
  iter = 4000,
  control = list(adapt_delta = 0.95)
)

summary(fit_bayes, prob = 0.95)
summary(fit_bayes, prob = 0.89)

rh <- rhat(fit_bayes)
range(rh)          # min / max Rhat
summary(rh)
bulk_ess <- fit_bayes$ess_bulk
tail_ess <- fit_bayes$ess_tail
summary(bulk_ess)
summary(tail_ess)

fit_bayes <- brm(
  yi | se(sqrt(vi)) ~ 0 + ggseg_region + Hemisphere + Age_Delta + Coca_Men_Perc +
    (1 | Entry_ID) + (1 | Study_ID),
  data = Subcortical_data_complete,
  prior = c(
    prior(normal(0, 1), class = "b"),
    prior(exponential(1), class = "sd")
  ),
  family = gaussian(),
  chains = 4,
  cores = 4,
  iter = 4000,
```

```
  control = list(adapt_delta = 0.95)
)

summary(fit_bayes, prob = 0.95)
summary(fit_bayes, prob = 0.89)
```

ANEXOS

Anexo 1. Produção científica do Mestrado e concluído durante o doutorado



Cingulate cortical thickness in cocaine use disorder: mediation effect between early life stress and cocaine consumption

Journal:	*Acta Neuropsychiatrica*
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Complete List of Authors:	Bittencourt, Augusto; PUCRS, Brain Institute (InsCer) Belmonte da Silveira, Bárbara; PUCRS, Brain Institute (InsCer) Tondo, Lucca; PUCRS, Brain Institute (InsCer) Melo Rothmann, Leonardo; PUCRS, Brain Institute (InsCer) Rosa Franco, Alexandre; Child Mind Institute Inc, Center for the Developing Brain, Center for Biomedical Imaging and Neuromodulation Ferreira, Pedro; PUCRS, Brain Institute (InsCer) Viola, Thiago ; PUCRS, Brain Institute (InsCer) Grassi-Oliveira, Rodrigo; Aarhus Universitet, Department of Clinical Medicine – Translational Neuropsychiatry Unit
Keywords:	Cocaine-Related Disorders, Neuroimaging, Gyrus Cinguli, Child Abuse, Crack Cocaine
Abstract:	Objective: The cingulate gyrus is implicated in the neurobiology of addictive behaviors, such as chronic cocaine consumption. Early-life stress (ELS) is an important risk factor for cocaine use disorder (CUD). Therefore, in this study we investigated the effect of CUD on cingulate cortical thickness and tested whether a history of ELS could influence the effects of CUD. Methods: Participants aged 18 to 50 years (78 with CUD due to crack cocaine consumption and 53 healthy controls) underwent MRI and the cingulate thickness (rostral anterior, caudal anterior, posterior, and isthmus regions) was analyzed. The clinical assessment comprised the Childhood Trauma Questionnaire (CTQ) and the Addiction Severity Index. Group comparisons adjusting by sex, age, and education where performed. Mediation models were generated where lifetime cocaine use,

	CTQ score, and cortical thickness corresponded to the independent variable, intermediary variable, and outcome, respectively. Results: Group comparisons revealed significant differences in six out of eight cingulate cortices, showing lower thickness in the CUD group compared with the control group. Negative correlations were found between CTQ scores and the isthmus cingulate (right hemisphere), as well as with the rostral anterior cingulate (left hemisphere). In the mediation analysis, we observed a significant negative direct effect of lifetime cocaine use on the isthmus cingulate and an indirect effect of cocaine use mediated by CTQ score. Conclusion: Our findings suggest that a history of ELS could aggravate the negative effects of chronic cocaine use on the cingulate gyrus, particularly in the right isthmus cingulate cortex.

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Manuscripts

Cingulate cortical thickness in cocaine use disorder: mediation effect between early life stress and cocaine consumption

Running title: Early stress, cocaine and cingulate

Augusto Martins Lucas Bittencourt[a,b], Bárbara Luiza Belmonte da Silveira[a], Lucca Pizzato Tondo[a], Leonardo Melo Rothmann[a], Alexandre Rosa Franco[c,d,e], Pedro Eugenio Mazzucchi Santana Ferreira[a], Thiago Wendt Viola[a,*], Rodrigo Grassi- Oliveira[a,f,*]

[a] Brain Institute (InsCer/BraIns), Pontifical Catholic University of Rio Grande do Sul (PUCRS), 90619900, Porto Alegre, Brazil.

[b] School of Medicine, Catholic University of Pelotas (UCPel), 96015560, Pelotas, Brazil.

[c] Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, 10962, USA.

[d] Center for the Developing Brain, Child Mind Institute, New York, NY, 10022, USA.

[e] Department of Psychiatry, NYU Grossman School of Medicine, New York, NY, 10016, USA.

[f] Department of Clinical Medicine – Translational Neuropsychiatry Unit, Aarhus University, 8000, Aarhus, Denmark.

[*] Senior authors with an equivalent contribution

Corresponding author: Prof. Rodrigo Grassi-Oliveira. Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. Postal Address: Universitetsbyen 13, Building 2b, 8000 Aarhus C. E-mail: rogo@clin.au.dk

Words: 3900; *Figures*: 3; *Tables*: 1

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Abstract

Objective: The cingulate gyrus is implicated in the neurobiology of addiction, such as chronic cocaine consumption. Early-life stress (ELS) is an important moderator of cocaine use disorder (CUD). Therefore, we investigated the effect of CUD on cingulate cortical thickness and tested whether a history of ELS could influence the effects of CUD.

Methods: Participants aged 18 to 50 years (78 with CUD due to crack cocaine consumption and 53 healthy controls) underwent MRI and the cingulate thickness (rostral anterior, caudal anterior, posterior, and isthmus regions) was analyzed. The clinical assessment comprised the Childhood Trauma Questionnaire (CTQ) and the Addiction Severity Index. Group comparisons adjusting by sex, age, and education were performed. Mediation models were generated where lifetime cocaine use, CTQ score, and cortical thickness corresponded to the independent variable, intermediary variable, and outcome, respectively.

Results: Group comparisons revealed significant differences in six out of eight cingulate cortices, showing lower thickness in the CUD group. Furthermore, years of regular cocaine use was the variable most associated with cingulate thickness. Negative correlations were found between CTQ scores and the isthmus cingulate (right hemisphere), as well as with the rostral anterior cingulate (left hemisphere). In the mediation analysis, we observed a significant negative direct effect of lifetime cocaine use on the isthmus cingulate and an indirect effect of cocaine use mediated by CTQ score.

Conclusion: Our findings suggest that a history of ELS could aggravate the negative effects of chronic cocaine use on the cingulate gyrus, particularly in the right isthmus cingulate cortex.

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Keywords: Cocaine-Related Disorders; Neuroimaging; Gyrus Cinguli; Child Abuse; Crack Cocaine.

Significant Outcomes

- Persons with cocaine use disorder presented lower cingulate cortical thickness, and years of cocaine use was the variable most associated with cingulate thickness.
- Negative correlations were found between early life stress and cingulate thickness.
- A partial mediation effect of early life stress on cingulate was found in cocaine use disorder.

Limitations

- The cross-sectional design cannot address the longitudinal developmental effects of exposure to early life stress.
- We only measured one aspect of gray matter integrity: cortical thickness.
- The results do not inform whether the observed cortical thinning found in cocaine use disorder could persist with successful treatment.

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1. Introduction

Cocaine use disorder (CUD) is a severe, complex, and debilitating disease characterized by changes in reward and inhibitory systems (Volkow et al., 2019). There are four key interrelated brain circuits that are involved in or affected by CUD, including the reward circuit (e.g., nucleus accumbens and additional striatum regions), the learning/memory circuit (e.g., amygdala and the hippocampus), the motivation/drive circuit (e.g., orbitofrontal/subcallosal cortices and motor cortex), and the cognitive control circuit (e.g., dorsolateral prefrontal cortex and the cingulate gyrus) (Volkow et al., 2016). The cingulate is implicated with the neurobiology of impulsivity, cocaine craving, and attentional bias toward cocaine-related cues preceding relapse (Volkow et al., 2012, Canterberry et al., 2016). In addition, findings suggest that persons with CUD have hypometabolism in the cingulate gyrus during the first months of withdrawal, suggesting that altered function, structure, and metabolism of specific cingulate cortices have clinical implications for the CUD treatment (Volkow and Fowler, 2000, Volkow et al., 2012).

Individual differences are highly relevant in the context of substance use disorders. Early life stress (ELS) is an environmental factor that substantially increases the risk of developing several psychiatric disorders, including CUD (Andersen and Teicher, 2009). Moreover, childhood maltreatment has been associated with worse clinical and treatment outcomes for CUD, as patients with a history of childhood physical neglect, for instance, exhibited higher levels of cocaine withdrawal symptoms during detoxification treatment when compared with patients with no such (Francke et al., 2013). In addition to the clinical perspective, neuroimaging evidence points to the existence of altered brain development trajectories associated with ELS exposure (Teicher and Samson, 2016), a finding that could be implicated with the vulnerability to substance use disorders later in adulthood (De Bellis et al., 2019). Consistent with that, studies have reported that ELS (Ross et al., 2021, Lim and Khor, 2022) and CUD are associated with alterations in structure, morphology, and function of brain regions involved in motivation, impulsivity, inhibitory control, emotional regulation (Teicher and Samson, 2013, Irizar et al., 2020, Tondo et al., 2021), including the cingulate. For instance, structural and functional alterations in the cingulate cortices have been reported following traumatic stress exposure (Baker et al., 2013, Calati et al., 2018). However, little is known about whether a history of ELS could interact with CUD effects on the cingulate structure, providing further insights into the relationship between stress and addiction at the neuropathophysiological level.

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Thus, this study had two main goals: 1) to compare the cortical thickness (CT) of four cingulate regions (rostral anterior, caudal anterior, posterior, and isthmus regions) between participants with CUD and healthy controls; and 2) to test a mediation model where the severity of exposure to ELS experiences would influence the association between lifetime cocaine consumption and cingulate CT alterations. As the cingulate gyrus has been associated with both ELS and cocaine addiction, we hypothesized that participants with CUD would have cingulate cortical thinning in comparison with controls. Moreover, a direct effect of lifetime cocaine use on cingulate CT was expected, as well as a mediation effect of ELS on this relationship. Therefore, we employed a hypothesis-driven region of interest approach to investigate CT alterations in cingulate subregions.

Importantly, this study was performed with participants who predominantly consumed smoked cocaine (i.e., crack) instead of snorted cocaine (Bittencourt et al., 2021). Crack cocaine is associated with shorter periods of sustained abstinence during treatment, greater propensity for dependence, higher plasmatic levels of the substance, greater intensity of psychotropic effects, easier administration, and lower costs when compared with intranasal and intravenous use of cocaine (Kiluk et al., 2013, Voon et al., 2016). Moreover, crack cocaine users are often socioeconomically disadvantaged, and previous studies have shown that over 80% of female crack cocaine users reported lifetime victimization, largely during childhood (Tractenberg et al., 2012, Perrenoud et al., 2021), suggesting that this population of substance users possess a high risk for the long-term negative consequences of ELS and CUD.

2. Methods

Participants

We conducted a cross-sectional study with 78 participants with CUD and 53 healthy controls. We recruited the CUD group from public drug-treatment inpatient facilities in southern Brazil. During hospitalization, they followed a standardized cocaine detoxification protocol. The treatment consisted of psychoeducation and support groups, moderate physical activity, a balanced diet (2200 Kcal/day), nursing care, and psychological and medical treatments. As inpatients, they were in an abstinence-controlled environment with no access to any type of drug, including alcohol and nicotine. We recruited the HC from the same community by word-of-mouth advertising.

For inclusion, all participants had to (a) be right-handed; (b) self-declare as being of

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low or middle socioeconomic status; (c) be 18-50 years old; (d) have graduated middle school

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(>8 years of educational attainment) in Brazil; and (e) have an IQ > 80. Other criteria for inclusion in the CUD group were having (f) a mental disorder primarily diagnosed as CUD, confirmed via the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV) (Kübler, 2013); (g) undergone 7-14 days of inpatient treatment; and (h) tested positive for cocaine in a urine screening test during the first three days of hospitalization (indicating they had used cocaine less than one week before the test). As previously mentioned, participants with CUD had a preference for smoking cocaine as a route of administration. Handedness was checked individually using the Handedness Inventory, with scores above nine indicating right-handedness (Briggs and Nebes, 1975). Participants were excluded if they presented potential contraindications for MRI scanning (metallic implants, recent tattoos, claustrophobia), acute or unstable clinical illnesses, abuse of other substances 14 days or less before the study, neurologic disorders, HIV, or syphilis. Participants took a fast-track blood exam to test for the latter two conditions. Concurrent severe psychotic mental disorders were also an exclusion criterion; however, we accepted patients who had other substance use disorders into the CUD group.

For healthy controls, the exclusion criteria also included psychiatric or neurological disorders aside from tobacco use disorder. This sample was screened for major psychiatric disorders using the SCID-IV (Kübler, 2013) and administered by a trained member of the research staff before the date of the MRI exam. Use of psychotropic medications within six months before the study and use of alcohol within a week before the study were also exclusion criteria.

