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Etude du système noradrenergique chez l'homme et dans la maladie de Parkinson

Chloé Laurencin

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L'UNIVERSITE CLAUDE BERNARD LYON 1**

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**Étude du système noradrénergique chez
l'homme et dans la maladie de Parkinson**

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Résumé

La maladie de Parkinson (MP) est une maladie fréquente, liée à des agrégats d' α -synucléine avec une dégénérescence des neurones dopaminergiques dans la substance noire. Un dysfonctionnement du système noradrénergique est également présent, avec une atteinte précoce et intense du locus coeruleus (LC). Une meilleure connaissance du rôle de la noradrénaline est nécessaire pour progresser sur notre compréhension de la MP.

Cette thèse débute par la validation d'un traceur, la ^{11}C -yohimbine, un antagoniste des récepteurs α_2 noradrénergique. Dans une deuxième étude, des IRM-TEP à la ^{11}C -yohimbine ont été réalisées chez des patients parkinsoniens et des témoins. Les patients présentaient une réduction de l'intensité du signal de la neuromélanine dans le LC et une diminution de fixation du traceur dans des régions corticales étendues, l'insula, le putamen et le thalamus. La baisse d'intensité du LC était corrélée à des symptômes moteurs (bradykinésie, fluctuations motrices) et non moteurs (fatigue, apathie, constipation). Une diminution de fixation du traceur dans le thalamus était associée aux tremblements tandis que l'anxiété était associée à une diminution dans le putamen, l'insula et le gyrus temporal supérieur. Nous confirmons l'absence de corrélation entre la dégénérescence du LC et des terminaisons noradrénergiques. Enfin, dans une troisième étude, l'efficacité de la clonidine sur les troubles du contrôle des impulsions a été testée. Les résultats sont en faveur d'une bonne tolérance du traitement mais l'efficacité devra être affirmée par un essai de phase 3.

Nos résultats soulignent l'altération substantielle et multimodale du système noradrénergique dans la MP.

Mots clefs : noradrénaline, maladie de parkinson, troubles du contrôle des impulsions, IRM-TEP, locus coeruleus, α_2 adrénorécepteurs, ^{11}C -yohimbine

Summary

Parkinson's disease (PD) is a common disorder, linked to α -synuclein aggregates with degeneration of dopaminergic neurons in the substantia nigra. Dysfunction of the noradrenergic system is also associated, with early and intense involvement of the locus coeruleus (LC). A better understanding of the role of noradrenaline is needed to advance our understanding of PD. This thesis begins with the validation of a tracer, ^{11}C -yohimbine, an α_2 noradrenergic receptor antagonist. In a second study, ^{11}C -yohimbine PET-MRI scans were performed in parkinsonian patients and controls. Patients showed reduced neuromelanin signal intensity in the LC and decreased tracer binding in extensive cortical regions, the insula, putamen and thalamus. Decreased LC intensity correlated with motor (bradykinesia, motor fluctuations) and non-motor (fatigue, apathy, constipation) symptoms. Decreased tracer binding in the thalamus was associated with tremor, while anxiety was associated with a decrease in the putamen, insula and superior temporal gyrus. We confirm the absence of correlation between LC degeneration and noradrenergic endings. Finally, in a third study, the efficacy of clonidine on impulse control disorders was tested. The results suggest that the treatment is well tolerated, but its efficacy needs to be confirmed by a Phase 3 trial.

Our results underline the substantial and multimodal alteration of the noradrenergic system in PD.

Keywords : Noradrenaline, Parkinson's disease, Impulse Control Disorders, PET-MRI, locus coeruleus, α_2 adrenoreceptors, ^{11}C -yohimbine

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Table des matières

Chapitre 1. La Maladie de Parkinson - Contexte	9
1. De l'origine dopaminergique et motrice... ..	9
2. A une origine non-dopaminergique et non-motrice	10
Chapitre 2. Pourquoi s'intéresser au système noradrénergique dans la maladie de Parkinson ?	13
1. Que savons-nous du système noradrénergique à l'état normal ?	13
a. Le locus coeruleus	13
b. Les récepteurs noradrénergiques	18
c. Rôle de la noradrénaline	19
2. Que savons-nous du système noradrénergique dans la maladie de Parkinson ?	21
a. Une dégénérescence précoce du locus coeruleus	21
b. Un rôle anti-inflammatoire et neuroprotecteur	23
c. Un rôle dans l'expression clinique de la maladie de Parkinson	25
Apathie.....	25
Douleurs.....	26
Dyskinésies.....	26
Tremblement	28
Troubles affectifs	29
Troubles cognitifs	30
Troubles du Contrôle des Impulsions (TCI).....	31
Dysautonomie.....	33
Troubles du sommeil	34
Chapitre 3. Enjeux et Limites.....	36
Chapitre 4. Présentation des objectifs	39
Chapitre 5. Le développement d'un traceur ¹¹ C-yohimbine et son utilisation chez l'homme .	41
Chapitre 6. Les altérations noradrénergiques dans la maladie de Parkinson : une approche TEP/IRM combinée.....	50
Chapitre 7. Vers une thérapeutique noradrénergique complémentaire : le cas des TCI	88
Chapitre 8. Conclusions et Perspectives	98
Annexes	102
Références	116

Abréviations

AD : Agoniste dopaminergique

AMS : Atrophie multi systématisée

DA : Dopamine

IRM : Imagerie par résonance magnétique

LC : Locus coeruleus

MP : Maladie de parkinson

PAF : Pure Autonome Failure

SNC : Système nerveux central

TCI : Troubles du contrôle des impulsions

Table des figures

Figure 1 : Expansion topographique des lésions histopathologiques au cours de la maladie de Parkinson.

Figure 2: “Body first” vs “brain first”.

Figure 3 : Localisation du locus coeruleus en coupe axiale d’un cerveau.

Figure 4 : IRM cérébrale en coupe axiale d’un patient sain sur une IRM 3T.

Figure 5 : Principales projection du locus coeruleus.

Figure 6 : Représentation des principales connections anatomiques entre le locus coeruleus et les autres régions cérébrales.

Figure 7 : Distribution de la variation de l’intensité du signal dans le locus coeruleus chez des témoins sains en fonction de l’âge.

Figure 8 : Synapse noradrénergique.

Figure 9 : Fonctionnement du système noradrénergique selon le niveau de NA.

Figure 10 : Résumé de l’étude de Doppler et Kinnerup.

Figure 11 : Le phénotype noradrénergique de la MP

Chapitre 1. La Maladie de Parkinson- Contexte

1. De l'origine dopaminergique et motrice...

Les recherches du XXème siècle ont permis de comprendre que la maladie de Parkinson (MP) relevait d'une dégénérescence dopaminergique à l'origine d'un dysfonctionnement de la voie nigro-striée (Hornykiewicz, 2006) et d'une triade de symptômes moteurs caractéristiques (Jankovic, 2008) décrite pour la première fois par James Parkinson en 1817 et incluant tremblements de repos, rigidité et bradykinésie. Ce déficit en dopamine (DA) observé nécessite donc de rétablir les voies dopaminergiques afin de réduire les symptômes moteurs. Pour ce faire, trois types de traitements sont proposés incluant la lévodopa (un précurseur de la DA agissant au niveau présynaptique), les inhibiteurs des enzymes qui dégradent la DA (COMT et MAO-B) pour potentialiser l'efficacité de la lévodopa, ou enfin les agonistes dopaminergiques (ADs) qui agissent au niveau post-synaptique sur les récepteurs D₁/D₂/D₃. La découverte et l'utilisation de la médication dopaminergique dans la MP a constitué une révolution thérapeutique (Cotzias et al., 1967). Son efficacité sur la symptomatologie extrapyramidale est très importante (on parle de « lune de miel » au début du traitement) et constitue même un facteur de diagnostic de la maladie.

Néanmoins, l'utilisation de ces traitements expose les patients à des effets indésirables. On voit en effet apparaître des fluctuations motrices et des dyskinésies (Mizuno et al., 2018). De même, la thérapie dopaminergique, et plus particulièrement les ADs peut provoquer des troubles du contrôle des impulsions (TCI) (Cilia & van Eimeren, 2011; Weintraub, Koester, et al., 2010a). Ces effets secondaires sont invalidants et obligent à une modification des doses de médication dopaminergique, faute de solution thérapeutique satisfaisante, mais au risque de voir s'aggraver les symptômes de la maladie (Rabinak & Nirenberg, 2010).

Enfin, si le diagnostic de maladie est principalement fondé sur la présence de symptômes moteurs caractéristiques, ceux-ci s'accompagnent de nombreux troubles non-moteurs qui débütent parfois même en amont de la triade extrapyramidale. La prise en charge de ces symptômes non moteurs reste aujourd'hui difficile du fait d'une réponse souvent médiocre aux traitements dopaminergiques (Katunina & Titova, 2017). Pendant longtemps largement inexplorés, l'attention se porte aujourd'hui sur une meilleure compréhension de cette symptomatologie non motrice (Langston, 2006) et une reconnaissance de la MP comme un syndrome complexe où d'autres systèmes de neurotransmetteurs sont possiblement impliqués (Borchert et al., 2016).

2. A une origine non-dopaminergique et non-motrice

Dans une approche descriptive, Braak et al. (H. Braak, Del Tredici, et al., 2003; H. Braak et al., 2004) proposent que le processus neuropathologique de la MP est topographiquement organisé (Figure 1). Il débuterait par le dysfonctionnement des structures non-dopaminergiques du noyau moteur dorsal, du nerf vague et des structures olfactives antérieures. L'affection progresserait ensuite selon un gradient caudo-rostral et ventro-dorsal vers les noyaux gris centraux puis le cortex cérébral. L'apparition d'une symptomatologie motrice et la dégénérescence de la substance noire (SN) n'interviendraient en fait qu'à partir du troisième ou quatrième stade. D'autres systèmes de neurotransmission comme le système noradrénergique seraient plus précocement atteints.

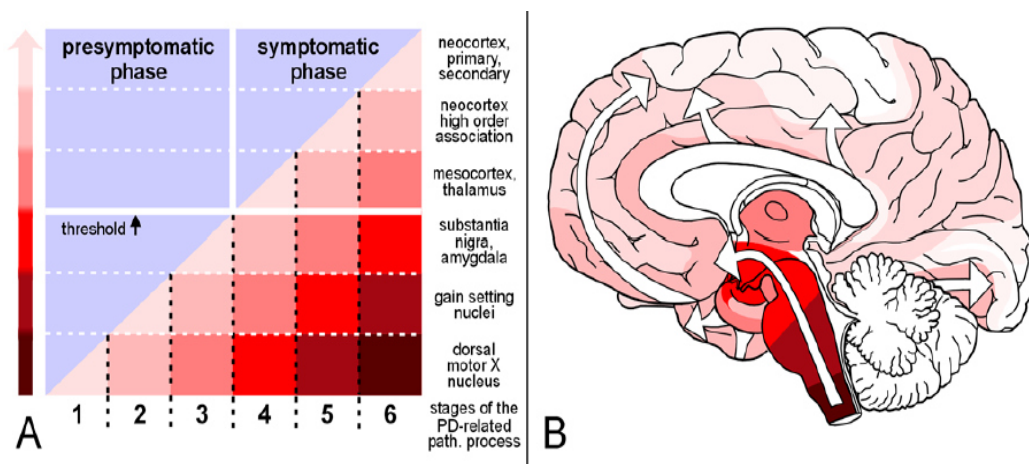


Figure 1 : Expansion topographique des lésions histopathologiques au cours de la MP.

Diagramme simplifié. B. Vue médiale. La phase pré-symptomatique est marquée par l'apparition de corps de Lewy sans symptôme chez les patients. Dans la phase symptomatique, le seuil neuropathologique est dépassé et les symptômes cliniques apparaissent. Les lésions intéressent initialement le noyau moteur des nerfs IX/X et fréquemment le noyau olfactif antérieur (stade 1). Ensuite, d'autres structures cérébrales sont progressivement impliquées. La pathologie s'étend plus rapidement au niveau du tronc cérébral que du bulbe olfactif. Elle implique ainsi le raphé, la formation réticulée, et le locus coeruleus (stade 2). Elle atteint ainsi les noyaux gris centraux, en particulier la SN (stade 3). Les lésions corticales débutent au niveau du mésocortex temporal antéromédian (stade 4) puis s'étendent vers les aires préfrontales et les aires sensorielles associatives de haut niveau (stade 5). Les aires prémotrices, motrices, et sensorielles primaires sont les plus tardivement affectées (stade 6). L'intensité de la couleur indique la sévérité de l'atteinte aux différents stades ; les flèches blanches indiquent le sens de propagation du processus dégénératif. Illustration issue de Braak et al. (2004).

Ce modèle permet ainsi d'expliquer l'apparition précoce de symptômes non-moteurs (anosmie, dépression) et les signes de perturbation du système nerveux autonome ainsi que les symptômes démentiels tardifs. L'atteinte de systèmes non-dopaminergiques (i.e. noradrénergique, sérotoninergique, cholinergique) jouerait donc un rôle clé dans la progression

de la MP, voir même précéderait la dégénérescence dopaminergique (H. Braak et al., 2004; Ferrer et al., 2012; Marien et al., 2004a; Zarow et al., 2003a). En parallèle, des données suggèrent néanmoins que la MP ne suit pas cette chronologie de distribution dans tous les cas (Parkkinen et al., 2008). En effet un autre modèle de propagation a été décrit avec une atteinte débutant au niveau dans les terminaisons nerveuses du système nerveux entérique (SNE), après quoi la pathologie se propage via les connexions parasympathiques et sympathiques (H. Braak, Rüb, et al., 2003) (Figure 2). Il a donc été émis l'hypothèse que la MP comprend deux sous-types : i) un sous-type "body-first" (ascendant), où la pathologie trouve son origine dans le système nerveux autonome entérique ou périphérique, puis remonte via le nerf vague et le système sympathique jusqu'au SNC (Borghammer & Van Den Berge, 2019) (ii) un sous-type de « brain first » (top-down), dans lequel la pathologie α -synucléine apparaît initialement dans le cerveau lui-même (l'amygdale ou parfois par le bulbe olfactif), et descend ensuite vers le système nerveux autonome périphérique. Des études en imagerie corroborent ces deux hypothèses (Horsager et al., 2020).

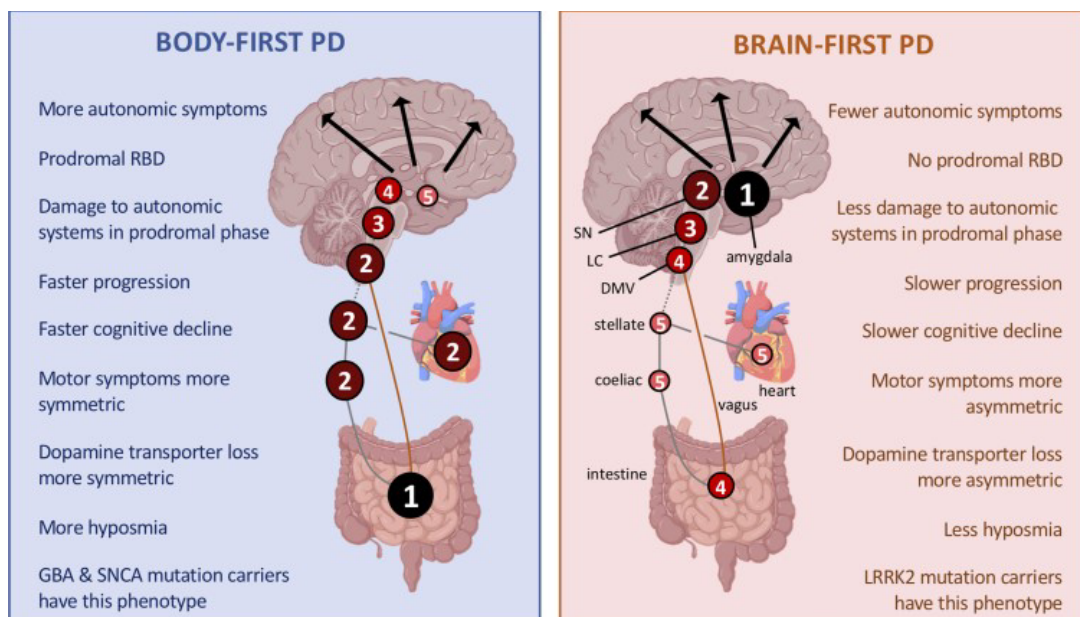


Figure 2 : Illustration des deux voies possibles de propagation de la dégénérescence dans la MP. Dans le sous-type « body-first », les dépôts pathologiques d' α -synucléine prennent naissance initialement dans le système nerveux entérique ou autonome et se propage au SNC par l'intermédiaire du connectome vagal et sympathique. Ces patients développent des troubles de comportements en sommeil paradoxal dans la phase prodromique, présentent davantage de symptômes dysautonomiques, une hyposmie importante, une progression motrice et non motrice plus rapide, ainsi qu'un déclin cognitif plus précoce. Dans le sous-type de la MP « brain-first » les dépôts pathologiques d' α -synucléine prennent naissance dans l'amygdale ou dans des structures étroitement liées, telles que le bulbe olfactif. Ces patients présentent moins de symptômes dysautonomiques, une hyposmie moins fréquente, une progression motrice et non motrice plus lente et un déclin cognitif moins rapide. Illustration issue de (Borghammer, 2021)

Il est important de noter que ces hypothèses supposent que l' α -synucléine provienne d'un seul site du système nerveux et se propage à partir de là d'une manière stéréotypée (Borghammer, 2021). C'est donc au début de la MP que les deux sous-types sont plus susceptibles de différer sur des biomarqueurs cliniques et d'imagerie, tandis qu'aux stades ultérieurs de la maladie, les deux phénotypes peuvent converger en raison de l'augmentation des quantités et de la dissémination de la pathologie de l' α -synucléine.

La physiopathologie de la MP est donc plus complexe que la dégénérescence dopaminergique nigro-striée communément admise (H. Braak & Del Tredici, 2008). Elle inclut notamment la perturbation des systèmes de neurotransmission non dopaminergiques (noradrénergique, sérotoninergique et cholinergique). L'intérêt pour ces derniers, s'est accru avec l'accumulation de données montrant que les lésions causés à d'autres zones anatomiques et systèmes neurochimiques précèdent la dégénérescence des neurones dopaminergiques dans la SN (Migueliz et al., 2020). Les autres systèmes affectés participent aux phases dites pré-symptomatiques et contribuent au mauvais fonctionnement des circuits moteurs et non moteurs. Parallèlement, les symptômes non moteurs sont de plus en plus reconnus dans la MP. Ils altèrent gravement la qualité de vie des patients car ils sont souvent plus débilissants que les symptômes moteurs et répondent mal aux thérapies dopaminergiques. Nous allons voir dans le prochain chapitre quelques éléments qui incitent à s'intéresser au système noradrénergique dans la physiopathologie de la MP.

Chapitre 2 : Pourquoi s'intéresser au système noradrénergique dans la maladie de Parkinson ?

Parmi les zones cérébrales qui subissent une dégénérescence dans la phase prodromique de la MP, le locus coeruleus (LC) mérite une attention particulière car il serait l'un des premiers noyaux à développer des corps de Lewy (Huynh et al., 2021). De plus, le dysfonctionnement du système noradrénergique serait lié à plusieurs des symptômes non moteurs observés dans la maladie comme nous allons le détailler ici.

1. Que savons-nous du système noradrénergique à l'état normal ?

a. LE LOCUS COERULEUS

Le LC est un petit noyau situé dans le tronc cérébral (tegmentum pontin dorsolatéral supérieur) (figure 3 et 4) qui contient la majorité des neurones noradrénergiques, lesquels constituent la principale source de noradrénaline (NA) dans l'ensemble du système nerveux central (SNC) (L. A. Schwarz & Luo, 2015).

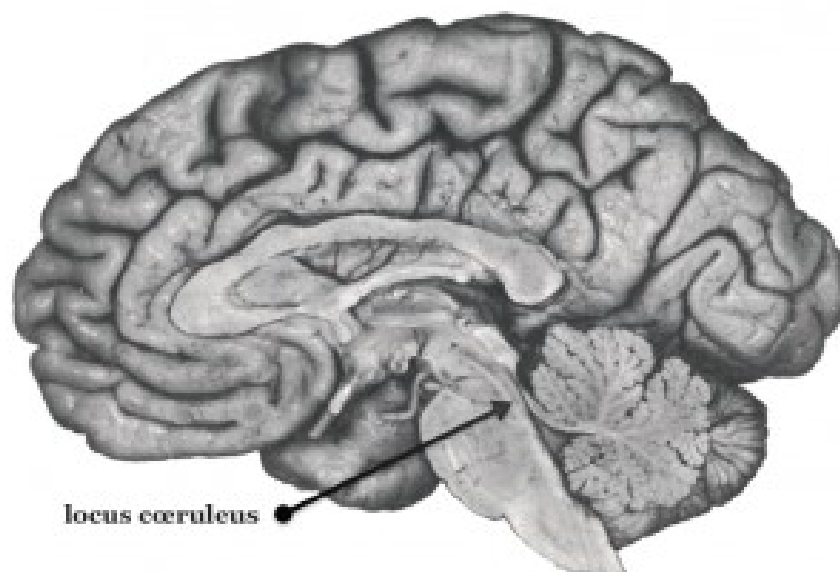


Figure 3 : Localisation du locus coeruleus en coupe axiale d'un cerveau *Source : Mather M, et al. The Locus Coeruleus: Essential for Maintaining Cognitive Function and the Aging Brain. Trends in Cognitive Sciences, 2016*

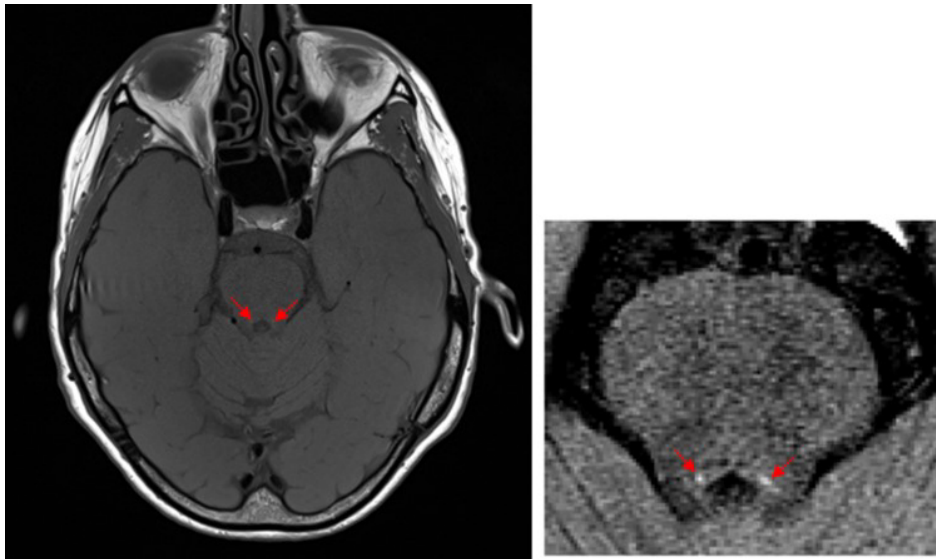


Figure 4 : IRM cérébrale en coupe axiale d'un patient sain sur une IRM 3T (7mm sous le niveau du colliculi inférieur), avec les LC visibles par deux points hyperintenses (flèches rouges). Source: Beardmore R, Hou R, Darekar A, Holmes C, Boche D. *The Locus Coeruleus in Aging and Alzheimer's Disease: A Postmortem and Brain Imaging Review. J Alzheimers Dis.* 2021;83(1):5-22.

Le LC envoie des projections descendantes vers la moelle épinière (Westlund et al., 1983) et innerve densément les zones ascendantes du SNC comme l'amygdale, le colliculus supérieur, le thalamus, l'hippocampe, le bulbe olfactif, le raphé dorsal et le cortex, notamment le cortex préfrontal, orbitofrontal, cingulaire antérieur et moteur primaire (Chandler et al., 2014; Fallon et al., 1978; Kempadoo et al., 2016; Loughlin et al., 1986; McLean & Shipley, 1991; L. A. Schwarz & Luo, 2015).

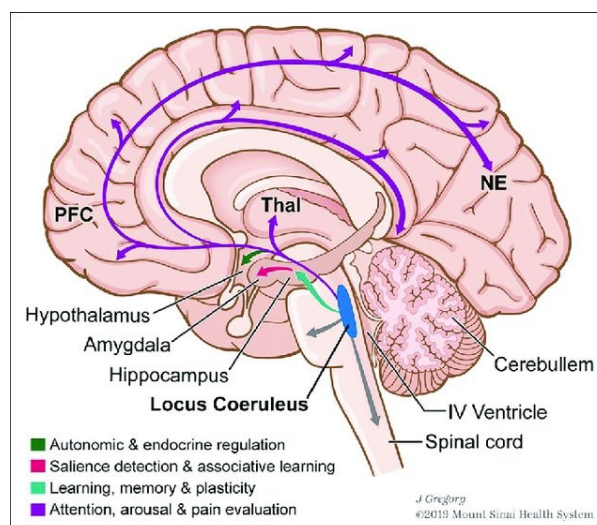


Figure 5 : Principales projection du locus coeruleus
 Issu de « *The role of the locus coeruleus in the generation of pathological anxiety* » (Morris et al., 2020)

Une innervation aussi étendue (figure 5) provenant d'un petit nombre de neurones nécessite une arborisation importante des axones. Cette collatéralisation favorise les phénomènes de neuromodulation (L. A. Schwarz & Luo, 2015). Les sous-populations de neurones du LC sont regroupées par rapport à leurs cibles efférentes, ce qui permet d'obtenir des effets sélectifs sur différentes fonctions (Poe et al., 2020). Par exemple, des sous-populations distinctes de neurones du LC, avec des phénotypes moléculaires et électrophysiologiques différents, se projettent préférentiellement dans le cortex préfrontal et moteur. Cette organisation permet à des populations distinctes de neurones du LC d'avoir des effets très spécifiques (Chandler et al., 2014). Des schémas d'activité distincts peuvent être observés dans ces sous-populations pendant une tâche en cours, ce qui suggère qu'elles peuvent jouer des rôles différents dans l'exécution et l'affinement des résultats comportementaux (Breton-Provencher et al., 2022).

Le LC reçoit également des afférences, moins diffuses, provenant du tronc cérébral et du cortex préfrontal principalement (Aston-Jones et al., 1986; Breton-Provencher & Sur, 2019; Delaville et al., 2011; Devoto et al., 2005). Beaucoup de ces entrées ne ciblent pas le LC, mais la zone peri-céruleenne, qui contient des neurones noradrénergiques et des neurones GABAergiques (Bajic et al., 2000; Ennis et al., 1991). Les neurones de cette zone péri-céruleenne exercent une influence inhibitrice sur le LC (Breton-Provencher & Sur, 2019; Kuo et al., 2019). Ensemble, le LC et la zone péri-céruleenne reçoivent des informations des régions impliquées dans les fonctions exécutives, l'éveil et l'état motivationnel (le cortex préfrontal, l'amygdale, l'hypothalamus latéral, raphé dorsal et noyau paragigantocellulaire). Les afférences provenant de différentes régions ont des propriétés électrophysiologiques et des probabilités de libération distinctes, et elles innervent des zones distinctes du LC (Barcomb et al., 2022). Cette organisation permet au système noradrénergique d'être efficace pour intégrer de riches informations sur l'environnement et, ensuite, pour influencer les comportements adaptatifs à ces environnements (L. A. Schwarz & Luo, 2015).

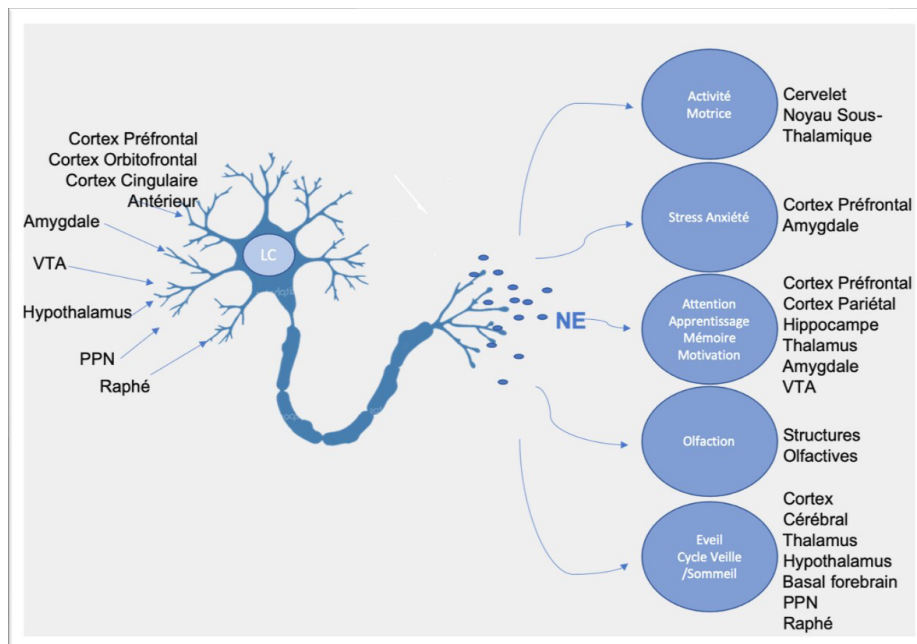


Figure 6 :
Représentation des principales connexions anatomiques entre le LC et les autres régions cérébrales. Cette connaissance est principalement issue des travaux chez l'animal. *PPN= noyau pédunculo-pontin, VTA= aire tegmentale ventrale. Adapté de Satoh & Iijima, 2019 et Delaville et al., 2011.*

Il est intéressant de mentionner que le LC ne se projette pas vers les noyaux fortement innervés par le système dopaminergique mais qu'il peut tout de même influencer la transmission dopaminergique de manière distale. Devoto et ses collaborateurs ont démontré que les fibres positives à la tyrosine hydroxylase du LC peuvent co-libérer non seulement la NA mais aussi la DA dans le cortex, y compris les cortex préfrontal, pariétal et occipital, en faisant intervenir des mécanismes médiés par les récepteurs α -adrénergiques (Devoto et al., 2005, 2020; Frau et al., 2022). Plus récemment, d'autres auteurs ont montré que l'activation du LC favorise la libération de DA dans le thalamus et l'hippocampe (Beas et al., 2018; Kempadoo et al., 2016; C. C. Smith & Greene, 2012; Yamasaki & Takeuchi, 2017). De plus, il a été démontré que le transporteur de la noradrénaline (NET) peut recapter non seulement la NA mais aussi la DA dans les régions où l'innervation DA est faible (Morón et al., 2002). Les interactions entre la NA et la DA sont donc nombreuses.

Par ailleurs, le LC possède une activité phasique et une activité tonique (Ma et al., 2023). L'activité tonique est caractéristique de l'état d'éveil, elle diminue au cours du sommeil et devient silencieuse lors du sommeil paradoxal. Le LC joue donc un rôle clé dans les cycles de veille/sommeil. L'activité tonique devient également plus soutenue lors d'un comportement exploratoire. L'activité phasique prend le pas sur l'activité tonique lors de processus attentionnels et lors de l'exécution de tâches précises. Ces éléments sont cruciaux concernant l'implication du système noradrénergique dans la cognition (Aston-Jones & Cohen, 2005). Les tirs phasiques sur un fond de niveaux toniques modérés se produisent donc en réponse à des stimuli pertinents pour la tâche, ce qui favorise une attention soutenue. Des niveaux toniques

plus élevés freinent ce rapport phasique et conduisent à un mode désengagé favorisant d'exploration d'autres stratégies. Cette relation en U inversé fonctionne également avec le niveau de NA: Des niveaux modérés de NA engagent les récepteurs α_2 , renforçant l'activité du réseau lié à la tâche et améliorant la performance ; Des niveaux plus élevés engagent les récepteurs α_1 ce qui a pour effet d'inhiber l'activité du réseau lié à la tâche et de nuire aux performances (Gamo & Arnsten, 2011).