All participants tested negative for cocaine, cannabis, amphetamines, opiates, and benzodiazepines in a urine screening test on the date of the MRI. Whenever a crack cocaine user checked into the drug treatment center and fulfilled the inclusion criteria, we invited them to participate in the study. After one week of hospitalization, professional psychiatrists interviewed each participant using the SCID-IV. Participants underwent an MRI exam between the eighth and fifteenth days of hospitalization.

All procedures were approved and carried out in accordance with the Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (PUCRS). After a complete description of the study, all subjects provided written informed consent.

Assessments

Sociodemographic characteristics and drug use patterns were obtained with the Addiction Severity Index – 6th version (ASI-6) (McLellan et al., 1980, Kessler et al., 2012).

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This is a semi-structured interview that gathers information on recent and lifetime problems related to substance misuse - including information on licit (tobacco and alcohol) and illicit drug (cannabis, smoked or snorted cocaine). A pattern of use of at least three times per week during a year was considered a regular year of substance use. Data on both snorted and smoked cocaine were grouped into a single variable.

We assessed childhood maltreatment history with the Childhood Trauma Questionnaire (CTQ). The CTQ is a self-answered, five-point, Likert-type questionnaire with 28 items that evaluate the severity of exposure to ELS. The CTQ generates a total score (possible score range: 25-125) accounting for five types of maltreatment experiences (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) (Bernstein et al., 1994, Grassi-Oliveira et al., 2006). In addition, there are quantitative scores for each type of maltreatment. Qualitatively, the presence of maltreatment was determined by using the suggested CTQ cutoff scores for cases of moderate severity.

MRI scanning

All magnetic resonance imaging (MRI) scans were performed in a 3.0T whole-body scanner (Signa, GE Healthcare, Milwaukee, USA). The three-dimensional, T1-weighted images were set to the following parameters: repetition time = 2400ms, echo time = 15ms, slice thickness = 1.6mm, scan matrix = 512 x 512, voxel size = 1mm^3, field of view = 256 mm, and resolution = 256 x 256. All T1 images were visually inspected for the quality of the image and for the absence of apparent motion artifacts. All subjects were invited to undergo a mock scan in a fake MRI machine before the actual MRI scan. The objective was to allow them to familiarize themselves with the procedures of this study.

FreeSurfer pre-processing

To assess the subjects' CT, we carried out cortical reconstructions using the FreeSurfer (version 5.3) image analysis suite (http://surfer.nmr.mgh.harvard.edu/). In short, the processing of cortical reconstructions involves motion correction and averaging (Reuter et al., 2010) of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep subcortical structures (Ségonne et al., 2004), intensity normalization tessellation of the gray matter/white matter boundary (Sled et al., 1998), automated topology correction (Ségonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid

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borders at the location where the greatest shift in intensity defines the transition into the other tissue class (Fischl and Dale, 2000). Cingulate CT (rostral anterior, caudal anterior, posterior, and isthmus regions) was extracted by parcellation of the cortex using the Desikan–Killiany atlas (Desikan et al., 2006). For each of the four cortical cingulate areas in both hemispheres, FreeSurfer calculates the average CT. Reconstructed images were visually inspected by three researchers with experience in neuroimaging and manually corrected for segmentation or processing mistakes in accordance with FreeSurfer's troubleshooting guidelines. Thus, all T1 images were visually inspected for the quality of the image and for the absence of apparent motion artifacts. The edited exams were then reprocessed, and CT data were extracted from the corrected images.

Statistical analyses

Descriptive analyses are presented as mean and standard deviation or absolute and relative frequencies. Differences involving continuous and categorical variables in sociodemographic clinical data were evaluated using independent t-tests, Yate's correction for chi-square, or Fisher's exact tests, respectively.

Analysis of covariance (ANCOVA) was used to estimate cingulate CT differences between groups adjusting by sex, age, and education. We estimated Cohen's D effect sizes for the CT group comparisons. Pearson's correlation was used to measure the association between sociodemographic/clinical variables and CT in the whole sample. Spearman's correlation was used to measure the associations only in the CUD group due to less sample size.

The cingulate regions with significant differences between groups and significant associations with CTQ scores were inserted in a mediation model in which lifetime cocaine use, CTQ scores, and cingulate thickness were defined, respectively, as the independent variable, the intermediary variable, and the outcome. Within these models, the direct effect corresponds to the effect of cocaine use on CT in the absence of the mediating variable (CTQ). The indirect effect corresponds to the effect of cocaine use on CT through the mediating variable. Indirect effects were estimated using the bootstrap bias-corrected method that generates 95% confidence intervals (CIs). CIs that do not contain zero or both positive/negative values indicate statistically significant direct or indirect effects in mediation models with 10,000 bootstrap samples. The total effect equals the sum of both direct and indirect effects. The graphical model is displayed in Figure 4. The covariates included in the mediation analyses were the same as in the ANCOVAs (i.e., sex, age, and education).

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Spearman's correlation was performed to evaluate relationships involving CTQ scores and the mediation result between CUD participants.

All statistical analyses were performed using SPSS v. 26.0 (SPSS Inc., Chicago, IL, USA). Mediation analysis was performed using PROCESS v. 3.5 by Andrew Hayes (Hayes and Preacher, 2014).

3. Results

Sample characteristics

Demographic and clinical characteristics are shown in Table 1. The CUD group was older, had fewer years of education, had higher rates of unemployment, and had fewer participants self-declared as white. Furthermore, the CUD group had more severe exposure to ELS experiences than the control group, with higher CTQ scores among CUD participants than healthy controls. Similarly, the CUD group presented a significantly higher prevalence of physical abuse ($p = .003$), emotional abuse ($p = .019$), emotional neglect ($p = .002$), and physical neglect ($p = .001$), considering the quantitative scores for each type of ELS. Qualitatively, among the CUD group 27 participants (34%) presented childhood physical abuse history, 17 participants (22%) presented childhood sexual abuse history, 26 participants (33%) presented childhood emotional abuse history, 25 participants (32%) presented childhood emotional neglect history, and 24 participants (30%) presented childhood physical neglect history, while among the control group 6 participants (11%) presented childhood physical abuse history, 5 participants (9%) presented childhood sexual abuse history, 8 participants (15%) presented childhood emotional abuse history, 4 participants (7%) presented childhood emotional neglect history, and 4 participants (7%) presented childhood physical neglect history.

Regular alcohol use was more common in the CUD group than in the control group, while regular tobacco use was more common in the control group than in the CUD group. No participant in the control group presented histories of regular cocaine/crack consumption.

Insert Table 1 here.

Cortical thickness

Freesurfer analyses revealed cingulate regions with significant CT in CUD participants compared with healthy controls (Fig. 1). Group comparisons controlled for sex, age, and

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60 education revealed significant differences between groups in six regions out of eight (LH –

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left hemisphere / RH – right hemisphere), showing lower CT in the CUD group compared with the control group (p-values < .05). Compared with controls, the CUD group showed lower CT in the LH caudal anterior cingulate (p = .009, Cohen's d = 1.01), LH rostral anterior cingulate (p < .001, Cohen's d = 1.11), RH rostral anterior cingulate (p = .003, Cohen's d = 0.76), LH posterior cingulate thickness (p = .018, Cohen's d = 0.87), RH posterior cingulate (p = .007, Cohen's d = 0.76), and RH isthmus cingulate (p = .003, Cohen's d = 0.69). Groups did not differ in RH caudal anterior cingulate and LH isthmus cingulate thickness.

Insert Figure 1 here.

Correlation analyses

Figure 2A shows the correlation matrix between substance use, sample characteristics, and cingulate CT. The correlation analysis between CTQ scores and cingulate thickness showed that CTQ scores were negatively correlated with RH isthmus cingulate and with LH rostral anterior cingulate thickness. At the same time, there were no significant associations with other cingulate regions. Furthermore, there were significant associations between cingulate thickness and age/education. Age was negatively correlated with almost all cingulate regions, except for the RH and LH isthmus cingulate. Similarly, education was positively correlated with almost all cingulate regions, except for the RH isthmus and the RH rostral cingulate. We also performed a scatter plot to show the association between CTQ scores and RH isthmus cingulate thickness (Fig. 2B).

Insert Figure 2 here.

Regarding licit/illicit drugs, years of regular cocaine use was the variable most associated with cingulate thickness, negatively correlated with LH caudal anterior cingulate, LH posterior cingulate, RH caudal anterior cingulate, RH isthmus cingulate, and posterior cingulate thicknesses. Additionally, the correlational analysis revealed that years of regular alcohol use were negatively correlated with LH caudal anterior cingulate, RH caudal anterior cingulate, and LH rostral anterior cingulate thicknesses. There were no associations between tobacco/cannabis and cingulate thickness.

Mediation model

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We ran mediation models in which years of regular cocaine use (if a control participant had never used cocaine, it was computed as zero years) was the predictor of cingulate thickness and tested whether CTQ scores could underlie this association. These analyses were controlled for age/education/sex and allowed us to identify the direct and indirect effects of cocaine use through childhood maltreatment. Thus, we tested the mediation effect only for the RH isthmus cingulate since this region was correlated with the total CTQ score in previous analyses.

In the mediation analysis, we found a negative significant direct effect of cocaine use on the RH isthmus cingulate (b= -.005, 95%CI [-.009, -.002]) and an indirect effect mediated by CTQ scores on the RH isthmus cingulate (b= -.001, 95%CI [-.002, -.0001]), suggesting partial mediation. The mediation model showed a significant improvement over a null model (R= 0.37; R-squared=S 0.14; Mean Square Error= 0.011; p = 0.0006. Specifically, 16.66% of the model's total effect (b= -.006, 95%CI [-.010, -.003]) was explained by the indirect effects mediated by ELS. Also, a marginal interaction effect was observed for sex (p = .055). The mediation model is shown in Figure 3. Additionally, Spearman's correlation analysis between the RH isthmus cingulate and CTQ scores for each type of maltreatment experience in the CUD group only, showed a negative correlation with childhood physical abuse score (rho = --0.25, p = 0.024), while there were no significant associations between other CTQ scores and RH isthmus.

Insert Figure 3 here.

Since we also found a negative correlation between alcohol use and LH rostral anterior cingulate thickness, we also tested the mediation model with alcohol instead of cocaine use as the main predictor. Neither a direct effect of alcohol (b= -.0009, 95%CI [-.004, .002]) nor an indirect effect of ELS/alcohol (b= -.0004, 95%CI [-.001, .0004]) were detected.

Discussion

Using structural MRI data, we compared cingulate CT between CUD patients and healthy control subjects. Group comparisons revealed significant differences in LH caudal anterior cingulate, LH rostral anterior cingulate, RH rostral anterior cingulate, LH posterior cingulate, RH posterior cingulate, and RH isthmus cingulate thicknesses, with a significantly lower CT in the CUD group than in the control group. We also observed higher CTQ scores in the CUD group than in the control group. Significant negative correlations were found

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between CTQ scores and CT of the RH isthmus cingulate and the LH rostral anterior cingulate. The mediation analysis showed a negative significant direct effect of cocaine use on isthmus cingulate CT and an indirect effect mediated by CTQ scores on isthmus cingulate CT, suggesting partial mediation. Particularly, 16,66% of the model's total effect was explained by the indirect effects mediated by ELS. We demonstrated that ELS is related to CUD and, in conjunction with it, mediates the effect of CUD on decreased isthmus cingulate thickness in the right hemisphere. This supports the role of ELS as a key environmental stressor that influences brain developmental trajectories associated with drug addiction.

Previous neuroimaging studies observed that the cingulate cortex of cocaine users has abnormalities in perfusion (Childress et al., 1999), white matter fractional anisotropy (Tondo et al., 2021) (Tondo et al. 2021), and gray matter density compared with controls (Ersche et al., 2012). Similar to our findings, Connolly et al. observed a negative association between years of cocaine use and grey matter volume of the cingulate gyrus (Connolly et al., 2013). More specifically, the anterior cingulate cortex is involved in reward processing and motivational salience and governs cognitive control processes such as attention and inhibition (Bubb et al., 2018, Zhao et al., 2020). Consistent with these observations, the rostral anterior cingulate cortex has been previously linked to encoding aversive emotional states (Rainville et al., 1997) and uncertainty in the decision-making framework (Bush et al., 2000), and particularly in the suppression of task-irrelevant emotional information (Davis et al., 2005). The posterior cingulate cortex is a primary node of the default mode network and is related to drug abuse (Li et al., 2013). Thus, the cingulate cortex serves not only as a crucial neural substrate characterizing the neurobiological mechanisms of addiction but also has the potential of a therapeutic target and neuroimaging-based biomarker of CUD (Zhao et al., 2021). Indeed, given that the cingulate cortex is also implicated in the modulation of cue-induced cocaine craving (Kilts et al., 2004), evidence suggests that bilateral transcranial stimulation over the prefrontal cortex changes the drug-cued reactivity in the cingulate cortex in patients with CUD (Conti and Nakamura-Palacios, 2014).

We also verified a mediation effect of ELS severity within the relationship between lifetime cocaine consumption and cingulate CT, suggesting that adverse experiences during childhood, such as abuse and neglect, could aggravate the effects of CUD later in life regarding thinning of the right isthmus cingulate CT. Importantly, the mediation model suggested that some percentage of the total model effect was due to the influence of a history of ELS (i.e. indirect effect), showing that years of substance consumption is not the only factor associated with altered brain cortical thickness. Indeed, evidence suggests that

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additional psychosocial factors (e.g. childhood maltreatment, adversity, poverty) account for a proportion of the detrimental effects of substance use disorders in the brain (De Bellis et al., 2019). For instance, it has been shown that highly traumatized Kurdish male refugees and repatriated French citizens from Algeria presented reduced bilateral isthmus cingulate cortex volume in comparison with healthy non-traumatized controls (Calati et al., 2018), suggesting that stressful experiences may increase the risk to the isthmus cingulate of the adverse effects of lifetime cocaine consumption.

The results of this study should be interpreted by taking some limitations into account. First, it must be pointed out that our findings suggest only a partial mediation effect of ELS on the relationship between lifetime cocaine use and decreased isthmus cingulate thickness. It suggests that other pathophysiological mechanisms underlie the association between lifetime cocaine use and cingulate thickness. Second, the CUD group was older and had lower educational attainment than the control group, which is important because age and education are associated with differences in brain structure. However, all statistical analyses were controlled for age and education. Third, our study is cross-sectional so it cannot address the longitudinal developmental effects of exposure to childhood maltreatment on CT. Despite the cross-sectional design, we used mediation analysis to investigate this relationship. Therefore, with all due caution given the nature of our data, the statistical method can facilitate an understanding of the relationships between these factors. Fourth, the results also do not inform whether the observed cortical thinning found in CUD subjects could persist with successful treatment and long abstinence periods. Thus, prospective studies also need to explore the relevance of these findings to the progression of drug addiction, prediction of relapse, and treatment outcomes. Lastly, we only measured one aspect of gray matter integrity: cortical thickness. Therefore, we cannot rule out the existence of other anatomical alterations associated with CUD. Future studies using other measures and analysis methods should help elucidate these functional changes to the underlying brain structure.

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Conclusion

Our results provide evidence of the interactive effects of both childhood maltreatment and lifetime cocaine use on the cingulate gyrus among persons with CUD, suggesting putative mechanisms by which exposure to ELS may create a vulnerable brain substrate for the effects of CUD later in life. This finding is important for our understanding of the effects of trauma, stress, and CUD on the gray matter structure of the brain. Because the cingulate gyrus is implicated in cognitive, emotional, and behavioral control processes, the effects of CUD on

the cingulate cortex may reflect a progressive loss of control related to addictive behaviors. Future longitudinal studies should build on the groundwork established by the analyses presented in this study to examine both structure and function of gray matter in clinical groups and to identify a clinical usage for these neuroimaging markers.

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Author Contributions

The study was designed by Bittencourt, Viola and Grassi-Oliveira. MRI acquisition and FreeSurfer analyses were carried out by Bittencourt, Tondo, Rothman, Belmonte, and Ferreira. Statistical analyses were carried out by Viola. The results were interpreted by all authors. Bittencourt wrote the first draft of the manuscript, which was subsequently revised for important intellectual content by the remaining authors. All authors approved the final version of the manuscript prior to submission.

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Statement of Interest

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1 Legend. HC: Healthy controls. CK: Crack-cocaine use disorder. Comparisons performed with ANCOVA adjusted for sex/age/education. Cingulate Cortex regions: rostral anterior, caudal anterior, posterior, and isthmus. Y-axis of figures in millimeter scales. * represents a p-value 0.05. ** represents a p-value 0.01.

Figure 2 Legend. A: Pearson's correlation matrix, only significant correlations are depicted within the matrix. Ethnicity = 1, caucasian. Cocaine (both snorted/smoked), alcohol, cannabis, and tobacco represent years of regular consumption. CTQ, represents the total score. B: Correlation between CTQ total score and isthmus cingulate (right hemisphere) cortical thickness.

Figure 3 Legend. The direct effect means the effect of cocaine use on CT when the mediating variable (CTQ) is not included. The indirect effect means the effect of cocaine use on CT through the mediating variable. 95% confidence intervals (CIs) that do not include zero, or both positive/negative values, indicate statistically significant effects. The total effect is the sum of the indirect/direct effect in the mediation model. A pattern of crack-cocaine use at least 3 times per week during a year, was considered as a regular year of crack-cocaine consumption. Univariate standardized regression coefficients are presented above lines, showing a positive association between the predictor and the mediator, and negative associations between the predictor/mediator with the outcome.

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Table 1. *Sample Characteristics*

Variables	HC (n=53)	CK (n=78)	*p*-value
Age (years; mean±SD)	28.39 (6.8)	33.83 (6.8)	0.001
Education (degree; mean±SD)	1.96 (0.47)	1.17 (0.69)	0.001
Sex (male:female)	18:35	40:38	0.051
Ethnicity (caucasian; %)	64.7%	44.9%	0.027
Employment (%)	86.3%	61%	0.002
Years in life that drank alcohol regularly. 3 or more days a week (mean±SD)	0.26 (0.97)	6.30 (7.41)	0.027
Years in life that smoked tobacco regularly. 3 or more days a week (mean±SD)	17.46 (3.1)	13.77 (3.7)	0.001
Years in life that smoked cannabis regularly. 3 or more days a week (mean±SD)	–	15.50 (4.3)	–

Legend. HC: Healthy controls. CK: Crack-cocaine use disorder. Education: 0 - no formal education. 1 - elementary/middle school. 2 - high school. 3 - college.

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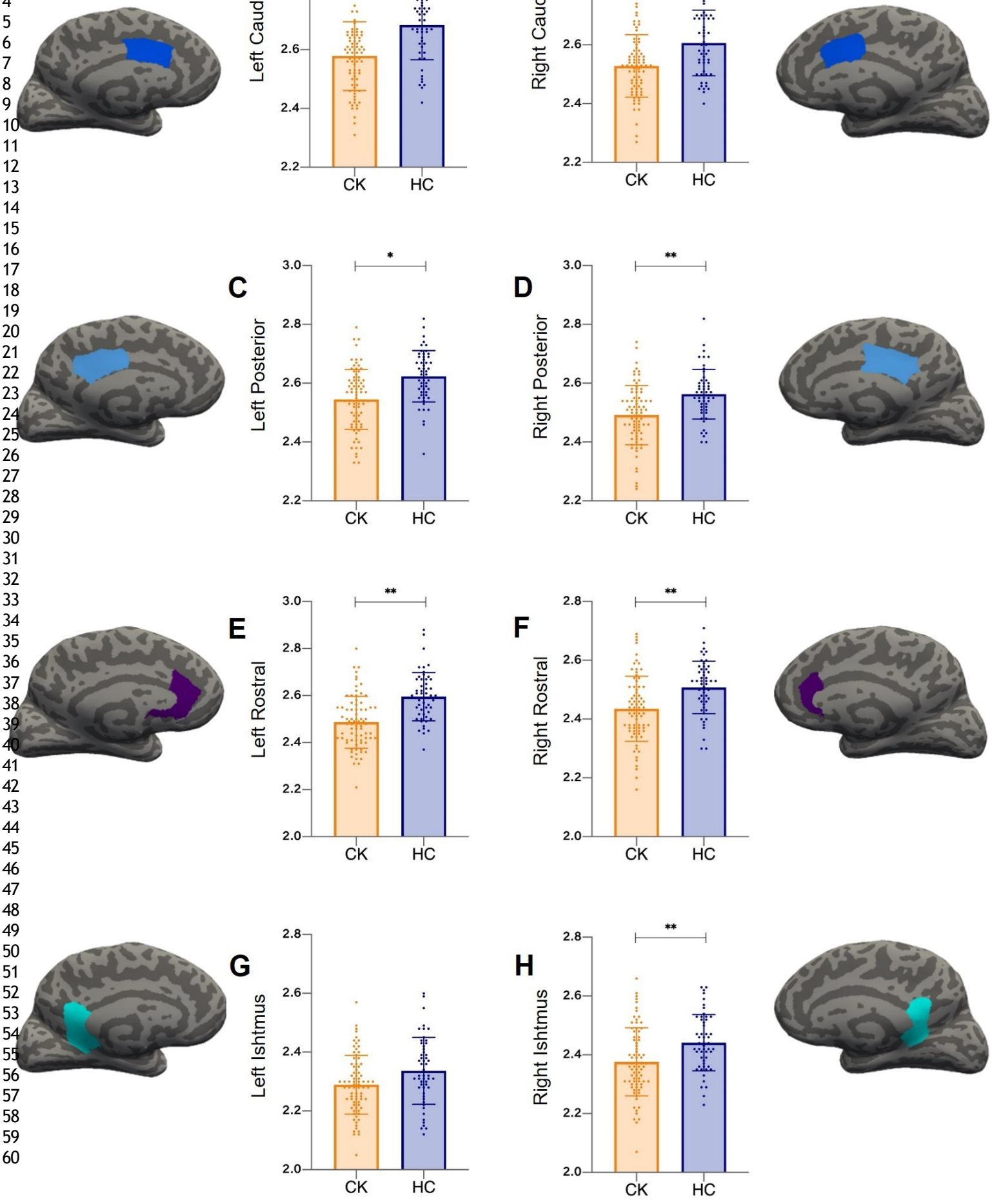
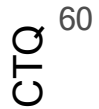

A
Left Caudal
B
Right Caudal
C
Left Posterior
D
Right Posterior
E
Left Rostral
F
Right Rostral
G
Left Ishtmus
H
Right Ishtmus
CK
HC
**
*

A

Pearson's correlation matrix

R_Rostral			−0.33				0.56	0.34	0.46	0.69	0.55	0.43	0.57	