Le LC contient de la neuromélanine, un polymère pigmenté résultant de l'oxydation de la NA dans le LC (comme la DA dans la substance noire) (Wakamatsu et al., 2015; Zucca et al., 2006). Ce sous-produit du métabolisme des neurotransmetteurs catécholaminergiques forme des complexes para-magnétiques avec le fer. Avec l'âge, la neuromélanine augmente dans le LC (Zucca et al., 2006). La neuromélanine sert elle-même d'agent de contraste endogène par résonance magnétique (RM) et sa relaxation en IRM est fortement renforcée par la fixation d'ions métalliques (Enochs et al., 1989, 1997; Trujillo et al., 2017). Les imageries par résonance magnétique (IRM) sensible à la neuromélanine constituent un outil précieux pour visualiser le LC. Le vieillissement « normal » en dehors de toutes pathologies, affecte le signal du LC. Dans une étude de Shibata en 2006, 64 volontaires sains âgés de 23 à 80 ans ont bénéficié d'une IRM sensible à la neuromélanine et l'intensité du signal du LC augmente progressivement jusqu'à 59 ans pour diminuer par la suite chez les personnes âgées (Sasaki et al., 2006) (Figure 7). Cette observation souligne pour la première fois in vivo la nécessité de considérer l'âge des participants lors de l'évaluation des anomalies de signal dans le LC. Les résultats de cette unique étude in vivo, sont en accord avec des études histologiques antérieures (Manaye et al., 1995; Mann, 1983). Il reste à comprendre les implications comportementales de cette altération dépendant de l'âge dans le LC.

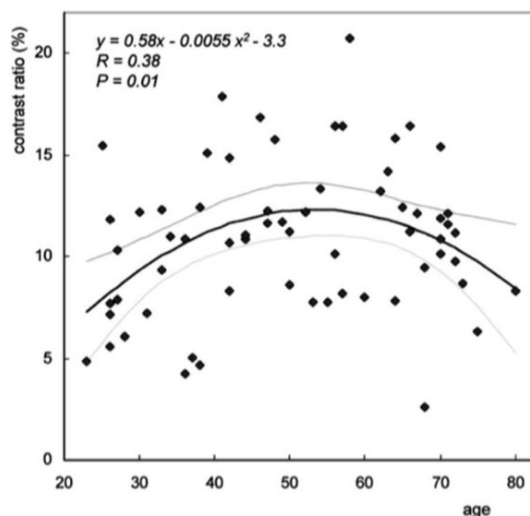


Figure 7 : Distribution de la variation de l'intensité du signal dans le LC chez des témoins sains en fonction de l'âge. *Issu de Shibata et al. 2006*

b. LES RECEPTEURS NORADRENERGIQUES

L'effet de la NA est médié par deux grands types de récepteurs, les α et β . Il s'agit de récepteurs métabotropiques couplés à des protéines G qui activent des cascades intracellulaires.

Il existe différents sous types de récepteurs :

- Les $\alpha 1$ qui existent en post synaptique et ont un effet stimulant de la production de NA (Molinoff, 1984). Il en existe différents sous types ($\alpha 1A$, $\alpha 1B$, $\alpha 1D$).
- Les $\alpha 2$ qui sont des autorécepteurs qui existent en pré- et post-synaptique, ils ont plutôt un rôle régulateur (Timmermans & van Zwieten, 1981). Il en existe différents sous types ($\alpha 2A$, $\alpha 2B$, $\alpha 2C$) (Civantos Calzada & Aleixandre de Artiñano, 2001).
- Les $\beta 1$ qui ont une haute affinité pour la NA et sont retrouvés en grande quantité dans le cœur, le cerveau et le tissu adipeux.
- Les $\beta 2$ qui ont une faible affinité pour la NA et sont impliqués dans la vasodilatation, la relaxation musculaire et la bronchodilatation.
- Les $\beta 3$ qui sont principalement retrouvés dans le tissu adipeux, où ils participent à la lipolyse, mais également dans la vessie et le système musculosquelettique.

Les récepteurs $\alpha 2$ présentent une plus grande affinité pour la NA que les récepteurs $\alpha 1$ et β et sont donc préférentiellement engagés à des taux de libération plus faibles (Arnsten, 2000).

Les récepteurs $\alpha 2C$ et $\alpha 2A$ partagent tous deux des fonctions d'autorécepteurs pour exercer un rétrocontrôle négatif sur la libération de NA.

- La majorité des récepteurs $\alpha 2$ -adrénergiques (ARs) du cerveau humain sont du sous-type $\alpha 2A$. Les $\alpha 2A$ -ARs servant d'autorécepteurs sur les neurones noradrénergiques fournissent un retour d'information pour diminuer la libération de NA lorsqu'ils sont activés par la NA extracellulaire (Milner et al., 1998). Le sous-type $\alpha 2A$ est largement exprimé dans le SNC et dans les tissus périphériques.
- Le sous-type $\alpha 2B$ est principalement non neuronal (MacDonald et al., 1997).
- Les récepteurs $\alpha 2C$ régulant la transmission non noradrénergique (par exemple, la sérotonine, la DA). L'expression de l' $\alpha 2C$ -AR est plus restreinte, les plus fortes densités se retrouvant dans le striatum ventral et dorsal (MacDonald et al., 1997), suggérant la possibilité de différences significatives dans la façon dont les $\alpha 2A$ et $\alpha 2C$ modulent la neurotransmission régionale. Cependant, l' $\alpha 2C$ -AR joue un rôle plus important dans les

états de faible activité endogène de la NA, tandis que l' $\alpha 2A$ -AR est relativement plus engagé dans les états de tonus noradrénergique élevé (Uys et al., 2017).

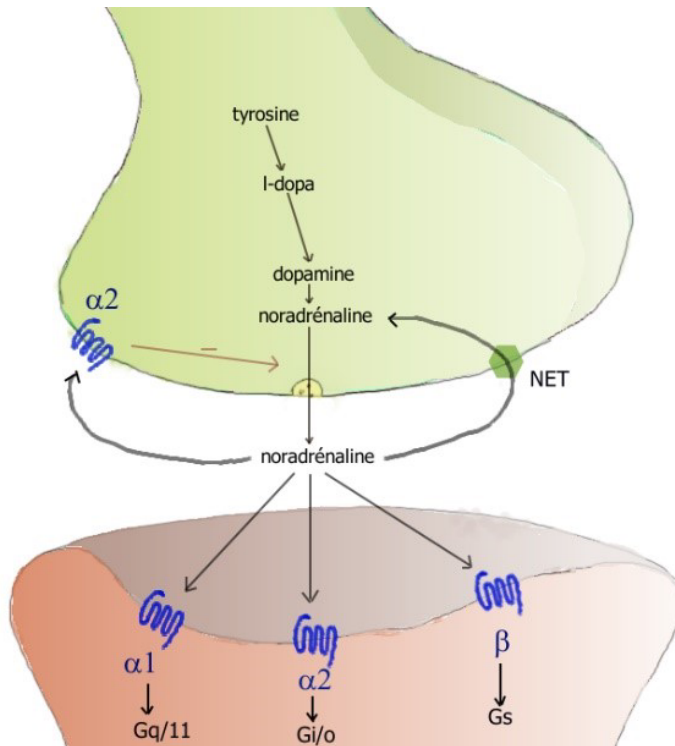


Figure 8 :

Représentation d'une synapse noradrénergique avec les trois grands sous types de récepteurs de la NA : $\alpha 1$ $\alpha 2$ et β .
NET : transporteur de la NA

C. ROLE DE LA NORADRENALINE

La NA est un neuromédiateur dont l'action a d'abord été caractérisée au niveau périphérique pour ses effets cardiovasculaires ou bronchiques. Au niveau central, la NA est principalement connue pour son rôle non spécifique dans l'attention et l'éveil (Aston-Jones & Cohen, 2005; Sara, 2009). Mais la NA présente aussi un rôle spécifique sur de nombreuses fonctions cognitives et motrices (Borodovitsyna, Flamini, & Chandler, 2017; Chamberlain & Robbins, 2013). En particulier, le système LC-NA semble impliqué dans la prise de décision et la sélection de réponse (voir Aston-Jones & Cohen, 2005 pour revue) et associé au contrôle exécutif de l'action (Mückschel, Dippel, & Beste, 2017). Enfin, la libération du neurotransmetteur NA a un rôle modulateur sur le traitement sensoriel, la douleur, l'anxiété, la dépression, les mécanismes du stress ainsi sur les fonctions thymiques.

Le fonctionnement du réseau noradrénergique est complexe (Figure 9). Sous des niveaux modérés de NA, les récepteurs $\alpha 2A$ post-synaptiques du cortex préfrontal sont stimulés. Cela inhibe l'AMPC et empêche l'ouverture des canaux HCN, ce qui renforce la

connectivité préfrontale (Arnsten, 2000). Au contraire, des niveaux élevés de NA stimulent les récepteurs $\alpha 1A$, activant la libération de calcium intracellulaire ce qui augmente l'ouverture des canaux potassiques induite par l'AMPc et affaiblit la connectivité du réseau. Les augmentations transitoires de NA qui engagent les récepteurs $\alpha 1$ et β peuvent également servir à déconnecter les circuits pour permettre la réorganisation de la configuration du réseau, afin de répondre aux demandes environnementales changeantes (Cools & Arnsten, 2022). En revanche, dans les régions cérébrales postérieures, notamment l'hippocampe et l'amygdale, la signalisation de l'AMPc a l'effet inverse, c'est-à-dire qu'elle renforce la connectivité synaptique. Dans ces circuits, l'excitation des récepteurs des voies de signalisation de l'AMPc (entre autres) a des effets positifs, notamment en facilitant la dépression à long terme et la potentialisation à long terme (Hagena et al., 2016). En résumé, au niveau de la mémoire de travail, les récepteurs $\alpha 2$ et $\alpha 1$ exercent des effets opposés, les récepteurs $\alpha 2$ favorisant et les récepteurs $\alpha 1$ altérant le réseau du cortex préfrontal et la fonction cognitive (Berridge & Spencer, 2016). Il est important de noter que la plupart de ces observations viennent de données chez l'animal.

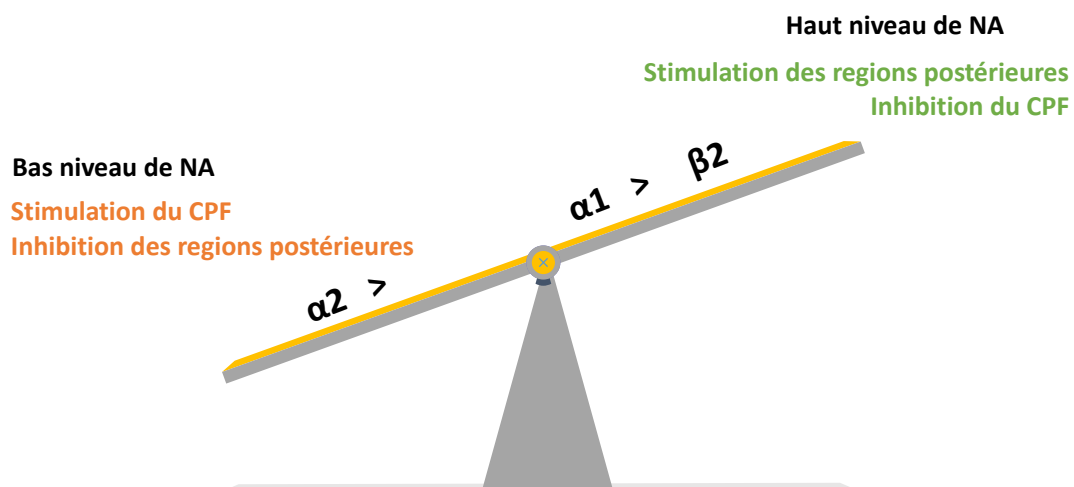


Figure 9 : Fonctionnement du système noradrénergique selon le niveau de NA. Avec un niveau de NA faible les récepteurs $\alpha 2$ sont activés avec un effet stimulation sur le cortex préfrontal (CPF). A un niveau de NA élevé les récepteurs $\alpha 1$ et $\beta 2$ sont activés avec un effet inverse. (Arnsten, 2000). Les récepteurs $\alpha 1$ de faible affinité, activés à des taux de libération plus élevés associés à des conditions d'excitation élevées (par exemple, le stress), nuisent aux performances de la mémoire de travail tout en favorisant la flexibilité de l'attention.

2. Que savons-nous du système noradrénergique dans la maladie de Parkinson ?

a. UNE DEGENERESCENCE PRECOCE DU LOCUS COERULEUS

Plusieurs études anatomopathologiques sur des cerveaux de patients atteints de la MP ont montré une perte modérée à sévère de cellules dans le LC (de 30 à 90%) et la présence de corps de Lewy (Bertrand et al., 1997; Chan-Palay & Asan, 1989; Gaspar & Gray, 1984; German et al., 1992; McMillan et al., 2011). Plus précisément, les neurones du LC contenant de la neuromélanine présentent des altérations, tandis que les neurones non noradrénergiques ne présentent pas de modifications sévères (Patt & Gerhard, 1993). La perte de cellules noradrénergiques est plus marquée dans la portion caudale du noyau (Bertrand et al., 1997; E. Braak et al., 2001; German et al., 1992).

Plus récemment, les études d'imagerie utilisant les séquences IRM sensible à la neuromélanine ont confirmé une perte progressive du signal dans le LC chez les patients atteints de MP (Castellanos et al., 2015; Sasaki et al., 2006; S. T. Schwarz et al., 2017; Wang et al., 2018). En particulier, il semblerait que cette diminution de contraste du LC soit plus importante du côté le plus affecté défini cliniquement et limitée au LC médian et caudal (Doppler, Kinnerup, et al., 2021; R. Ye et al., 2022).

Il a également été proposé que les dépôts d' α -synucléine dans le LC précèdent et sont d'une plus grande ampleur que dans la SN (Zarow et al., 2003b). Ces résultats suggèrent que le dysfonctionnement du LC peut contribuer à l'apparition et à la progression de la maladie plutôt que d'en être une simple conséquence. Conformément aux stades de Braak, les différentes caractéristiques cliniques dues au dysfonctionnement noradrénergique peuvent être observées tout au long de la progression de la maladie et apparaissent souvent avant l'apparition des symptômes moteurs (R. C. K et al., 2023). Braak postule également que l' α -synucléine peut se propager de l'intestin au cerveau via le nerf vague. Dans une étude de Kim et al, ce postulat a été testé en évaluant l' α -synucléinopathie dans le cerveau d'un nouveau modèle murin (Kim et al., 2019). Des cellules de fibrilles préformées d' α -synucléine phosphorylées à la sérine 129 ont été prélevées dans le SNC et ont été injectées dans les muqueuses musculaires duodénales et pyloriques. Dans le cerveau, l' α -synucléine phosphorylée à la serine 129 a d'abord été détectée dans le noyau moteur dorsal du nerf vagal, puis dans le LC et, seulement plus tard, dans les neurones dopaminergiques du SNpc. Les souris présentaient également plusieurs symptômes

non moteurs de la MP, notamment l'anxiété, la dépression et des troubles cognitifs. Cette étude confirme l'atteinte précoce du LC.

Une étude sur le taux de catécholamines dans le liquide céphalo-rachidien (LCR) de patients porteurs d'une MP, d'une atrophie multi systématisée (AMS) et d'une « pure autonome failure » (PAF) montre une diminution du taux de catécholamines évocatrices d'un déficit noradrénergique central (Goldstein et al., 2021). Dans la PAF, il n'y a pas d'atteinte dopaminergique mais c'est une pathologie qui peut ensuite évoluer vers une MP ou une AMS. Les auteurs avancent l'hypothèse d'un mécanisme « norépinephrine first » avec une dégénérescence des neurones noradrénergiques du LC précédant la perte des neurones dopaminergiques de la SN.

En outre, le concept de dégénérescence précoce a aussi été illustré grâce à l'imagerie en tomographie par émission de positon (TEP). Ainsi, en utilisant la ^{18}F -Dopa, Pavese et ses collègues ont montré une absorption réduite du radiotracteur dans le LC sur des patients évalués en début de maladie à l'inclusion puis trois ans plus tard, indiquant une perte progressive de la fonction noradrénergique (Pavese et al., 2011). Dans cette étude, la réduction du signal en fluorodopa est interprétée comme une perte progressive de la fonction terminale noradrénergique. Le signal de départ chez les patients était plus élevé que les témoins sains. Bien que non significative cette préservation du signal en début de maladie pourrait indiquer une régulation en réponse à la présence de corps de Lewy avec un processus complexe de modification du système noradrénergique. En effet, dans les pathologies neurodégénératives il semble que la modification du système noradrénergique se fasse de façon non linéaire. Par exemple, dans la maladie d'Alzheimer, il a été observé des inclusions tau précocement dans le LC (avant même le stade MCI) et une perte de cellules dans le LC avec la progression de la maladie (Matt et al., n.d.). Toutefois, ces inclusions et cette perte de cellules ne s'accompagnent pas d'une diminution du taux de NA. En effet, il est rapporté une diminution du taux de NA dans les tissus mais une augmentation des métabolites de la NA dans le LCR, ce qui indique un taux de renouvellement et une disponibilité cellulaire accrue (Hoogendijk et al., 1999; Palmer et al., 1987). Il y a donc dans la MA un effet compensatoire des cellules du LC restantes. En parallèle, il y a des études chez l'animal qui montre une hyperactivité du LC avant la mort cellulaire (Weinshenker, 2018). Ces changements peuvent avoir des conséquences positives et négatives car l'activation excessive des neurones survivants pourrait contribuer à la toxicité cellulaire (Blesa et al., 2022).

b. UN ROLE ANTI-INFLAMMATOIRE ET NEUROPROTECTEUR

Bien que la MP soit une maladie neurodégénérative, il existe des signes de microgliose réactive, caractéristique de la neuroinflammation, qui peuvent contribuer à la dégénérescence neuronale. La TEP avec des traceurs de translocation de la protéine 18 KDa (TSPO) est un outil pour évaluer la neuroinflammation chez les patients. La TSPO est une protéine de translocation de la membrane mitochondriale externe et sa présence dans les structures cérébrales est considérée comme un signe indirect d'inflammation, principalement en relation avec l'activation de la microglie. Chez les patients atteints de MP, une liaison accrue du radiotracer a été constatée dans le putamen et la SN (Iannaccone et al., 2013). De plus, il convient de noter que les gènes Parkin et LRRK2, codent pour des protéines impliquées dans la régulation de l'activité de la microglie (Beilina & Cookson, 2016). En particulier, la mutation de Parkin est associée à une atteinte plus sévère des neurones DA et à une production accrue de cytokines M1, tandis que LRRK2 est exprimée dans la microglie activée et participe à la modulation de l'inflammation en réponse à des stimuli pathologiques (Dionísio et al., 2019; Russo et al., 2014). Les neurones dopaminergiques sont très sensibles aux lésions inflammatoires. Dans des modèles animaux exposés au lipopolysaccharide (LPS) (une molécule qui provoque une forte réaction inflammatoire systémique) une dégénérescence significative des neurones dopaminergiques a été observée. En effet, les cellules dopaminergiques sont particulièrement sensibles au stress oxydatif, car elles sont dépourvues de défenses antioxydantes efficaces (Hartmann et al., 2003; Qin et al., 2007).

Des études expérimentales ont montré que la NA peut exercer un contrôle inhibiteur sur la neuroinflammation, en activant des voies cellulaires anti-inflammatoires et neuroprotectrices. Le système noradrénergique pourrait réduire la production d'interleukines pro-inflammatoires et le LC modulerait l'activation de la microglie et des astrocytes, en stabilisant ces cellules dans leur état de repos grâce à l'activation de médiateurs anti-inflammatoires (Ağaç et al., 2018; Klotz et al., 2003; Szabó et al., 1997).

Le rôle des neurones producteurs de NA dans la MP a également été étudiée en stimulant chroniquement les neurones catécholaminergiques du LC par manipulation chimio génétique (Jovanovic et al., 2022). Il a été retrouvé que les neurones à NA envoient des projections axonales complexes vers les neurones dopaminergiques de la SN et qu'une activité accrue des neurones à NA augmente la survie des neurones dopaminergiques chez les souris surexprimant la mutation faux sens A53T de l' α -synucléine et prévient le dysfonctionnement moteur.

Toutefois, l'action des neurones à « NA élevée » ne parvient pas à atténuer l'agrégation de l' α -synucléine et la microglie dans la SN.

En outre, la déplétion noradrénergique interagirait avec la pathophysiologie du système dopaminergique en favorisant la susceptibilité des neurones dopaminergiques à la dégénérescence (Fornai et al., 2007). Ainsi, dans un modèle expérimental de la MP chez le rat, la lésion du LC était associée à une sensibilité accrue des cellules dopaminergiques aux dommages et à un degré plus élevé de dégénérescence nigrostriatale (Af Bjerkén et al., 2019). De même, des études *in vitro* ont montré que, dans des cultures de DA mésencéphalique, l'administration de NA réduit le risque d'inflammation et taux de mort neuronale. Des résultats similaires ont été observés dans des modèles animaux. Chez les rats, le traitement par la DSP-4 (modèle de souris dans lequel la NA a été initialement épuisée par la DSP-4) est utilisé. Ces souris sont ensuite exposées au LPS. Le prétraitement par la DSP-4 potentialise la neurodégénérescence induite par le LPS dans le SNpc, l'hippocampe et le cortex moteur. Le DSP-4 renforce l'activation microgliale induite par le LPS et augmente le stress oxydatif neuronal. La DSP-4 a accéléré les déficits progressifs des symptômes non moteurs, notamment l'hyposmie, la constipation, l'anxiété, la réaction de sursaut exagérée et l'altération de l'apprentissage. En outre, des diminutions notables des fonctions motrices ont été observées chez les souris traitées (Song et al., 2019). Le rôle protecteur du système noradrénergique sur les cellules dopaminergiques nigrostriatales est donc bien connu (Gesì et al., 2000)

D'un point de vue pharmacologique, l'atomoxétine, inhibiteur de la recapture de la NA, et l'idazoxan, antagoniste des α 2-ARs, ont été évalués dans un modèle animal de la MP. Le traitement systémique concomitant par l'atomoxétine et l'idazoxan, une combinaison qui sert à améliorer la disponibilité extra-synaptique de la NA, exerce des effets anti-inflammatoires et neuroprotecteurs après l'administration d'un stimulus inflammatoire, (LPS), dans la SN. Les déficits de la fonction motrice induits par la lésion (akinésie, asymétrie d'utilisation des membres antérieurs) et la perte de DA striatale ont été compensés à des degrés divers selon le traitement noradrénergique (Yssel et al., 2018).

Enfin, il a été suggéré que la stimulation indirecte du système noradrénergique pourrait réduire la neuroinflammation. Ainsi, la stimulation du nerf vagal (SNV), connue pour son effet activateur sur le LC par le biais des projections cholinergiques du noyau du tractus solitaire (Bonaz 2016), réduirait l'activation gliale et l'accumulation d' α -synucléine, à la fois chez les rats ayant subi une lésion du LC et chez les rats dont le LC était intact (Hosomoto 2023). Des études supplémentaires sont nécessaires pour confirmer cet effet (Borghammer & Hamani, 2017).

C. UN ROLE DANS L'EXPRESSION CLINIQUE DE LA MALADIE DE PARKINSON

Apathie

L'apathie est un signe non moteur comportemental fréquent dans la MP. La prévalence est d'environ 40 % et celle-ci augmente avec la progression de la maladie, jusqu'à atteindre 50% au stade avancé (Chagraoui et al., 2018; Mele et al., 2020). L'apathie a été définie par l'International Society for Central Nervous System Clinical Trials Methodology (ISCTM) comme une réduction quantitative et persistante des comportements orientés vers un but, entraînant une altération significative du fonctionnement de la vie quotidienne des patients (Miller et al., 2021). Au stade précoce et fluctuant de la MP, l'apathie peut être considérée comme une apathie motivationnelle qui répond, dans une certaine mesure, à la DA (Béreau et al., 2023). Sa physiopathologie est sous-tendue par une dénervation dopaminergique et sérotoninergique (Maillet et al., 2016a; Pagonabarraga et al., 2015). Au stade avancé de la MP, l'apathie peut être associée au déclin cognitif. Il est important de noter que cette apathie cognitive n'est plus sensible à la DA. L'apathie cognitive peut refléter la propagation de la pathologie de Lewy et l'implication concomitante d'autres systèmes de neurotransmetteurs, y compris les circuits cholinergiques et noradrénergiques (Dujardin et al., 2013; Hezemans et al., 2022; D. K et al., 2009).

Des éléments récents posent la question de l'implication de la NA dans l'apathie de la MP. Par exemple, il a été montré une dégénérescence des régions caudales du LC, associée à une détérioration de la cognition mais également à des scores d'apathie plus élevés chez des patients parkinsoniens (R. Ye et al., 2022). De même, une récente étude randomisée en double aveugle, avec l'atomoxétine (Hezemans et al., 2022) a été menée chez des patients parkinsoniens. L'effet de l'atomoxétine dépendait de l'intégrité du LC (évaluée à l'aide de l'IRM 7T) : les participants dont le LC était plus atteint présentaient une amélioration plus importante de l'apathie sous atomoxétine que sous placebo. Les résultats indiquent une contribution du système noradrénergique à l'apathie et un bénéfice potentiel du traitement noradrénergique sous réserve d'une stratification en fonction de l'intégrité du LC. D'un point de vue physiopathologique, l'hypoactivité du LC pourrait réduire l'exploration de nouveaux aspects de l'environnement, car les niveaux toniques requis pour promouvoir un comportement flexible ne sont pas atteints. Ceci est cohérent avec les dimensions de l'apathie liées à l'initiation ou à l'auto-activation (par opposition aux aspects de l'apathie liés à l'émotion ou à la récompense) (Passamonti et al., 2018). Il semble donc que la dénervation noradrénergique participe à l'apathie et notamment plutôt l'apathie cognitive rencontrée dans des stades avancés de la MP.

Douleurs

La douleur chronique est un symptôme non moteur très fréquent qui affecte jusqu'à 80% des patients atteints de la MP, tant dans les phases prodromiques qu'au cours des stades ultérieurs de la maladie. La douleur chez les personnes atteintes de la MP est assez hétérogène et peut être due à différents mécanismes (de Andrade et al., 2023). Le traitement dopaminergique ne permet de contrôler que partiellement la douleur liée à la MP. La NA et la DA jouent un rôle dans la transmission de la douleur. La plupart des études ont rapporté que la L-Dopa réduit la perception de la douleur (Brefel-Courbon et al., 2005; Gerdelat-Mas et al., 2007; Nebe & Ebersbach, 2009; Schestatsky et al., 2007). Néanmoins, l'apomorphine, qui est un agoniste de la DA n'a pas modifié le seuil de la douleur ni les activations cérébrales induites par une stimulation douloureuse (Dellapina et al., 2011). De plus, dans une étude de corrélation par imagerie (DaTSCAN), le seuil subjectif de la douleur n'était pas corrélé avec le ratio de liaison ²³I-ioflupane-FP-CIT dans le striatum, mais il y avait une corrélation significative avec le taux de liaison dans les régions extra-striatales (cortex cingulaire postérieur et insula) suggérant que les anomalies de la perception de la douleur peuvent être liées à d'autres systèmes monoaminergiques (Dellapina et al., 2019).

Les inhibiteurs de la recapture de la NA et de la sérotonine diminuent ou empêchent l'hyperalgésie chez les rats 6-OHDA (Campos et al., 2019; Cao et al., 2016). Ainsi, l'hyperalgésie dans le modèle de la MP chez le rat est médiée par d'autres systèmes monoaminergiques qui modulent le système opioïde. Récemment, une étude chez des rats traités à la 6-OHDA a montré que le système noradrénergique participe à la régulation du seuil de nociception. Ces rats étaient traités au DSP-4 pour créer une déplétion noradrénergique. (Gao et al., 2023). Les seuils de douleurs du groupe de rats traités par 6-OHDA et DSP-4 étaient plus altérés que le groupe de rats traités uniquement à la 6-OHDA.

Au final il semble que plusieurs neurotransmetteurs tels que la DA, la NA, la sérotonine et les opioïdes pourraient participer au traitement anormal de la douleur dans la MP.

Dyskinésies

Les dyskinésies, ainsi que les fluctuations motrices, sont des complications motrices du traitement chronique par la DA, qui entraînent une altération de la qualité de vie (Hechtner et al., 2014). Les mécanismes physiopathologiques qui sous-tendent les dyskinésies sont partiellement compris. Elles impliquent des activités oscillatoires spécifiques des neurones du cortex moteur et des ganglions de la base ainsi que des variations du métabolisme de la lévodopa (en termes de schéma de stimulation des récepteurs de la DA et de taux de renouvellement) qui

apparaissent avec l'évolution de la maladie. La compréhension plus précise de la pathophysiologie des dyskinésies nécessite d'explorer les systèmes modulateurs de neurotransmetteurs susceptibles d'influencer la transmission dopaminergique (di Biase et al., 2023).

Concernant la NA, les études donnent des résultats contradictoires chez l'animal. Dans une étude de Shin et al. (Shin et al., 2014a), les rats ont subi une double lésion utilisant des injections de 6-OHDA en combinaison de l'anti-DBH-Saporine, pour éliminer les neurones NA dans le LC et les noyaux pontins associés. Ces rats étaient plus enclins à développer des dyskinésies induites par la L-DOPA que ceux ayant subi uniquement le traitement 6-OHDA. La perte de cellules dans la SN était similaire chez les animaux ayant subi une lésion simple ou double, ce qui montre que l'aggravation n'est pas due à une perte accrue de neurones DA dans la SN (Shin et al., 2014b). D'autres études (Fulceri et al., 2007; Miguelez et al., 2011; Pérez et al., 2009) n'ont pas retrouvé d'effet de la déplétion noradrénergique voire un effet inverse. Il est à noter toutefois que l'intensité de la déplétion noradrénergique n'est probablement pas homogène entre les études du fait des différents protocoles de déplétion utilisés dans ces études.

Chez le primate, une équipe a étudié l'effet des médicaments antagonistes α_2 sur les dyskinésies avec un effet prometteur. Le fipamezole notamment permettait d'augmenter la proportion de temps « on » sans dyskinésie invalidante (Fox et al., 2001; Henry et al., 1999; Savola et al., 2003). Chez l'homme, les résultats ont été néanmoins décevants. Dans une étude en double aveugle, randomisée, contrôlée par placebo menée sur 115 patients américains et 64 patients indiens, le fipamezole a réduit les dyskinésies uniquement chez les Américains (Lewitt et al., 2012). Une étude clinique a évalué les effets de l'idazoxan sur les dyskinésies par un test aigu à la lévodopa chez 18 patients atteints de MP à un stade avancé : la sévérité des dyskinésies s'est améliorée après un prétraitement par 20 mg d'idazoxan (Rascol et al., 2001). Malheureusement, ces résultats n'ont pas été confirmés par d'autres essais (Manson et al., 2000).

Des essais se sont intéressés à l'efficacité du propranolol (antagonistes des récepteurs β) sur les dyskinésies. L'effet est démontré chez le rongeur (Bhide et al., 2015; Shi et al., 2020), et un petit essai en ouvert retrouvait également un effet chez l'homme (Carpentier et al., 1996). Toutefois les mécanismes impliqués restent à discuter, un effet anxiolytique des bêtabloquants ne pouvant être exclu. Les autres hypothèses seraient la modulation des interneurons cholinergiques du striatum (Shi et al., 2020) ou l'atténuation de l'efflux de DA (Bhide et al., 2015).

Globalement, ces données ne permettent pas encore de conclure sur l'implication précise du système noradrénergique et son intérêt thérapeutique dans les dyskinésies, des études complémentaires sont nécessaires.

Tremblement

La physiopathologie des tremblements de la MP reste incomplètement comprise et, contrairement à la bradykinésie et à la rigidité, leur gravité n'est pas liée au degré global de dénervation dopaminergique nigro-striatale (Vingerhoets et al., 1997). Alors qu'il existe une corrélation claire entre le degré de bradykinésie et de rigidité dans la MP, ni la sévérité du tremblement de repos ni celle du tremblement d'action ne sont liées aux scores de bradykinésie ou de rigidité (Louis et al., 2001). Plusieurs phénotypes de la maladie de Parkinson ont été identifiés en fonction de l'ensemble des symptômes cliniques qu'ils présentent. Les phénotypes les plus répandus sont le phénotype akinéto-rigide (avec ou sans instabilité posturale et difficulté de marche) et le phénotype avec prédominance de tremblements (Jankovic et al., 1990).