R_Posterior	0.21	0.25	−0.35		−0.34		0.61	0.33	0.81	0.66	0.54	0.38		
R_Ishtmus					−0.29	−0.3	0.43	0.72	0.4	0.46	0.4			
R_Caudal		0.22	−0.4	−0.24	−0.28		0.64	0.34	0.47	0.63				
L_Rostral		0.25	−0.46	−0.19		−0.22	0.7	0.4	0.65					
L_Posterior		0.32	−0.34		−0.25		0.67	0.33						
L_Ishtmus		0.19		0.34			0.35							
L_Caudal		0.3	−0.41	−0.26	−0.34									
CTQ		−0.17	0.21	0.27	−0.26									
Cocaine			0.37	−0.22	0.27									
Cannabis						0.26								
Tobacco		0.32			−0.28									
Alcohol	0.26	−0.23	0.32											
Ethnicity														





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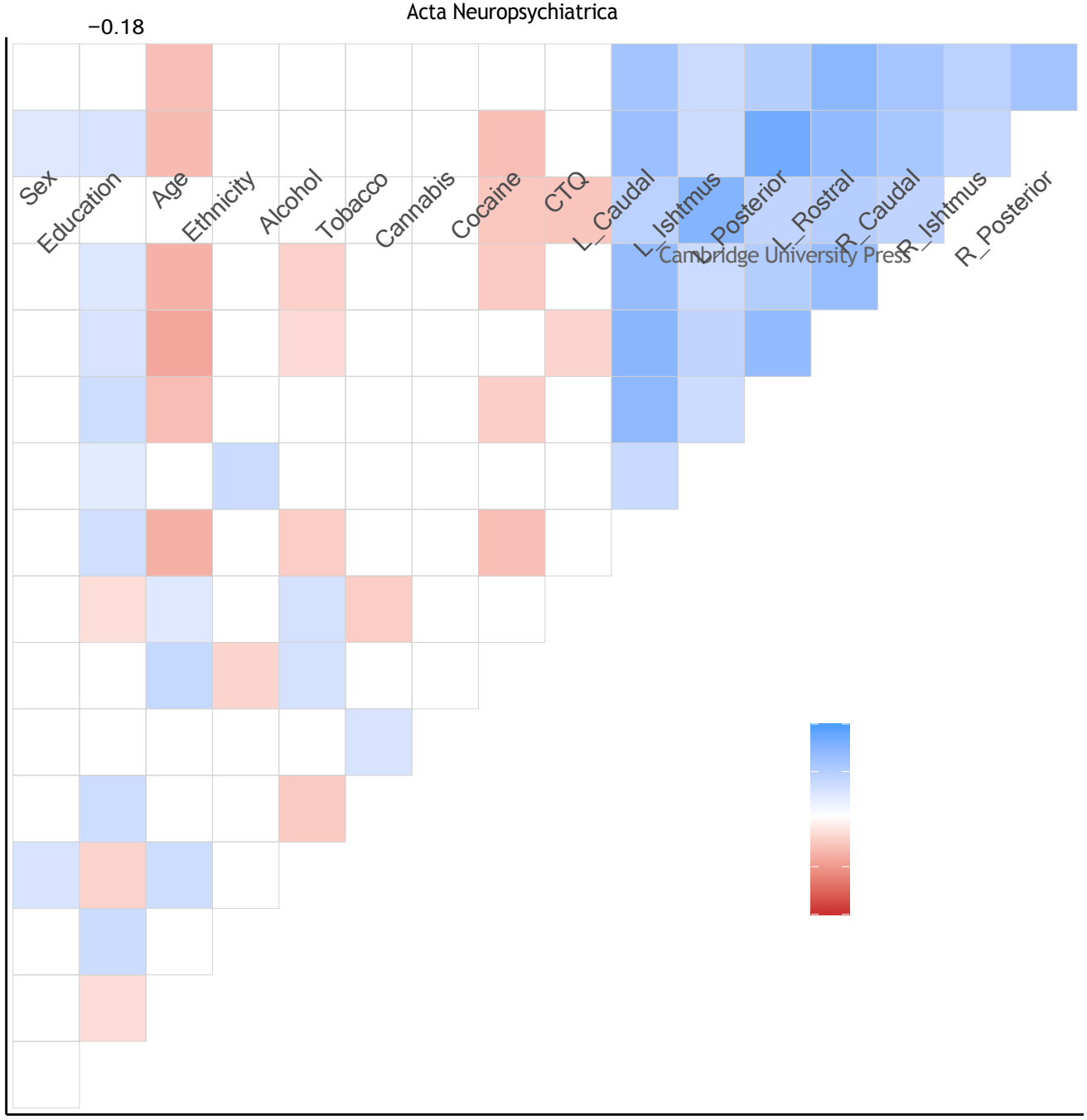

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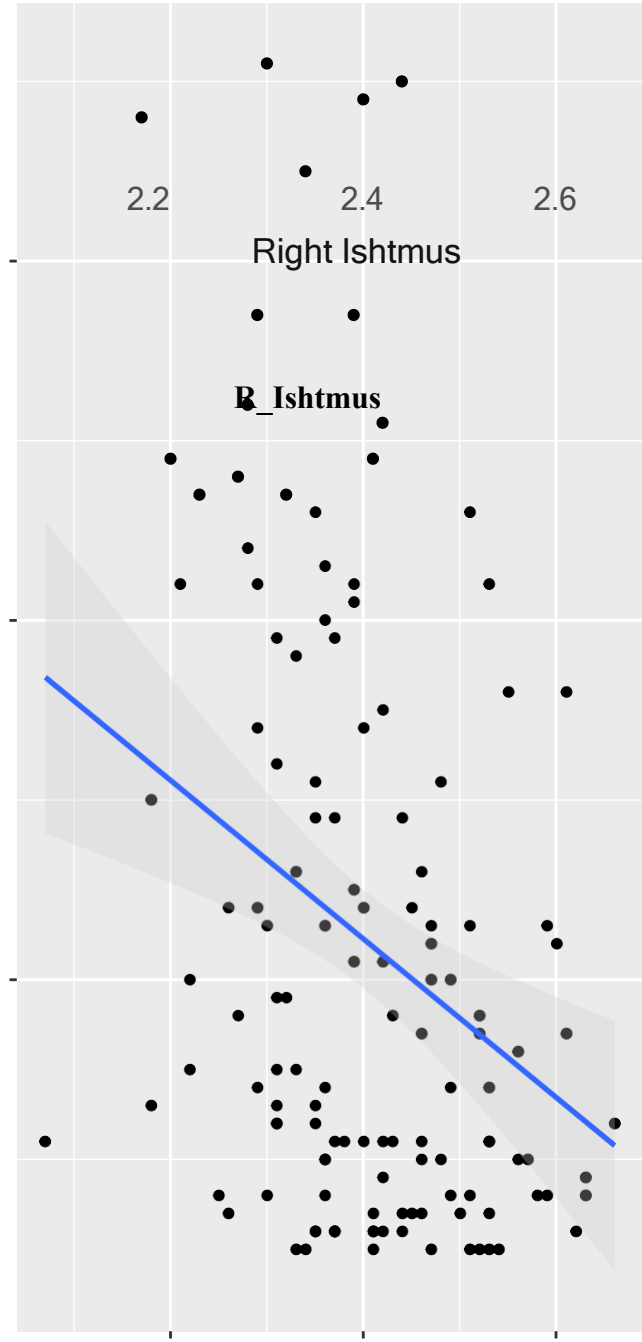

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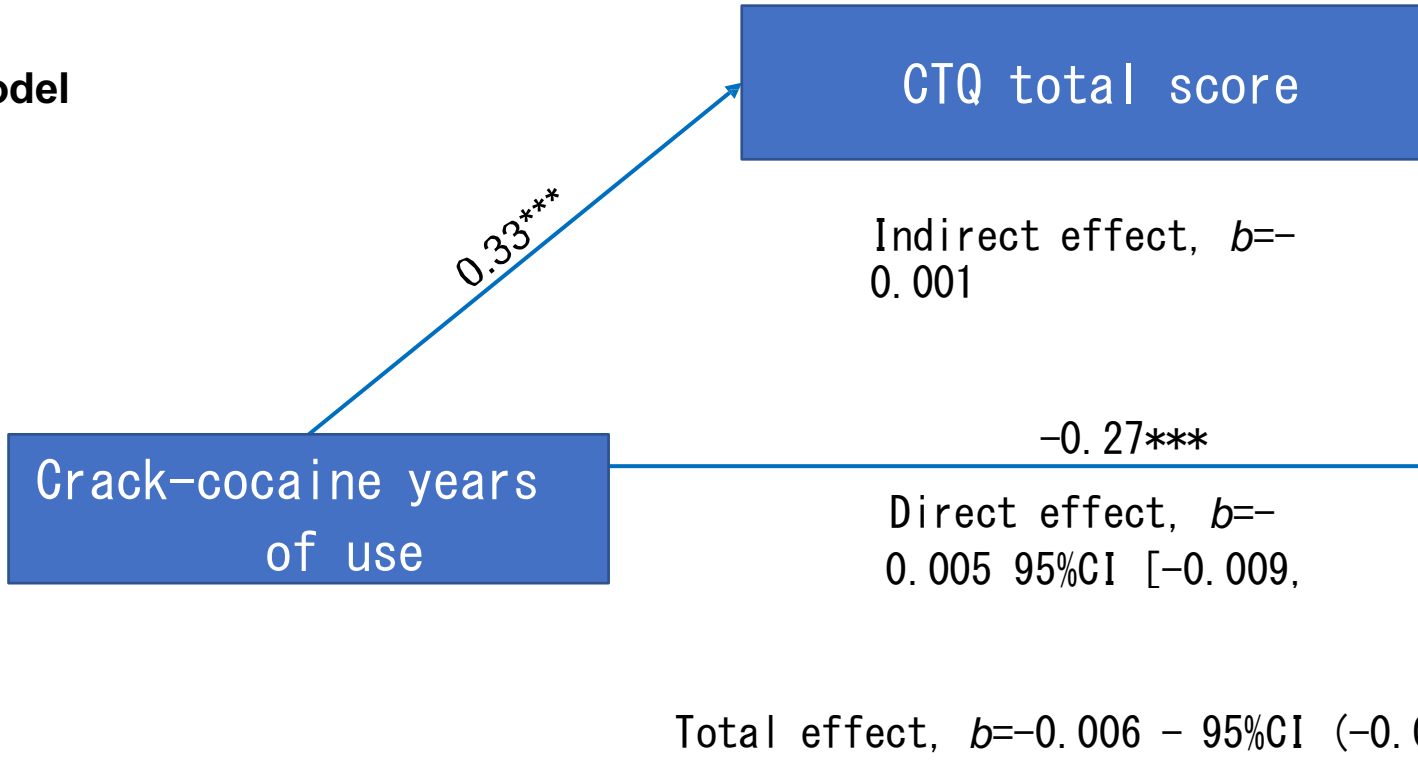

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Review

Patterns of structural brain differences in cocaine use disorder: Integrating multilevel frequentist, Bayesian, and coordinate-based meta-analyses

Augusto Martins Lucas Bittencourt [a,b,c], Bernardo Penteado Favero [d], Camila Haas [e], Eduardo Tavares Portolan [e], Enzo Gallardo [e], Leonardo Melo Rothmann [f], Rodrigo Grassi-Oliveira [a,e,f], Thiago Wendt Viola [a,e,*]

[a] Brain Institute (InsCer), Pontifical Catholic, University of Rio Grande do Sul (PUCRS), Porto Alegre 90619900, Brazil
[b] School of Medicine, Catholic University of Pelotas (UCPel), Pelotas 96015560, Brazil
[c] School of Medicine, Federal University of Rio Grande (FURG), Rio Grande 96203900, Brazil
[d] School of Medicine, Federal University of Pelotas (UFPel), Pelotas 96030-000, Brazil
[e] School of Medicine, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Porto Alegre 90610-970, Brazil
[f] Department of Clinical Medicine – Translational Neuropsychiatry Unit, Aarhus University, Aarhus 8000, Denmark

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ABSTRACT

Background: Cocaine Use Disorder (CUD) has been associated with differences in gray matter (GM) measures, but prior meta-analyses have yielded inconsistent results due to methodological variability, publication bias, and selective reporting. To address these gaps, this study integrates multilevel frequentist, Bayesian, and coordinate- based approaches to provide a comprehensive, anatomically resolved synthesis of structural neuroimaging findings in CUD.

Methods: Following PRISMA guidelines (PROSPERO: CRD42024585260), 47 studies were included that compared GM indices between individuals with CUD and healthy controls. Multilevel random-effects meta-an- alyses were conducted to quantify cortical and subcortical group differences while accounting for clinically relevant moderators. Bayesian hierarchical models were used to conduct sensitivity analyses addressing potential reporting bias, and a coordinate-based Activation Likelihood Estimation (ALE) analysis evaluated spatial convergence across voxel-based morphometry studies.

Results: The analyses indicated that CUD showed lower GM measures in prefrontal and temporal cortical regions, particularly the ITG and the rostral middle frontal gyrus. Subcortical analyses showed lower GM volume in the amygdala, hippocampus, thalamus, pallidum, nucleus accumbens, brainstem, and cerebellum. Longer duration of cocaine use and greater clinical severity were associated with larger negative effect-size estimates for cortical measures. Bayesian regularization yielded consistent cortical effect-size estimates across sensitivity analyses, whereas the coordinate-based ALE analysis identified no clusters surviving family-wise error correction.

Conclusions: Together, results from this meta-analysis identify consistent patterns of GM differences across cortico-subcortical regions in individuals with CUD. These findings provide an integrated neuroanatomical reference framework that may inform future longitudinal studies and the evaluation of candidate neuroimaging biomarkers.

1. Introduction

Cocaine Use Disorder (CUD) is characterized by persistent cocaine consumption, impaired self-regulation, and continued use despite adverse consequences (Abuse, 2020; Hasin et al., 2013; Koob and Vol- kow, 2010; Poisel et al., 2023; Schwartz et al., 2022). In 2023, about 25 million people globally (0.47 % of those aged 15–64) reported using cocaine ("World Drug Report 2025 - Statistical Annex," n.d.; "World Drug Report 2025," n.d.). The associated physical, psychological, social, and legal risks make CUD a significant public health concern (Karila et al., 2012; Sanvisens et al., 2021; Schwartz et al., 2022). To better understand the neuroanatomical basis of CUD, recent advances in structural neuroimaging have highlighted lower gray matter (GM) vol- ume throughout cortical and subcortical regions involved in addictive

* Corresponding to: School of Medicine, Pontifical Catholic University of Rio Grande do, Sul, No.6681 Ipiranga Avenue, Porto Alegre, Rio Grande do Sul, Brazil.
E-mail address: thiago.wendt@pucrs.br (T.W. Viola).

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behaviors (Beheshti, 2023; Bittencourt et al., 2021; Dang et al., 2022; McCurdy et al., 2024; Pando-Naude et al., 2021; Rothmann et al., 2024; Schinz et al., 2023; Trevisan et al., 2023). However, previous studies have produced heterogeneous findings, primarily due to methodological variability, including differences in analytical approaches, diversity in the neuroanatomical measures examined, and considerable heteroge- neity across clinical and demographic factors of the included samples (Garza-Villarreal et al., 2017; McCurdy et al., 2024; Meade et al., 2020; Narayana et al., 2010; Schinz et al., 2023). Therefore, these findings have not yet been translated into reliable neuroimaging biomarkers or contributed to more effective clinical interventions.

Meta-analyses have reported GM group differences between in- dividuals with CUD and healthy controls (HC), most consistently within the prefrontal and temporal cortices (Ersche et al., 2013; Hall et al., 2015; Pando-Naude et al., 2021), regions implicated in executive control and cue reactivity (Koob and Volkow, 2016). Several studies have described lower GM indices in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Ersche et al., 2013; Pando-Naude et al., 2021), whereas others have emphasized differences in temporal and limbic regions, including the insula and hippocampus (Barro´s-Loscertales et al., 2011; Dang et al., 2022). Evidence for subcortical involvement has been less consistent, with some meta-analyses reporting group differences in striatal (Barro´s-Loscertales et al., 2011; Bittencourt et al., 2021; Garza-Villarreal et al., 2018; Schuch-Goi et al., 2017) and thalamic measures (Pando-Naude et al., 2021; Sim et al., 2007), while others did not find statistically significant differences in these regions (Garza-Villarreal et al., 2017; Narayana et al., 2010). Such inconsistencies may reflect substantial methodolog- ical heterogeneity across studies, including differences in analytic stra- tegies, sample characteristics, and susceptibility to statistical and reporting biases (Bartoˇs et al., 2024; Dang et al., 2022; Ersche et al., 2013; Kunz et al., 2024; Rhodes et al., 2017).

High-quality quantitative reviews established a robust regional pattern of lower GM volume in CUD and provided critical support for neurocircuitry models of addiction (Ersche et al., 2013; Hall et al., 2015; Pando-Naude et al., 2021). However, their findings were constrained by heterogeneity and reporting practices in the primary literature, which limited the systematic integration of multiple morphometric measures, the statistical dependence among regional estimates, clinically relevant moderators, and the impact of selective reporting in whole-brain ana- lyses. The present study builds on prior work by providing an integrative quantitative framework that systematically accounts for key sources of methodological and clinical variability in the structural neuroimaging literature on CUD.

Across the four available quantitative reviews of structural brain differences in CUD, route of cocaine administration was not examined as a moderator in any quantitative analysis (Dang et al., 2022; Ersche et al., 2013; Hall et al., 2015; Pando-Naude et al., 2021), despite evidence that rapid delivery methods such as crack smoking or intravenous injection are associated with more severe cognitive impairments, earlier relapse, and larger-magnitude GM differences compared to intranasal use (Bittencourt et al., 2021, 2024; Poireau et al., 2024; Rothmann et al., 2024). Furthermore, physiological studies have reported increased ce- rebrovascular risk in samples characterized by intravenous administra- tion (Kaufman et al., 1998). These observations highlight the need to systematically evaluate the route of cocaine administration as a moderating variable in structural neuroimaging analyses.

Psychiatric and medical comorbidities, along with polysubstance use, constitute significant yet often overlooked sources of heterogeneity in CUD research. Empirical studies indicate that comorbid mental dis- orders and concurrent substance use are associated with larger- magnitude group differences in GM measures, particularly in prefron- tal, insular, and hippocampal regions (Alia-Klein et al., 2011;

Dang et al., 2022; Kaag et al., 2014; Noyan et al., 2016; Pando-Naude et al., 2021; Stoychev, 2019). The exclusion of these variables from quantita- tive reviews likely contributes to inconsistencies in prior meta-analyses (Dang et al., 2022; Ersche et al., 2013; Hall et al., 2015; Mackey et al., 2019; Pando-Naude et al., 2021).

To address different dimensions of heterogeneity in the literature, we combined complementary quantitative approaches. Bayesian meta- analytic models were used to provide a probabilistic characterization of uncertainty and a coherent framework for prior-regularized sensi- tivity analyses, complementing the primary frequentist multilevel syn- thesis (Cao et al., 2023), while coordinate-based techniques, such as Anatomic Likelihood Estimation (ALE), were used to assess whether structural differences converge spatially across independent samples (Li et al., 2022; Pando-Naude et al., 2021; Tolomeo and Yu, 2022).

In addition, we incorporated clinically relevant moderators, including route of cocaine administration, psychiatric and medical comorbidities, and polysubstance use, to examine how methodological and clinical variability are associated with differences in the magnitude and spatial distribution of GM measures in CUD. Rather than testing a narrow confirmatory hypothesis, the primary aim of this meta-analysis was to identify and prioritize structural brain differences that remain consistent across heterogeneous study designs and clinical pre- sentations, thereby refining the neuroanatomical characterization of CUD and enhancing the clinical and translational interpretability of prior findings.

2. Methods

2.1. Literature search

A systematic review was conducted in accordance with the PRISMA guidelines. The protocol was preregistered in PROSPERO (CRD42024585260). Embase, MEDLINE, Web of Science, and PsycINFO were searched for studies published up to August 2024. Search strategies were constructed using three conceptual domains: (1) cocaine use dis- order, (2) structural neuroimaging, and (3) neuroanatomy. Terms related to cocaine use disorder included

"cocaine use disorder," "cocaine dependence," and "cocaine addiction." Structural neuroimaging terms included "structural MRI," "voxel-based morphometry," "VBM," "cortical thickness," "surface area," and "gray matter." Neuroanatomical terms included "brain," "cortex," "subcortical," and related anatomical descriptors. Within each domain, terms were combined using the OR operator; domains were combined using the AND operator.

2.2. Eligibility criteria

Studies were included if they reported original data in full-length articles and used structural Magnetic Resonance Imaging (MRI) to compare GM (volume, cortical thickness (CT), or surface area) between people with CUD and HC. For inclusion, studies were required to report quantitative structural neuroimaging results, including effect size esti- mates or sufficient statistical information to derive them (e.g., means and standard deviations, test statistics), or, for coordinate-based ana- lyses, clearly specified stereotactic coordinates derived from whole- brain analyses. These criteria ensured the inclusion of studies that pro- vided relevant, quantitative comparisons using robust imaging methods, thereby enhancing the validity and comparability of the analyses. Exclusion criteria were qualitative reports, narrative reviews, confer- ence abstracts, and studies that reported only qualitative descriptions or lacked extractable quantitative data. Three independent reviewers per- formed data extraction in duplicate, with all discrepancies resolved by consensus to maintain rigor.

To increase data inclusion and maintain comparability, we used a tiered approach. Studies with complete group comparison statistics (e. g., *t*-values, *p*-values, effect sizes) were included in both frequentist and Bayesian syntheses. Studies reporting only stereotactic coordinates, without summary statistics, were included only in the coordinate-based meta-analysis (ALE). This allows us to use spatial data without intro- ducing incomplete statistics to effect-size analyses. For example, Rando

et al. provided coordinates but not test statistics, so they were included only in the ALE analysis (Rando et al., 2013).

Fig. 1 summarizes the study selection process, following PRISMA, 2020 (Page et al., 2021; "PRISMA, 2020 Flow Diagram," n.d.; "PRISMA, 2020 statement," n.d.). During title and abstract screening, records were excluded when they clearly failed to meet eligibility criteria, including non-original publications (e.g., reviews or editorials), non-human studies, studies not involving CUD, or studies not reporting structural neuroimaging outcomes. Two hundred seventy-three records were identified (PubMed: 81; ISI Web of Science: 121; PsycINFO: 70; included by literature review: 1). After removing 119 duplicates, 154 records were screened by title and abstract, and 90 were excluded. Sixty-four full-text articles were checked, and 17 were excluded for reasons such as publication type, lack of access, or insufficient sample information. In total, 47 studies were included in this review, with 46 contributing to frequentist and Bayesian meta-analyses, and 15 used in the coordinate-based ALE analysis.

2.3. Data extraction

Extracted variables included demographic information, such as the number of participants, mean age, mean years of education for CUD and HC, and male proportion in the CUD group. To account for group dif- ferences, we calculated the age delta (mean CUD age minus the control age) and the education delta (mean years of education in the CUD minus the control group).

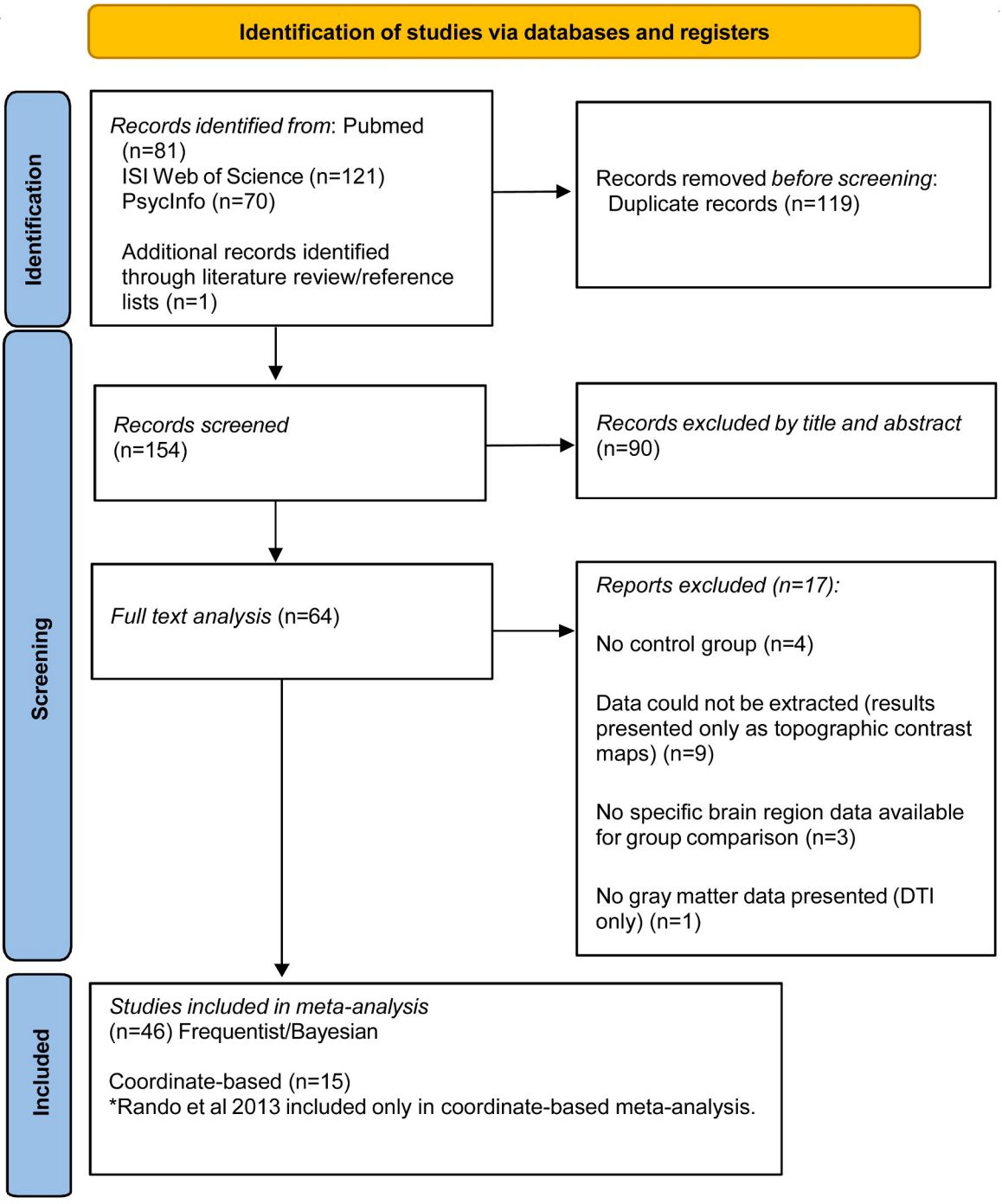

Fig. 1. PRISMA 2020 flow diagram of study selection for the meta-analysis.

Clinical variables extracted included route of cocaine administration, time of assessment in longitudinal studies (baseline vs. follow-up), duration of cocaine use, and psychiatric or medical comorbidities. Duration of use was quantified as years of cocaine exposure, and route of administration was coded as intranasal versus non-intranasal (smoked or intravenous), given the low representation of the latter routes. Given the high heterogeneity in reported comorbidities across studies, we derived a sample-level indicator of clinical severity that combines the timing of assessment and comorbidity burden. Samples were classified as presenting less severe clinical profiles when no substantial psychiatric or medical comorbidities were reported or, in longitudinal designs, when follow-up assessments reflected milder withdrawal symptoms and longer abstinence. More severe clinical profiles were defined by the presence of psychiatric (e.g., ADHD, major depression, alcohol or cannabis use disorders) or medical (e.g., HIV+) comorbidities in at least 50 % of the sample, or by baseline assessments characterized by stronger withdrawal symptoms and shorter abstinence durations. This stratification is supported by empirical evidence showing that psychiatric comorbidities and concurrent substance use in CUD are associated with higher relapse rates, shorter abstinence durations, and increased treatment dropout (Andersson et al., 2019; Go´mez Pe´rez et al., 2025; Palazo´n-Llecha et al., 2024; Wang et al., 2021). Nicotine use was not included as a moderator because it was inconsistently defined and reported across studies and showed limited between-study variability, precluding reliable quantitative integration. In contrast, alcohol and cannabis use demonstrated greater variability and more consistent reporting, allowing their inclusion in moderator analyses.

Neuroimaging descriptors included the analytical strategy (whole-brain vs. region-of-interest [ROI]), the morphometric MRI outcome (GM volume, CT, or surface area), the cerebral hemisphere, and the anatomical label reported by the authors. A single study could contribute more than one effect-size entry if it reported results for multiple brain regions, stratified participants by clinical status (e.g., with vs. without comorbidities), stratified by sex, or included longitudinal MRI assessments. In longitudinal designs, each time point was treated as an independent entry in the dataset.

Both whole-brain and ROI studies were included in this meta-analysis. We included ROI designs because they often target brain regions linked to addiction, such as the prefrontal cortex, striatum, and limbic areas. Including both types maximizes the evidence base and provides a more comprehensive assessment of structural changes related to cocaine use. To ensure transparency and reduce bias, we recorded the analytic strategy (whole-brain vs. ROI) as a descriptor for each effect size and considered it in heterogeneity analyses. This approach follows previous neuroimaging meta-analyses in substance use disorders (Dang et al., 2022; Ersche et al., 2013; Hall et al., 2015), which demonstrate the benefits of integrating ROI data to improve coverage and account for methodological differences. Design and neuroimaging data from the included studies are summarized in Supplementary Table S1.

2.4. Outcome

For each comparison, we extracted, when available, the mean and standard deviation (SD) of the neuroimaging metric for both groups. When only standard errors were reported, these were converted to SDs using the square root of the sample size. When mean and SDs, or error estimates, were available only in graphical format (e.g., bar plots), values were extracted using GetData Graph Digitizer (v2.26.0.20, © S. Fedorov) (Fedorov, n.d.). If neither descriptive statistic was available, we collected t- or z-statistics, assuming a normal distribution. When only p-values were provided, they were recorded for subsequent estimation of effect size. Also, when available for whole-voxel-based analysis studies, specific peak coordinates (x, y, z) were recorded. All anatomical labels were mapped to regions of the Desikan-Killiany cortical atlas (aparc) (Desikan et al., 2006)

or to the Automatic Subcortical Segmen- tation (aseg) atlas (Fischl et al., 2002), as implemented in the ggseg package (v1.6.6) (Mowinckel and Vidal-Pin˜eiro, 2020).