Le thalamus reçoit une riche innervation depuis le LC et il s'agit d'une structure centrale dans la genèse des tremblements (Blesa et al., 2016). Une étude en IRM-TEP au ^{11}C -MeNER (un inhibiteur du transporteur de la NA) a pu étudier les terminaisons noradrénergiques chez des patients parkinsoniens et des témoins. La fixation baisse dans toutes les régions sous corticales étudiées mais avec une différence significative pour le thalamus et le noyau rouge uniquement. La diminution de la fixation du ^{11}C -MeNER résulterait d'une altération de la neurotransmission noradrénergique dans la MP. Les patients avec un score de tremblement élevé étaient associés à une diminution moins marquée que les autres patients (Nahimi, Kinnerup, et al., 2018). Dans une autre étude utilisant le ^{11}C -MeNER il a également été retrouvé que les patients avec un tremblement au premier plan avaient une fonction noradrénergique relativement préservé par rapport aux autres patients (Kinnerup et al., 2021). Par rapport au sous-type akinéto-rigide, les patients avec une forme tremblante de MP présentent donc potentiellement des neurones noradrénergiques mieux préservés (Fereshtehnejad et al., 2015). Ces résultats sont concordant avec une étude anatomopathologique dans laquelle les patients avec une forme de MP marquée par des troubles de la marche au premier plan avaient une perte plus importante de neurones dans la SN et le LC que les patients avec des formes tremblantes de MP (Paulus & Jellinger, 1991a). Il semble donc que la NA pourrait avoir un impact sur le phénotype clinique moteur de la MP.

Troubles affectifs

Les prévalences rapportées des troubles affectifs dans la MP sont disparates, les études faisant état de taux allant de 2 % à 90 % pour la dépression (Ishihara & Brayne, 2006) et de 5 % à 69 % pour l'anxiété (Kulisevsky et al., 2008; Lauterbach & Duvoisin, 1991). Ces deux symptômes sont présents à tous les stades de la maladie. D'un point de vue thérapeutique, la lévodopa et le pramipexole (un agoniste dopaminergique) ont montré leur efficacité sur les symptômes dépressifs dans la MP (Barone et al., 2006; Nègre-Pagès et al., 2010), mais l'optimisation du traitement dopaminergique est rarement suffisante pour améliorer les patients avec un syndrome dépressif caractérisé (Eskow Jaunarajs et al., 2011). Des études récentes suggèrent qu'une atteinte diffuse impliquant non seulement la DA, mais aussi les systèmes glutamatergique, noradrénergique et sérotoninergique est probablement à l'origine des symptômes affectifs de la MP (Prange et al., 2022).

Les comportements de type dépressif et anxieux chez les modèles rongeurs de MP, sont aggravés par la diminution de la dopamine, de la sérotonine et de la noradrénaline (Schintu et al., 2012), ce qui met en évidence les effets complexes des systèmes monoaminergiques. Par exemple, bien que le traitement de la 6-hydroxydopamine ne provoque pas d'anxiété, la combinaison de la 6-hydroxydopamine et de la DSP4 entraîne un comportement anxieux chez les rongeurs (Delaville et al., 2012). Cette étude démontre que les états de type anxieux nécessitent une déplétion en DA mais également une déplétion en 5-HT ou en NA. L'anhédonie et les comportements de type dépressif ne sont apparus que lors de la déplétion combinée des trois monoamines.

Certaines études font état d'un degré plus élevé d'atrophie du LC chez les patients atteints de la MP qui présentent davantage de symptômes non moteurs, tels que la dépression notamment (Wang et al., 2018). Comme citées auparavant, des études en IRM sensible à la neuromélanine ont révélées une perte progressive du signal dans le LC chez les patients atteints de MP, et même un signal plus faible chez les patients atteints de MP présentant des symptômes dépressifs (Castellanos et al., 2015; Sasaki et al., 2006; Wang et al., 2018). Les modifications de la liaison des transporteurs de NA et de DA ont été étudiées à l'aide d'un double ligand TEP ¹¹C-RTI-32 (un marqueur du transport de la dopamine et de la noradrénaline) chez des patients atteints de la MP (Remy et al., 2005) : 8 patients avec et 12 sans antécédents de dépression. Par rapport aux patients qui ne présentaient pas de caractéristiques dépressives, les patients souffrant de dépression présentaient une fixation plus faible du ¹¹C-RTI-32 dans le LC et les régions du système limbique, cingulaire antérieur, le thalamus, l'amygdale et le striatum ventral. Les scores d'anxiété dans les deux sous-groupes de patients atteints de MP étaient inversement

corrélés à l'absorption du ^{11}C -RTI-32 dans ces régions. Les auteurs concluent que la dépression et l'anxiété dans la MP sont associées à la perte d'innervation de la dopamine et de la noradrénaline dans le système limbique. D'un point de vue thérapeutique, les inhibiteurs de recapture doubles sérotoninergique et noradrénergiques (nortryptiline, amitriptyline, venlafaxine) ou principalement noradrénergiques (désipramine) sont particulièrement efficaces comme le confirme une méta-analyse où la désipramine avait une efficacité plus rapide que le citalopram (inhibiteur de recapture sérotoninergique) (Liu et al., 2013). Ces données confortent l'idée d'une implication noradrénergique dans la genèse des troubles affectifs de la MP mais des études supplémentaires sont nécessaires.

Troubles cognitifs

Des études épidémiologiques ont retrouvés des taux élevés (de 25% à 50%) de Mild Cognitive Impairment (MCI) au moment du diagnostic de MP, ce qui montre que le développement des troubles cognitifs peut précéder l'atteinte motrice (Weil et al., 2018). Généralement, le déficit cognitif se présente sous la forme d'un syndrome dysexécutif dans lequel les troubles de l'attention jouent un rôle central (Dujardin et al., 2013). La physiopathologie de ces troubles implique notamment le cortex préfrontal (CPF), l'hippocampe, le LC, la SN et les régions striatales reliées au CPF (Owen, 2004; Sawamoto et al., 2007). Le dysfonctionnement de plusieurs neurotransmetteurs, notamment cholinergiques (Jellinger, 2012; Lee et al., 2019; Yarnall et al., 2013, 2014) dopaminergiques, et noradrénergiques serait impliqué. Il est intéressant de noter que bien que le déficit dopaminergique joue un rôle dans la physiopathologie des troubles cognitifs, le traitement dopaminergique peut en fait aggraver les fonctions cognitives (Chaudhuri & Odin, 2010). Le rôle du système noradrénergique semble particulièrement important dans les premiers stades de la MP (Halliday et al., 2014; Ko et al., 2013). Une étude anatomopathologique a pu montrer que la perte de neurones noradrénergique dans le LC était plus rapidement progressive que la perte de neurones dopaminergiques dans la substance noire particulièrement pour les patients avec une démence parkinsonienne (Huynh et al., 2021). Il a également été montré que la modulation de l'activité noradrénergique par clonidine aggrave les troubles attentionnels chez les patients parkinsoniens modérément sévères tandis qu'elle n'avait pas d'effet sur des patients plus sévères (Riekkinen et al., 1998). D'un point de vue thérapeutique, l'atomoxétine (l'inhibiteur de la recapture de la NA) a notamment été déjà testée dans la MP en ouvert, avec une amélioration des fonctions exécutives (Marsh et al., 2009). Un autre essai contrôlé randomisé montrait un effet sur les symptômes cognitifs (évaluation globale par le Mini-Mental State Evaluation (MMSE)), (Weintraub, Mavandadi, et

al., 2010). Mais les résultats des études sur l'atomoxétine dans la cognition et l'attention dans la MP sont contrastés. Une méta-analyse récente de trois études ne montre pas d'efficacité sur les troubles attentionnels et la cognition (Ghosh et al., 2020). Plusieurs explications à ces résultats contradictoires : Premièrement, avec la dégénérescence du système noradrénergique, l'atomoxétine a potentiellement moins de substrat à lier. En effet, comme le montrait une étude en imagerie il existe une diminution du transporteur de la NA dans la MP (Nahimi, Sommerauer, et al., 2018), ce qui pourrait freiner l'efficacité du traitement. Deuxièmement, comme nous l'avons vu plus haut, la NA a une faible affinité pour les α_1 et une forte pour les α_2 qu'elle lie à faible dose et on sait qu'une stimulation accrue des récepteurs α_1 altère le fonctionnement du CPF (Arnsten, 2000; Birnbaum et al., 1999; Ramos & Arnsten, 2007), alors qu'une stimulation accrue des récepteurs α_2 améliore le fonctionnement du CPF (Jäkälä et al., 1999). D'autre part il semble qu'il existe une diminution des récepteurs α_2 avec la MP (Cash et al., 1984). Ainsi, dans la MP, une augmentation sous-optimale de la disponibilité extracellulaire de la NE peut n'avoir aucun effet en raison possiblement d'une modification de l'équilibre des récepteurs vers une augmentation du rapport α_1/α_2 . Cela expliquerait pourquoi l'atomoxétine peut rester inefficace dans la MP. L'impact de l'atomoxétine semble être dépendant de l'innervation noradrénergique restante (problème non soulevé par le traitement du TDAH dans lequel l'atomoxétine est efficace). Cette molécule est donc difficile à utiliser sans d'avantage de connaissance sur le niveau de récepteurs chez les patients parkinsoniens.

Troubles du Contrôle des Impulsions (TCI)

Les TCI, définis comme une incapacité à résister à l'impulsion ou à la tentation d'accomplir un acte qui nuit à soi-même ou à autrui (Evenden, 1999), sont principalement représentés par les achats pathologiques, le jeu, les compulsions alimentaires et l'hypersexualité. Il existe également le phénomène de répétition stéréotypée de tâches sans but (punding), qui est classiquement intégrée à ces troubles. On parle également de « syndrome de dysrégulation dopaminergique » pour les addictions à la lévodopa (Faouzi et al., 2021). En termes de fréquence, les TCI se rencontrent chez 14% à 39% des patients parkinsoniens (Faouzi et al., 2021; K. M. Smith et al., 2016). Il a été rapporté que ces patients étaient fréquemment atteints de comorbidités psychiatriques comme l'anxiété, la dépression et les troubles obsessionnels compulsifs (Voon, Sohr, et al., 2011). Les traitements dopaminergiques, constituent le principal facteur de risque de TCI. Parmi les traitements dopaminergiques, les ADs sont les médicaments les plus pourvoyeurs de TCI, avec un risque de 2 à 3,5 fois plus important (Weintraub, Koester, et al., 2010b). Tous les ADs se lient au récepteur

dopaminergique D3 (Ahlskog, 2011) principalement localisés dans le système mésolimbique. Les TCI sont supposés liés à une sensibilisation anormale du système dopaminergique mésolimbique impliqué directement dans le système de récompense (Abler et al., 2009; Claassen et al., 2017; Rao et al., 2010; Voon, Gao, et al., 2011). En effet, les études d'imagerie fonctionnelle centrées sur l'analyse des voies dopaminergiques soulignent l'implication du réseau dopaminergique méso-cortico-limbique dans la survenue des TCI au cours de la MP, incluant notamment une augmentation de la libération de DA au niveau du striatum ventral (Pagano et al., 2021; Steeves et al., 2009). Il a été démontré que les patients parkinsoniens sans traitement dopaminergique sont plus sensibles aux conséquences négatives et ont des difficultés à apprendre d'une conséquence positive. A l'inverse, les patients sous traitements dopaminergiques deviennent plus sensibles aux conséquences positives d'une action et ont des difficultés d'apprentissage des conséquences négatives de celle-ci (Frank et al., 2004). Cet état, retrouvé sous traitement dopaminergique est le point de départ des TCI du fait de cette surestimation des bénéfices et d'une sous-estimation des conséquences négatives. Actuellement, aucun traitement n'existe pour les TCI et la diminution des traitements par AD n'est pas toujours possible en raison de la survenue d'un syndrome de sevrage.

En outre, le lien entre médication dopaminergique et TCI n'est aujourd'hui pas clair. En effet, tous les patients parkinsoniens sous agoniste dopaminergique ne développent pas de TCI (Isaias et al., 2008) ; alors que des TCI sont observés chez des patients de novo qui ne sont pas encore sous traitement (Antonini et al., 2011). Il semble donc que : 1/ certains facteurs de risque puissent prédisposer les patients parkinsoniens au développement des TCI et 2/ que la physiopathologie de ces troubles soient plus complexes et impliquent d'autres systèmes de neurotransmetteurs. Alors que certains facteurs de risque comme le sexe masculin ou l'âge de début de la maladie ont été évoqués, des prédispositions individuelles pourraient être en rapport avec une topographie différente des lésions de la MP ou des prédispositions génétiques (Marques et al., 2018; Robbins et al., 2012). De même, bien que des avancées fondamentales ait été faites dans notre compréhension des TCI, d'autres recherches sont nécessaires pour aller au-delà de la DA (Callesen et al., 2013; Williams & Potenza, 2008)

De manière intéressante, le système noradrénergique a été impliqué dans le jeu pathologique (Potenza, 2013; Potenza et al., 2002). L'activité noradrénergique centrale est en effet augmentée chez les joueurs pathologiques. En dehors de la MP, des études ont suggéré que l'administration de traitement noradrénergique aurait une action sur l'impulsivité. Comme nous l'avons vu, il semblerait que des changements relativement faibles dans les niveaux de NA pouvaient produire des changements significatifs dans la fonction du cortex préfrontal. La

guanfacine par exemple (qui stimule les récepteurs α_2), renforcerait ainsi la connectivité du réseau du CPF (Arnsten, 2020). En outre, les traitements inhibiteurs de la recapture de NA (qui agissent en augmentant la transmission noradrénergique comme l'atomoxétine) améliorent également les patients atteints de troubles de l'attention avec hyperactivité (TDAH) (Del Campo et al., 2011). Le renforcement de la régulation de l'attention, du comportement et des émotions par le PFC contribue probablement aux effets thérapeutiques de ces médicaments dans le traitement du TDAH. Chez les héroïnomanes, un essai randomisé a montré que la clonidine améliorait la prise de décision et diminuait l'impulsivité (Zhang et al., 2012). En théorie, l'activation des α_2 -ARs présynaptiques entraîne l'inhibition de la libération neuronale de NA, mais il a été rapporté qu'une dose élevée de clonidine engageait les récepteurs post-synaptiques, entraînant une augmentation de la transmission noradrénergique (Miyazaki et al., 2004).

Dans la MP, on observe également une diminution des comportements impulsifs suite à l'augmentation du tonus noradrénergique par un inhibiteur sélectif de la recapture de la NA (atomoxétine) (Kehagia et al., 2014). De plus, un rôle de la NA sur les fonctions exécutives a donc été proposé à l'origine de l'impulsivité chez les patients parkinsoniens (Kehagia et al., 2014). Mais peu d'études se sont intéressées à l'effet de la manipulation noradrénergique sur le contrôle inhibiteur chez les patients parkinsoniens (Chamberlain & Robbins, 2013). De récentes études suggèrent également un effet de la médication noradrénergique (atomoxétine) sur l'inhibition de réponse chez les patients parkinsoniens (Rae et al., 2016; Z. Ye et al., 2015) en restaurant la connectivité des réseaux préfrontaux liés aux fonctions exécutives (Borchert et al., 2016). Au final, l'engagement des réseaux préfrontaux-striataux semble être la clé d'une inhibition réussie et la NA joue un rôle important dans ces réseaux (Tomassini et al., 2022).

Dysautonomie

La dysautonomie est un problème fréquemment rencontré dans la MP. L'hypotension orthostatique (hypoTO) notamment concerne 30 à 58% des patients (Goldstein, 2006) et c'est un symptôme qui augmente la mortalité des patients (De Pablo-Fernandez et al., 2017). La NA est impliquée dans la gestion du système nerveux autonome. Dans le système nerveux périphérique, la NA est le principal neurotransmetteur des neurones postganglionnaires sympathiques qui vont innervier les vaisseaux sanguins et le cœur ; elle agit comme vasoconstricteur et maintient la pression artérielle. La vasoconstriction défectueuse à l'origine de l'hypotension orthostatique neurogène repose sur la libération insuffisante de NA par les terminaux sympathiques postganglionnaires en raison de la dénervation sympathique

postganglionnaire. Il existe des données d'imagerie et de neuropathologie montrant que les neurones sympathiques efférents post-ganglionnaires innervant le myocarde sont affectés par les dépôts d' α -synucléine (Amino et al., 2005; Goldstein et al., 1997). Les fibres sympathiques innervant les vaisseaux sanguins sont également affectées. Il en résulte une altération de la libération de NA et une vasoconstriction défectueuse en position debout, ce qui entraîne une chute de la tension artérielle. Le taux de NA plasmatique, est plus faible chez les patients atteints de la MP et d'hypoTO que chez ceux qui n'ont pas d'hypoTO (Goldstein et al., 2021).

D'un point de vue thérapeutique, la midodrine est un agoniste des récepteurs α 1 qui induit une vasoconstriction et augmente la tension artérielle, et qui est largement utilisée pour le traitement de l'hypoTO dans la MP. Un autre traitement, la droxydopa est un précurseur de la NA qui est également efficace pour le traitement de l'hypoTO (Hauser et al., 2022). L'atomoxetine a été montré efficace dans des essais cliniques (Ramirez et al., 2014; Shibao et al., 2007) mais l'ampreloxetine, un inhibiteur à longue durée d'action du transporteur de la NA n'a pas pu montrer son efficacité dans un essai de phase 3 qui s'est arrêté prématurément (Lamotte & Millar Verneti, 2021). Ces traitements ne sont donc pas utilisés en pratique.

Au niveau du SNC, des corps de Lewy sont retrouvés dans des zones de régulation du système nerveux autonome telles que l'hypothalamus, le LC, la formation réticulaire de la moelle et le noyau dorsal du vague et pourraient être responsable de la dysautonomie (Asahina et al., 2013). Le rôle du LC est discuté, une étude d'IRM à 7 T chez des patients atteints de la MP montre un signal réduit de neuromélanine dans le LC caudal gauche était associé à l'hypoTO (Madelung et al., 2022). Une autre étude anatomopathologique n'avait pas retrouvé de lien entre les dépôts dans le LC et l'hypotension orthostatique (Tong & Chen, 2021) suggérant que l'atteinte seule du LC n'expliquait pas l'hypotension orthostatique. Des études supplémentaires sont donc nécessaires.

Troubles du sommeil

Parmi les troubles du sommeil de la MP, les troubles du comportement en sommeil paradoxal (TCSP) sont une parasomnie fréquente, caractérisée par l'absence d'atonie musculaire pendant le sommeil paradoxal. La prévalence des TCSP est estimée à 46% (Maggi et al., 2023). Les études en imagerie par IRM à la neuromélanine ont montré une diminution du contraste de la région du LC dans les TCSP, y compris les TCSP idiopathiques sans MP associée. Une première étude en IRM sensible à la neuromélanine avait retrouvé une diminution de l'intensité du signal du LC chez les patients parkinsoniens qui était encore plus marquée chez les patients qui présentaient des TCSP (Ehrming et al., 2016). Dans une étude avec des

patients atteints de MP avec et sans TCSP, il était montré une réduction de l'intensité du signal du complexe locus coeruleus/subcoeruleus chez les patients atteints de MP, qui était plus marquée chez les patients parkinsoniens avec TCSP. L'intensité réduite du signal est en corrélation avec le pourcentage d'augmentation anormale du tonus musculaire pendant le sommeil paradoxal (García-Lorenzo et al., 2013). Une étude sur un plus large panel de patients et de témoins montrait que l'intensité du signal était réduite dans tous les syndromes parkinsoniens par rapport aux sujets témoins sains, sauf dans la MP sans TCSP (Nobileau et al., 2023). On suppose que les neurones glutamatergiques du noyau subcoeruleus régulent le sommeil paradoxal (Fraigne et al., 2015). Le noyau subcoeruleus est situé en position ventrale et légèrement rostrale par rapport au locus coeruleus (LC). Le modèle de génération du sommeil paradoxal est cependant beaucoup plus complexe et implique d'autres régions du cerveau et plusieurs systèmes de neurotransmetteurs qui agissent comme des modulateurs (Iranzo, 2018). Il existe notamment plusieurs études qui permettent d'affirmer l'existence également d'une base noradrénergique dans les TCSP. Une étude en IRM et TEP au ^{11}C -MeNER (transporteur de la NA) montrait que les patients parkinsoniens qui avaient une diminution du volume du LC en IRM, avaient également une diminution de la fixation du traceur qui était corrélée avec les TCSP (Sommerauer, Fedorova, et al., 2018). Enfin, une étude plus récente a également examiné des polysomnographies de patients parkinsoniens et leur TEP au ^{11}C -MeNER (Doppler, Smit, et al., 2021) : les patients atteints de la MP présentaient des anomalies de la microstructure du sommeil, corrélées à une diminution de la densité des transporteurs de NA sur la TEP ^{11}C -MeNER dans le LC et les noyaux du raphé, ainsi que dans le thalamus et le cortex bitemporal. Les auteurs ont conclu que l'altération de la microstructure du sommeil est associée à un dysfonctionnement noradrénergique.

En conclusion, il semble que le système noradrénergique :

- 1/ joue un rôle crucial dans l'apparition de la MP,***
- 2/ aurait un rôle anti-inflammatoire et neuroprotecteur,***
- 3/ pourrait être impliqué dans la symptomatologie de la MP.***

Mais à ce jour, le système noradrénergique et ses implications dans la physiopathologie de la MP sont largement inexplorés.

Chapitre 3. Enjeux et Limites

La MP est la deuxième maladie neurodégénérative la plus fréquente après la maladie d'Alzheimer. En France, selon le dernier rapport de santé publique France, plus de 175 000 personnes étaient traitées pour une MP en 2020 avec 25 000 nouveaux cas par an. Les hommes sont 1.5 fois plus touchés que les femmes. L'âge constitue le principal facteur de risque de la maladie : la prévalence passe ainsi d'un pour 1000 chez les personnes âgées de 50 à 59 ans à 19 pour 1000 chez celles âgées de 80 à 89 ans (Elbaz et al., 2016). Ces données françaises sont proches de celles rapportées par une méta-analyse incluant 47 études réalisées partout dans le monde (Pringsheim et al., 2014). Par conséquent, il est estimé que le vieillissement de la population devrait conduire à une augmentation de 56% du nombre de malades parkinsoniens entre 2015 et 2030 en France, pour atteindre 260 000 personnes (Wanneveich et al., 2018). Les conséquences de cette maladie sont considérables pour la personne atteinte, entraînant une diminution de l'espérance de vie (Hoogland et al., 2019), de la qualité de vie (Den Oudsten et al., 2007), de l'autonomie mais aussi une invalidité importante et donc une charge importante pour leurs proches (Mosley et al., 2017). Ainsi, du fait de sa prévalence et de ses conséquences, mieux comprendre et prendre en charge la MP est un enjeu important de santé publique.

Comme nous venons de le voir dans les deux premiers chapitres, l'intérêt de l'étude des systèmes non-dopaminergiques est grandissant en vue du développement de nouvelles stratégies thérapeutiques pour pallier les symptômes résistants aux traitements dopaminergiques standards (Fox et al., 2008). En effet, la dégénérescence précoce de ces systèmes pourrait être impliquée dans le développement de nombreux symptômes moteurs et non-moteurs de la maladie (Fox et al., 2008; Martínez-Fernández et al., 2016). A l'heure actuelle, il existe de nombreux radiotraceurs pour l'imagerie TEP du système sérotoninergique (5HT) (e.g. récepteurs 5HT_{1A} ; Halldin, Gulyás, & Farde, 2001; Kumar & Mann, 2007; Pike, Halldin, & Wikström, 2001 ; Pagano et al., 2017). Ainsi, il a pu être montré que les dysfonctionnements sérotoninergiques étaient impliqués dans le tremblement, la genèse des dyskinesies (Doder et al., 2003; Loane et al., 2013; Politis et al., 2014) mais également dans l'anxiété, la dépression et l'apathie (Maillet et al., 2016; Paulus & Jellinger, 1991; Thobois et al., 2017). Il existe également des radiotraceurs pour l'imagerie TEP du système cholinergique (e.g. acétylcholinestérase et acétylcholine vesicular transporter, Brooks, JNM 2010). Ainsi, les dysfonctionnements cholinergiques seraient eux impliqués notamment dans la genèse des

troubles de la marche et des troubles cognitifs (Bohnen & Albin, 2011; Müller & Bohnen, 2013).

Pendant longtemps, les moyens d'investigation du système noradrénergique se sont limités à l'anatomopathologie, qui apporte des données cruciales mais incomplètes. Le développement de nouvelles séquences d'IRM spécifiques (i.e. pondération T1 Turbo Spin Echo (TSE)) a permis d'identifier avec succès le LC au moyen d'un contraste sensible à la neuromélanine (Sasaki et al., 2006; Yi et al., 2023) et ainsi d'obtenir enfin des informations *in vivo*. En effet, la petite taille du LC a contribué à limiter les recherches *in vivo* de cette structure chez l'homme. Cette approche est aujourd'hui considérée comme un biomarqueur *in vivo* du LC chez l'homme, prometteur (Clewett et al., 2016; Keren et al., 2015). Mais les données de volume et de l'intensité du LC ne répondent pas à toutes les questions concernant le fonctionnement du système noradrénergique.

Jusqu'à peu, aucun traceur TEP du système noradrénergiques n'était disponible. En 2018, une première étude de l'équipe du Professeur Borghammer est publiée, utilisant le ^{11}C -MeNER, inhibiteur du transporteur de la NA, et montre une diminution de fixation du traceur (i.e des projections noradrénergiques) chez 15 patients parkinsoniens par rapport à 10 témoins (Nahimi, Sommerauer, et al., 2018) avec des baisses significatives dans le thalamus et le noyau rouge. La même équipe a publié ensuite plusieurs études d'imagerie en TEP au ^{11}C -MeNER (Nahimi, Kinnerup, et al., 2018) permettant notamment de confirmer l'implication du système noradrénergique dans les TCSP. Dans une étude hybride IRM/TEP au ^{11}C -MeNER, les patients avec une MP et des TCSP présentaient une diminution du signal de la neuromélanine du LC à l'IRM mais également une réduction généralisée de la fixation du ^{11}C -MeNER plus marquée que les patients avec une MP mais sans TCSP (Sommerauer, Fedorova, et al., 2018)

Ces études ont également permis de démontrer qu'il existait une diminution de fixation du traceur ^{11}C -MeNER dans le cortex moteur chez les patients parkinsoniens (sans lien avec l'atrophie du cortex) avec une analyse en sous-groupe qui montrait que la fixation était plus abaissée chez les patients avec un score de Hoehn & Yahr élevé, permettant de supposer qu'il existe une perte des projections noradrénergiques sur le cortex moteur avec l'évolution de la maladie (Sommerauer, Hansen, et al., 2018). Par ailleurs, dans une autre publication, il a été montré une diminution des projections noradrénergiques ascendantes chez les patients parkinsoniens par rapport aux témoins sains dans toutes les régions cérébrales échantillonnées, mais aucune corrélation n'a été établie entre les données du LC en IRM et les diminutions de captation du ^{11}C -MeNER par la TEP (Doppler, Kinnerup, et al., 2021) (figure 10). De plus,

l'étude met en évidence des différences régionales dans les lésions du LC, les parties médiane et caudale du LC étant plus touchées que la partie rostrale.

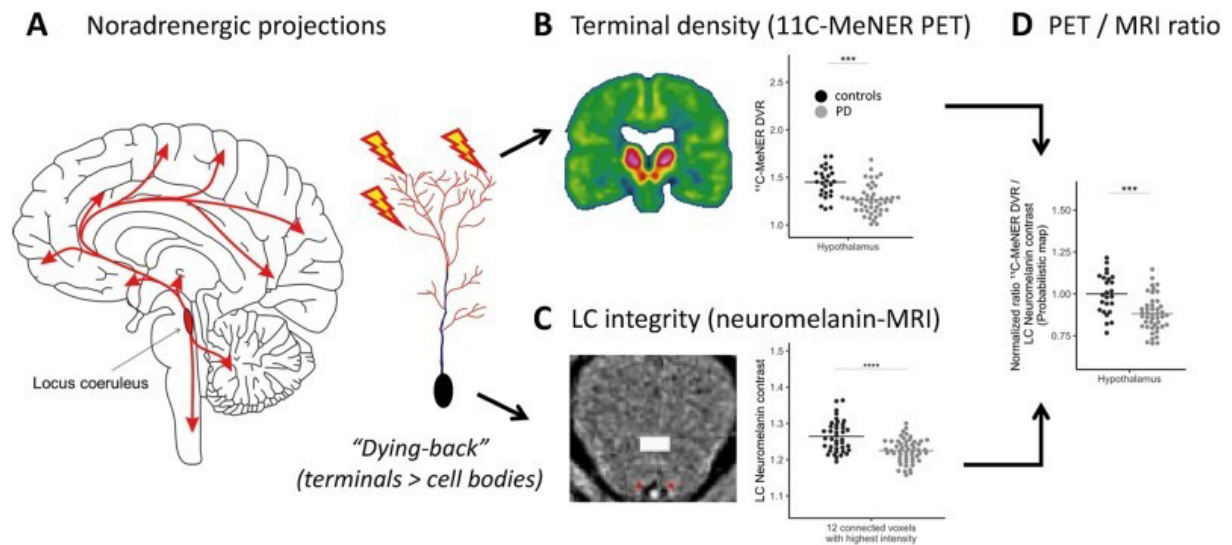


Figure 10 : Résumé de l'étude de Doppler et Kinnerup.

(A) Les projections des neurones noradrénergiques du LC (modifié d'après (Augusto & Gambino, 2019)) (B) La densité des terminaux noradrénergiques, montrée par 11C-MeNER PET (tiré de la figure 5 et de la figure supplémentaire 1 de Doppler et al.6). (C) L'intégrité structurelle du LC (indiqué en rouge), comparée à une région témoin (pont) : IRM sensible à la neuromélanine (d'après la figure 1 de Doppler et al.6). (D) Le rapport entre le signal TEP et le signal IRM est indiqué pour l'hypothalamus (d'après la figure 7 de Doppler et al.6). Les données ont été normalisées par rapport à la moyenne des sujets témoins sains. Chez les patients, le rapport significativement plus faible signifie que le dysfonctionnement noradrénergique des terminaisons (TEP) a dépassé celui des corps cellulaires (IRM). DVR = ratio de volume de distribution. Figure Issue de (Helmich & Lehéricy, 2021)

Enfin, sur le plan moteur, une étude a pu montrer une relative préservation du signal noradrénergique chez des patients parkinsoniens tremblants par rapport aux non tremblants. (Kinnerup et al., 2021). En effet, alors que la fixation du traceur était globalement plus basse chez les patients parkinsoniens que chez les contrôles mais les patients parkinsoniens avec un tremblement prédominant avaient une fixation du 11C-MeNER significativement plus élevée dans le LC et le thalamus. Un résumé des études d'imagerie moléculaire sur le système noradrénergique et la MP est présenté en annexe (tableau 1)

Alors que les systèmes sérotoninergiques et cholinergiques ont fait l'objet de nombreuses études, les études sur le système noradrénergique dans la MP *in vivo* sont peu nombreuses car les traceurs sont récents. Beaucoup de points restent à éclaircir concernant le rôle et le fonctionnement du système noradrénergique dans la MP.

Chapitre 4. Présentation des objectifs

Notre objectif premier dans ce travail de thèse était d'avancer sur la compréhension du rôle du système noradrénergique dans la pathophysiologie de la MP. En effet, bien que les protocoles pharmacologiques et les études en imagerie cérébrale aient apporté des preuves de concepts importantes sur l'implication de la NA dans les troubles moteurs et non moteurs de la MP, ils n'autorisent aucune conclusion ferme quant à l'impact des modulations noradrénergiques d'activité cérébrale obtenues pharmacologiquement.

Dans un premier temps, en collaboration avec le centre lyonnais d'imagerie du vivant (Cermep), nous avons choisi de pallier un certain nombre de points méthodologiques non abordés dans la publication princeps de Nahimi et ses collègues (Nahimi et al., 2015) étape cruciale pour l'utilisation de ce nouveau radiotracer via une approche non-invasive, en mettant en place une étude méthodologique. Les objectifs étaient multiples. Il s'agissait de (i) créer un modèle compartimental *in vivo* de pharmacocinétique TEP de la ^{11}C -Yohimbine via la mesure TEP combinée à la fonction d'entrée artérielle du radiotracer, (ii) valider un modèle simplifié de quantification non-invasif, (iii) évaluer la reproductibilité de la quantification de ces paramètres et (iv) tester la sensibilité de fixation de la ^{11}C -Yohimbine en compétition avec une variation des concentrations de NA extracellulaire dans le cerveau. Au final, ce projet doit fournir une solution de protocole non-invasif permettant alors de cartographier *in vivo* chez l'homme, sur de larges populations, la densité des récepteurs α_2 . Il s'agira de la première publication de ce travail de thèse présentée chapitre 5.

Fort de ce développement méthodologique, nous poursuivrons notre travail en mettant en place une seconde étude qui mesurera directement l'altération du système LC-NA spécifique à la MP et tentera, le cas échéant, d'expliquer l'évolution physiopathologique de la maladie en combinant les solutions récentes d'imagerie du LC aux nouvelles données d'imagerie moléculaire et en systématisant le recueil de données comportementales et cliniques. En d'autres termes, notre objectif ici sera double. Il s'agira de (i) montrer l'influence d'un dysfonctionnement du système noradrénergique dans la MP à partir de la comparaison des données TEP/IRM issues de patients parkinsoniens par rapport à des sujets sains de même âge et sexe, et (ii) montrer le rôle des modifications du système noradrénergique dans la symptomatologie de la MP à partir de la corrélation des données comportementales aux données d'imagerie TEP/IRM. Ce travail est présenté chapitre 6 et fait l'objet d'une deuxième publication.

Enfin, convaincu de l'intérêt d'une modulation pharmacologique du système noradrénergique dans la MP, nous avons exploité les résultats de nos précédents travaux fondamentaux suggérant que la modulation du tonus NA induite par la clonidine, un agoniste spécifique des récepteurs α_2 , agissait directement sur les mécanismes d'inhibition de réponse dans la MP (Criaud et al., 2022). Nous avons donc mis en place un essai clinique randomisé contre placebo, de phase 2b, multicentrique (Lyon, Clermont-Ferrand, St Etienne, Nice, Strasbourg, NCT03552068), destiné à tester l'effet prédit de réduction de l'impulsivité des patients parkinsoniens (TCI) par l'administration chronique de clonidine. Il s'agit de la troisième publication présentée chapitre 7.

Chapitre 5. Le développement d'un traceur ^{11}C -yohimbine et son utilisation chez l'homme

En 2015, le développement du traceur ^{11}C -Yohimbine par une équipe danoise ouvre de nouvelles perspectives en permettant pour la première fois une quantification *in vivo* directe de la disponibilité des récepteurs α_2 -adrénergiques (Nahimi et al., 2015). Toutefois, dans cette étude, plusieurs points méthodologiques clés n'étaient pas abordés :

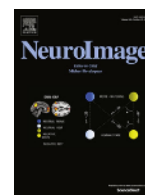
- 1) L'identification d'une région de référence appropriée, étape cruciale pour l'utilisation chez l'homme de ce nouveau traceur via une approche non-invasive.
- 2) L'évaluation de la reproductibilité et le contrôle de la variabilité de la mesure. Sans cette estimation, il est difficile de déterminer avec précision la signification clinique des modifications pharmacologiques et/ou physiopathologiques de la disponibilité des récepteurs α_2 -adrénergiques.
- 3) Enfin, il était important de s'assurer que ce nouveau traceur était sensible à des variations de la concentration synaptique de NA.

Nous avons donc décidé de proposer un développement méthodologique en collaboration avec la plateforme d'imagerie du CERMEP, permettant :

- 1) De dériver un modèle non-invasif adapté à une utilisation clinique du ligand ^{11}C -yohimbine en mesurant la concentration plasmatique artérielle d'activité du ^{11}C -yohimbine non métabolisé (nommée « fonction d'entrée ») nécessaire pour l'extraction des paramètres pharmacocinétiques ;
- 2) D'évaluer la fiabilité de la quantification de ces paramètres ;
- 3) De tester la sensibilité de fixation de la ^{11}C -yohimbine en compétition avec l'augmentation des concentrations de NA extracellulaire dans le cerveau.

Les résultats attestent clairement de la fiabilité du traceur pour mesurer quantitativement le taux d'occupation des récepteurs α_2 *in vivo* dans le cerveau humain, en particulier avec l'utilisation de la *Simplified Reference Tissue Method* (Laurencin et al., 2021).

Ce traceur est intéressant car il cible des récepteurs α_2 -adrénergiques, connus pour avoir un rôle majeur dans la régulation de la neurotransmission noradrénergique (Szabadi, 2013) et dont la perte sélective serait impliquée dans la physiopathologie de maladies neurodégénératives incluant la MP (Marien et al., 2004b). De plus, ils constituent une cible d'intérêt d'un point de vue pharmacologique



Modeling [¹¹C]yohimbine PET human brain kinetics with test-retest reliability, competition sensitivity studies and search for a suitable reference region



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ABSTRACT

Previous work introduced the [¹¹C]yohimbine as a suitable ligand of central α 2-adrenoreceptors (α 2-ARs) for PET imaging. However, reproducibility of [¹¹C]yohimbine PET measurements in healthy humans estimated with a simplified modeling method with reference region, as well as sensitivity of [¹¹C]yohimbine to noradrenergic competition were not evaluated. The objectives of the present study were therefore to fill this gap. **Methods:** Thirteen healthy humans underwent two [¹¹C]yohimbine 90-minute dynamic scans performed on a PET-MRI scanner. Seven had arterial blood sampling with metabolite assessment and plasmatic yohimbine free fraction evaluation at the first scan to have arterial input function and test appropriate kinetic modeling. The second scan was a simple retest for 6 subjects to evaluate the test-retest reproducibility. For the remaining 7 subjects the second scan was a challenge study with the administration of a single oral dose of 150 μ g of clonidine 90 min before the PET scan. Parametric images of α 2-ARs distribution volume ratios (DVR) were generated with two non-invasive models: Logan graphical analysis with Reference (*LREF*) and Simplified Reference Tissue Method (*SRTM*). Three reference regions (cerebellum white matter (CERWM), frontal white matter (FLWM), and corpus callosum (CC)) were tested. **Results:** We showed high test-retest reproducibility of DVR estimation with *LREF* and *SRTM* regardless of reference region (CC, CERWM, FLWM). The best fit was obtained with *SRTM*_{CC} ($r^2=0.94$). Test-retest showed that the *SRTM*_{CC} is highly reproducible (mean ICC>0.7), with a slight bias (-1.8%), whereas *SRTM*_{CERWM} had lower bias (-0.1%), and excellent ICC (mean>0.8). Using *SRTM*_{CC}, regional changes have been observed after clonidine administration with a significant increase reported in the amygdala and striatum as well as in several posterior cortical areas as revealed with the voxel-based analysis. **Conclusion:** The results add experimental support for the suitability of [¹¹C]yohimbine PET in the quantitative assessment of α 2-ARs occupancy in vivo in the human brain.

Trial registration EudraCT 2018-000380-82

1. Introduction

Investigations of the noradrenergic system function in the brain have mainly emerged from animal studies so far. Indeed, the lack of suitable imaging tools has hampered its understanding in human. Nevertheless, we now have the possibility to overcome this difficulty as in vivo imag-

ing of the noradrenergic system has recently become feasible with the development of a novel PET radiotracer: [¹¹C]yohimbine (Nahimi et al., 2015). Yohimbine is an antagonist of the α 2-adrenoreceptors (α 2-ARs) and a partial agonist of the 5-HT_{1A} receptors (Millan et al., 2000). The radiotracer [¹¹C]yohimbine binds with high selectivity to all α 2-ARs subtypes (Jakobsen et al., 2006). This represents a great opportunity

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towards the collection of missing data in the living human brain by direct quantification of regional $\alpha 2$ -ARs availability. Indeed, $\alpha 2$ -ARs play a key role in regulating noradrenergic neurotransmission (Szabadi, 2013) as altered noradrenergic transmission with specific loss of $\alpha 2$ -ARs is currently theorized to play a critical role in both symptoms and progression of some neurodegenerative and mood disorders (Marien et al., 2004; Ordway et al., 2003). Human in vivo imaging of $\alpha 2$ -ARs is therefore essential. Previous work showed that [^{11}C]yohimbine PET tissue data can be described by a 1 tissue compartment (1-TCM), and $\alpha 2$ -ARs binding potential can be estimated using the corpus callosum (CC) as reference tissue (Nahimi et al., 2015). Simplified Reference tissue methods (SRTM) have been widely used to estimate neuroreceptor binding potential because they eliminate the invasive arterial input function (AIF) step. However, reproducibility of non-displaceable binding potential (BP_{ND}) in healthy humans, as well as displaceability with an $\alpha 2$ -ARs agonist, were not evaluated. Yet, demonstration of a reproducible [^{11}C]yohimbine PET outcome measure is critical and preliminary to accurately determine the clinical significance of pharmacologic or pathophysiological $\alpha 2$ -ARs changes.

The objectives of the present study were therefore (1) to identify an optimal [^{11}C]yohimbine PET full kinetic modeling with AIF, (2) assess the validity of non-invasive kinetic modeling, (3) identify the best reference region, (4) estimate the reproducibility of [^{11}C]yohimbine PET measurements with test-retest scans and (5) examine the sensitivity of [^{11}C]yohimbine with a noradrenergic pharmacological competition using acute administration of clonidine, a drug known to decrease NA release through pre-synaptic $\alpha 2$ -ARs activation.

2. Materials and methods

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Sud Méditerranée III (EudraCT: 2018–000380–82) and pre-registered before being conducted on the ClinicalTrials.gov database under the trial record number NCT03520543. The subjects gave written informed consent to participate in the study.

2.1. Participants

Over sixteen healthy men included, two were discontinued, and four completed the study. The mean age was 25 years old (standard deviation, SD, 3 years) and the mean weight was 74.4 ± 7.2 kg (range, 63–87). All subjects were free of medical or neuropsychiatric illness and none of them were smokers or under medication. Each subject underwent two [^{11}C]yohimbine PET scans separated by an interval of 7 to 21 days. For the first scan (test), an arterial catheter was inserted into the radial artery after completion of the Allen test and infiltration of the skin with 1% lidocaine. For the second scan, 7 subjects had a repeated baseline PET (retest), and 7 other subjects had a second PET 74 ± 11 min after administration of a 150 μg oral dose of clonidine (challenge). For all subjects, this second scan was performed without blood sampling. Subjects were also genotyped for the cytochrome P450 (CYP) system with regard to the CYP2D6 isoform, as this latter is involved in the metabolism of yohimbine in the liver, yielding two metabolites that may have some action at $\alpha 2$ -ARs (Le Corre et al., 1999).

2.2. PET procedures

[^{11}C]yohimbine was synthesized as previously described (Jakobsen et al., 2006). The radiochemical purities of syntheses

used for the study were greater than 95%, with corresponding molar activities of 53.4 ± 16.4 GBq/ μmol at the end of synthesis.

All subjects received an intravenous bolus injection of 370 MBq \pm 10% of [^{11}C]yohimbine (Table 1). List-mode PET data were acquired, during 90 min from the injection of the tracer, simultaneously with 3T MRI data (Dixon T1, anatomic MPRAGE T1, venous and arterial TOF), on a Siemens mMR Biograph system.

2.3. Input function measurement

AIF (C_a) and metabolite levels in the plasma were measured from 25 heparinized arterial blood samples manually collected with the following timing: every 5 s for the first minute, every 10 s until second minute, and at times 5, 10, 30, 45, 60, and 90 min post-injection. Eight whole blood aliquots (100 μL), at times of 1, 2, 5, 10, 30, 45, 60, and 90 min post injection, were counted in gamma counter (Perkin-Elmer) to evaluate whole blood to plasma ratio (f_{wb}). Twenty-five blood samples were centrifuged for 3 min (4000 g) and plasma aliquots (100 μL) were counted in gamma counter to measure uncorrected plasma curve (C_p). For metabolite analysis, other plasma aliquots were filtrated using a 0.45 μm membrane filter. Two hundred micromilliliter plasma filtrates were injected in HPLC system with a C8 CAPCELL PAK MF column (Osaka Soda). Fractions were collected and counted for radioactivity in gamma counter. The activity of [^{11}C]yohimbine was divided by the total activity recovered from the gamma counter to give the plasma parent fraction of unmetabolized [^{11}C]yohimbine (PPf). Plasma-free fraction of [^{11}C]yohimbine freely diffusible to tissue (f_p) was measured by ultrafiltration at 1, 2, 5, 10, 30, 45, 60, and 90 min post-injection as previously described (Moore et al., 2003). Arterial blood samples were centrifuged, and 1 mL of plasma was placed in ultracentrifugation devices (Centrifree®, Millipore) and spun for 10 min at 2000 g. One hundred micromilliliter aliquots of whole plasma and ultrafiltrate were counted in gamma counter. After counting, all samples were weighed, and counts were corrected. The f_p was determined from the ratio of concentrations in the ultrafiltrate and whole plasma. AIF was the plasma curve corrected from the plasma parent fraction curve $AIF(t) = PPf(t) \cdot C_p(t)$. The whole blood curve was determined by the mean f_{wb} and the plasma curve $C_{wb}(t) = f_{wb} \cdot C_p(t)$.

2.4. Image processing

Raw PET data were motion corrected (Reilhac et al., 2018), then rebinned into 24-time frames (variable length frames, 8×15 s, 3×60 s, 5×120 s, 1×300 s, 7×600 s) sinograms for dynamic reconstruction. Images were reconstructed using 3D ordinary Poisson-ordered subsets expectation maximization (OP-OSEM 3D), incorporating the system point spread function using 3 iterations of 21 subsets. Sinograms were corrected for scatter, randoms, normalization and attenuation (Mérida et al., 2017). Reconstructions were performed with a zoom of 2, yielding a voxel size of $2.03 \times 2.03 \times 2.08$ mm³ in a matrix of 172×172 voxels with a 4 mm 3D post-reconstruction gaussian filtering. The mean PET image of the session 2 was coregistered (rigid transform) onto the mean PET image of the session 1. Individual MRI T1 of the first session was normalized to the MNI space (Montreal Neurological Institute template of the International Consortium for Brain Mapping Project) with the Segment function of SPM 12 (Ashburner and Friston, 2005). Labeling of the structural brain regions was performed using the multi-atlas propagation with enhanced registration (MAPER) methodology (Heckemann et al., 2010), and the 83-region Hammersmith atlas (Hammers et al., 2003). After projection of the atlas onto the two sessions, regional time activity curves (TAC) were extracted for a selection of brain regions including the amygdala, cerebellum, corpus

Table 1

Details of the CYP2D6 status for each subject and Injected Radioactivity Dose, Molecular Activity, Free fraction in plasma (f_p), Plasma to whole blood fraction (f_{wb}).

Subject	Gaedigk Activity Score		Scan 1 Test		f_p (%)	f_{wb} (%)	Scan 2 ReTest		Scan 2 Challenge	
	MBq		GBq/ μ mol				MBq	GBq/ μ mol	MBq	GBq/ μ mol
1	1.5 (E)	319	27		–	70.3	Not available			
2	1.5 (E)	351	24		7.8	66.3	355	21		
3*	1 (I)	376	22		6.8	66.3		366	30	
4*	2 (E)	376	12		10.5	71.3			355	22
5	1 (I)	351	31		7.6	59.8	414	45		
6*	1.5 (E)	355	44		8.0	62.9			373	33
7*	2 (E)	374	19		6.3	66.4			362	34
8	1 (I)	362	36		–	–			393	14
9*	1 (I)	363	42		8.0	66.1	370	29		
10	1 (I)	367	25		7.4	66.5	367	24		
11	1.5 (E)	341	33		8.7	63.2			361	24
12	1 (I)	384	31		–	–	385	27		
13*	2 (E)	351	28		11.3	69.9			381	20
14*	1.25 (E)	355	48		10.7	64.4	357	39		
Mean\pmSD		359\pm17	30\pm 10		8.5\pm 1.7	66.1 \pm 3.3	375\pm 22	31\pm 9	370\pm 13	25\pm 7

*subjects included in the kinetic modeling analysis. CYP2D6 activity score calculated according to Gaedigk's method (2008) (I and E = Intermediate and Extensive metabolizers respectively).

callosum, frontal lobe, gyrus cinguli, insula, occipital lobe, parietal lobe, striatum, temporal lobe, and thalamus.

2.5. Kinetic modeling

Modeling of the PET TAC was performed with the AIF corrected for metabolite and plasma free fraction using the Turku PET center utilities library (TPCCLIB, <https://gitlab.utu.fi/vesoik/tpcclib>). Invasive models including the 1-TCM (*fitk2*), the 2-TCM (*fitk4*), and the Logan graphical analysis (LGA) (Logan, 2000) were used to estimate the volume of distribution (V_T , mL.g⁻¹) across regions. Fitting accuracy was evaluated with the Akaike information criteria (AIC) (Akaike, 1974). Reference tissue modeling techniques were also evaluated using SRTM (Lammertsma and Hume, 1996) and the non-invasive Logan reference tissue model (LREF) (Logan, 2000). The CC was chosen as reference region based on the recommendations of previous work (Nahimi et al., 2015). In addition, the cerebellar white matter (CERWM) and the frontal lobe white matter (FLWM) were also tested as potential reference tissue because white matter has previously been proposed to represent a region of non-specific binding (Landau et al., 2012). The distribution volume ratio (DVR) was the parameter of interest of the simplified modeling techniques: DVR_{SRTM}, DVR_{LREF}, and DVR_{1-TCM} (DVR computed as the ratio of the V_T of the target region to the V_T in the reference region, derived from the 1-TCM with AIF).

Reference tissue modeling was also performed at the voxel level to compute intra-cerebral DVR parametric maps with SRTM (Gunn et al., 1997) and with LREF (Varga and Szabo, 2002). DVR parametric images were then transformed from the subject's space to the MNI space using the nonlinear deformation fields derived from the spatial normalization of the individual's MR image. Finally, normalized parametric images were smoothed using an 8 × 8 × 8-mm³ full width at half maximum isotropic gaussian kernel to account for the interindividual anatomy variability, normalization uncertainties, and to improve the sensitivity of the SPM analysis. Additionally, regional mean DVR values were computed from the parametric maps in the subject's space.

2.6. Test-retest reproducibility study

2.6.1. Bias and variability

The test-retest bias was calculated as the difference between the test and retest DVRs, divided by the mean of the test and retest values, and the variability as the SD of the bias. These parameters were expressed as percentage.

2.6.2. Reliability

The reliability of the measurements was assessed by the intraclass correlation coefficient (ICC) calculated as (BSMSS-WSMSS)/(BSMSS+WSMSS) where BSMSS is the mean sum of square between subjects and WSMSS is the mean sum of square within subjects (Shrout and Fleiss, 1979). This statistic estimates the relative contributions of between- and within-subject variability and assumes values from -1 (i.e., BSMSS = 0) to 1 (identity between test and retest, i.e., WSMSS = 0).

2.7. Test-challenge study

Clonidine is highly selective and exerts potent agonistic effects at pre-synaptic α_2 -ARs (Delaville et al., 2011). Regional changes induced by the challenge with clonidine were computed as the relative difference of DVR between scans in selected ROIs, expressed as percentage. Binding changes were also observed at the voxel level.

2.8. Statistical analysis

Statistical analysis was performed using Rstudio (<https://github.com/rstudio/rstudio>). Paired Student's t-tests were used to test for differences in the injected dose and molar activity of the [¹¹C]yohimbine between Scan 1 and Scan 2 and also applied to test whether DVRs after retest or clonidine challenge significantly differed from baseline condition. Results with $p < 0.05$ were considered statistically significant. SPM12 was used for voxel-wise comparison with spatially normalized smoothed DVR images. Statistical parametric maps of the t statistic were computed with a threshold of $p < 0.05$ uncorrected at the voxel level and an extent voxels threshold the "Expected number of voxel per cluster". Significant clusters were selected at a corrected cluster level of $p < 0.05$ ("False discovery rate") (Poline et al., 1997).

3. Results

3.1. Subject demographics

In total, over the fourteen subjects scanned, only thirteen completed the study according to the protocol. One subject's retest scan (subject 1) was not evaluated because of PET camera malfunction during the acquisition and was excluded from the test-retest analysis. Additionally, over the thirteen subjects, two subjects did not have arterial sampling in scan 1 but completed the study. For three subjects, the metabolite data were non-exploitable. At the end, for the modeling study, seven

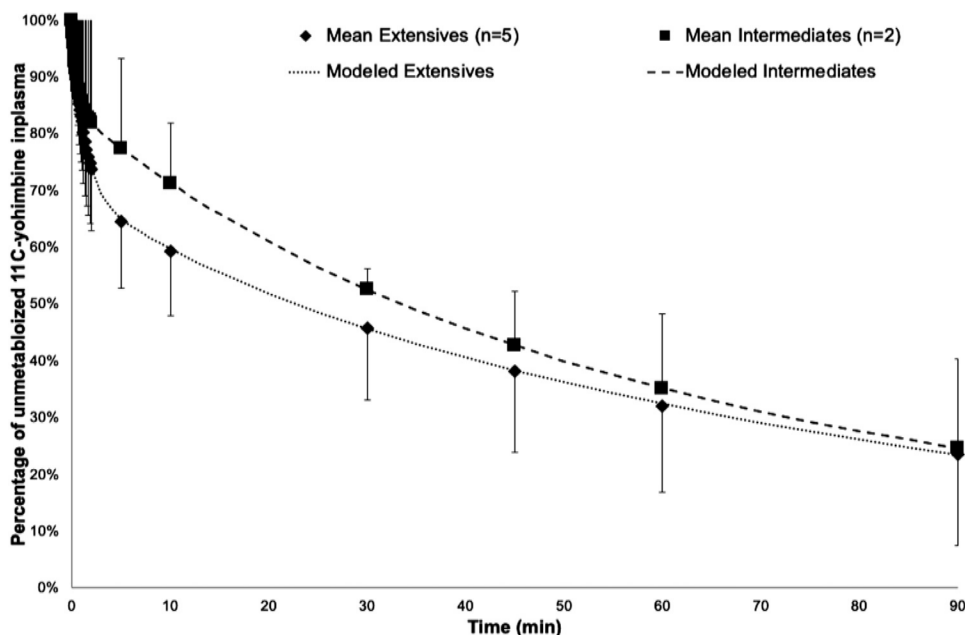


Fig. 1. Plasma parent fraction (PPF) of unmetabolized [^{11}C]yohimbine calculated for the group of intermediate metabolizers and the group of extensive metabolizers (mean and SD across subjects in each group).

datasets were available (PET scan, AIF, metabolite function and free fraction), for the test-retest, six datasets were available (six subjects, two PET scans), and for the test-challenge study, seven datasets were available (seven subjects, two PET scans) (Table 1). Mean age for both groups was identical (25 ± 4 years old for the test-retest group and 25 ± 2 for the test-challenge group).

3.2. Modeling study

Fig. 1 shows metabolization curve (mean and SD plasma parent fractions across subjects) and its modeling depending on the CYP2D6 activity. The best modeling curve of the mean plasma parent fraction curve was a 3-exponentials model:

$$PPf(t) = A1.e^{-\frac{t}{T1}} + A2.e^{-\frac{t}{T2}} + A3.e^{-\frac{t}{T3}}$$

with $A1 = 0.16$, $T1 = 0.41$, $A2 = 0.27$, $T2 = 21.45$, and $A3 = 0.57$, $T3 = 68.97$ for the group of intermediate metabolizers, and with $A1 = 0.30$, $T1 = 0.88$, $A2 = 0.09$, $T2 = 11.49$, and $A3 = 0.61$, $T3 = 65.77$ for the group of extensive metabolizers.

Free plasma fraction was constant over time and had a mean value of $8.5 \pm 1.7\%$. Note that intermediate metabolizers presented mean lower fp values compared to extensive metabolizers ($7.4 \pm 0.5\%$ and $9.1 \pm 1.8\%$, respectively) not statistically significant ($W = 22$, $p = 0.16$). Whole blood to plasma ratio was constant over time with a mean value of $66.1 \pm 3.3\%$ (Table 1) without significant differences between both types of genotypes ($W = 21$, $p = 0.46$). Fig. 2 shows an example of AIF corrected for metabolites and whole blood concentration curve for one subject with intermediate CYP2D6 activity and one subject with extensive profile.

Overall, the Akaike information (AIC) showed slightly lower values for the 2-TCM (225 ± 21) compared to the 1-TCM (244 ± 18) approach, indicating better fits for the 2-TCM. However, as previously highlighted (Nahimi et al., 2015), the 1-TCM approach is much more robust and produced less non-physiological estimates of the kinetic parameters. Accordingly, the 1-TCM was judged as the most appropriate model for analysis of [^{11}C]yohimbine imaging data. Kinetic parameters and V_T using 1-TCM and LGA in the investigated brain regions are reported in Table 2. The V_T were higher in almost all the cortical regions (>0.4). Lower V_T were observed in the cerebellum and the striatum (<0.35) as well as in the three potential reference tissues (CERWM, CC, FLWM).

Although, the regression between V_T values computed by the 1-TCM model and V_T values computed with LGA were extremely well correlated ($V_{T,LGA} = 0.99 \cdot V_{T,1-TCM} + 0.04$; $r^2 = 0.98$; $p < 0.001$), this latter model slightly but significantly overestimated V_T in all regions compared to 1-TCM ($p < 0.0002$).

3.3. Model with tissue reference regions

Regression of DVR_{LREF} and DVR_{SRTM} to DVR_{1-TCM} for the three tested reference regions are shown in Table 3. Regression coefficients were over 0.8 for all regressions, with the best fit obtained for $SRTM_{CC}$ (0.94). Regression slopes were close to 1 for both methods (ranging from 0.81 for $SRTM_{CERWM}$ to 1.13 for $SRTM_{CC}$). Intercepts ranged from 0.03 ($SRTM_{CC}$) to 0.24 ($SRTM_{CERWM}$).

3.4. Test-retest study

There were no significant differences between test and retest scans in neither the amount of radioactivity injected (MBq mean \pm SD: Scan 1: 361.8 ± 12.6 ; Scan 2: 374.7 ± 22.1 ; $Student_t = -1.3$; $p = 0.26$) nor the molar activity of [^{11}C]yohimbine (GBq/ μmol mean \pm SD: Scan 1: 33.5 ± 9.5 ; Scan 2: 30.8 ± 9.2 ; $Student_t = 0.71$; $p = 0.51$). The biases, variabilities and ICC values of the [^{11}C]yohimbine binding parameters are presented in Table 3 (right part) for both compartmental models with the three potential reference tissues. Reliability was very good (>0.74) for both models using either the CC or the CERWM as reference region, while it was acceptable when using the FLWM (around 0.5). The mean values of bias were low ($<2\%$) for all models, and the average variability ranged from 3.8% for the $SRTM_{CERWM}$ to 6.3% for the $LREF_{CC}$ model. Test and retest DVR values were highly correlated ($R^2 > 0.98$). Test-retest performance based on averaged values across subjects are presented in detail, region by region, in Table 4 for the most reproducible methods, namely the $LREF$ and the $SRTM$ with CC and CERWM as reference regions. Using the CC, the test-retest DVR reliability was moderate to high, ranging from 0.67 (gyrus cinguli) to 0.93 (cerebellum) with the $LREF$ and from 0.52 (striatum) to 0.98 (cerebellum) with the $SRTM$. Using the CERWM, the test-retest DVR reliability was also moderate to high, ranging from 0.59 (frontal lobe) to 0.92 (amygdala) with the $LREF$ and from 0.70 (cerebellum) to 0.92 (amygdala) with the $SRTM$. The test-retest DVR variability was excellent ranging from 2.6% (cerebellum) to 7.1% (insula) using the $SRTM$ with CC, while this

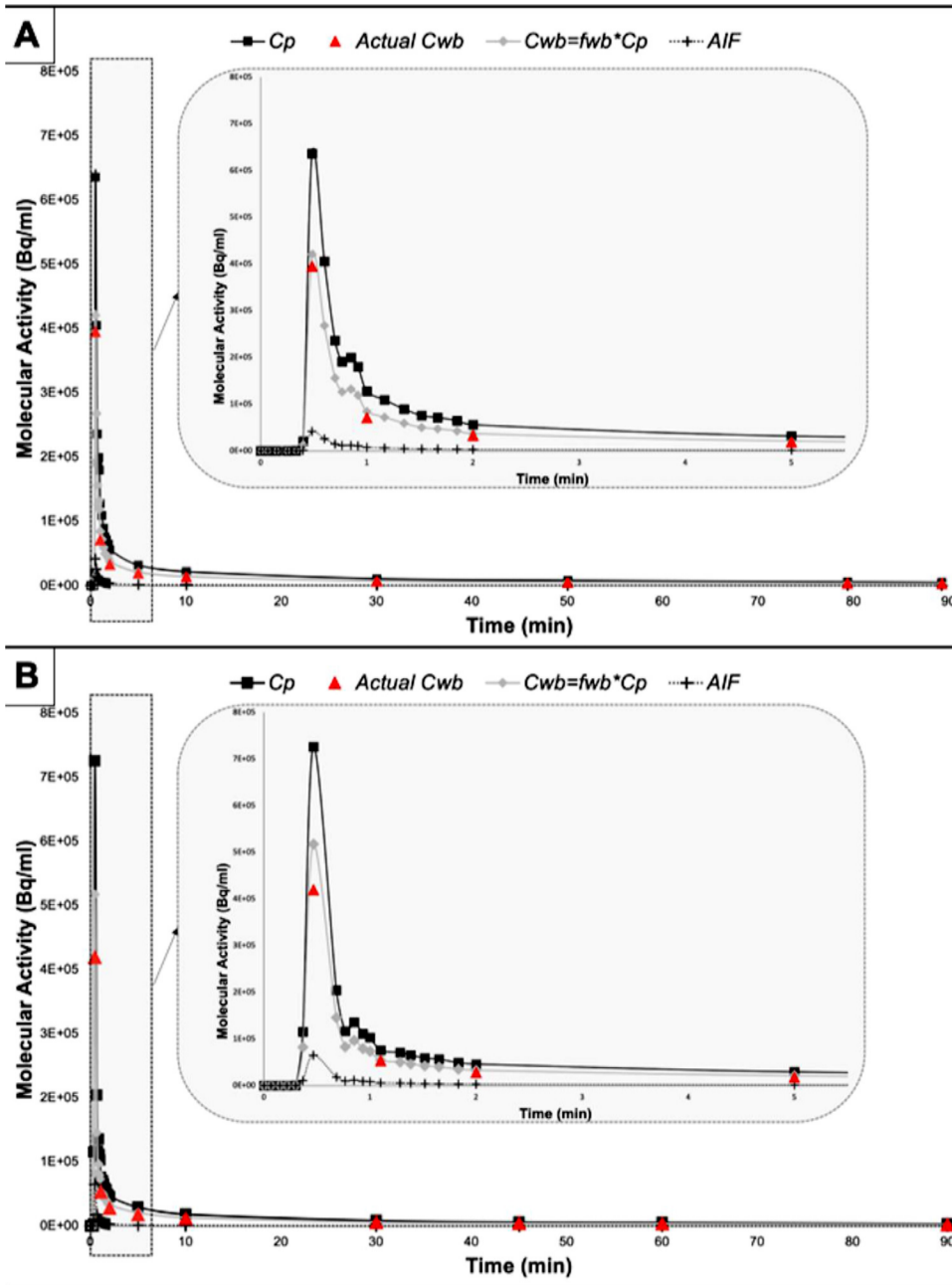


Fig. 2. Illustration of arterial input function (AIF), whole blood plasma (C_{wb}), uncorrected plasma (C_p) curves for one intermediate metabolizer subject (Part A) and one extensive metabolizer (part B). f_{wb} : plasma to whole blood fraction.

Table 2
Kinetic parameters and V_T estimated with 1-TCM and LGA in 7 healthy volunteers.