2.5. Data analysis

Effect sizes (Cohen's d) and their sampling variances were calculated using the escalc() function from the metafor package (v0.5–7) (Viechtbauer, 2010) in R (v2.10.0) ("mlR Core Team 2022 R A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. - References - Scientific Research Publishing," n.d.; Viechtbauer, 2010). Because studies contributed multiple entries, we used a multilevel random-effects meta-analysis model (rma.mv() func- tion) (Viechtbauer, 2010). This included two levels: effect-size entries nested within studies. The model accounted for both within- and between-study variability. Weights were based on inverse-variance estimation, incorporating sampling variance and estimated between-study variance (τ^2). All analyses were performed separately for cortical and subcortical datasets.

First, univariate meta-regressions were used to test whether meth- odological and demographic factors affected heterogeneity. Factors included morphometric outcome, analysis method, hemisphere, age delta, education delta, and male proportion, as measured by the Q-sta- tistic and p-value. Next, we examined whether clinical characteristics in the CUD groups, including years of use, primary route of use, and less versus more severe clinical presentation, operated as moderators. Last, models included brain region (ggseg_region) (Mowinckel and Vidal-Pi- n˜eiro, 2020) and significant univariate moderators. Pseudo-R^2 measured the explained heterogeneity.

Fourth, to address selective reporting bias, particularly in whole- brain neuroimaging studies that often report only statistically signifi- cant findings, we conducted a Bayesian multilevel meta-analysis as a sensitivity analysis using the brms package in R (Bürkner, 2017, 2018). Studies employing whole-brain analyses without reporting null results were identified, and missing regional entries were imputed for anatomical regions not

explicitly reported. The Bayesian model mirrored the frequentist multilevel structure and included weakly informative, zero-centered Normal priors on standardized regional ef- fect sizes (Normal(0, 0.3) and Normal(0, 1.0)) and exponential priors on variance components. These priors reflect the conservative assumption that unreported neuroimaging effects are likely small and centered near zero, thereby reducing the risk of false-positive inflation due to selective reporting. Fixed effects included anatomical region (ggseg_region) and significant methodological and sample-level moderators identified in prior analyses, with random intercepts specified at the Study_ID and Entry_ID levels. Full model specifications and code are provided in Supplemental Material 7.

In the fifth and final stage, we conducted a coordinate-based meta- analysis restricted to studies reporting peak stereotactic coordinates from whole-brain voxel-wise comparisons. Coordinates from voxel- based morphometry (VBM) studies were analyzed using GingerALE (v3.0.1) (Turkeltaub et al., 2002; Frahm et al., 2023). When necessary, Talairach coordinates were converted to MNI space using the Lancaster transform (icbm2tal) (Lancaster et al., 2007). To ensure robustness of voxel-level inference, analyses were performed only when at least 14 independent experiments were available (Frahm et al., 2023). When multiple contrasts were reported from the same sample, the primary whole-brain CUD versus control contrast was retained.

ALE maps were generated using a random-effects model accounting for between-study variability (Eickhoff et al., 2009). Statistical signifi- cance was assessed using a family-wise error (FWE)–corrected threshold of $p < 0.05$ based on 5000 permutations (Eickhoff et al., 2012), with a minimum cluster volume of 1 mm^3 .

2.6. Quality and bias assessment

Study quality was evaluated using a 10-item framework adapted from recommendations for neuroimaging meta-analyses (Müller et al.,

2018), covering diagnostic rigor, characterization of controls, absti- nence/treatment status, route reporting, comorbidity reporting, de- mographics, covariate control, longitudinal design, and full reporting of findings. Scoring details are provided in Supplementary Material 2.

3. Results

3.1. Associations of methodological and clinical variables with structural neuroimaging findings

Table 1 summarizes the associations between methodological and clinical variables and effect-size heterogeneity in MRI findings in com- parisons between individuals with CUD and HC. For cortical data, age delta ($p = 0.02$) and the proportion of male participants ($p = 0.03$) significantly explained heterogeneity in the meta-analyses. These results indicate that larger negative effect-size estimates were observed when the CUD group was older than the control group. In contrast, samples with a higher proportion of males in the CUD group showed smaller- magnitude group differences in CT, surface area, and volume.

No significant associations were observed between morphometric outcome type (thickness, surface area, or volume), analysis type (ROI vs. Whole-brain), brain hemisphere (bilateral, left, or right), or education level with heterogeneity in either cortical or subcortical meta-analyses. However, a trend toward larger group differences in the right hemi- sphere was observed in the CT meta-analysis ($p = 0.059$). Therefore, the brain hemisphere was retained for further meta-regression analyses alongside age delta and the proportion of male participants.

Regarding clinical variables, Fig. 2 summarizes these analyses, and the complete meta-regression estimates are presented in Table 1. Years of cocaine use significantly explained heterogeneity in the cortical meta- analysis (Q-value = 7.44; p-value = 0.02; Fig. 2A), but not in the subcortical meta-analysis (Q-value = 0.01; p-value = 0.90; Fig. 2B). This indicates that longer duration of cocaine use was associated with larger- magnitude negative effect-size estimates for cortical measures (estimate = —0.037; error = 0.017; pseudo-R^2 = 9.84 %). The clinical level factor was also significantly associated with heterogeneity in the cortical analysis (Q-value = 3.96; p-value = 0.046; Fig. 2C), but not in the

subcortical meta-analysis (Q-value = 1.12; p-value = 0.288; Fig. 2D). Samples characterized by greater clinical severity, including higher levels of abstinence-related symptoms and a higher prevalence of psy- chiatric (e.g., ADHD, major depression, alcohol or cannabis depen- dence) or medical (e.g., HIV+) comorbidities, showed larger-magnitude negative cortical effect-size estimates (estimate = —0.186; error = 0.093; pseudo-R^2 = 1.53 %). In a post-hoc analysis restricted to samples with more severe clinical presentations, no significant differences were found between substance use disorder-related features, primarily referred to as comorbid alcohol use disorder and cannabis use disorder, compared to other psychiatric/medical comorbidities in terms of cortical effect sizes (Q-value = 0.12; p-value = 0.727). Additionally, although the primary route of cocaine administration (i.e., snorted versus smoked or intravenous) did not significantly explain heteroge- neity (cortical data: Q-value = 1.11; p-value = 0.291; subcortical data: Q-value = 0.55; p-value = 0.458), both analyses showed a tendency toward larger negative effect-size estimates when snorting was not the primary route of administration.

3.2. GM group differences across brain regions in CUD

Fig. 3 summarizes the meta-analyses of cortical and subcortical re- gion segmentations. These meta-analyses included the moderator vari- able of ggseg-mapped regions in addition to brain hemisphere, age delta, and the proportion of male participants. Volume, thickness, and area were grouped in the primary analysis of the cortical subset (k = 419). The meta-analytic estimates for each mapped region, along with the corresponding number of observations, are provided in Supplementary Material 3. Available effect sizes ranged from 5 (i.e., bankssts, frontal pole, paracentral, pericalcarine, and transverse temporal gyri) to 37 (i.
e., pars triangularis). Fig. 3A highlights cortical regions with significant differences (p-value < 0.05) compared to the reference region, the temporal pole, which was the only region that showed a positive coef-
ficient. This indicates that the superior temporal gyrus, rostral middle frontal gyrus, lateral occipital gyrus, superior frontal gyrus, inferior temporal gyrus (ITG), fusiform gyrus, lateral OFC, and middle temporal gyrus showed the largest-magnitude negative group differences in

Table 1
Testing the effects of methodological and clinical variables on effect sizes.

	Cortical dataset						Subcortical dataset					
	K (samples)	Estimate	SE	95 % CI	Q-test *p*-val	pR^2	*K* (samples)	Estimate	SE	95 % CI	Q-test *p*-val	pR^2
Morphometric outcome	419				0.138	-	56				-	-
Volume (reference)	230				-		56				-	
Area	21	+ 0.113	0.09	-0.08–0.30	0.256							
Thickness	168	-0.052	0.04	-0.14–0.03	0.242							
Analysis type	419				0.182	-	56				0.226	-
ROI (reference)	175				-		38				-	
Whole brain	244	-0.267	0.20	-0.66–0.12	0.182		18	-0.366	0.30	-0.96–0.22	0.226	
Hemisphere	419				0.122	-	56				0244	-
Bilateral (reference)	96				-		18				-	
Left	145	-0.225	0.14	-0.49–0.04	0.108		18	-0.492	0.29	-1.06–0.08	0.094	
Right	178	-0.263	0.13	-0.53–0.01	0.059		20	-0.436	0.28	-0.99–0.12	0.127	
Age delta[ca]	408	**-0.057**	**0.02**	**-0.10–0.01**	**0.027**	4.1 %	53	+ 0.021	0.03	-0.05–0.09	0.568	-
Education delta[cb]	399	+ 0.059	0.07	-0.07–0.19	0.399	-	47	-0.048	0.01	-0.26–0.16	0.661	-
Male sex (%)[cd]	414	**+ 0.005**	**0.01**	**0.00–0.01**	**0.032**	4.0 %	54	-0.001	0.01	-0.03–0.01	0.349	-
Years of cocaine use	410	**-0.0371**	**0.01**	**-0.07 to —0.01**	**0.020**	9.8 %	53	-0.001	0.02	-0.05–0.04	0.904	-
Route of cocaine use	419				0.291	-	56				0.458	-
Intranasal (reference)	384				-		43				-	
Smoked or Intravenous	35	-0.1406	0.26	-0.66–0.37	0.291		13	-0.1294	0.34	-0.80–0.54	0.458	
Clinical severity level	419				0.046	1.5 %	56				0.288	-
Less	294				-		21				-	
More	125	**-0.1861**	**0.13**	**-0.58 to —0.07**	**0.046**		35	-0.3012	0.25	-0.80–0.20	0.458	

Legend. Meta-regression and subgroup comparisons. Negative coefficient estimates indicate larger between-group differences (i.e., greater reduction associated with CUD); c = continuous variable; a (age delta) = mean sample age of the CUD group minus mean sample age of the control group (positive values: CUD group older; negative values: control group older); b (education delta) = mean sample education years of the CUD group minus mean sample education years of the control group (positive values: CUD with higher education; negative values: control group with higher education); d = percentage of males in the CUD group; pR^2 = pseudo-R^2 indicating the proportion of heterogeneity explained for each significant model.

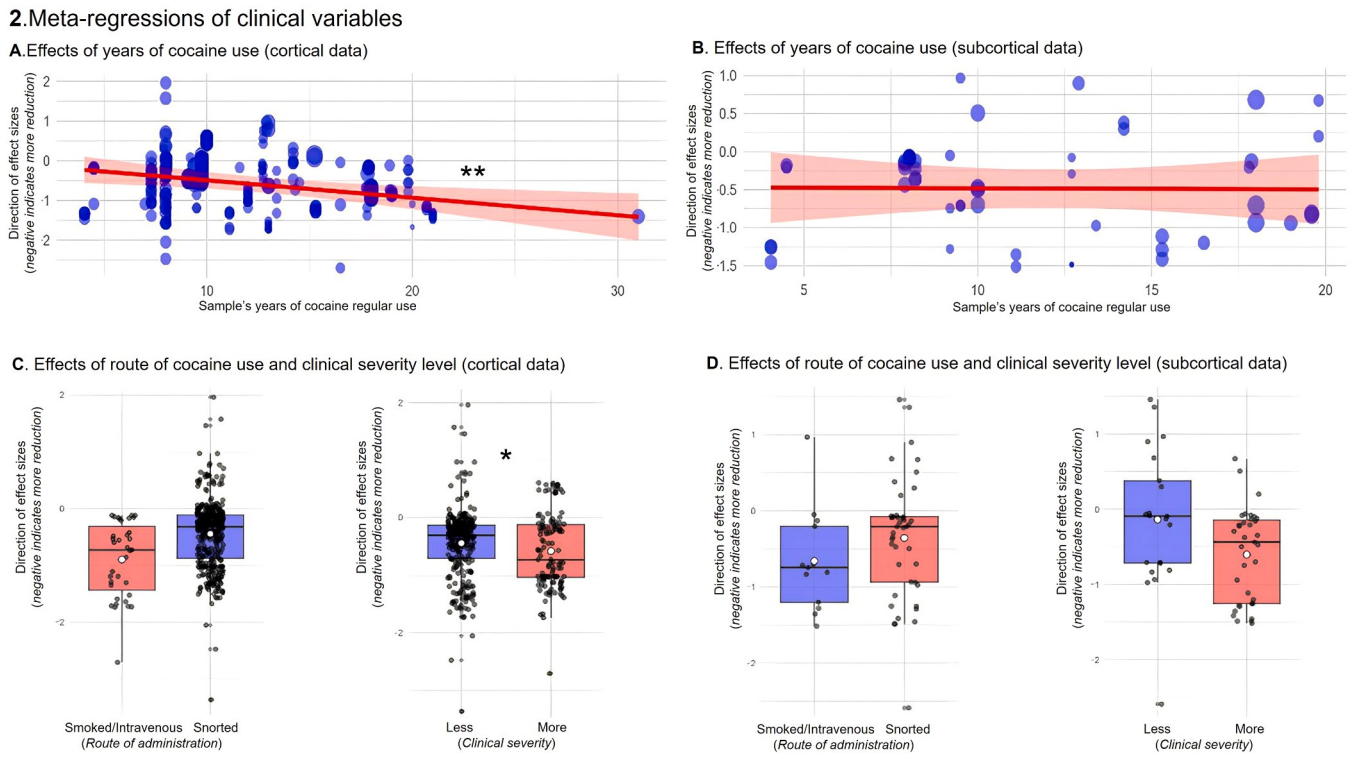

Fig. 2. Testing clinical variables as potential sources of heterogeneity in the meta-analysis. (A) Cortical meta-regression testing years of cocaine consumption (k = 410), snorted (k = 384) versus smoked/intravenous cocaine use (k = 35), and less severe (k = 294) versus more severe (k = 125) clinical presentation. (B) Subcortical meta-regression testing years of cocaine consumption (k = 53), snorted (k = 43) versus smoked/intravenous cocaine use (k = 13), and less severe (k = 21) versus more severe (k = 35) clinical presentation. * indicates a p-value < 0.05. ** indicates a p-value < 0.01.