Regions	1-TCM V_b (%)	LGA K_1 (mL/cm ³ /min)	k_2 (min ⁻¹)	V_T (mL/cm ³)	V_T (mL/cm ³)
Amygdala	2.3 ± 0.8	0.007 ± 0.002	0.019 ± 0.004	0.39 ± 0.08	0.41 ± 0.08
Cerebellum	2.3 ± 0.9	0.010 ± 0.003	0.029 ± 0.004	0.34 ± 0.07	0.39 ± 0.07
Frontal Lobe	1.7 ± 0.8	0.011 ± 0.003	0.025 ± 0.004	0.42 ± 0.10	0.45 ± 0.10
Gyrus Cinguli	2.3 ± 0.8	0.011 ± 0.003	0.023 ± 0.005	0.45 ± 0.10	0.49 ± 0.10
Insula	2.4 ± 0.8	0.009 ± 0.003	0.022 ± 0.004	0.41 ± 0.10	0.45 ± 0.09
Occipital Lobe	2.0 ± 0.9	0.011 ± 0.003	0.025 ± 0.004	0.42 ± 0.10	0.46 ± 0.10
Parietal Lobe	2.0 ± 0.8	0.011 ± 0.003	0.025 ± 0.004	0.42 ± 0.10	0.46 ± 0.10
Striatum	1.6 ± 0.7	0.010 ± 0.003	0.029 ± 0.004	0.34 ± 0.09	0.37 ± 0.08
Temporal Lobe	1.9 ± 0.8	0.009 ± 0.003	0.023 ± 0.004	0.41 ± 0.10	0.45 ± 0.10
Thalamus	2.3 ± 0.9	0.010 ± 0.003	0.024 ± 0.005	0.42 ± 0.09	0.46 ± 0.09
Cerebellum White Matter (CERWM)	1.5 ± 0.6	0.008 ± 0.002	0.025 ± 0.004	0.31 ± 0.06	0.35 ± 0.06
Corpus Callosum (CC)	1.5 ± 0.6	0.005 ± 0.001	0.015 ± 0.002	0.32 ± 0.07	0.36 ± 0.07
Frontal Lobe White Matter (FLWM)	1.1 ± 0.5	0.007 ± 0.002	0.019 ± 0.003	0.34 ± 0.08	0.36 ± 0.08

Data are presented as mean values (± SD).

Table 3

Validation and reproducibility of the distribution volume ratio (DVR) computed with models with reference region, against gold standard 1-TCM model with AIF.

		Mean Regression parameters over DVR _{1-TCM}			Mean Test-Retest reproducibility parameters					
		Slope	Intercept	R ²	ICC	Bias (%)	VAR (%)	Slope	Intercept	R ²
DVR_{LREF}	CC	1.07 ± 0.13	0.16 ± 0.16	0.84 ± 0.06	0.75 ± 0.08	-1.2	6.3	0.96	0.05	0.99
	CERWM	0.94 ± 0.14	0.06 ± 0.15	0.81 ± 0.07	0.75 ± 0.10	0.8	4.1	0.97	0.05	0.99
	FLWM	0.98 ± 0.12	0.14 ± 0.14	0.82 ± 0.07	0.56 ± 0.22	0.7	4.3	0.97	0.05	0.99
DVR_{SRTM}	CC	1.13 ± 0.05	0.03 ± 0.08	0.94 ± 0.04	0.74 ± 0.12	-1.8	4.9	0.94	0.06	0.98
	CERWM	0.81 ± 0.09	0.24 ± 0.10	0.85 ± 0.07	0.82 ± 0.07	-0.1	3.8	0.93	0.09	0.98
	FLWM	0.94 ± 0.08	0.14 ± 0.10	0.92 ± 0.05	0.45 ± 0.31	-0.1	4.2	0.95	0.06	0.98

Data are presented as mean values (± SD).

Table 4

Mean regional DVR test-retest reproducibility and test-challenge variations.

Model	Structures	Test-Retest Study				Challenge Study				
		DVR Test	DVR Retest	ICC	Bias (%)	VAR (%)	DVR Test	DVR Challenge	Change (%)	
LREF_{CC}	Amygdala	1.23 ± 0.08	1.23 ± 0.08	0.71	-0.14	4.82	1.30 ± 0.16	1.36 ± 0.13	5.2 ± 5.9	
	Cerebellum	1.30 ± 0.15	1.28 ± 0.20	0.93	-1.88	4.74	1.36 ± 0.19	1.39 ± 0.13	2.5 ± 8.3	
	Frontal Lobe	1.49 ± 0.13	1.47 ± 0.17	0.70	-1.57	7.94	1.61 ± 0.14	1.56 ± 0.15	-2.5 ± 5.1	
	Gyrus Cinguli	1.56 ± 0.13	1.54 ± 0.16	0.67	-1.58	7.80	1.64 ± 0.15	1.63 ± 0.15	-0.7 ± 3.0	
	Insula	1.41 ± 0.14	1.39 ± 0.13	0.73	-1.55	6.97	1.47 ± 0.13	1.48 ± 0.13	0.5 ± 4.5	
	Occipital Lobe	1.47 ± 0.10	1.44 ± 0.14	0.78	-2.23	5.44	1.53 ± 0.18	1.55 ± 0.15	1.7 ± 6.7	
	Parietal Lobe	1.49 ± 0.11	1.48 ± 0.16	0.68	-0.90	7.21	1.58 ± 0.14	1.56 ± 0.15	-1.1 ± 3.4	
	Striatum	1.27 ± 0.11	1.26 ± 0.11	0.68	-0.57	7.10	1.31 ± 0.10	1.32 ± 0.11	1.0 ± 3.6	
	Temporal Lobe	1.40 ± 0.12	1.37 ± 0.14	0.80	-1.80	5.76	1.46 ± 0.15	1.48 ± 0.14	1.4 ± 4.6	
	Thalamus	1.43 ± 0.13	1.43 ± 0.14	0.83	0.01	5.32	1.55 ± 0.19	1.55 ± 0.17	0.6 ± 3.2	
	SRTM_{CC}	Amygdala	1.23 ± 0.06	1.21 ± 0.06	0.82	-1.38	2.72	1.28 ± 0.16	1.36 ± 0.12	6.3 ± 7.9
		Cerebellum	1.14 ± 0.14	1.13 ± 0.15	0.98	-1.56	2.60	1.19 ± 0.16	1.23 ± 0.13	4.5 ± 9.7
		Frontal Lobe	1.48 ± 0.11	1.45 ± 0.11	0.79	-1.90	5.10	1.58 ± 0.14	1.57 ± 0.14	-0.9 ± 6.1
Gyrus Cinguli		1.54 ± 0.11	1.51 ± 0.12	0.73	-2.37	5.89	1.61 ± 0.15	1.62 ± 0.14	0.4 ± 4.4	
Insula		1.38 ± 0.13	1.33 ± 0.10	0.64	-3.37	7.13	1.43 ± 0.12	1.44 ± 0.11	0.8 ± 5.2	
Occipital Lobe		1.44 ± 0.08	1.39 ± 0.09	0.79	-3.64	4.02	1.48 ± 0.17	1.51 ± 0.14	2.7 ± 8.7	
Parietal Lobe		1.45 ± 0.09	1.44 ± 0.11	0.68	-0.85	5.35	1.53 ± 0.12	1.53 ± 0.14	0.4 ± 6.4	
Striatum		1.19 ± 0.08	1.19 ± 0.08	0.52	-0.33	6.21	1.20 ± 0.08	1.25 ± 0.11	4.4 ± 6.5	
Temporal Lobe		1.39 ± 0.10	1.35 ± 0.11	0.81	-3.16	4.45	1.44 ± 0.14	1.48 ± 0.14	2.4 ± 6.0	
Thalamus		1.36 ± 0.10	1.37 ± 0.10	0.67	0.23	5.32	1.45 ± 0.18	1.49 ± 0.14	3.0 ± 5.4	
LREF_{CERWM}		Amygdala	1.13 ± 0.10	1.15 ± 0.10	0.92	1.94	3.20	1.13 ± 0.10	1.16 ± 0.07	2.7 ± 6.8
		Cerebellum	1.18 ± 0.03	1.18 ± 0.06	0.71	0.01	2.85	1.18 ± 0.02	1.17 ± 0.04	-0.3 ± 2.0
		Frontal Lobe	1.36 ± 0.07	1.36 ± 0.07	0.59	0.51	4.49	1.41 ± 0.25	1.33 ± 0.08	-4.5 ± 11.1
	Gyrus Cinguli	1.42 ± 0.10	1.43 ± 0.09	0.77	0.48	4.52	1.44 ± 0.16	1.39 ± 0.07	-2.9 ± 8.3	
	Insula	1.29 ± 0.09	1.29 ± 0.08	0.66	0.46	5.30	1.29 ± 0.11	1.26 ± 0.06	-2.1 ± 5.9	
	Occipital Lobe	1.34 ± 0.08	1.34 ± 0.07	0.76	-0.29	3.59	1.33 ± 0.07	1.32 ± 0.06	-1.1 ± 3.8	
	Parietal Lobe	1.36 ± 0.07	1.37 ± 0.07	0.65	1.14	4.35	1.38 ± 0.14	1.32 ± 0.06	-3.3 ± 8.2	
	Striatum	1.15 ± 0.11	1.17 ± 0.09	0.88	1.55	4.00	1.14 ± 0.12	1.12 ± 0.07	-1.4 ± 6.6	
	Temporal Lobe	1.27 ± 0.09	1.28 ± 0.08	0.79	0.18	4.50	1.28 ± 0.10	1.26 ± 0.08	-1.2 ± 6.6	
	Thalamus	1.30 ± 0.08	1.33 ± 0.08	0.73	2.09	4.06	1.35 ± 0.06	1.32 ± 0.06	-1.9 ± 6.1	
	SRTM_{CERWM}	Amygdala	1.14 ± 0.08	1.16 ± 0.09	0.92	2.13	2.82	1.14 ± 0.10	1.17 ± 0.09	3.0 ± 8.6
		Cerebellum	1.16 ± 0.03	1.15 ± 0.05	0.70	-0.63	2.62	1.15 ± 0.02	1.15 ± 0.04	-0.1 ± 2.1
		Frontal Lobe	1.39 ± 0.07	1.38 ± 0.10	0.79	-0.90	3.82	1.44 ± 0.25	1.35 ± 0.08	-4.9 ± 10.9
Gyrus Cinguli		1.45 ± 0.11	1.44 ± 0.12	0.87	-0.58	3.93	1.46 ± 0.16	1.40 ± 0.07	-3.6 ± 8.0	
Insula		1.30 ± 0.09	1.30 ± 0.09	0.74	-0.50	5.02	1.31 ± 0.11	1.27 ± 0.06	-2.6 ± 6.2	
Occipital Lobe		1.36 ± 0.08	1.34 ± 0.09	0.81	-1.63	3.83	1.34 ± 0.07	1.33 ± 0.07	-1.4 ± 3.8	
Parietal Lobe		1.38 ± 0.08	1.38 ± 0.10	0.78	-0.02	4.03	1.40 ± 0.15	1.34 ± 0.07	-3.7 ± 8.1	
Striatum		1.17 ± 0.10	1.18 ± 0.09	0.87	0.92	4.19	1.17 ± 0.10	1.14 ± 0.06	-1.7 ± 6.5	
Temporal Lobe		1.30 ± 0.10	1.29 ± 0.11	0.87	-1.23	4.15	1.30 ± 0.10	1.28 ± 0.08	-1.6 ± 6.4	
Thalamus		1.30 ± 0.08	1.32 ± 0.10	0.80	1.22	4.03	1.34 ± 0.06	1.32 ± 0.06	-1.9 ± 5.7	

Data are presented as mean values (± SD). Data in bold indicate significant differences between sessions ($p < 0.05$).

variability was slightly higher, ranging from 4.7% (cerebellum) to 7.9% (frontal lobe) with the *LREF*. Using the CERWM as reference region, the test-retest DVR variability ranged from 2.8% (cerebellum) to 5.3% (insula) with the *LREF* and from 2.6% (cerebellum) to 5% (insula) with the *SRTM*. The mean bias across all ROIs was trivial (< 4%). Of note, using *SRTM* method, the R1 parameter in any ROI was not significantly different between test and retest using the CC or the CERWM as reference tissue ($p = 1$ and $p = 0.97$ respectively).

3.5. Challenge study

There were no significant differences between test and challenge scans in neither the amount of injected radioactivity (Scan 1: 362 ± 14

MBq; Scan 2: 370 ± 13 MBq; $Student_{t_6} = -0.98$; $p = 0.367$) nor the molecular activity of [¹¹C]yohimbine (Scan 1: 27.7 ± 10.9 GBq/ μ mol; Scan 2: 25.3 ± 7.4 GBq/ μ mol; $Student_{t_6} = 0.47$; $p = 0.652$). The mean systolic and diastolic arterial blood pressures were 120 and 76 mmHg, respectively at the time of administration. Ninety minutes after administration, clonidine produced a transient 24% decrease only in the mean diastolic blood pressure ($\chi^2(6)=17.81$, $p = 0.007$). This effect of clonidine on the cardiovascular system is in good agreement with the literature (Talke et al., 2001). At the anatomical regional level, results of the challenge study are given in Table 4 (right part). Significant increase of DVR in the challenge compared to the baseline condition was only observed in the amygdala (+6%) and striatum (+4%) with *SRTM_{CC}*. Im-

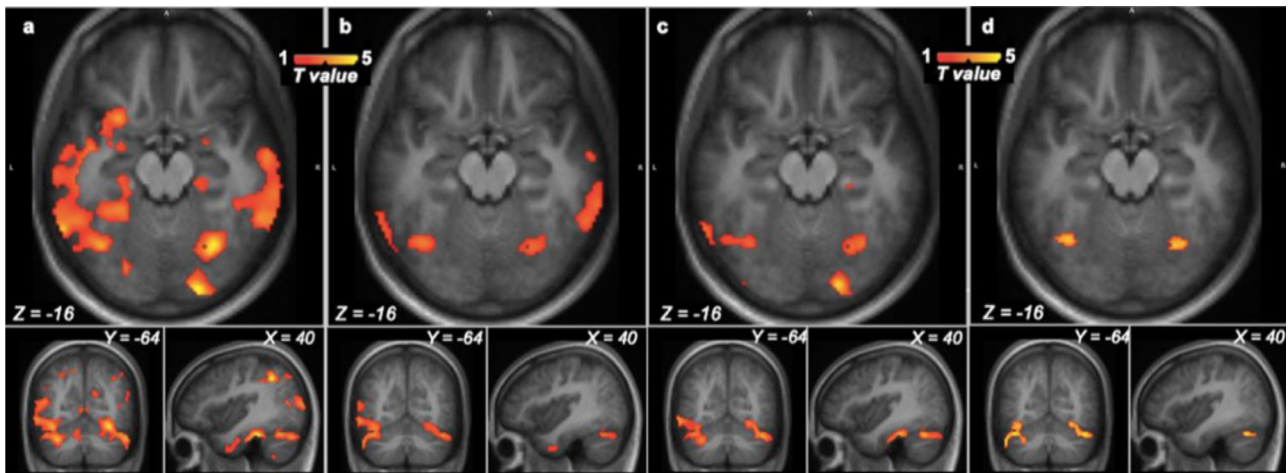


Fig. 3. MRI overlaid with t-statistic maps comparing DVR values with CC as reference region and *SRTM* method (a), *LREF* method (b), and with CERWM as reference region and *SRTM* method (c), *LREF* method (d) and obtained from SPM comparing test and challenge minus test and retest studies using height threshold of $P < 0.05$ uncorrected at the voxel level and an extent voxels threshold the “Expected number of voxel per cluster” (246, 427, 260 and 294 voxels respectively for (a), (b) (c) and (d) maps).

portantly, using *SRTM* method, the R_1 parameter in any ROI was not significantly different between test and challenge using the CC or the CERWM as reference tissue ($p = 0.99$ and $p = 0.91$ respectively).

3.5.1. Statistical parametric mapping

Statistical parametric maps present the results of the comparison between challenge and test conditions, for the challenge group, with respect to the same comparison in test-retest control group (t contrast of condition effect: $(DVR_2 - DVR_1)_{\text{challenge}} - (DVR_2 - DVR_1)_{\text{control}}$). Fig. 3 shows the thresholded maps for the *SRTM*_{CC} (3a), the *LREF*_{CC} (3b), and the *SRTM*_{CERWM} (3c), and the *LREF*_{CERWM} (3d).

Table 5 gives the cluster parameters that elicited differences according to the parametric imaging method (*SRTM* or *LREF*) and the reference region (CC or CERWM). Using *SRTM* and the CC, two clusters showed significant activities including bilaterally the temporal and occipital fusiform gyrus, the cerebellum, the lateral part of the occipital cortex, the middle temporal gyrus, as well as the right occipital pole, inferior temporal gyrus and angular gyrus. Same contrast with *SRTM* and the CERWM reference region or with the *LREF* model did not show any significant cluster. Yet, these contrasts showed activities mainly located in the posterior part of the brain encompassing the temporal and occipital cortex as well as the cerebellum, as observed significantly using the *SRTM*_{CC} imaging method.

4. Discussion

The regional distribution of [¹¹C]yohimbine binding corresponds with the known distribution of α_2 -ARs in post mortem human brain studies (Ordway et al., 1993; Vos et al., 1992). The most prominent uptake of the tracer was seen in cortical brain regions, especially in the cingulum, frontal, parietal and occipital cortices whereas uptake was less prominent in the striatum and the cerebellum (Fig. 4).

4.1. The kinetic modeling study

In order to evaluate a reliable and suitable method for α_2 -ARs quantification, we compared various invasive and non-invasive models, often used for brain receptor quantification.

Using invasive models and direct fitting of the PET kinetics with tissue compartmental model and AIF, the 1-TCM was found to be sufficient for describing the tracer kinetics of [¹¹C]yohimbine in the healthy human brain (Nahimi et al., 2015). Testing the LGA alternative to 1-TCM as a simpler resolution method from an algorithmic point of view led to

results quite similar despite a very limited higher V_T values found with LGA (around 12%). This might be attributed to the fact that blood volume, V_b , is not taken into account in LGA model. However, since V_b is fairly stable over the regions, this overestimation does not exclude the use of LGA as an alternative method to 1-TCM for a reliable estimate of the volume of distribution.

With non-invasive models, our findings show, for the first time, the feasibility of using a simple acquisition protocol for kinetic modeling avoiding arterial blood sampling. In particular, DVR estimated using non-invasive kinetic models (*LREF* and *SRTM*) showed an excellent correlation to the invasive 1-TCM whatever the reference region (CC, CERWM or FLWM) with the best fit obtained for *SRTM*_{CC} ($R^2=0.94$). Of note, the results indicated a slight tendency toward an overestimation with CC (slope equal to 1.07 using *LREF* and 1.13 with *SRTM*). However, since the correlation with the 1-TCM is excellent and stable across brain regions, the induced bias can be predicted and should not have an impact on comparative studies. In parallel, tendency toward a slight underestimation was reported with CERWM and FLWM, which was more pronounced with *SRTM* (slope equal to 0.81 and 0.94 respectively) than *LREF* (slope equal to 0.94 and 0.98 respectively). Using reference tissue methods with cerebral regions, underestimation of DVR values can be explained by a possible specific binding within the reference region as well as spill-over effect (Salinas et al., 2015). Nonetheless, CERWM or FLWM are valuable reference regions in the event of the impossibility of using the CC due to lesion of this zone in a patient, for instance.

4.2. Test-Retest reproducibility

In addition to the accuracy of the reference tissue methods, we evaluated their test-retest performance. Using FLWM as reference region, our results showed poor test-retest reliability of DVR measurements with both parametric imaging methods. However, the *SRTM* with the CERWM as reference region showed excellent test-retest reproducibility of DVR measurements, with variability ranging from 2.6% to 5.0% and a small negative bias (−0.1%). Using the *SRTM* with the CC, test-retest reproducibility of DVR measurements were a bit more spread, with a slightly higher variability ranging from 2.6% to 7.0% and a slightly higher negative bias (2%). Of importance, whatever the reference region, R_1 values, also computed with *SRTM*, did not differ between test and retest across all ROIs. In addition, the *LREF* method showed comparable very good test-retest reliability of DVR measurements (ICC=0.75) for both reference region with a slightly lower variability when using the CERWM (~ 4%) compared to the CC (~ 6%). This demonstration of

Table 5
Increase of [¹¹C]yohimbine induced by clonidine administration compared to baseline (SPM analysis).

Areas	BA	Side	MNI coordinates			T value	P corr cluster	Cluster size
			x	y	z			
<i>SRTM_{CC}</i>								
Posterior Temporal Fusiform Cortex	20	R	42	-34	-26	6.28	0.001	6944
Cerebellum_VI	-	R	26	-48	-30	5.93		
Occipital Pole	18	R	20	-92	-16	5.14		
Angular Gyrus	40	R	38	-50	42	5.01		
Inferior Temporal Gyrus	20	R	64	-40	-20	4.91		
Occipital Fusiform Gyrus	19	R	30	-64	-16	4.67		
Cerebellum_Crus 1	-	R	56	-68	-32	4.64		
Lateral Occipital Cortex	19	R	28	-74	26	3.99		
Middle Temporal Gyrus	20	R	68	-24	-24	3.91		
Middle Temporal Gyrus	37	L	-60	-56	-12	6.15		
Temporal Occipital Fusiform Cortex	37	L	-32	-46	-12	5.84		
Lateral Occipital Cortex	19	L	-46	-84	12	5.55		
Cerebellum_VI	-	L	-28	-40	-30	4.51		
Cerebellum_V	-	L	-22	-36	-30	4.43		
Lateral Occipital Cortex	19	L	-52	-76	-2	4.24		
Cerebellum_Crus 1	-	L	-38	-66	-28	4.19		
Cerebellum_VIIb	-	L	-20	-76	-52	4.17		
Occipital Fusiform Gyrus	19	L	-38	-66	-18	3.99		
Amygdala	-	R	26	-4	-20	3.46	0.970	271
Parahippocampal Gyrus	36	R	26	-16	-22	3.03		
<i>LREF_{CC}</i>								
Inferior Temporal Gyrus	20	R	64	-40	-20	4.71	0.979	710
Middle Temporal Gyrus	21	R	60	-10	-20	2.61		
Lateral Occipital Cortex	19	L	-50	-76	-4	4.44	0.979	1197
Lateral Occipital Cortex	19	L	-48	-82	10	4.31		
Middle Temporal Gyrus	37	L	-60	-58	-10	3.93		
Cerebellum_Crus 1	-	L	-40	-66	-26	3.83		
Occipital Fusiform Gyrus	37	L	-38	-64	-18	3.13		
Cerebellum_Crus 1	-	R	44	-62	-26	3.32	0.979	556
Lateral Occipital Cortex	19	R	26	-66	-16	2.67		
Cerebellum_VI	-	R	34	-64	-20	2.49		
Cerebellum_Crus 1	-	R	34	-74	-26	2.34		
<i>SRTM_{CERWM}</i>								
Middle Temporal Gyrus	37	L	-60	-58	-12	4.72	0.714	1718
Lateral Occipital Cortex	19	L	-46	-84	12	4.46		
Cerebellum_VIIb	-	L	-22	-70	-52	3.44		
Lateral Occipital Cortex	19	L	-52	-72	-2	3.44		
Cerebellum_Crus 1	-	L	-40	-62	-24	3.24		
Occipital Pole	18	R	18	-90	-14	4.59	0.971	1084
Cerebellum_Crus 1	-	R	44	-60	-28	4.55		
Cerebellum_Crus 1	-	R	32	-72	-28	3.19		
Lateral Occipital Cortex	19	R	26	-64	-12	3.07		
Posterior Temporal Fusiform Cortex	20	R	42	-34	-26	4.59	0.971	284
Fusiform Gyrus	20	R	32	-30	-26	3.60		
<i>LREF_{CERWM}</i>								
Cerebellum_Crus 1	-	L	-52	-66	-34	3.38	0.973	320
Cerebellum_Crus 1	-	L	-40	-66	-26	3.08		
Temporal Occipital Fusiform Cortex	37	L	-36	-62	-16	2.52		
Cerebellum_Crus 1	-	R	42	-62	-26	3.18	0.973	332
Lateral Occipital Cortex	19	R	26	-66	-14	2.96		
Cerebellum_VI	-	R	34	-64	-24	2.50		

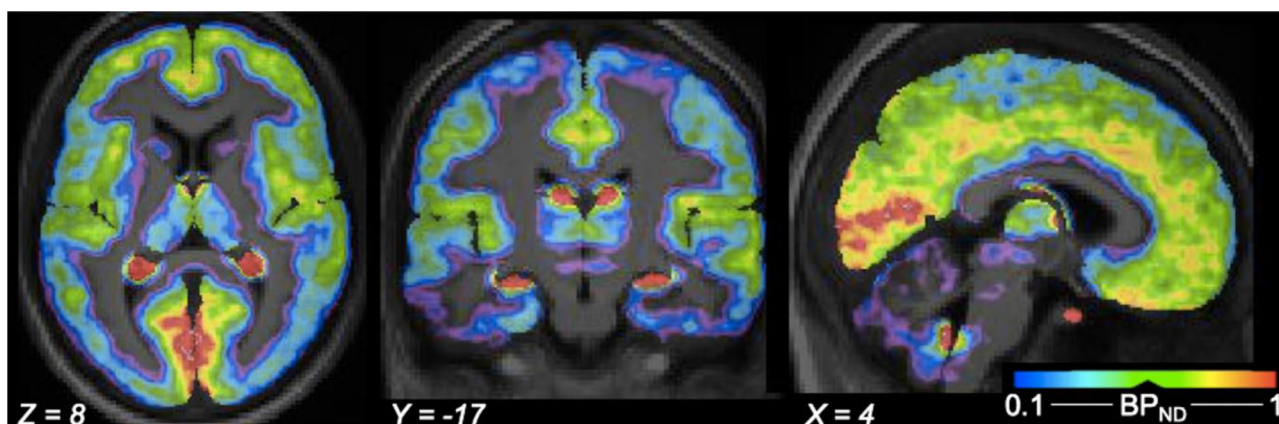


Fig. 4. Average parametric images of BP_{ND} values estimated with CC as reference region and *SRTM* method overlaid on the mean MRI images of the 14 participants during the first scan. Color bar gives estimates of BP_{ND} in units of $mL.cm^{-3}$.

a reproducible [^{11}C]yohimbine PET outcome measure using CERWM or CC is critical for further clinical investigations in larger studies.

4.3. Challenge study

So far, very limited evidence has been presented to support PET imaging of noradrenaline neurotransmission in humans. The brain uptake and receptor binding of [^{11}C]yohimbine was found to be reduced by unlabeled yohimbine challenge, amphetamine administration or by acute vagus nerve stimulation in rats and/or Landrace pig brain (Jakobsen et al., 2006; Landau et al., 2015, 2012; Phan et al., 2017, 2015).

In our study, regional analyses showed significant regional change induced by the challenge with clonidine within the amygdala and the striatum, only when using the *SRTM* with the CC as reference region. In parallel, we conducted a voxel-based analysis as this latter has several advantages over the ROI-based approach, including the use of SPM to identify alterations in receptor binding in all brain areas without anatomical *a priori*. Interestingly, the voxel-based analysis showed changes that were not discernable with the ROIs analysis, where delineation of regions is deterministic and based on anatomo-functional considerations. In particular, statistical parametric maps of [^{11}C]yohimbine binding under clonidine administration showed significant specific increases in the posterior part of the brain including the temporal and occipital lobes, as well as the cerebellum. However, this increase was again reported only when using *SRTM* with the CC as reference region. Overall, the pattern of increased [^{11}C]yohimbine uptake observed with this voxel-based analysis is consistent with previous studies demonstrating that α 2-ARs agonists changed regional cerebral blood flow (CBF) in posterior cortical regions including the cerebellum, the temporal cortex and the angular gyrus (Bonhomme et al., 2008; Fu et al., 2001). This increase in [^{11}C]yohimbine binding is likely the consequence of clonidine acting at presynaptic α 2-ARs sites resulting in reduced noradrenergic neurotransmission (Dennis et al., 1987; Starke, 1981) and leading to a state of low tonic arousal. Indeed, all of our volunteers reported that time spent in the scanner during the challenge condition had seemed shorter than during the first baseline scan. Considering the known effect of clonidine on vigilance (Coull et al., 2004; Hall et al., 2001), we can reasonably assume that our participants had a low level of consciousness during the challenge scan. Interestingly, many studies have previously highlighted the role of a posterior network in the deleterious effect of clonidine on attention and arousal (Bonhomme et al., 2008; Coull et al., 2004; Fu et al., 2001). In particular, the results of the present study reinforce the nonmotor role of the cerebellum (Strick et al., 2009) through α 2-ARs modulation (Schambra et al., 2005) as well as the role of the fusiform gyrus and lateral occipital cortex in attention (Tallon-Baudry et al., 2005).

4.4. Limitations of the study

There are some limitations in this study that has to be mentioned. First, the experimental design did not provide for arterial blood sampling during the second scan session. In fact, the first objective of the present study was to validate the use of a simplified reference tissue model, and the second objective was to assess both the reproducibility and the sensitivity of [^{11}C]yohimbine PET measurements estimated with this simplified modeling method. To this end, we limited the use of the invasive sampling of arterial blood only to the first scan in order not to lose volunteers for the second scan who might not want to repeat this unpleasant experience. Yet, it would have made sense to have arterial input in the clonidine challenge to evaluate the impact of the challenge on peripheral metabolism, if any, as well as to quantify the true volume of non-displaceable volume of distribution in the potential reference regions. This point would merit further investigations. Then, another shortcoming is the proportion of clonidine that binds to plasma protein. Indeed, free plasma fraction can change upon pharmacological

challenge due to displacement of ligand binding to plasma proteins. For instance, Phan et al. (2017) have shown an elevation of *fp* in response to challenge with unlabeled yohimbine. However, it has to be highlighted that the bound fraction of yohimbine to plasma proteins is around 80% (Berlan et al., 1993) while this bound fraction for clonidine is reported to be of 20% (Khan et al., 1999). Although we cannot completely rule out the possibility of a change of *fp* upon clonidine challenge, we believe this is very unlikely since the reported protein binding is relatively low. Indeed, within the same range (around 20%, (de la Torre et al., 2004) no change of *fp* has been observed with amphetamine challenge (Phan et al., 2015). In the same vein, the potential effects of clonidine on CBF should also be considered. Since [^{11}C]yohimbine was administered as a systemic bolus, potential changes in CBF might affect the kinetics of the tracer in the brain and influence its binding. In humans, clonidine is known to decrease blood pressure and reduce CBF (James et al., 1970; Lee et al., 1997). In our study, administration of clonidine produced a transient 26% decrease in mean diastolic arterial blood pressure. A clonidine-induced decrease in CBF could decrease the delivery of the tracer, which would induce a smaller *V_t*, therefore an underestimation of the clonidine-induced increase in α 2-ARs binding. In other terms, the effect of clonidine in the present study, might have been underestimated. Finally, the results of the present study cannot completely rule out a possible effect of genotype (see supplementary materials). Further studies are needed to confirm this observation. In the meantime, the authors recommend to genotype volunteers for the cytochrome P450 system with regard to the CYP2D6 isoform if between groups comparisons have to be performed.

Conclusion

Our results support the use of [^{11}C]yohimbine PET in the in vivo assessment of human brain α 2-ARs. Rapid tracer uptake associated with low test-retest variability and good reproducibility was demonstrated in the regions with the highest densities of the α 2-ARs. In particular, the authors recommend the use of [^{11}C]yohimbine parametric imaging of DVR by non-invasive *SRTM* using the CC as reference tissue for imaging α 2-ARs. This method was able to evidence moderate occupancy with concurrent drug on α 2-ARs. Alternatively, CERWM might be considered when measurements in the CC would not be reliable for structural or lesional reason. In other terms, simplified imaging protocols can be used for reliable [^{11}C]yohimbine PET quantification which opens the possibility to investigate, in large human samples, the role of α 2-ARs in various neuropsychiatric disorders including schizophrenia, depression, Parkinson's disease and Alzheimer's disease.

Declaration of Competing Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Data/code availability statement

Public access to the data online is not permitted without the approval of the study's sponsor namely the Hospices Civils de Lyon (Protocol ID 69HCL17_0196). The authors will be happy to support request for a formal data sharing agreement.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2021.118328](https://doi.org/10.1016/j.neuroimage.2021.118328).

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Chapitre 6. Les altérations noradrénergiques dans la maladie de Parkinson : une approche TEP/IRM combinée

Fort de nos résultats sur le développement méthodologique, nous avons mis en œuvre une étude permettant d'étudier pour la première fois *in vivo* le rôle du système noradrénergique dans la MP.

Nous avons inclus 30 patients parkinsoniens et 30 témoins (appariés en âge et sexe). Chaque participant a passé une acquisition IRM/TEP à la ^{11}C -Yohimbine. Dans cette étude, nous avons en effet choisi d'utiliser la technologie d'imagerie bimodale IRM/TEP. Ce système hybride fournit simultanément une information fonctionnelle et structurale avec une bonne performance en résolution spatiale. De plus, il était crucial d'acquérir en même temps les données moléculaires (TEP, disponibilité des récepteurs α_2) et les données structurales (IRM) notamment pour nos études ultérieures sur l'IRM fonctionnelle (afin d'éviter les problèmes liés aux différences dans l'état d'excitation des participants permettant ainsi une investigation appropriée sur la relation entre ces variables). Ici, l'un des objectifs de cette étude était d'examiner, pour la première fois, si des changements structurels dans le LC étaient fonctionnellement liés à la perte des récepteurs α_2 dans la MP. Plus particulièrement, l'imagerie cérébrale en TEP avec la ^{11}C -Yohimbine nous a permis pour la première fois d'évaluer la vulnérabilité des récepteurs α_2 dans la MP. En parallèle, nous avons cherché à déterminer si des changements du système noradrénergique liés à la MP étaient corrélés à des changements dans les habiletés cognitives, motrices et/ou olfactives. L'IRM cérébrale nous a permis de comprendre le lien entre une altération de l'intégrité du LC et de la symptomatologie parkinsonienne. Nous ne présentons pas toutes ces données dans l'article qui suit. Il nous reste beaucoup de données à analyser que ce soit au niveau du bilan neuropsychologique, du bilan olfactif ou des échelles non motrices que nous avons recueillies et cela fera l'objet de prochains articles qui se focaliseront davantage sur les signes non moteurs de la MP grâce à des échelles cliniques dédiées, comme pour l'étude plus précise des liens avec l'anxiété notamment.

Ici nous montrons que les patients parkinsoniens présentent une réduction de l'intensité du signal de la neuromélanine dans le LC, corrélée à des symptômes moteurs (bradykinésie, fluctuations motrices) et non moteurs (fatigue, apathie, constipation). Les patients présentent également une diminution de fixation du traceur ^{11}C -Yohimbine dans des régions corticales étendues, notamment le cortex moteur, ainsi que dans l'insula, le putamen et le thalamus. Une

diminution de fixation du traceur dans le thalamus était associée aux tremblements tandis que l'anxiété était associée à une diminution dans le putamen, l'insula et le gyrus temporal supérieur. Nous montrons que l'atteinte noradrénergique est profonde et étendue dans la MP.

Noradrenergic alterations in Parkinson's disease: a combined ^{11}C -yohimbine PET/neuromelanin MRI study

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Abstract

Degeneration of the noradrenergic system is now considered a pathological hallmark of Parkinson's disease but little is known about its consequences in terms of parkinsonian manifestations. Here, we evaluate two aspects of the noradrenergic system using multimodal in vivo imaging in patients with Parkinson's disease and healthy controls: the pigmented cell bodies of the locus coeruleus with neuromelanin sensitive MRI and the density of $\alpha 2$ -adrenergic receptors (ARs) with PET using [^{11}C]yohimbine. Thirty patients with Parkinson's disease and thirty age- and sex-matched healthy control subjects were included. Patient's symptoms characteristics were assessed using the MDS-UPDRS scale. Patients showed reduced neuromelanin signal intensity in the locus coeruleus compared to controls, and diminished [^{11}C]yohimbine binding in widespread cortical regions including the motor cortex as well as in the insula, the thalamus and the putamen. Clinically, locus coeruleus neuronal loss was correlated with motor (bradykinesia, motor fluctuations, tremor) and non-motor (fatigue, apathy, constipation) symptoms. A reduction of $\alpha 2$ -ARs availability in the thalamus was associated with tremor, while a reduction in the putamen, the insula and the superior temporal gyrus was associated with anxiety. These findings highlight a multifaceted alteration of the noradrenergic system in Parkinson's disease since locus coeruleus and $\alpha 2$ -ARs degenerations were found to be partly uncoupled. These findings raise important issues about noradrenergic dysfunctions that may encourage the search for new drugs targeting this system, including $\alpha 2$ -ARs, for the treatment of Parkinson's disease.

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15 **Running title:** Noradrenergic parkinsonian alterations

16

17 **Keywords:** Parkinson's disease; Noradrenaline; PET/MRI; locus coeruleus; α 2-adrenergic
18 receptors

19 **Abbreviations:** ARs = adrenergic receptors; BP_{ND} = non-displaceable binding potential; CNR =
20 contrast-to-noise ratio; FSL = FMRIB Software Library; FWE = family-wise error; LC = locus
21 coeruleus; LEDD = levodopa equivalent daily doses; MDS = Movement Disorder Society; MNI
22 = Montreal Neurological Institute; MoCA = Montreal Cognitive Assessment; PDQ-39 = 39-item
23 Parkinson's Disease Questionnaire; ROI = region of interest; TSE = turbo spin-echo; UPDRS =
24 Unified Parkinson's disease Rating Scale; VBM = voxel-based morphometry

25

1 Introduction

2 Parkinson's disease is mostly characterized by the loss of dopaminergic neurons in the substantia
3 nigra pars compacta. However, the neurodegenerative process also extends to other
4 neurotransmission systems such as serotonin, or acetylcholine and noradrenaline, which
5 contribute to motor and non-motor symptoms.¹⁻⁴ The modulation and interactions of the complex
6 interconnected non-dopaminergic networks with dopaminergic circuits are far from being fully
7 understood, and the cascade of perturbations in these interconnected systems and associated
8 circuits is still a central issue. Among these neurotransmitters, the noradrenergic system is
9 probably the most least well known.^{5,6-8}

10 Firstly, the direct role of the noradrenergic system in various cognitive functions is well
11 documented.⁹ This includes specific functions like vigilance, attention and executive control, but
12 also more transversal functions like learning, cognitive flexibility and working memory,⁸ or an
13 even more general role in adaptive adjustments in gain that serve to optimize performance.¹⁰ It is
14 important to point out that there is a major gap in our understanding of how these modulations
15 apply to the motor circuits.¹¹ The alteration of these functions might thus contribute to various
16 parkinsonian manifestations.⁸ However, it is often under-recognized and its association with
17 specific symptoms, in particular with the motor manifestations of the disease, is still unclear.
18 Secondly, the effect of noradrenergic dysfunction in the manifestations of the disease might also
19 be related to its antiparkinsonian and neuroprotective properties.¹² The loss of noradrenergic
20 neurons in the locus coeruleus (LC), the sole source of noradrenaline to the neocortex,
21 hippocampus, cerebellum and thalamus (¹³ for review) which is estimated between 20 and 90%,
22 precedes and exceeds the characteristic loss of dopaminergic neurons in the substantia nigra.¹⁴
23 There is evidence mainly based on animal studies that noradrenergic loss may enhance
24 neurotoxic damage to nigrostriatal dopaminergic neurons,^{15,16} and that, conversely, restoration of
25 LC damaged system positively influences the recovery process of degenerated dopaminergic
26 neurons.^{17,18} Taken together, these observations suggest that enhancing noradrenergic
27 neurotransmission may facilitate both specific functions affected by the disease and the recovery
28 process of dopaminergic neurons.¹⁹ Yet, therapeutic strategies targeting this system in
29 Parkinson's disease are still currently limited.^{7,20}

1 The use of $\alpha 2$ -adrenergic receptors (ARs) antagonists has recently been considered as a major
2 possible target²¹ as it might potentiate noradrenaline availability by blocking presynaptic $\alpha 2$ -ARs
3 whose normal function is to regulate noradrenaline release.^{22–24} However, direct *in vivo* evidence
4 of alteration of $\alpha 2$ -ARs in parkinsonian manifestations is still lacking. This critical lack of
5 knowledge, accompanied by substantial controversies on the neurofunctional bases of the
6 noradrenergic system and its alteration in Parkinson's disease,^{25,26} is mainly due to the lack of
7 specific *in vivo* molecular imaging tools in humans. To date, *in vivo* imaging studies have only
8 used presynaptic noradrenergic tracers of the noradrenergic transporter with [¹¹C]MeNER. These
9 studies have shown reduced tracer uptake, suggesting a diminished density of noradrenergic
10 terminals, mainly in the thalamus, hypothalamus, LC and raphe nuclei.^{2,27} Regarding $\alpha 2$ -ARs,
11 most of our knowledge derives from animal studies or post-mortem samples of human brains.^{28,29}
12 Autoradiography studies suggest an alteration in $\alpha 2$ -ARs in different brain regions (thalamus,³⁰
13 cerebellum,³¹ hypothalamus,³² and prefrontal cortex³³). Here, we take advantage of recent
14 methodological developments allowing *in vivo* imaging of the noradrenergic system in human
15 with the novel PET radiotracer [¹¹C]yohimbine,^{34–36} now available for use in large samples of
16 human subjects to map differences in $\alpha 2$ -ARs distribution between parkinsonian patients and
17 matched controls. The [¹¹C]yohimbine binds with high selectivity to all $\alpha 2$ -ARs subtypes.³⁷ It is
18 displaced when there is competition at the receptor with endogenous noradrenaline, as shown by
19 preclinical studies reporting reduced receptor binding by unlabeled yohimbine challenge,
20 amphetamine administration or acute vagus nerve stimulation in preclinical studies^{37–39} and
21 human studies reporting increased receptor binding after clonidine administration.³⁴

22 The objectives of the present study are to assess two aspects of noradrenergic neurodegeneration
23 in Parkinson's disease by means of hybrid MRI/PET imaging: lesions of pigmented cell bodies
24 of the LC with neuromelanin-sensitive MRI and alterations of $\alpha 2$ -ARs density with
25 [¹¹C]yohimbine PET. Assessing simultaneously noradrenergic terminals (with PET) and LC cell
26 bodies (with MRI) is of primary importance given that their respective deficits may be
27 uncoupled.⁴⁰ To inform the disputed pathophysiological mechanisms of the disease, correlations
28 between the observed noradrenergic dysfunctions and the standard clinical measures of
29 Parkinson's disease have been systematically tested.

30

1 **Materials and methods**

2 **Participants**

3 The demographics and clinical characteristics of the participants are listed in Table 1. We
4 enrolled 30 Parkinson's disease patients and 30 healthy controls matched for age, gender, and
5 global cognitive functioning using the Montreal Cognitive Assessment (MoCA) score. Patients
6 were diagnosed with Parkinson's disease for at least 1 year in accordance with the Movement
7 Disorder Society criteria.⁴¹ The Movement Disorder Society Revised Unified Parkinson's
8 Disease Rating Scale (MDS-UPDRS) was used to assess Parkinson's disease symptoms,
9 including separate assessments of non-motor symptoms (UPDRS-I), daily activity (UPDRS-II),
10 motor symptoms (UPDRS-III), and motor complications (UPDRS-IV).⁴² In addition, the 39-item
11 Parkinson's Disease Questionnaire (PDQ-39) was used to evaluate quality of life.⁴³ All patients
12 were assessed in the "ON" state with their usual antiparkinsonian medication. Levodopa
13 equivalent daily dose (LEDD) was calculated according to previously published conversion
14 rules.⁴⁴ Most of the patients with PD were in the early and middle stage of their disease with a
15 mean Hoehn & Yahr score of 1.8 and MDS-UPDRS-III score in the "on" state of 17.7 (± 12.3).
16 Exclusion criteria were medications that interfere with the noradrenergic system, a diagnosis of
17 other neurological or psychiatric disorders, and the presence of major dyskinesia or tremor in the
18 patients for technical imaging purposes. The study was conducted in accordance with the
19 Declaration of Helsinki and approved by the local Ethical Committee in Biomedical Research
20 (N^o CPP 19_01_02/N^o EudraCT 2018-003999-13). Written informed consent was obtained from
21 all the subjects before the study.

22 **Magnetic Resonance Imaging**

23 MRI data were acquired on a Biograph mMR (hybrid MRI/PET) including a whole brain high-
24 resolution anatomical 3D T1-weighted MPRAGE sequence in the sagittal plane (matrix size 256
25 $\times 256 \times 176$, voxel size $1 \times 1 \times 1 \text{ mm}^3$), and a 2D axial turbo spin-echo (TSE) sequence (in plane
26 resolution $0.4 \times 0.4 \text{ mm}^2$, slice thickness 3 mm, matrix size $464 \times 512 \times 15$) which provided a
27 neuromelanin-sensitive MRI.

1 **Voxel-based morphometry analysis**

2 To exclude the possibility that structural degeneration affects the results of [¹¹C]yohimbine
3 binding, voxel-based morphometry (VBM) analysis was conducted. Standard VBM
4 preprocessing protocol of the Computational Anatomy Toolbox (CAT12, [http://www.neuro.uni-](http://www.neuro.uni-jena.de/cat/)
5 [jena.de/cat/](http://www.neuro.uni-jena.de/cat/)) running on Statistical Parametric Mapping (SPM12; Welcome Trust Centre for
6 Neuroimaging, University College, London, UK) was employed. Briefly, each 3D T1-weighted
7 image was bias-corrected and segmented into grey matter, white matter and cerebrospinal fluid
8 tissue classes using SPM's unified segmentation function. The grey matter segmentation
9 probability maps were spatially transformed to the Montreal Neurological Institute (MNI)
10 standard space using the ICBM-152 template according to the DARTEL approach with default
11 settings in 1.5 mm cubic resolution, and then smoothed with a Gaussian kernel of 8 mm full-
12 width-at-half-maximum. Lastly, to correct for individual differences in brain size, the Total
13 Intracranial Volume (TIV) was estimated for each subject using CAT12 interface (Statistical
14 Analyses – Estimate TIV), as the sum of the grey matter, white matter, and CSF volumes.

15 **Neuromelanin-sensitive MRI analysis**

16 To calculate signal intensity in the LC, an approach similar to that published by García-Lorenzo
17 and colleagues⁶ was implemented. First, two regions were manually drawn on the T1 MRI high
18 resolution MNI template using FSLEyes (FSL v5.0.11, FMRIB, Oxford, UK). These two regions
19 (one for each side) were defined as large 3D bounding boxes and placed around the hyperintense
20 voxels at the lateral border of the fourth ventricle so that they included the LC, but excluded the
21 substantia nigra which also contains neuromelanin.⁴⁵ In addition, we used the central reference
22 mask freely available to normalize the intensity of the LC.⁴⁶ These three regions were then
23 wrapped and resampled onto the subject's neuromelanin-sensitive T1 image using SPM12. Using
24 FSL functions, the LC was defined as the area of the 10 voxels with the brightest intensity within
25 each bounding box. We considered the intensity of the LC as the average of the intensities of the
26 10 voxel region (Fig. 1). The contrast-to-noise ratio (CNR) was calculated for each LC (right and
27 left) as $CNR_{LC} = (S_{LC} - S_{REF}) / S_{REF}$ where S_{LC} and S_{REF} correspond to the mean signal intensity of
28 the LC and the reference region respectively. Normalization of the LC signal to a central
29 reference region (pons) to calculate the CR by relative difference has been the most commonly
30 used and recommended method in previous studies.⁴⁷

1 **[¹¹C]yohimbine PET**

2 Radiosynthesis of [¹¹C]yohimbine was performed as previously described.³⁷ The radiochemical
3 purities of syntheses used for the study were greater than 95%, with molar activities of 85 ± 30
4 GBq/μmol at the end of synthesis. All subjects received an intravenous bolus injection of 370
5 MBq ± 10% of [¹¹C]yohimbine. List-mode PET data were acquired during the 90 min from the
6 injection of the tracer. MRI data were acquired simultaneously.

7 Raw PET data were corrected for motion,⁴⁸ and then rebinned into 24 time frames (variable
8 length frames, 8 × 15 s, 3 × 60 s, 5 × 120 s, 1 × 300 s, 7 × 600 s) sinograms for dynamic
9 reconstruction. Sinograms were corrected for scatter, randoms, normalization, and attenuation.⁴⁹
10 Images were reconstructed using 3D ordinary Poisson-ordered subsets expectation maximization
11 (OP-OSEM 3D), incorporating the system point spread function using 3 iterations of 21 subsets.
12 Reconstructions were performed with a zoom of 2 in a matrix of 172 × 172 voxels, yielding a
13 voxel size of 2.03 × 2.03 × 2.08 mm³, with a 4 mm 3D post-reconstruction Gaussian filtering.
14 Regional time activity curves were extracted based on labelling of structural brain regions
15 obtained with the multi-atlas propagation with enhanced registration methodology (MAPER)⁵⁰
16 and the 83-region Hammers atlas.⁵¹ [¹¹C]yohimbine non-displaceable binding potential (BP_{ND})
17 parametric maps were then generated using the simplified reference tissue model (SRTM), with
18 the corpus callosum as reference region.³⁴ PET parametric images were spatially normalized to
19 the MNI space with parameters derived from the individual T1 MRI.

20 **Statistics**

21 Statistical analyses on demographic data were performed using Rstudio
22 (<https://github.com/rstudio/rstudio>). All data were tested for normal distribution using the
23 Shapiro-Wilk test and the Levene test for homogeneity of variance. Independent samples t-tests
24 or Wilcoxon tests, as appropriate, were used to compare demographics group mean differences.
25 We assessed group differences in the CNR_{LC} with an analysis of covariance accounting for age
26 and sex as covariates. A two-tailed t-test was generated in the SPM12 toolbox to assess between-
27 group differences on grey matter concentration using family-wise error (FWE) correction with *p*
28 < 0.05 threshold. The extend threshold was set to 100 voxels and total intracranial volume was
29 used as covariate of no interest.

1 SPM12 in Matlab2020a was used for between-group comparisons of [¹¹C]yohimbine BP_{ND} at the
2 voxel level (2-sample t-test) controlling for age and gender. Spatially normalized parametric
3 images were smoothed with an 8-mm Gaussian filter, and an average cortical grey-matter mask
4 was used for explicit masking within the SPM software. The voxel-level analysis threshold was p
5 < 0.001 (uncorrected), and subsequently a FWE cluster-level correction at $p < 0.05$ was applied.

6 We assessed the association of MRI and PET signals and interrogated nonparametric (partial)
7 correlations between CNR_{LC} and [¹¹C]yohimbine BP_{ND} values extracted from the ROIs,
8 employing Spearman correlation test adjusted for age and sex.

9 We assessed the links between both noradrenergic markers and specific clinical characteristics
10 within our group of Parkinson's disease patients by means of partial correlation coefficients
11 adjusted for age and sex. Indeed, it is known that both variables influence the phenotypical
12 expression of Parkinson's disease,⁵² that healthy ageing influences neuromelanin accumulation
13 in the LC,⁵³ and that [¹¹C]yohimbine BP_{ND} might be influenced by gender.³⁶ All correlations
14 were two-sided and significance was set at $p < 0.05$.

15

16 **Results**

17 **Altered LC integrity in patients with Parkinson's disease**

18 Parkinson's disease patients had lower CNR_{LC} than healthy controls (0.29 ± 0.04 vs 0.31 ± 0.04 ,
19 respectively; $F(1, 99) = 5.72$, $p = 0.019$). CNR was higher in the left than the right LC ($0.32 \pm$
20 0.03 versus 0.28 ± 0.04 , respectively; $F(1,99) = 22.02$, $p < 0.001$). No significant effect of
21 gender and no interaction were found ($p > 0.3$). Because of the side effect, all other analyses
22 have been conducted for both sides separately.

23 **Reduced [¹¹C]yohimbine binding in Parkinson's disease patients**

24 Reduced binding of [¹¹C]yohimbine was observed in the Parkinson's disease group compared to
25 healthy controls in four significant clusters including mainly cortical regions across all lobes and
26 the insula, the putamen and the thalamus (Table 2, Fig. 2). VBM was additionally employed to
27 assess grey matter volume loss in Parkinson's disease patients compared to controls as a

1 potential confounding factor within the ROI. No significant effect was found between the two
2 groups using FWE with corrected p value < 0.05 in the t-test.

3 **Correlation between $\alpha 2$ -ARs availability and LC MRI data**

4 No significant correlation was found between regional [^{11}C]yohimbine BP_{ND} values and CNR_{LC}
5 (all $p > 0.1$).

6 **Correlation of neuromelanin MRI data with clinical scores in Parkinson's** 7 **disease**

8 **Clinical characteristics**

9 CNR_{LC} correlated negatively with LEDD (right: $r = -0.52$, $p = 0.011$ and left: $r = -0.49$, $p =$
10 0.017).

11 **Non-motor scores**

12 CNR_{LC} correlated negatively with UPDRS-I total score (right: $r = -0.43$, $p = 0.035$ and left: $r = -$
13 0.47 , $p = 0.02$). We explored within this scale which items mostly driven this effect and found
14 that apathy sub-score was negatively correlated with the right and left CNR_{LC} ($r = -0.48$, $p =$
15 0.018 and $r = -0.46$, $p = 0.025$ respectively), constipation and light headedness on standing sub-
16 scores correlated negatively with the left CNR_{LC} ($r = -0.52$, $p = 0.008$ and $r = -0.47$, $p = 0.02$
17 respectively), while the fatigue sub-score showed significant negative correlation with the right
18 CNR_{LC} ($r = -0.48$, $p = 0.017$).

19 **Motor scores**

20 Although we did not observe any significant correlation between CNR_{LC} and UPDRS-II and -III
21 total scores (all $p > 0.1$), we also specifically explored the relationship between CNR_{LC} and rest
22 tremor, rigidity and bradykinesia. Those were calculated using the following items for MDS-
23 UPDRS-III: rest tremor - 3.17, rigidity - 3.3, bradykinesia - 3.4-3.8. Interestingly, the left CNR_{LC}
24 correlated negatively with the bradykinesia sub-score ($r = -0.42$, $p = 0.043$) while a trend in the
25 right side was also observed ($r = -0.39$, $p = 0.056$), and the right CNR_{LC} correlated positively
26 with the tremor sub-score ($r = 0.45$, $p = 0.026$). Finally, we also found that the left CNR_{LC}
27 correlated negatively with the UPDRS-IV score ($r = -0.44$, $p = 0.03$) with a trend in the right side
28 ($r = -0.38$, $p = 0.069$). Interestingly, this effect was mostly driven by the motor fluctuation sub-

1 score (sum of items 4.3 and 4.4) which showed significant negative correlation with the left and
2 right CNR_{LC} ($r = -0.43$, $p = 0.035$ and $r = -0.41$, $p = 0.044$ respectively) while such correlations
3 were not observed for the dyskinesia sub-score (sum of items 4.1 and 4.2) (all $p > 0.1$).

4 **Correlation of $\alpha 2$ -ARs PET data with clinical scores in Parkinson's disease**

5 We found no correlation between [¹¹C]yohimbine BP_{ND} values in the ROI derived from the
6 between-group SPM contrast and the total scores of the MDS-UPDRS scales. However,
7 significant correlations were found with sub-scores within the different sections of the scale.

8 **Non-motor scores**

9 The item assessing anxiety in the UPDRS-I part correlated negatively with [¹¹C]yohimbine BP_{ND}
10 values in three regions within the right hemisphere : the putamen ($r = -0.50$, $p = 0.008$), the
11 insula ($r = -0.44$, $p = 0.02$) and the superior temporal gyrus ($r = -0.41$, $p = 0.034$).

12 **Motor scores**

13 The item assessing rest tremor in the UPDRS-III part correlated negatively with [¹¹C]yohimbine
14 BP_{ND} values in the right thalamus ($r = -0.46$, $p = 0.015$). In other words, the lower the binding in
15 the thalamus, the more the patients suffered from tremor.

16 **Discussion**

17 In the present study, we investigated two aspects of the noradrenergic system using multimodal
18 *in vivo* imaging in Parkinson's disease patients and healthy controls with hybrid MRI/PET: the
19 density of pigmented cell bodies of the LC with neuromelanin sensitive MRI and the availability
20 of the $\alpha 2$ -ARs with [¹¹C]yohimbine PET. Both show marked reductions in signal intensity in
21 patients, confirming that noradrenergic damage is profound and widespread in Parkinson's
22 disease. Clinical, behavioral and anatomical data suggest, however, that noradrenergic
23 dysfunction is multifaceted and may involve different circuits underlying specific motor and
24 non-motor symptoms.

25 **Noradrenergic system integrity in Parkinson's disease**

26 The reduction in signal intensity within the LC in Parkinson's disease patients confirms previous
27 MRI studies^{2,40,54-57} and provides a robust and replicable *in vivo* indication of the loss of

1 pigmented LC neurons previously suggested in post-mortem histological studies.⁵⁸⁻⁶⁰ On the
2 contrary, there was only very sparse evidence about the loss of $\alpha 2$ -ARs in Parkinson's disease
3 patients, including only one *in vitro* autoradiography study reporting a decrease of density in the
4 prefrontal cortex³³ and one preliminary *in vivo* study using [¹¹C]yohimbine in a small group of
5 PD patients reporting a global reduction in [¹¹C]yohimbine distribution volume in the temporal,
6 parietal and occipital cortices, the insula and the cingulate gyrus.⁶¹ Our data provide a precise
7 mapping of [¹¹C]yohimbine binding reduction in Parkinson's disease patients (Fig. 2). Within the
8 parietal lobe, the angular gyrus, the superior parietal lobule and the postcentral gyrus are
9 especially affected. The occipital cortex also shows multiple sources of binding differences both
10 in the primary and associative visual cortices. In the frontal lobe, only motor structures (primary
11 motor cortex, supplementary motor area and premotor cortex) and the inferior frontal gyrus
12 reveal binding reduction in patients. The temporal lobe seems also relatively preserved since
13 only one region in the superior temporal gyrus shows group differences. Medially, the posterior
14 cingulate/precuneus region is particularly affected. Finally, binding reduction in Parkinson's
15 disease also concerns the insula, the putamen and the thalamus (Fig. 2). This latter observation is
16 in good agreement with previous post-mortem and animal studies showing severe reductions of
17 noradrenaline levels in almost all subregions of the thalamus.^{30,62}

18 Interpreting [¹¹C]yohimbine binding reduction is not straightforward. Indeed, as $\alpha 2$ -ARs are
19 located both pre- and post-synaptically,^{63,64} the decrease in [¹¹C]yohimbine binding could reflect
20 both a reduction of presynaptic $\alpha 2$ -ARs due to the diminished innervation caused by the
21 degeneration of noradrenergic neurons, and/or a reduction in the availability of postsynaptic $\alpha 2$ -
22 ARs which can be relatively independent of the degeneration of noradrenergic neurons (as
23 observed for the dopaminergic system).⁶⁵ The former hypothesis predicts strong correlations
24 between neuromelanin MRI and [¹¹C]yohimbine PET signals. Our results are not consistent with
25 this prediction. They are rather reminiscent of the conclusion obtained from [¹¹C]MeNER -a
26 marker of noradrenaline transporter availability- PET studies that deficits in noradrenergic
27 terminals and LC cell bodies are partly uncoupled.^{2,40} It seems that the number of noradrenergic
28 cells in the LC would be a major determinant of $\alpha 2$ -AR density only in the LC itself.⁶⁶ Our data
29 are in line with the overall hypothesis according to which monoaminergic receptors undergo
30 adaptive changes in Parkinson's disease that make the availability of their receptors non
31 proportional to the extent of neuronal death of the corresponding cell bodies.^{65,67} It is therefore

1 essential to disentangle, within the global clinical picture, the symptoms that might be more
2 related to the loss of $\alpha 2$ -ARs and/or to the loss of noradrenergic cells in the LC.

3 **Non-motor symptoms**

4 **Fatigue**

5 Fatigue was found to be associated with LC neuronal loss. This is in line with the idea that
6 fatigue results from disruption of nondopaminergic pathways, including the noradrenergic
7 system.⁶⁸⁻⁷⁰ This is not incompatible with the hypothesis that fatigue in Parkinson's disease is
8 also associated with serotonergic dysfunction in prefrontal-basal ganglia and limbic circuits.⁷¹
9 Indeed, it is well known that there are strong interactions between the noradrenergic and
10 serotonergic systems (mainly through the LC-dorsal raphe nucleus connection)⁷²⁻⁷⁴ suggesting
11 that both are likely to contribute to the appearance of the symptom. However, the argument that
12 fatigue characterizes a specific serotonergic phenotype of Parkinson's disease is based on
13 associations between fatigue and other non-motor symptoms related to the degeneration of
14 serotonergic pathways (apathy, anxiety, sleep problems and daytime sleepiness)⁷⁵ that are most
15 often moderate⁶⁹ and that are not all reported in the present study as only apathy was also found
16 to be associated with LC neuronal loss. Anxiety was just associated with a reduction of $\alpha 2$ -ARs
17 availability in the putamen, the insula and the superior temporal gyrus, but not with a reduction
18 in signal intensity within the LC. Yet, neither LC neuronal loss nor $\alpha 2$ -ARs availability were
19 found to account for sleep disorders. This observation is in line with several pharmacological
20 studies of physical exercise in healthy humans suggesting that the role of the serotonergic
21 system in central fatigue might be overestimated⁷⁶ while the role of the noradrenergic system
22 might conversely be underestimated.⁷⁷ In addition, given that fatigue is a non-dopaminergic
23 symptom, the fact that Methylphenidate -a reuptake inhibitor of dopamine and noradrenaline- is
24 proposed as a treatment against fatigue in Parkinson's disease^{78,79} is also consistent with the idea
25 that the pathophysiological mechanism leading to fatigue involves the degeneration of the
26 noradrenergic system. Beyond Parkinson's disease, the association of fatigue with a loss of
27 noradrenergic cells in the LC but not with a loss of $\alpha 2$ -ARs in other specific brain regions is not
28 trivial. It relates the global perception of an internal state of energy to the general function of the
29 noradrenergic system which is to mobilize the whole brain and body for action from a unique but

1 widely distributed source. This association is not put forward in current biological theories of
2 fatigue.⁶⁹

3 **Apathy**

4 Apathy is a complex and multifactorial alteration of the internal and external drives of goal-
5 directed behavior.⁸⁰ It has been associated with dysfunctions of different neural networks
6 supporting emotional/affective, cognitive and auto-activation circuits,^{3,81,82} for which meso-
7 cortico-limbic dopaminergic and serotonergic lesions are thought to play a major role. The
8 present study provides new insight into apathy pathophysiology and suggests that there is a role
9 of noradrenergic alteration since we found a correlation between apathy and LC neuronal loss.
10 This observation is reminiscent of a former recent study using pharmacological MRI and testing
11 more specifically predictive processing (i.e., executive functions) of goal-directed behavior.⁸³
12 Although we cannot disentangle cognitive from motivational apathy in the present study, it is
13 tempting to speculate that the noradrenergic dysfunction identified in our empirical observations
14 may be more closely associated with cognitive apathy (which includes dysfunction of a set of
15 executive mechanisms required for achieving a goal) than with motivational apathy.⁸⁴ Our results
16 also strengthen the idea that fatigue is associated with apathy (both relying on the general
17 activation function of the LC-NA system, not on specific losses of α 2-ARs) but not with
18 anxiety⁸⁵ (which does not involve LC neuronal loss in the present study).

19 **Anxiety**

20 Anxiety is commonly associated with apathy and depression to constitute a behavioral « non-
21 motor triad » in Parkinson's disease governed by serotonergic and dopaminergic
22 degeneration.^{3,86} However, while anxiety symptoms are clearly linked to alterations of limbic
23 cortico-striato-thalamo-cortical circuits, several studies have proposed that basal ganglia and
24 brainstem nuclei could be at the root of such disorders,^{87,88} including a loss of noradrenaline
25 innervation in the locus coeruleus and the limbic system.^{87,89} Our data are consistent with the
26 involvement of noradrenergic dysfunction in anxiety as its severity is associated with a reduction
27 of α 2-ARs availability in a brain network including the putamen, the insula and the superior
28 temporal gyrus (but not with a loss of noradrenergic cells in the LC). However, we found no
29 evidence for a common noradrenergic dysfunction of the “non-motor triad” as they all seem to

1 have different origins: anxiety was associated with alteration of noradrenergic terminals, apathy
2 with alteration of LC cell bodies, while depression was not linked to any of these dysfunctions.