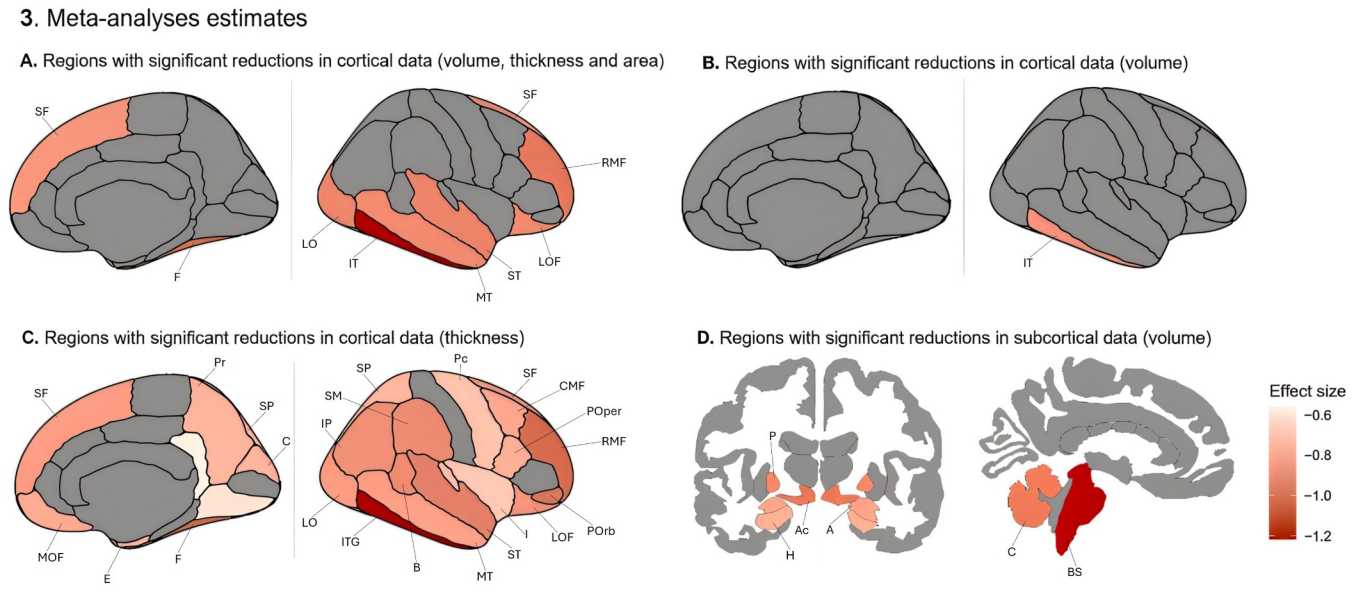

Fig. 3. (A) Cortical regions showing significant group differences in GM measures when combining volume, thickness, and surface area. (B) Cortical regions showing significant group differences in GM volume. (C) Cortical regions showing significant group differences in cortical thickness. (D) Subcortical regions showing sig- nificant group differences in GM volume. Effect-size estimates are color-coded, with darker red indicating larger negative effect-size values. Group differences are displayed on lateral and medial views of the cortical surface and on coronal and sagittal slices for subcortical regions. SF – Superior frontal. F – Fusiform. LO – Lateral occipital. IT – Inferior temporal. MT – Middle temporal. ST – Superior temporal. LOF – Lateral orbitofrontal. RMF – Rostral middle frontal. SF – Superior frontal. Pr – Precuneus. MOF – Middle orbitofrontal. E – Entorhinal. C – Cuneus. SP – Superior parietal. IP – Inferior parietal. SM – Supramarginal. Pc – Precentral. CMF – Caudal middle frontal. POper – Pars opercularis. POrb – Pars orbitalis. I – Insula. B – Bankssts. P – Pallidum. Ac – Accumbens. A – Amygdala. H – Hippocampus. C – Cerebellum. BS – Brain stem.

cortical measures. Notably, the ITG and the rostral middle frontal gyrus exhibited the largest-magnitude negative effect-size estimates (p-value < 0.001). This model explained 10.6 % of the total heterogeneity (p- value < 0.0001).

Although the cortical morphometric outcome did not significantly explain heterogeneity (Table 1), two stratified analyses were performed separately for volume (k = 230) and thickness (k = 168). After adjust- ing for brain hemisphere, age difference, and the proportion of male participants, negative associations between CUD and ITG measures were observed in both volumetric (estimate = —0.293; SE = 0.119; p = 0.014) and CT analyses (estimate = —1.111; SE = 0.240; $p < 0.001$). Notably, the ITG was the only brain region with significant differences in the volumetric analysis (Fig. 3B), while several other areas showed decreased CT (e.g., rostral middle frontal, pars triangularis, middle temporal, lateral orbitofrontal, caudal middle frontal, etc.; Fig. 3C) compared to the temporal pole reference region (complete data in Supplementary Material 3).

Similarly, although the analysis type variable did not significantly explain heterogeneity (Table 1), two stratified analyses were performed separately for ROI (k = 175) and whole-brain (k = 244) data in the cortical dataset. After adjusting for brain hemisphere, age difference, and the proportion of male participants, both models indicated that the ITG showed the largest negative effect-size estimates in comparisons between individuals with CUD and HC (ROI model: estimate = —1.284; SE = 0.233; $p < 0.001$; whole-brain model: estimate = —0.484; SE = 0.111; $p < 0.001$).

Subcortical estimates (k = 56) are presented in Fig. 3D. Available effect sizes ranged from 2 (i.e., lateral ventricle and brainstem) to 15 (i. e., caudate) volumetric data (Supplementary Material 3). Fig. 3D high- lights subcortical regions with significant differences (p-value < 0.05) compared to the reference region, the lateral ventricle, which showed a positive coefficient. This indicates that the amygdala, brainstem, cere- bellum, hippocampus, pallidum, thalamus, and accumbens showed the largest-magnitude negative effect-size estimates among subcortical re- gions, with the brainstem, cerebellum, and accumbens exhibiting the largest group differences (p-value < 0.01). This model explained 3.1 % of the total heterogeneity (p-value = 0.024). For the subcortical data, we did not perform stratified analyses by whole-brain versus ROI studies due to the small number of studies contributing to the whole-brain type.

3.3. Sensitivity analysis using a Bayesian approach

To evaluate the influence of selective reporting and sparsely observed data in whole-brain studies, we expanded the cortical dataset from 419 reported effect sizes to 1769 by imputing effect sizes for unreported brain regions. Regarding the subcortical dataset, the number of effect sizes increased from 56 to 262. These additional entries corresponded to studies that used a whole-brain analysis approach but did not report all regional outcomes. Missing effect sizes and their variances were modeled as unknowns and estimated in a Bayesian framework.

The first Bayesian model used a weakly informative Normal(0, 0.3) prior on the standardized effect sizes, encoding the expectation that most true effects are small and centered around zero, while still allowing moderate effects to remain plausible. This prior was chosen to provide conservative regularization, partly counteracting potential bias arising from selective reporting of statistically significant effects in the literature. In regions with limited data, it shrinks estimates toward zero, whereas in regions with more data, its influence is comparatively smaller, as shown by the similarity with the wider-prior model. To assess the robustness of our conclusions to this prior choice, we fitted a second model using a wider Normal(0, 1.0) prior on the effect sizes, which places substantial prior probability on larger positive and negative effects while remaining centered at zero.

Table 2 shows that in the first Bayesian model only two cortical regions, the ITG and the rostral middle frontal gyrus, displayed strong posterior evidence of negative group differences, as their credible intervals lay entirely below zero. Convergence diagnostics were satisfactory, with R^values for all sampled parameters ranging from 0.9997 to 1.0038 (median ≈ 1.0004) and effective sample sizes between 2084 and 3789 for the Study_ID random effects and between 3310 and 5398 for the Entry_ID random effects. No subcortical regions showed such evidence under this specification. For the subcortical model, convergence diagnostics were again satisfactory, with R^values ranging from 0.9998 to 1.0022 (median ≈ 1.0003) and effective sample sizes between 2926 and 3321 for Study_ID and between 2347 and 3964 for Entry_ID. Full posterior estimates are reported in Supplementary Material 4.

In the model with the wider Normal(0, 1.0) prior, the ITG and rostral middle frontal gyrus again showed strong posterior evidence of negative group differences, and additional cortical regions (fusiform, lateral orbitofrontal, and superior temporal gyri) also exhibited credible

Table 2
Bayesian meta-analysis findings.

Brain region	Narrow Prior (0, 0.3)				Wider Prior (0, 1.0)			
	Estimate	SE	-95 % CrI	+ 95 % CrI	Estimate	SE	-95 % CrI	+ 95 % CrI
Cortical dataset								
Fusiform	-0,21	0,13	-0,47	0,04	**-0,46**	**0,19**	**-0,83**	**-0,07**
Inferior temporal	**-0,45**	**0,12**	**-0,63**	**-0,26**	**-0,69**	**0,17**	**-1,02**	**-0,36**
Lateral occipital	-0,13	0,12	-0,37	0,10	-0,36	0,18	-0,71	0,01
Lateral orbitofrontal	-0,11	0,09	-0,29	0,06	**-0,33**	**0,16**	**-0,64**	**-0,01**
Middle temporal	-0,11	0,1	-0,32	0,08	-0,34	0,17	-0,67	0,01
Rostral middle frontal	**-0,22**	**0,09**	**-0,39**	**-0,05**	**-0,43**	**0,16**	**-0,74**	**-0,11**
Superior frontal	-0,08	0,08	-0,24	0,09	-0,29	0,16	-0,60	0,02
Superior temporal	-0,14	0,1	-0,34	0,06	**-0,37**	**0,17**	**-0,69**	**-0,03**
Subcortical dataset								
Amygdala	-0,1	0,21	-0,51	0,30	-0,13	0,41	-0,92	0,66
Brain stem	-0,23	0,25	-0,71	0,27	-0,58	0,45	-1,44	0,31
Cerebellum	-0,16	0,19	-0,52	0,21	-0,25	0,35	-0,36	1,02
Hippocampus	-0,05	0,21	-0,46	0,37	-0,05	0,41	-0,85	0,76
Pallidum	-0,03	0,22	-0,46	0,40	-0,12	0,39	-0,89	0,64
Thalamus	0,03	0,22	-0,40	0,46	0,04	0,39	-0,73	0,83
Accumbens	-0,18	0,25	-0,66	0,30	-0,24	0,47	-1,16	0,69

Legend: Bayesian meta-analyses incorporating both observed and imputed missing effect sizes. Values are posterior means (Estimate) and posterior standard deviations (SE) with 95 % credible intervals (CrI). Negative coefficients indicate smaller brain volumes in individuals with CUD relative to controls. The left panel shows results from a model with a weakly informative Normal(0, 0.3) prior on the population-level effects ("narrow prior"), whereas the right panel shows results from a model with a wider Normal(0, 1.0) prior.

Declaration of Interest Statement

The authors declare there is no conflict of interest.

negative effect-size estimates associated with CUD, whereas subcortical regions continued to show no clear evidence of group differences.

3.4. Complementary coordinate-based analyses

To examine spatial convergence across independent studies, we performed a coordinate-based meta-analysis, restricting it to the 15 experiments that reported peak stereotactic coordinates from whole-brain VBM comparisons between individuals with CUD and HC. In total, 101 foci were analyzed using the ALE algorithm implemented in GingerALE (v3.0.1) (Eickhoff et al., 2012, 2009; Frahm et al., 2023). The analysis applied a FWE correction at $p < 0.05$ with 5000 permutations and a minimum cluster volume of 1 mm^3, consistent with established recommendations for coordinate-based meta-analyses (Lancaster et al., 2007). The resulting maximum ALE value (0.017257173) did not exceed the FWE-corrected significance threshold (0.019126007); therefore, no clusters survived correction for multiple comparisons. Thus, no regions showed statistically significant spatial convergence of GM differences in samples with CUD.