3 **Constipation**

4 Constipation is one of the most common nonmotor symptoms that emerge from the very early
5 phase.^{90,91} The underlying mechanisms of constipation in Parkinson's disease are still unknown,
6 but neurodegeneration of autonomic centers of both the enteric and central nervous systems are
7 likely.⁹² Our observation that constipation is associated with a reduction of signal intensity in the
8 LC fits with the general idea that dysfunction of the noradrenergic system is closely linked to
9 numerous premotor symptoms of Parkinson's disease.⁹³⁻⁹⁶ But most importantly, it is also
10 consistent with rodent studies providing specific evidence that: 1) the LC participates in the
11 regulation of colorectal motility (via activation of $\alpha 1$ -ARs in the lumbosacral defecation
12 center),⁹⁷ 2) noradrenaline plays a major role in regulating colon immune homeostasis,⁹⁸ and 3)
13 the reduction of noradrenaline level in the intestine causes colon inflammation, α -synuclein
14 pathology, neuronal loss and, in fine, constipation.^{98,99}

15 **Motor symptoms**

16 LC neuronal loss in Parkinson's disease has been associated with the disease, but not directly
17 with motor symptoms.^{6,100} Here, we provide evidence for a direct link with bradykinesia, rest
18 tremor, and motor fluctuations. By contrast, while noradrenergic denervation of the motor
19 areas¹⁰¹ and noradrenergic transporters density decrease in the motor cortex¹⁰² have been
20 associated with motor cortical dysfunction in Parkinson's disease,^{103,104} the substantial reduction
21 of $\alpha 2$ -ARs availability in the motor cortices of Parkinson's disease patients found in the present
22 study revealed no direct relationship with a global motor dysfunction (i.e, neither with the
23 UPDRS-II nor with the UPDRS-III scores). However, it is possible that the potential
24 consequences of cortical $\alpha 2$ -ARs loss are more indirect and more specific. Indeed, as $\alpha 2$ -ARs
25 would be located on inhibitory interneurons, a reduced availability could contribute to the broad
26 reduction of intracortical inhibition at rest and to the increase in cortical excitation frequently
27 observed in PD.¹⁰⁵⁻¹⁰⁷ Future studies are needed to clarify this possible masked relationship.

1 **Bradykinesia**

2 Bradykinesia is a multifaceted concept including potentially distinct motor abnormalities with
3 distinct pathophysiological backgrounds that are all mixed in one single clinical term.¹⁰⁸ Here,
4 we did not find specific correlates of bradykinesia as assessed by means of UPDRS-III in
5 [¹¹C]yohimbine binding data, but report a significant association with a global alteration of LC
6 integrity. Although this observation does not address the problem of the “bradykinesia complex”
7 (ibid), it contributes to the debate about its incomplete response to dopaminergic drugs. Indeed,
8 levodopa only improves overall bradykinesia but does not normalize all other abnormal
9 movement parameters.¹⁰⁹ Our data support the suggestions of several studies promoting the role
10 of noradrenaline in the control of motor behavior¹¹ and the fact that its depletion results in motor
11 deterioration in Parkinson’s disease.^{16,19,30,102} It can be assumed that the role of noradrenaline is
12 indirect. First because it would facilitate nigro-striatal dopamine transmission.¹¹⁰ Second because
13 the noradrenergic system would play a major role in executive functions like response inhibition
14 whose alteration might lead to movement control disorders.^{111–114} Future work on the
15 noradrenergic bases of movement disorders in Parkinson’s disease should include a more
16 detailed clinical evaluation of bradykinesia and its related features.¹⁰⁸

17 **Motor fluctuations**

18 The present study pinpoints a correlation between the decrease in LC signal intensity and the
19 severity of levodopa-induced motor complications (UPDRS-IV total score). However we did not
20 find any relationship with α 2-ARs availability change despite previous studies having reported a
21 potent effect of α 2-ARs antagonists on dyskinesia in a monkey model of Parkinson’s disease^{115–}
22 ¹¹⁸ as well as in patients with Parkinson’s disease when given in combination with levodopa.¹¹⁹
23 In addition, although there are very few investigations of the role of the LC in motor fluctuations,
24 LC denervation in rodents was not found to potentiate levodopa-induced motor complications.¹²⁰
25 These contradictions clearly require further investigations comparing notably Parkinson’s
26 disease patients with and without motor fluctuations and dyskinesias. Nevertheless, the present
27 data bring back to the forefront the issue of the links between motor and non-motor
28 fluctuations,¹²¹ and suggest that alteration of LC integrity might be a common denominator.

1 **Rest tremor**

2 Tremor in Parkinson's disease does not closely correlate with nigrostriatal dopaminergic
3 deficits¹²² and is not fully restored by dopaminergic medication.¹²³ Increasing evidence also
4 involves the noradrenergic system in the network dynamics of parkinsonian tremor.^{27,122,124} Our
5 data are consistent with this view. Both the amount of neuronal loss in the LC inferred from
6 neuromelanin MRI and $\alpha 2$ -ARs availability in the thalamus inferred from [¹¹C]yohimbine
7 binding have been associated with tremor level in the present dataset. The direction of the
8 relationship between neuromelanin MRI and clinical data indicates that tremor is higher in
9 patients for whom LC integrity is better preserved, as previously observed in post-mortem
10 analyses comparing tremor-dominant to akinetic-rigid patients^{125,126} or in *in vivo* investigations
11 using [¹¹C]MeNER PET.¹²⁴ This relationship was also predicted by former observations linking
12 the presence of tremor to a more benign course of disease¹²⁷ or to a relatively preserved LC-NA
13 system.^{27,124} Our data are in line with a group of studies implicating a cerebello-thalamo-cortical
14 circuit in the genesis of tremor^{128–132} as they provide evidence that $\alpha 2$ -ARs availability in the
15 thalamus decreases with the severity of rest tremor. This is particularly consistent with the recent
16 observation that distribution volume ratio of noradrenaline transporters in the thalamus correlates
17 with resting tremor amplitude in patients with Parkinson's disease, suggesting that noradrenaline
18 transporters density is relatively preserved in this region for patients with tremor-dominant
19 Parkinson's disease.¹²⁴

20 **Limitations**

21 There are some limitations to this study that should be acknowledged. First, due to ethical
22 reasons and to the need to reduce movements within the scanner for imaging small brainstem
23 structures like the LC, patients with Parkinson's disease were scanned in the ON medication
24 state. There is evidence from animal studies that administration of levodopa might foster the
25 accumulation of neuromelanin.¹³³ However, these effects are expected to be relatively long-
26 lasting rather than fluctuating between medication states. In the present study, LEDD in patients
27 did correlate with CNR_{LC} indicating that PD patients with higher dose of dopaminergic treatment
28 were those with lower signal in the LC. This was observed for both sides of the LC. A second
29 possible effect of the ON medication state is that postsynaptic $\alpha 2$ -ARs may be

1 downregulated.^{134,135} However, we did not find any correlation between LEDD and
2 [¹¹C]yohimbine BP_{ND}, at least in the regions that have been sampled.

3 Second, it is not possible to distinguish the pre- and post-synaptic locations of the α 2-ARs with
4 [¹¹C]yohimbine. Future studies should consider multitracer approaches with specific presynaptic
5 tracer (such as [¹¹C]MeNER) in order to assess whether changes in α 2-ARs with Parkinson's
6 disease mainly occur at the pre- or at the post-synaptic level (or both). Furthermore, it is also
7 worth mentioning that [¹¹C]yohimbine does not differentiate either between the different
8 subtypes of α 2-ARs that have been characterized pharmacology (α 2A, α 2B, α 2C).¹³⁶ Therefore,
9 there is still a strong need in the future to pursue the effort in developing specific radiotracers to
10 further investigate this noradrenergic system *in vivo*.

11 **Conclusions**

12 In conclusion, the present work is the first multimodal comparative *in vivo* imaging study to
13 assess the association between Parkinson's disease symptoms and the integrity of two aspects of
14 the noradrenergic system: the distribution of α 2-ARs in the brain and the density of cell bodies in
15 the LC. Our results highlight the substantial and multimodal alteration of the noradrenergic
16 system in humans and its possible role in the pathophysiology of Parkinson's disease, not only in
17 terms of non-motor impairments (supporting the noradrenergic phenotype recently proposed by
18 Chaudhuri and colleagues)⁷ but also with regard to some motor aspects of the disease
19 (bradykinesia, motor fluctuations and rest tremor). Overall, our findings may encourage the
20 search for new drugs targeting the α 2-ARs system for the treatment of Parkinson's disease.
21 However, future studies are warranted to shed more light on the specific role of the α 2-ARs and
22 their different subtypes in the pathophysiology of the disease. In particular, further research is
23 needed to sharpen the clinical picture and better characterize the different phenotypes of this
24 heterogeneous and multisystem disease.

25 **Data availability**

26 Data are available upon reasonable request.

27

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6

7 **Competing interests**

8 The authors report no competing interests.

9

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16
17

18 **Figure legends**

19 **Figure 1 Data pipeline.** [¹¹C]yohimbine and LC Neuromelanin data were acquired
20 simultaneously from hybrid PET/MRI. *Left side:* [¹¹C]yohimbine BP_{ND} parametric maps were
21 used for contrasting the healthy control and the Parkinson's disease groups. The outcome of the
22 voxel-based analysis allowed identification of four significant clusters that provided the ROI for
23 the analysis of the links between [¹¹C]yohimbine BP_{ND} and clinical scores in patients. *Right side:*
24 LC identification was performed for each individual from neuromelanin sensitive T1 images
25 with a three-steps procedure. First, the regions of interest were manually drawn as large 3D
26 bounding boxes in the MNI space, then wrapped and resampled onto the subject's native space.
27 Finally, the clusters of connected voxels with the highest signal intensity were selected to define
28 LC areas. The CNR between the LC and the reference region was calculated to estimate LC

1 signal intensity and these values were referred to the clinical scores of the Parkinson's disease
2 patients.

3

4 **Figure 2 Statistical parametric maps comparing Parkinson's disease patients to control**
5 **subjects.** Decrease in [^{11}C]yohimbine binding is observed in patients with Parkinson's disease
6 with regard to healthy control subjects.

7

8

9 **Table 1 Demographics and clinical characteristics of participants**

	Healthy Controls	Parkinsonian patients	Statistics
N	30	30	
Sex (female/male)	12/18	12/18	
Age (years)	60.3 \pm 8	60.1 \pm 7.5	ns ^a
MoCA	27.9 \pm 1.5	27.9 \pm 2	ns ^b
Parkinson's disease characteristics			
Disease duration (years)		6.5 \pm 4	
LEDD (mg/day)		1006 \pm 703	
Hoehn & Yahr		1.8 \pm 0.4	
PDQ39		39.6 \pm 22.1	
MDS-UPDRS I		8.5 \pm 5.1	
MDS-UPDRS II		7.1 \pm 4.3	
MDS-UPDRS III		17.7 \pm 12.3	
MDS-UPDRS IV		2.3 \pm 3	

10 Data are presented as mean \pm standard deviation.

11 ^aParametric test (Student's t-test).

12 ^bNon-parametric test (Wilcoxon test).

13

1 **Table 2 SPM results of the two samples t test on [¹¹C]yohimbine binding**

Areas	BA	Side	MNI coordinates			T value	P corr cluster	Cluster size
			x	y	z			
Reduced [¹¹C]yohimbine binding in Parkinson's disease versus healthy controls								
Angular Gyrus	40	R	46	-38	52	5.37	0.000	3775
Superior Temporal Gyrus	22	R	52	-12	0	5.08		
Postcentral Gyrus (Opercular)	48	R	50	-8	16	5.06		
Inferior Frontal Gyrus (pars opercularis)	44	R	46	14	10	4.22		
Insula	13	R	36	-12	6	4.18		
Precentral gyrus	4	R	40	-26	58	3.97		
Putamen	-	R	30	-10	6	3.90		
Postcentral gyrus	3	R	52	-14	30	3.73		
Thalamus (PuM)	-	R	6	-24	4	5.18	0.000	1354
Insula	13	L	-32	-6	16	4.59		
Precentral Gyrus (Premotor cortex)	6	L	-48	-4	12	3.84		
Posterior Cingulate Cortex (Dorsal)	31	R	2	-36	40	4.95	0.000	3836
Superior Parietal Cortex	7	R	18	-76	40	4.55		
Lateral Occipital Cortex	19	L	-10	-82	36	4.43		
Cuneus	18	R	4	-80	34	4.41		
Posterior Cingulate Cortex (Ventral)	23	R	8	-52	10	4.37		
Posterior Cingulate Cortex (Mid Cingulate)	23	R	8	-20	46	4.28		
Lateral Occipital Cortex	19	R	32	-80	26	4.27		
Lingual Gyrus	18	L	-6	-72	0	4.07		
Precentral Gyrus	6	R	4	-22	60	3.89		
Lingual Gyrus	17	R	4	-66	12	3.87		
Precuneus	31	L	-6	-52	38	3.80		
Precuneus	31	R	2	-56	42	3.80		
Superior Parietal Cortex	7	L	-32	-50	56	4.41	0.013	614
Angular Gyrus	40	L	-42	-52	46	4.23		
Postcentral Gyrus	3	L	-50	-14	38	3.76		
Postcentral Gyrus	4	L	-36	-28	56	3.66		

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3

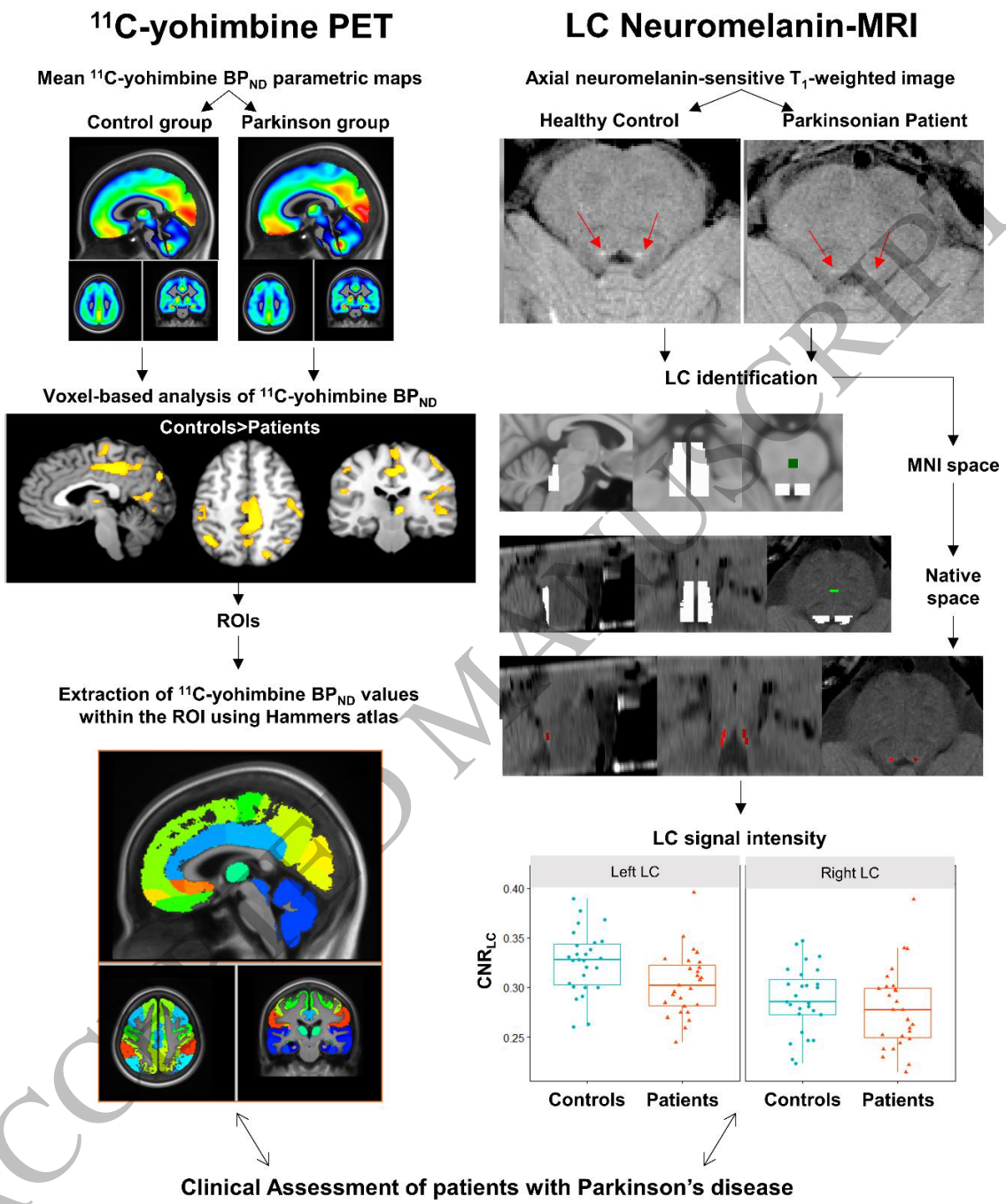


Figure 1
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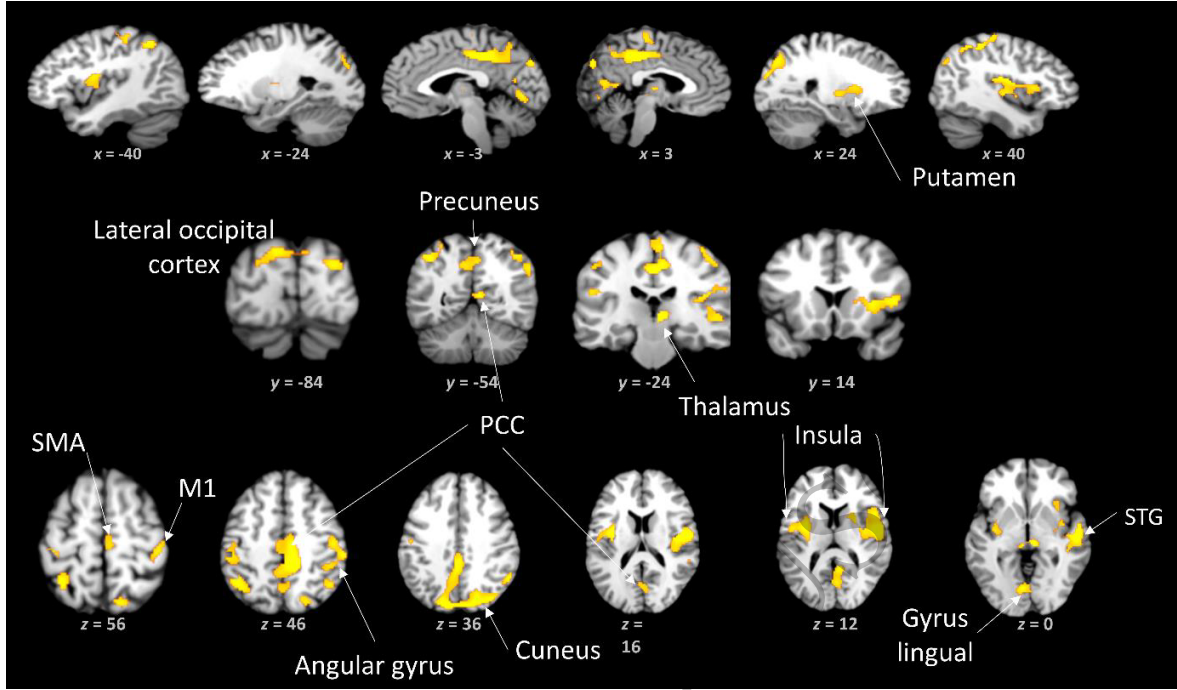


Figure 2
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Chapitre 7. Vers une thérapie noradrénergique complémentaire : le cas des TCI

Actuellement, il reste beaucoup à apprendre sur le bénéfice des médicaments noradrénergiques dans le traitement symptomatique. Les essais dans la MP sont finalement menés avec des cibles diverses en termes de récepteurs. Comme nous l'avons vu précédemment, le système noradrénergique est impliqué dans les phénomènes d'impulsivité et même possiblement de jeux pathologiques. Mais peu d'études se sont intéressées à l'effet des traitements noradrénergiques chez les patients parkinsoniens impulsifs. Les TCIs sont un effet secondaire fréquent des traitements dopaminergiques de la MP. A ce jour, la solution thérapeutique consiste essentiellement à réduire le dosage des ADs, au risque d'une dégradation des symptômes moteurs. Bien que l'interaction entre systèmes noradrénergiques et dopaminergiques reste à élucider, nous nous sommes appuyés sur nos travaux antérieurs montrant le rôle du système noradrénergique dans le contrôle exécutif et l'inhibition de réponse (Albares et al., 2015 ; Spay et al., 2018). Plus particulièrement, nous avons exploité les travaux fondamentaux suggérant que la modulation du tonus noradrénergique induite par la clonidine agissait directement sur les mécanismes d'inhibition de réponse dans la MP (Criaud et al., 2022). La clonidine est un agoniste des récepteurs α_2 -adrénergiques qui diminuerait la libération de NA en activant le récepteurs α_2 de façon présynaptique. Il faut toutefois être prudent car il a aussi été rapporté qu'une dose élevée de clonidine engagerait les récepteurs post-synaptiques, entraînant une augmentation de la transmission noradrénergique (Miyazaki et al., 2004). Par analogie, il a été montré que la guanfacine (un agoniste α_2) améliorerait la connectivité du réseau préfrontal par un effet post synaptique et il s'agit d'un traitement validé aux États Unis dans le traitement des TDAH (Arnsten, 2020) tout comme la clonidine (Neuchat et al., 2023) car ils ont un effet sur l'impulsivité. Nous avons donc initié un essai clinique de phase II, multicentrique dans les centres de Lyon, Clermont-Ferrand, Grenoble, St Etienne et Nice (NCT03552068), destiné à tester l'effet prédit de réduction de l'impulsivité des patients parkinsoniens avec TCI par l'administration chronique de clonidine. Malheureusement, notre critère principal de réussite (probablement trop strict) n'est pas atteint dans l'étude. Une étude de phase 3 est nécessaire pour trancher la question. Néanmoins, nous parvenons à démontrer ici que le traitement est bien toléré dans la population de patient sélectionné.



Efficacy and safety of clonidine for the treatment of impulse control disorder in Parkinson's disease: a multicenter, parallel, randomised, double-blind, Phase 2b Clinical trial

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Abstract

Background Impulse control disorders (ICDs) are frequently encountered in Parkinson's disease (PD).

Objectives We aimed to assess whether clonidine, an α 2-adrenergic receptor agonist, would improve ICDs.

Methods We conducted a multicentre trial in five movement disorder departments. Patients with PD and ICDs ($n = 41$) were enrolled in an 8-week, randomised (1:1), double-blind, placebo-controlled study of clonidine (75 μ g twice a day). Randomisation and allocation to the trial group were carried out by a central computer system. The primary outcome was the change at 8 weeks in symptom severity using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) score. A reduction of the most elevated subscore of the QUIP-RS of more than 3 points without any increase in the other QUIP-RS dimension defined success.

Results Between 15 May 2019 and 10 September 2021, 19 patients in the clonidine group and 20 patients in the placebo group were enrolled. The proportion difference of success in reducing QUIP-RS at 8 weeks, was 7% (one-sided upper 90% CI 27%) with 42.1% of success in the clonidine group and 35.0% in the placebo group. Compared to patients in the placebo group, patients in the clonidine group experienced a greater reduction in the total QUIP-RS score at 8 weeks (11.0 points vs. 3.6).

Discussion Clonidine was well tolerated but our study was not enough powerful to demonstrate significant superiority compared to placebo in reducing ICDs despite a greater reduction of total QUIP score at 8 weeks. A phase 3 study should be conducted.

Trial Registration The study was registered (NCT03552068) on clinicaltrials.gov on June 11, 2018.

Keywords Clonidine · Noradrenergic system · Parkinson's disease · Impulse control disorder · QUIP-RS

Introduction

Impulse control disorders (ICDs) are behavioural disorders frequently encountered in Parkinson's disease (PD) treated by dopamine replacement therapies (DRT). The main ICDs are pathological gambling, binge eating, compulsive shopping, and hypersexuality [1].

A recent study reported a 5-year cumulative ICD incidence rate of 46% [1]. Risk factors for ICDs are duration and dose of DA treatment, male gender, comorbid apathy,

anxiety, depression, and bipolar disorders [2–4]. Genetic factors of susceptibility are also suspected [5]. ICDs are underdiagnosed because patients sometimes do not recognise these disorders and often underestimate their severity [6]. The lack of insight and a defence mechanism (with denial or feeling of shame) are the main explanations reported [6]. ICDs reduce patients' quality of life and place a heavy burden on their caregivers [7]. No treatment exists for ICDs. The classical approach consists of reducing or discontinuing DA with a risk of dopamine withdrawal syndrome, which associates anxiety, irritability, apathy and worsening of motor symptoms, and concern approximately a third of PD patients [2, 8]. However, in a retrospective study, only 40%

Extended author information available on the last page of the article

of the PD patients with ICDs were in remission following a reduction or discontinuation of DA after 3.5 years of follow-up [9].

The mechanism of ICDs is not entirely understood but dysfunction of the mesocorticolimbic dopaminergic pathway plays a key role and abnormal sensitization of the limbic dopaminergic system, combined with a relatively preserved dopaminergic mesocorticolimbic pathways and reduced dopamine transporter (DAT) expression in ventral striatum have been clearly shown [10]. Beyond the dopaminergic system, glutamatergic and opioidergic neurotransmission dysfunction could also participate in ICD pathophysiology, which led to clinical trials with controversial or negative results. A small clinical trial with amantadine showed positive results on pathological gambling, because it was hypothesized that dyskinesia and ICDs depend on common mechanisms involving alterations of glutamate homeostasis [11]. However, amantadine was also demonstrated to be associated with the development of ICDs [12]. Naltrexone, an opioid receptor antagonist, was also tested in ICDs because of its efficacy in alcohol dependence but the study failed to demonstrate any efficacy [13]. Recently evidence in PD has pointed to early neuronal loss in the locus coeruleus (LC), which is the primary component of the noradrenergic system that is involved in functions such as arousal, behavioural flexibility, executive function, learning, memory, and wakefulness [14]. In addition, noradrenergic dysfunction is involved in some non-motor symptoms of PD such as depression [15] and dysexecutive symptoms [16], but also in proactive inhibition that is disproportionate in PD favouring akinesia [17]. More specifically, clonidine, an α 2-adrenergic agonist, was found to cancel the positive action of subthalamic nucleus-deep brain stimulation (STN-DBS) on akinesia, consistent with the role of noradrenalin (NA) in movement initiation via the modulation of α 2-adrenoceptors and inhibitory control [18]. Many effects of clonidine have been attributed to presynaptic α 2-adrenoreceptors, resulting in the inhibition of neural release of NA, however, higher doses of clonidine may preferentially [19, 20] engage post-synaptic receptors, enhancing noradrenergic transmission [15]; these effects may have an impact on the top-down control role of the prefrontal cortex [21].

There is also evidence of a role of the noradrenergic system in decision-making and reward processes in rodents [21]. In humans, α 2-adrenergic antagonists, such as yohimbine, raise impulsivity [22]. Furthermore, atomoxetine, a NA re-uptake inhibitor, may reduce motor impulsivity in PD [23]. In heroin addicts, a randomised trial found that clonidine improved decision-making performance as assessed by the Iowa Gambling Test and decreased impulsivity [24]. Furthermore, clonidine is commonly used in attention deficit hyperactivity disorder and Tourette's syndrome and provides benefits on hyperactivity and impulsivity [25]. Based

on these results it would be of great interest to analyse the impact of clonidine on ICDs in PD, which has never been done so far.

In this context, we conducted a multicentre prospective, randomised, double-blind placebo-controlled trial to investigate the efficacy of clonidine on ICDs and its safety in PD patients in a phase 2b study in preparation for a phase 3 trial.

Patients and methods

Patients

Patients were screened in five university hospital movement disorder departments in France (Lyon, Clermont-Ferrand, Saint Etienne, Grenoble, and Nice). We included patients diagnosed with PD at least 1 year previously and in accordance with the Movement Disorder Society criteria, who were aged [30–80] years, and who weighed [40–95] kg. ICD symptoms had to start after PD onset and initiation of DRT. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) was used to assess the presence and severity of ICDs. The QUIP-RS is a screening instrument for ICDs [26]. Its three sections focus on: (i) the four most common ICDs; (ii) punting and hobbyism; and (iii) compulsive medication use; the higher the score the more severe are the ICDs. Inclusion criteria consisted of a QUIP-RS total score ≥ 10 or a sub-score > 5 for pathological gambling, > 7 for compulsive shopping or hypersexuality, or > 6 for binge eating. All therapeutic classes of antiparkinsonian treatments were allowed, including DA, but had to be stable in the last 2 months and remain stable during the study. Exclusion criteria were depression (Beck Depression Inventory [BDI II] > 19), dementia (Montreal Cognitive Assessment [MOCA] < 20), orthostatic hypotension, renal failure (glomerular filtration rate < 30 ml/min/1.73m²), bradyarrhythmia, heart failure or coronary disease, Raynaud disease, or addiction to a substance defined by the DSM-IV (except tobacco); in addition, patients with a treatment that could interact with the noradrenergic system (see list in supplemental data) were also excluded. Furthermore, based on the judgement of a study investigator (neurologist), patients with severe ICD necessitating immediate tapering of dopaminergic medication were excluded.

Approval from the institutional ethical standards committee on human experimentation (Comité de protection des personnes Ouest IV -Nantes) was obtained before study initiation and the trial was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent before randomisation (EudraCT number 2019-000165-20). The study was registered (NCT03552068) on clinicaltrials.gov.

Methods

Patients received oral clonidine (75 µg twice a day, a morning and an evening) or a placebo for 8 weeks without any titration. Patients were instructed not to change their PD treatment (medications and/or DBS settings) during the study and treatment was checked at each visit. Randomisation and allocation to the trial group were carried out by a central computer system. Assignment was masked from the patients, study staff, investigators, and data analysts. The QUIP-RS was administered by a neuropsychologist specialised in PD. The neuropsychologists were trained before the beginning of the study in order to standardise, between centres, the administration of the questionnaire. When two sub-scores were equal, we the most disabling for the patient according to the neurologist was retained. Depression symptoms were assessed using the BDI II [27]. We studied hyper- and hypodopaminergic mood and behaviour using the Arduin scale [28], anxiety using the State-Trait-Anxiety Inventory (STAI-Y), and sleepiness using the Epworth scale [29]. The 39-item Parkinson's Disease Questionnaire (PDQ-39) [30] was used to evaluate quality of life. We assessed the tolerability (general physical examination, electrocardiogram, blood pressure, pulse measurement) and adherence (capsule counts and patient journal) at weeks 2, 4 and 8. Orthostatic hypotension was searched for (measurement of blood pressure after 5 min lying down, and at 1, 3, 5 and 10 min after standing up) at baseline, as well as at 2, 4 and 8 weeks. Adverse events were monitored throughout the study with a specific interest on orthostatic hypotension and related falls that were considered as serious adverse events. A visit was scheduled at 2 weeks after the inclusion visit, in order to check the tolerance and adherence. At 4 and 8 weeks after randomisation, the primary and secondary criteria were collected in addition to the tolerance and adherence parameters. One visit was scheduled one month after the end of the study.

Primary endpoint

The efficacy of the clonidine after 8 weeks of treatment was determined using the QUIP-RS. Success corresponded to a decrease of more than 3 points of the more elevated sub-score, without elevation of another sub-score of the QUIP-RS. This criterion was chosen to consider the most marked ICD for a given patient, which seemed more clinically relevant.

Secondary endpoints

Change in ICD severity was assessed by the variation of the total QUIP-RS score between baseline and week 4 and between baseline and week 8. Secondary outcomes were the changes between baseline and week 8 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale MDS-UPDRS part I (Non-Motor Aspects of Experiences of Daily Living), part II (motor aspects of experiences of daily living), part III (motor symptoms), and part IV (motor complications) scores [31].