4. Discussion

This meta-analysis identified consistent negative group differences in GM measures between individuals with CUD and HC, particularly in the prefrontal and temporal cortices, which are key regions responsible for executive control, decision-making, emotional regulation, and drug-related cue reactivity (Pando-Naude et al., 2021; Volkow et al., 2019, 2016). These findings are congruent with models of impaired top-down regulation and increased cue reactivity in addiction (Goldstein and Volkow, 2011; Koob and Volkow, 2016), and they build on previous meta-analyses that emphasized prefrontal, temporal, and limbic group-level differences (Dang et al., 2022; Ersche et al., 2013; Pando-Naude et al., 2021). By combining traditional effect-size synthesis, Bayesian inference, and coordinate-based (ALE) methods, we improved spatial precision, reduced selective reporting bias, and provided complementary validation. This combination raises confidence in the reproducibility of the observed group differences and highlights their potential relevance for hypothesis generation and for future evaluation of candidate neuroimaging markers and intervention-relevant circuits.

A key finding of this meta-analysis is that the ITG emerged as the cortical region showing the largest and most consistent group differences between individuals with CUD and HC. After adjustment for methodological and sample-level covariates, the ITG remained the region with the largest negative effect-size estimates and was the only cortical area demonstrating statistically significant group differences across both volumetric and CT analyses. These results indicate that the ITG represents a robust anatomical correlate within the structural neuroimaging literature on CUD. From a neurobiological perspective, prior experimental and clinical studies have proposed that processes such as glutamatergic dysregulation, oxidative stress, and altered dopaminergic signaling may be particularly relevant to cortical regions characterized by high plasticity and metabolic demand, including the ITG (Cunha-Oliveira et al., 2008; Dietrich et al., 2005; Goyal et al., 2014; Herculano-Houzel, 2011; Kalivas, 2004; Koob and Volkow, 2016). However, given the cross-sectional nature of the available data, these mechanisms should be interpreted as plausible explanatory frameworks rather than direct causal pathways. Consistent negative posterior estimates observed in the Bayesian analyses support the reproducibility of this finding.

The ITG, frequently implicated in cue-reactivity paradigms, supports perceptual and semantic processing by integrating visual input with associative and emotional information via projections to the amygdala and hippocampus,

thereby contributing to the attribution of motivational salience to drug-related cues (Hanlon et al., 2014; Hill-Bowen et al., 2021; Miyashita, 1993). Accordingly, ITG alterations may represent a downstream marker of cue sensitization within fron- to–temporo–limbic circuits (Garavan et al., 2000; Jasinska et al., 2014; Kosten et al., 2006). Structural differences in this region may therefore help identify individuals at higher risk of cue-induced relapse and inform network-based neuromodulation strategies targeting prefrontal or parietal control nodes connected to temporal cortices (Balderston et al., 2022; Dejoie et al., 2024; Madeo et al., 2020; Pettorruso et al., 2019; To et al., 2018; Vasileiadi et al., 2023).

In addition, lower GM measures in the orbitofrontal cortex, rostral middle frontal gyrus, and anterior cingulate cortex are consistent with neurocognitive models implicating these regions in inhibitory control and decision-making processes relevant to CUD (Goldstein and Volkow, 2011; Koob and Volkow, 2016). Group differences in these areas have been repeatedly observed in prior neuroimaging studies and may relate to behavioral patterns characterized by compulsive drug use and impaired self-regulation (Goldstein and Volkow, 2011; Koob and Vol- kow, 2016; Volkow et al., 2003). Similarly, group differences involving the hippocampus and temporal cortices may be associated with vari- ability in memory-related processes, including the encoding and retrieval of drug-related cues, which are central to models of maladap- tive learning in addiction (Avchalumov and Mandyam, 2021; Kober et al., 2016). Lower GM volumes in the insula have also been linked to interoceptive processing and salience attribution, functions frequently implicated in craving and cue reactivity (Droutman et al., 2015; Naqvi et al., 2014). Taken together, these patterns of group differences align with theoretical frameworks emphasizing executive control, compul- sivity, and cue salience as core dimensions of CUD, underscoring the relevance of interventions that engage these neural systems (Dang et al., 2022; Ersche et al., 2013; Koob and Volkow, 2016; Zilverstand et al., 2018).

Our effect-size analyses found lower GM indices in frontal and temporal regions. However, the coordinate-based meta-analysis found no clusters

passing FWE correction ($p < 0.05$, 5000 permutations). The highest ALE value (0.017) was below the corrected threshold (0.019), showing insufficient spatial overlap across studies. This likely results from the small number of available coordinate-based studies (n = 15, 101 locations) and inconsistent reporting. Simulations suggest that at least 14 experiments are needed for reliable ALE results (Eickhoff et al., 2016); our sample just surpassed this, limiting sensitivity (Frahm et al., 2023). Previous meta-analyses with fewer than 14 studies also failed to find consistent ALE results in small datasets (Dang et al., 2022; Ersche et al., 2013; Mackey et al., 2019; Pando-Naude et al., 2021). Many VBM studies only report significant clusters and exclude null findings, resulting in less comprehensive datasets (Button et al., 2013; Eickhoff et al., 2017; Müller et al., 2018). Therefore, the lack of convergent clusters is likely due to a limited sample size and reporting bias, rather than an actual absence of consistent spatial convergence (Nichols et al., 2017; Poldrack et al., 2017; Salimi-Khorshidi et al., 2009). This matches evidence that ALE is sensitive to small samples, flexible thresholds, and incomplete null reporting (Eklund et al., 2016; Salimi-Khorshidi et al., 2009; Woo et al., 2014). Future studies should standardize whole-brain reporting, including null results, to clarify the spatial patterns of CUD-related differences (Müller et al., 2018; Nichols et al., 2017; Pol- drack et al., 2017; Turkeltaub et al., 2012).

In moderator analyses, the primary route of cocaine administration did not account for between-study heterogeneity in either cortical (Q = 1.11, p = 0.291) or subcortical data (Q = 0.55, p = 0.458). Neverthe- less, point estimates were more negative in the non-intranasal category in both datasets, although the corresponding uncertainty was substan- tial. Interpretation is limited by sparse and inconsistent reporting: only 12 studies in the dataset clearly reported the predominant route of use among participants (Supplementary Material 2), and few directly con- trasted routes within comparable cohorts. Accordingly, the current ev- idence does not support consistent route-specific differences at the meta-analytic level, but it underscores route-of-administration reporting as a key variable for future, adequately powered studies.

A key contribution of this meta-analysis is the explicit assessment of clinically relevant moderators. The results indicate that greater clinical severity and longer duration of cocaine use are associated with larger negative effect-size estimates for cortical GM measures, but not for subcortical structures. This pattern is consistent with prior longitudinal and cross-sectional studies reporting associations between prolonged cocaine use and lower CT or volume, particularly in frontal and temporal regions, as well as partial normalization following sustained reductions in use (Bittencourt et al., 2021; Crunelle et al., 2014; Hirsiger et al., 2019; Ide et al., 2014; McCurdy et al., 2024; Parvaz et al., 2017; Roth- mann et al., 2024; Schinz et al., 2023).

The preferential involvement of cortical regions may reflect differ- ences in metabolic demand and structural plasticity relative to subcor- tical regions, although causal mechanisms cannot be established within the constraints of the available evidence (Clare et al., 2024; Du et al., 2021; Serra et al., 2023; Wang et al., 2025). More severe clinical profiles, including psychiatric comorbidities (e.g., depression, ADHD, alcohol or cannabis use disorders) and medical conditions such as HIV infection, were associated with larger-magnitude cortical group differences. This observation aligns with prior studies indicating that dual pathology and polysubstance use are associated with poorer clinical outcomes and more pronounced structural differences across substance use disorders (Bachi et al., 2018; Haorah et al., 2025; Kroll et al., 2020; Meade et al., 2020; Stoychev, 2019; Tesselaar et al., 2025; Wakim et al., 2021). Taken together, these findings suggest that structural brain differences, clinical severity, comorbidities, and polysubstance use co-occur as markers of a more severe clinical phenotype in CUD, rather than reflecting isolated or disorder-specific effects (Meyerhoff, 2017; Pando-Naude et al., 2021; Unterrainer et al., 2019). Notably, post-hoc analyses did not reveal significant differences between substance-related and other psychiatric or medical comorbidities, indicating that the cumulative burden of multimorbidity, rather than specific diagnostic categories, is associated with greater cortical involvement. These findings highlight the need for longitudinal designs to clarify temporal trajectories and for clinical trials evaluating tailored or multimodal interventions for high-severity subgroups.

Several limitations should be considered when interpreting these findings. Substantial methodological heterogeneity exists across studies, including differences in neuroanatomical assessment techniques, diag- nostic criteria, routes of cocaine administration, and clinical sample characteristics, which may limit consistency and generalizability. In addition, publication bias and selective reporting of positive findings remain possible despite the use of Bayesian sensitivity analyses to mitigate these biases. We did not contact the authors of primary studies to request additional unpublished data, which may have limited the availability of specific clinical or regional information. However, this issue was addressed through conservative analytic strategies designed to attenuate the effects of selective reporting and missing data. Most included studies were cross-sectional, precluding causal inferences regarding the temporal relationship between cocaine use and structural brain differences. Although efforts were made to minimize overlapping samples across publications, residual non-independence cannot be fully excluded.

Additionally, variability in psychiatric and medical comorbidities among participants may substantially contribute to heterogeneity in results. Few studies rigorously controlled concomitant substance use, such as alcohol, nicotine, and cannabis, which may have influenced observed group differences. Our operationalization of clinical severity also represents a limitation. Due to substantial heterogeneity and sparse reporting of specific comorbidities across studies (e.g., diverse psychi- atric diagnoses, polysubstance use, and medical conditions such as HIV infection), we aggregated these features into a single sample-level severity indicator instead of modeling psychiatric comorbidities, medi- cal comorbidities, and polysubstance use as separate

moderators. Another limitation is that the primary route of cocaine administration was analyzed dichotomously (intranasal vs. non-intranasal), rather than separately comparing intranasal, smoked, and intravenous use. This decision reflected the low and heterogeneous representation of smoked and intravenous routes across studies, which precluded stable three- level meta-regression models. Consequently, potential route-specific structural patterns associated with smoked or intravenous cocaine on brain structure could not be fully disentangled in the present meta- analysis. Additional limitations are inherent to coordinate-based ALE approaches, which rely exclusively on studies reporting precise stereo- tactic coordinates and may therefore introduce selection bias. Finally, the scarcity of longitudinal data limits insights into the temporal evo- lution and potential reversibility of structural brain differences. Minor inaccuracies in coordinate transformations or anatomical conversions may also affect spatial precision, particularly in less frequently exam- ined brain regions.

Despite these limitations, this study makes significant contributions to the literature in several keyways. First, it offers a more anatomically precise and statistically reliable characterization of GM changes in CUD. Second, it shows the benefits of combining Bayesian and coordinate- based methods to address biases and clarify inconsistencies. Third, it emphasizes the importance of clinical moderators, such as route of use, comorbidity, and polysubstance involvement, and highlights the need to move beyond “one-size-fits-all” models of CUD.

Abbreviations

ACC, Anterior cingulate cortex; ALE, Activation Likelihood Estima- tion; CT, Cortical thickness; CUD, Cocaine Use Disorder; FWE, Family- wise error; GM, Gray matter; HC, Healthy controls; ITG, Inferior tem- poral gyrus; MRI, Magnetic resonance imaging; OFC, Orbitofrontal cortex; ROI, Region-of-interest; VBM, Voxel-based morphometry;

Authors contribution

Augusto Martins Lucas Bittencourt originated the research question and developed the study design in collaboration with Bernardo Penteado Favero, Camila Haas, Eduardo Tavares Portolan, Enzo Galhardo, Leo- nardo Melo Rothman, Rodrigo Grassi-Oliveira, and Thiago Wendt Viola. Augusto Martins Lucas Bittencourt, Bernardo Penteado Favero, and Camila Haas performed literature review, literature search, coding of studies, data entry, and manuscript preparation. Enzo Galhardo evalu- ated the quality and bias assessment of the studies. Eduardo Tavares Portolan, Leonardo Melo Rothmann, and Thiago Wendt Viola supplied statistical and methodical consultation and performed the statistical analyses. All authors edited and revised the manuscript.

CRediT authorship contribution statement

Enzo Gallardo: Investigation, Data curation. **Leonardo Melo Rothmann:** Validation, Data curation. **Rodrigo Grassi-Oliveira:** Writing – review & editing, Supervision. **Viola Thiago:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation. **Bernardo Penteado Favero:** Investigation, Data curation. **Camila Haas:** Investigation, Data curation. **Eduardo Tavares Portolan:** Methodology, Investigation, Data curation. **Augusto Martins Lucas Bittencourt:** Writing – original draft, Methodology, Conceptualization.

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Declaration of Competing Interest

The authors report no potential conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2026.113064.

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Pontifícia Universidade Católica do Rio Grande do Sul
Pró-Reitoria de Graduação
Av. Ipiranga, 6681 - Prédio 1 - 3º. andar
Porto Alegre - RS - Brasil
Fone: (51) 3320-3500 - Fax: (51) 3339-1564
E-mail: prograd@pucrs.br
Site: www.pucrs.br