Changes in depression symptoms were assessed using the BDI II [27], in hyper- and hypodopaminergic mood and behaviour using the Arduin scale or ECMP [28], in anxiety with the STAI-Y, and sleepiness with the Epworth scale [32]. The 39-item Parkinson's Disease Questionnaire (PDQ-39) [30] evaluated the modification of the quality of life [32].

Statistical analysis

The primary outcome was a reduction of QUIP-RS score between baseline and 8 weeks. We defined a success as a reduction by 3 points or more between baseline and 8 weeks of the highest QUIP-RS subscore at baseline, without any augmentation in the other QUIP-RS dimension. The minimal clinical difference was set at a 15% difference of success between placebo and clonidine. Using a confidence interval (CI) approach [33], we estimated that 19 patients per group will produce a one-sided upper 90% CI, which excludes 15% assuming that the difference between placebo and clonidine is 0% or less. If the one-sided 90% CI contains 15%, a phase 3 RCT could be considered. We performed a post hoc analysis using a linear mixed effect model to test for time by group differences for treatment response, using fixed effect for randomisation group, time and their interaction, and a random intercept and slope by subject as random effects. The primary outcome analysis included all patients who were enrolled (intention to treat [ITT] analysis). We used the maximum bias approach for handling missing values. We imputed a success for the placebo participant missing primary outcome and a failure for the clonidine participant missing primary outcome. We defined the per protocol population (PP population) as all the patients enrolled who completed the primary outcomes measure. The PP population was used only for the calculation of the primary endpoint. No hypothesis test was performed on secondary outcomes to avoid type I error inflation. Statistics were done using SAS (Statistical Analysis Software 9.4, SAS Institute Inc, Cary, NC, USA).

Role of the funding source

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author has full access to all the data and takes final responsibility to submit for publication.

Results

Between 15 May 2019 and 10 September 2021, 41 patients were screened and 39 enrolled and randomly assigned. Nineteen received clonidine and 20 placebos (ITT population). One patient in the placebo arm decided to stop the study because of a personal issue independent of ICD. 19 patients in the clonidine arm and 19 patients in the placebo arm completed the study (PP population; Fig. 1). The groups were balanced in terms of baseline demographic characteristics; the mean (\pm standard deviation, SD) total QUIP-RS score at baseline was higher in the clonidine arm (28.8 ± 13.2) than in the placebo arm (23.1 ± 7.8 ; Table 1). In addition to the fulfilling of inclusion and exclusion criteria, no patients had

a history of bipolar disorders nor presented mania at inclusion based on DSM V criteria.

Primary endpoint

The difference of success rate in reducing QUIP-RS at 8 weeks, was of 7% between groups (one-sided upper 90% CI 27%), with 8/19 patients experiencing success in the clonidine group (42.1%) and 7/20 in the placebo group (35.0%) in the ITT population. In the PP population, the proportion difference was of 10% (one-sided upper 90% CI 30.5) with 42.1% of success in the clonidine group and 31.6% in the placebo group.

Secondary endpoints

At 4 weeks, compared to patients in the placebo arm, patients receiving clonidine had a larger reduction of the mean total QUIP-RS score (7.9 versus 2.9 points). At 8 weeks, this difference became greater; 11.0 points under clonidine versus 3.6 under placebo (Fig. 2).

Fig. 1 Flow chart

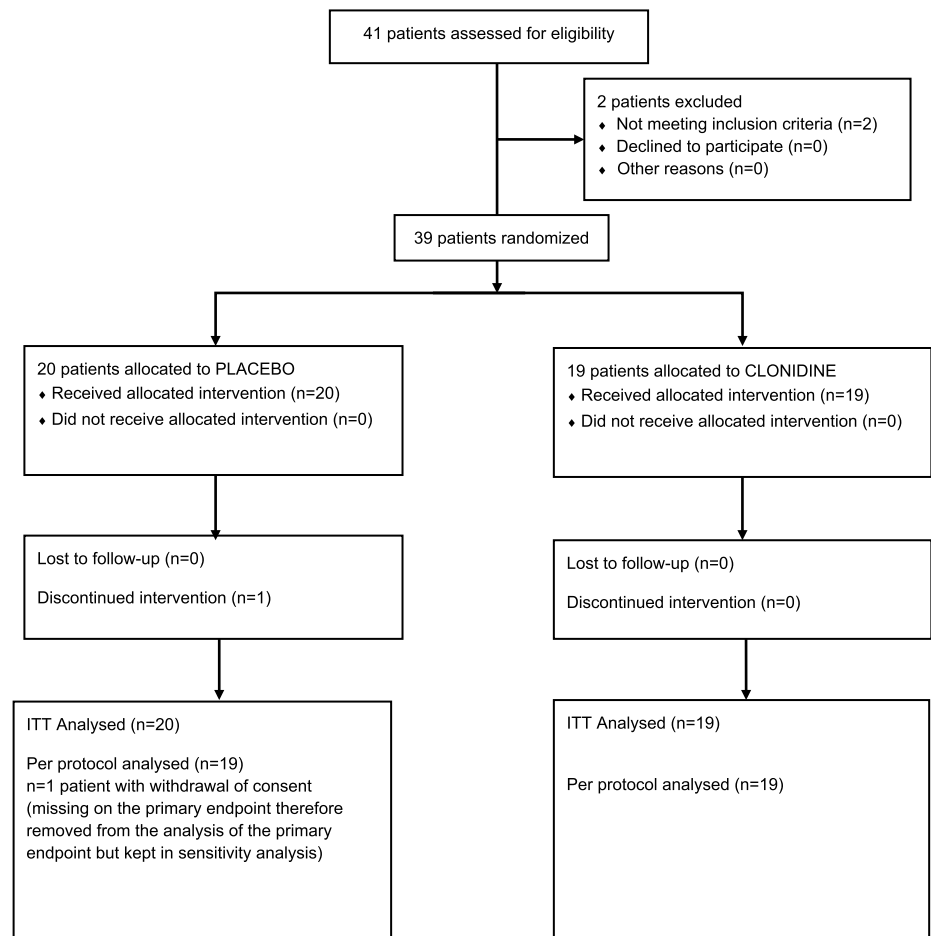


Table 1 Baseline characteristics

Variable	Placebo	Clonidine
<i>N</i>	20	19
Age (years)		
Median (range)	56 (38–75)	61 (45–72)
Mean (SD)	56.3 (9.3)	59.0 (8.2)
Male sex		
<i>N</i> (%)	13 (65)	15 (79)
Time since diagnosis (years)		
Median (min–max)	6 (2–19)	9 (2–17)
Mean (SD)	7.3 (4.7)	8.7 (4.9)
QUIP-RS total score		
Median (min–max)	23 (10–39)	27 (10–62)
Mean (SD)	23.1 (7.8)	28.8 (13.2)
Highest QUIP-RS sub-score at baseline <i>N</i> (%)		
Pathological gambling	2 (10.0)	1 (5.3)
Hypersexuality	8 (40.0)	5 (26.3)
Compulsive buying	0	1 (5.3)
Eating disorder	6 (30)	6 (31.6)
Hobbyism	4 (20)	3 (15.8)
Punding	0 (0)	3 (15.8)
Dopamine dysregulation syndrome	0 (0)	0 (0)
Total levodopa equivalent daily dosage (mg/day)		
Median (min–max)	830 (250–1808)	889 (100–2500)
Mean (SD)	946.6 (458.9)	1076.1 (655.2)
Agonist dopaminergic, (% yes)		
<i>N</i> (%)	20 (100)	15 (78.9)
MDS-UPDRS 1: (/52)		
Median (min–max)	14.5 (9–22)	14.0 (5–27)
Mean (SD)	14.2 (3.9)	14.6 (6.5)
MDS-UPDRS 2: (/52)		
Median (min–max)	9 (4–2)	11 (3–3)
Mean (SD)	11.3 (6.2)	13.0 (7.6)
MDS-UPDRS 3: (/132)		
Median (min–max)	15.5 (4–50)	17.0 (8–48)
Mean (SD)	18.9 (12.0)	20.5 (10.3)
MDS-UPDRS 4: (/24)		
Median (min–max)	4 (0–9)	4 (0–13)
Mean (SD)	3.6 (3.0)	5.21 (4.2)
MDS-UPDRS total score: (/260)		
Median (min–max)	50 (25–80)	44 (27–102)
Mean (SD)	48.8 (16.8)	53.3 (22.1)

The frequency of success in reducing QUIP-RS at 4 weeks did not differ between groups (4/20 in the placebo arm (20%) and 4/19 in the clonidine arm (21%).

In the mixed effect model, the estimated mean difference of QUIP-RS evolution between clonidine and placebo groups was -3.8 (95%CI $[-7.2; 0.4]$) (see details in supplemental data).

There was no worsening of motor or non-motor manifestations under clonidine.

The MDS UPDRS total and component scores, STAI-Y-A and B, ECMP, and the Epworth scale remained stable at 8 weeks in the ITT population. The PDQ39 score was better at 8 weeks than inclusion in the clonidine group and worse in the placebo group (Table 2).

Fig. 2 QUIP-RS total score at baseline, 4 and 8 weeks for placebo and clonidine group

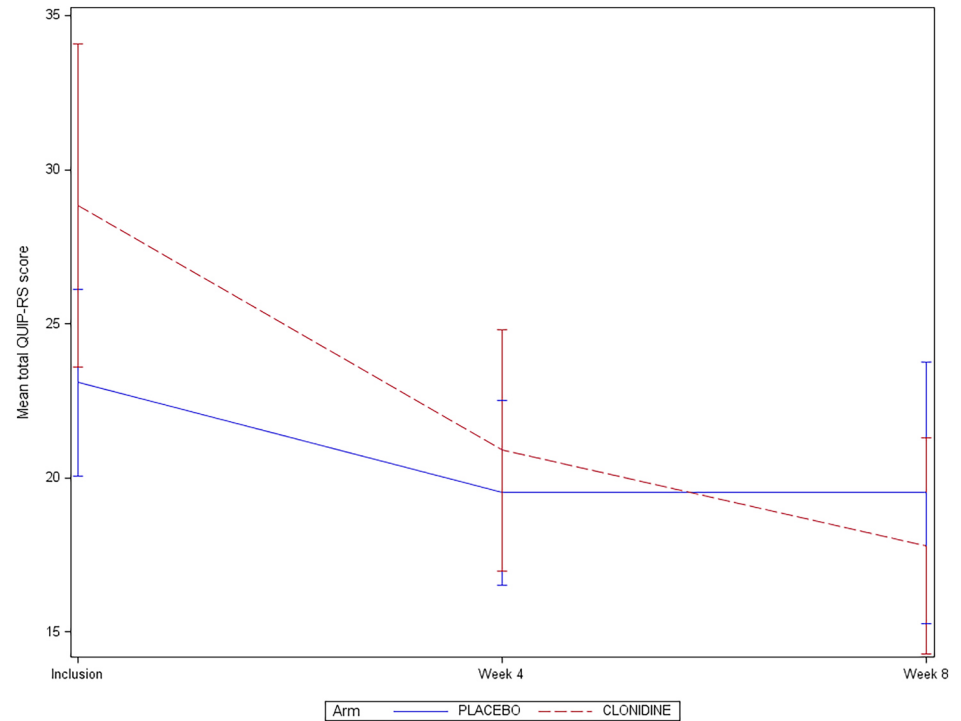


Table 2 Secondary objectives

	Inclusion		Week 8	
	Placebo (N=20)	Clonidine (N=19)	Placebo (N=20)	Clonidine (N=19)
QUIP-RS	23.10 (7.8)	28.8 (13.2)	19.5 (10.7)	17.8 (8.8)
UPDRS total score (/260) Mean (SD)	48.8 (16.9)	53.3 (22.1)	48.9 (21.9)	52.6 (21.2)
UPDRS I (/52) Mean (SD)	14.2 (3.9)	14.6 (6.5)	12.5 (5.3)	13.8 (6.7)
UPDRS II (/52) Mean (SD)	11.3 (6.2)	12.9 (7.6)	12.7 (7.9)	12.8 (8.0)
UPDRS III (/132) Mean (SD)	18.9 (12.1)	20.5 (10.3)	19.6 (11.6)	19.4 (11.1)
UPDRS IV (/24) Mean (SD)	3.6 (3.0)	5.2 (4.2)	3.7 (4.0)	4.1 (3.8)
BDI II (/63) Mean (SD)	8.8 (5.7)	9.2 (5.3)	7.1 (5.8)	8.7 (8.6)
STAI-Y-A (State) (/80) Mean (SD)	28.8 (10.3)	27.7 (11.0)	28.4 (11.9)	27.3 (9.0)
STAI-Y-B (Trait) (/80) Mean (SD)	43.6 (10.5)	38.8 (10.1)	37.4 (11.2)	36.7 (9.9)
PDQ-39 (/100) Mean (SD)	40.3 (19.5)	41.7 (23.9)	48.7 (20.9)	36.5 (31.0)
Epworth (/24) Mean (SD)	11.7 (5.1)	9.3 (4.4)	13.5 (5.4)	8.9 (5.0)
ECMP I Hypodopaminergic disorders Median (range)	4.0 (3, 6)	4.0 (2, 7)	3.5 (2, 6)	3.0 (2, 5)
ECMP II Non motor fluctuations Median (range)	1.5 (0, 3.5)	2.0 (0, 4)	1.5 (0, 3)	1.0 (0, 4)
ECMP II Hyperdopaminergic disorders Median (range)	12.5 (6, 17)	12.0 (9, 12)	7.5 (4, 11)	7.0 +

Adherence

Patients in the clonidine group had a good adherence monitored using capsule count; 74% of the patients received at least 75% of treatment doses for all periods between visits.

Safety

Overall, clonidine was well tolerated with no unexpected safety issues (Table 3). During the study, there were three positive orthostatic hypotension tests in the clonidine arm and two in the placebo arm. Orthostatic hypotension was not

Table 3 Adverse events related to the treatment

	Placebo group	Clonidine group
Fatigue	3	2
Asymptomatic bradycardia < 60 bpm but > 50 bpm	0	1
Restless legs syndrome	0	1
Fall (without orthostatic hypotension)	0	1
Nausea	0	1
Orthostatic hypotension	2	3
Sleepiness	2	1

associated with any falls or other symptoms. One fall was notified in a patient of the clonidine arm but unrelated to orthostatic hypotension. One asymptomatic bradycardia was detected during follow-up in the clonidine group (between 50 and 60 bpm). Sleepiness was reported in one patient in the clonidine arm and two patients in the placebo arm.

Discussion

This study found that clonidine was well tolerated by PD patients, and the results indicate that a phase 3 trial should be conducted. Although the rate of success was not significantly different between groups, patients receiving clonidine had a greater and faster reduction of the total QUIP-RS score at 8 weeks; it is of note that this phase 2b study was not calibrated to conclude on clonidine efficacy but on the conduct a phase 3 study. Of course, the pathophysiology of ICD in PD being still controversial and complex, we cannot exclude that targeting only the noradrenergic system could be insufficient to suppress ICD [2]. Furthermore, it is worth mentioning the importance of the placebo effect which has been reported to be strong in PD [34]. This suggests also that patients can modify their addictive behaviour thanks to a close follow-up with regular neuropsychologists interviews, neurological follow-up and support. It would be interesting to evaluate more precisely the impact of psychological intervention for the treatment of ICDs [35]. In terms of tolerance, induced orthostatic hypotension was not an issue and was found in three patients in the clonidine arm and two in the placebo arm, despite the reduction of peripheral vascular resistance induced by clonidine. Moreover, the Epworth score at 8 weeks was slightly better in the clonidine group and only one case of sleepiness was reported in the clonidine arm (2 in the placebo group), which was another potential limitation for the use of this drug in PD patients. Finally, PDQ39 was better in the clonidine group after 8 weeks of treatment.

Despite the randomisation, an imbalance was observed between groups for several variables, which, in turn, could have affected the results. Indeed, patients in the clonidine group had higher QUIP-RS total scores at baseline, meaning that they experienced more severe ICD. Moreover, patients in the clonidine groups were less systematically on agonist dopaminergic (78.9% vs 100% in the placebo group), which could, again, reflect more important ICD persisting despite the discontinuation of this treatment. Altogether, we cannot rule out that patients in the clonidine group may present more severe and more difficult to tackle ICD. It was however hard, because of the difficulty of recruiting these patients, to perfectly match them based on ICD score for this early-phase study. Although this could have affected our findings, we hypothesize that the differences of trends in terms of QUP-RS score reduction could have been more pronounced with better matching, which reinforces the need for a larger study to smooth out inter-group differences. In addition, with our mixed-effects model considering this difference, the difference in slopes remains statistically significant between the arms at the 10% alpha threshold (with $p = 0.06$).

The precise mechanisms of action of clonidine remain to be elucidated. It could, however, impact ICDs via the modification of noradrenergic transmission affecting, in turn, the inhibitory role of the prefrontal cortex; this lack of inhibitory and executive top-down control is one of the mechanisms of behavioural addictions in PD, in combination with aberrant motivation and reward circuits activations [36]. In theory, activation of presynaptic α_2 -adrenoceptors results in the inhibition of neural release of NA, but a high dose of clonidine has been reported to engage post-synaptic receptors leading to an enhancement of noradrenergic transmission [18]. Herein, the dose used is considered as high suggesting that the observed trend might be related to increased noradrenergic tonus, which fits well the positive effect of atomoxetine, a NA transporter antagonist increasing noradrenergic release, on response inhibition during a stop signal task in PD [37]. Interestingly, a higher dose is used in Tourette syndrome [25], which could suggest a higher dose of clonidine in future studies on ICDs in PD, but it seems more appropriate that a longer treatment duration be explored to maximize clonidine efficacy. This is supported herein by the clonidine-induced reduction of the total QUIP-RS score that was more pronounced after 8 than 4 weeks, suggesting a progressive action. In addition, as suggested in a recent clinical trial of atomoxetine in PD patients with apathy, the effect of atomoxetine appears dependent on locus coeruleus integrity [38] and it would therefore be useful to include this aspect using imaging approaches (MRI or PET) in future studies investigating clonidine in such patients. To conclude, this phase 2b study paves the way for a large phase 3 study with a longer treatment duration to demonstrate or rule out an effect of clonidine on ICDs in PD.

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Declarations

Conflicts of interest The authors have no competing interests to declare that are relevant to the content of this article.


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Chapitre 8. Conclusions et Perspectives

Nos résultats montrent que la compréhension de la neurotransmission noradrénergique est essentielle pour progresser sur la prise en charge de la MP.

La mise au point du traceur ^{11}C -Yohimbine (Laurencin et al., 2021) était une étape fastidieuse mais indispensable pour les études suivantes. Cela nous a permis également de cartographier pour la première fois *in vivo* chez l'homme, sur de larges populations, la densité des récepteurs α_2 (Laurencin et al., 2023). Ce travail chez le sujet sain, présenté en annexe 2, contribue à mieux comprendre leur distribution dans le cerveau, mais alerte aussi sur la nécessité d'ajuster les études sur le sexe des participants, des différences significatives étant constatées.

Sur le plan physiopathologique, notre étude d'imagerie chez les patients (Chapitre 6) met en évidence l'altération substantielle et multimodale du système noradrénergique dans la MP et son implication dans la symptomatologie motrice et non motrice. Ces éléments supportent l'hypothèse d'un phénotype noradrénergique de la MP comme proposé par Chaudhuri (R. C. K et al., 2023). Dans cet article, Chaudhuri et al, rappellent que diverses études de phénotypage clinique, étayées par des données neuropathologiques et d'imagerie, suggèrent l'existence d'endophénotypes distincts de la MP de manière précoce. Le déclin du système noradrénergique chez les patients atteints de MP, se traduirait par un sous type avec une prédominance de symptômes non moteurs, au premier plan desquels les TCSP, la douleur, l'anxiété et la dysautonomie. D'un point de vue moteur, ces patients présenteraient un phénotype akinéto-rigide principalement akinétique qui peut être compliqué par un freezing et une anxiété à long terme (ibid). Le phénotype de ces patients correspond étroitement au modèle "body first".

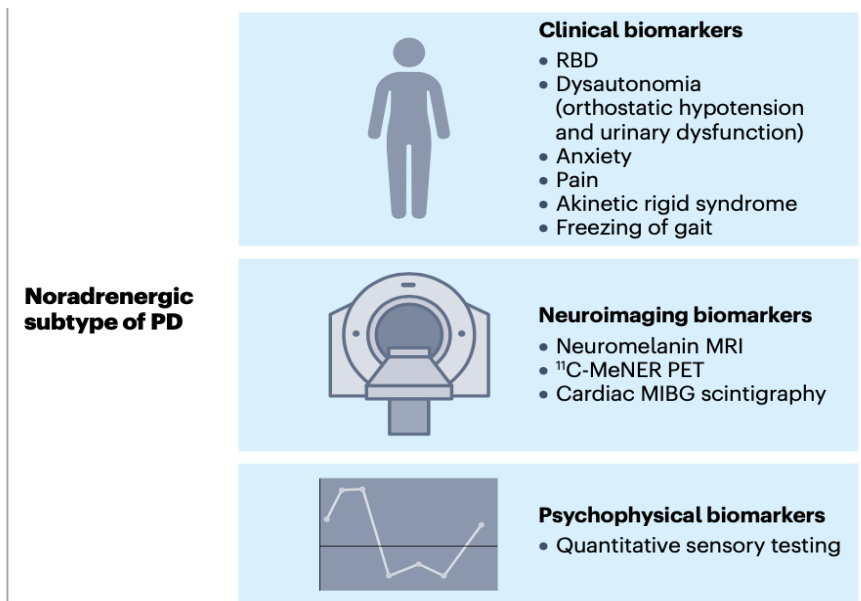


Figure 11 : Identification du sous-type clinique noradrénergique de la maladie de Parkinson. Issu de Chaudhuri et al. (R. C. K et al., 2023).

Notre étude renforce l'idée d'une influence du système noradrénergique sur les symptômes moteurs de la MP en montrant la présence d'une altération de la transmission noradrénergique dans le cortex moteur chez les patients atteints de la MP. En outre, la perte de neurones pigmentés dans le LC était négativement corrélée à la bradykinésie et aux fluctuations motrices. Inversement, le signal du LC était mieux préservé chez les patients avec un score de tremblement plus élevé. En outre, la disponibilité des récepteurs α_2 dans le thalamus diminue avec l'intensité du tremblement. Nos résultats confortent donc l'idée que le dysfonctionnement noradrénergique peut contribuer aux symptômes moteurs de la MP. Nous n'avons pas des patients à des stades évolués de la MP et notamment très peu de patients avec du freezing, ce qui peut expliquer l'absence de corrélation. Des études ciblées sur cette population serait intéressante. Sur le plan non moteur, nos résultats mettent en avant un rôle du système noradrénergique dans l'anxiété, l'apathie, la fatigue et la constipation. Des études supplémentaires sont toutefois nécessaires avec des échelles dédiées concernant notamment l'anxiété et l'apathie. Enfin, dans notre étude, il est confirmé l'absence de corrélation apparentes entre la dégénérescence du LC et des terminaisons noradrénergiques comme déjà montré par Doppler et al. (Doppler, Kinnerup, et al., 2021). Ces résultats suggèrent que les récepteurs subissent des changements adaptatifs qui rendent leur disponibilité non proportionnelle à l'ampleur de la mort neuronale dans le LC.

D'un point de vue pharmacologique, notre essai de phase 2b (Chapitre 6) destiné à tester l'effet de la clonidine sur les TCIs est négatif. Il serait toutefois intéressant de réaliser un essai de phase 3 car la présence d'un critère trop strict a pu limiter nos résultats. De plus, l'effet de la clonidine n'est pas complètement nul et il est probablement limité par l'effet placebo. Si nos données semblent encourageantes pour la mise en place d'essais cliniques ciblant les récepteurs α_2 adrénergiques dans la MP (notamment par la bonne tolérance de ces traitements et leur potentielle efficacité), de futures études précliniques nous semblent encore nécessaires pour mieux comprendre le rôle spécifique des récepteurs α_2 . En effet, les perspectives thérapeutiques visant les voies noradrénergiques centrales sont potentiellement considérables, mais nécessitent au préalable une compréhension claire des mécanismes d'action et de modulation de la NA.

Dans le futur, des études supplémentaires avec des patients à différents stades de la maladie mais aussi sur différents sous-types de patients sont nécessaires. Notamment, le degré d'atteinte noradrénergique sera un élément important à prendre en compte, du fait du fonctionnement particulier du système noradrénergique. De plus, si la ^{11}C -Yohimbine possède l'avantage de donner une image globale de la densité des récepteurs α_2 , elle ne permet pas de différencier les différents sous-types de récepteurs aux propriétés fonctionnelles probablement spécifiques (Slater et al., 2022). Ce d'autant plus que les cibles thérapeutiques de certains traitements sont plus spécifiques de certains sous type de récepteurs α_2 (la guanfacine par exemple cible préférentiellement les $\alpha_2\text{A}$). Enfin, la capacité d'explication des phénomènes de variation de fixation sera limitée dans la mesure où il sera impossible de savoir si ces effets proviennent d'une modulation des afférences présynaptiques ou de la densité des récepteurs post-synaptiques. Il est donc essentiel également de caractériser l'activité des transporteurs noradrénergiques pour comprendre sans ambiguïté la complexité des mécanismes présynaptiques et leur plasticité. En nous appuyant sur nos développements méthodologiques récents, notre prochain objectif est de compléter la collection de ligands noradrénergiques du CERMEP en synthétisant et en évaluant le radiotracer ^{11}C -ORM-13070 (traceur des récepteurs $\alpha_2\text{C}$) et le radiotracer ^{11}C -MeNER (traceur du NET). Ces développements ont d'ores et déjà été planifiés pour les prochaines années. Le ^{11}C -ORM-13070, selon les premières études de Lehto et collaborateurs (Lehto et al., 2016; Lehto, Hirvonen, et al., 2015; Lehto, Johansson, et al., 2015), permet de mesurer la densité des récepteurs $\alpha_2\text{C}$ chez l'homme. Bien que le rôle spécifique des récepteurs $\alpha_2\text{C}$ dans les fonctions altérées dans la MP soit encore flou, on peut supposer qu'ils jouent probablement un rôle substantiel. En effet, le ciblage de ces récepteurs contribuera à l'interprétation des données acquises dans le cadre de ce travail doctoral, avec un

intérêt particulier concernant leur concentration striatale et leur rôle dans la modulation de la transmission dopaminergique (Rommelfanger & Weinshenker, 2007).

En conclusion, le système noradrénergique joue un rôle important dans la MP. Cette thèse confirme cette hypothèse et apporte de nouveaux éléments sur les modalités de l'atteinte de ce système. Nos travaux s'inscrivent dans la lignée des premières données d'imagerie *in vivo* du système noradrénergique dans la MP et de nombreuses études sont encore à réaliser pour mieux comprendre l'implication du système noradrénergique et développer des traitements efficaces.

Annexes

Annexe 1 : Tableau 1 : Récapitulatif des études TEP sur le système noradrénergique et la MP.

Annexe 2 : Article concernant la cartographie des récepteurs noradrénergiques α_2 chez

l'homme : Laurencin C, Lancelot S, Merida I, Costes N, Redouté J, Le Bars D, Boulinguez P,

Ballanger B. **Distribution of α_2 -Adrenergic Receptors in the Living Human Brain Using**

[11C]yohimbine PET. *Biomolecules*. 2023 May 15;13(5):843. doi: 10.3390/biom13050843.

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Annexe 1 - Tableau 1 : Récapitulatif des études TEP sur le système noradrénergique et la MP




Recrutement	Type d'imagerie	Résultats	Référence
15 patients avec MP 10 témoins sains	TEP ¹¹ C-MeNER	Réduction de la fixation du traceur dans le LC et le thalamus chez les patients MP par rapport aux témoins La fixation du LC était relativement préservée chez les patients atteints de la MP avec tremblement.	(Nahimi, Kinnerup, et al., 2018)
16 patients avec MP et TCSP 14 patients avec MP sans TCSP 12 témoins sains	IRM neuromélanine TEP ¹¹ C-MeNER	Les patients avec une MP et TCSP présentaient une diminution du signal de la neuromélanine du LC à l'IRM et une réduction généralisée de la fixation du ¹¹ C-MeNER plus marquée que les patients avec une MP sans TCSP	(Sommerauer, Fedorova, et al., 2018)
17 TCSP idiopathique 30 patients avec MP sans TCSP 11 témoins sains	TEP ¹¹ C-MeNER IRM neuromélanine Scintigraphie ¹²³ I-MIBG TEP ¹⁸ F-DOPA TEP ¹¹ C-donepezil	Réduction du signal neuromélanine dans le LC chez les patients avec TCSP et patients avec MP Fixation du ¹¹ C-MeNER plus faible dans le thalamus et le noyau rouge pour les patients TCSP par rapport aux témoins, mais différence significative uniquement dans une analyse post hoc dans le thalamus gauche	(Knudsen et al., 2018)
30 patients avec MP 12 témoins	TEP ¹¹ C-MeNER	Réduction de la fixation du ¹¹ C-MeNER dans le cortex moteur primaire sans lien avec l'atrophie., Les patients ayant un stade Hoehn & Yahr plus élevé présentaient des réductions plus prononcées de la fixation	(Sommerauer, Hansen, et al., 2018)
53 patients avec MP 40 témoins sains	IRM neuromélanine TEP ¹¹ C-MeNER	La réduction du contraste IRM était limitée au LC moyen et caudal. La fixation du traceur était plus faible chez les patients dans toutes les zones examinées. Pas de corrélation entre le contraste IRM du LC et la densité des transporteurs de noradrénaline.	(Doppler, Kinnerup, et al., 2021)
65 patients avec MP (dont 28 avec tremblement) 28 témoins sains	TEP ¹¹ C-MeNER	Diminution de fixation du traceur chez les patients par rapport aux témoins, La diminution de fixation était moins marquée pour les patients tremblants dans le LC et le thalamus.	(Kinnerup et al., 2021)
52 patients avec MP (16 sans freezing, 10 avec freezing dopa sensible, 21 avec freezing résistant)	TEP ¹¹ C-MeNER	Réduction significative et globale de la fixation dans le groupe freezing dopasensible par rapport au groupe sans freezing et régionalement dans le lobe frontal, le thalamus gauche et droit, le lobe temporal et le LC avec l'effet le plus fort obtenu dans le thalamus droit	(McKay et al., 2023)

MP = maladie de Parkinson ; TCSP = troubles du comportement en sommeil paradoxal ;

Annexe 2

Article

Distribution of α_2 -Adrenergic Receptors in the Living Human Brain Using [^{11}C]yohimbine PET

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Abstract: The neurofunctional basis of the noradrenergic (NA) system and its associated disorders is still very incomplete because in vivo imaging tools in humans have been missing up to now. Here, for the first time, we use [^{11}C]yohimbine in a large sample of subjects (46 healthy volunteers, 23 females, 23 males; aged 20–50) to perform direct quantification of regional alpha 2 adrenergic receptors' (α_2 -ARs) availability in the living human brain. The global map shows the highest [^{11}C]yohimbine binding in the hippocampus, the occipital lobe, the cingulate gyrus, and the frontal lobe. Moderate binding was found in the parietal lobe, thalamus, parahippocampus, insula, and temporal lobe. Low levels of binding were found in the basal ganglia, the amygdala, the cerebellum, and the raphe nucleus. Parcellation of the brain into anatomical subregions revealed important variations in [^{11}C]yohimbine binding within most structures. Strong heterogeneity was found in the occipital lobe, the frontal lobe, and the basal ganglia, with substantial gender effects. Mapping the distribution of α_2 -ARs in the living human brain may prove useful not only for understanding the role of the NA system in many brain functions, but also for understanding neurodegenerative diseases in which altered NA transmission with specific loss of α_2 -ARs is suspected.

Keywords: α_2 -adrenoceptor; [^{11}C]yohimbine; hybrid PET/MRI; human; cartography; in vivo



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1. Introduction

The noradrenergic (NA) system has been implicated in the regulation of brain regions involved in numerous motor and non-motor functions, in particular arousal, sensory processing, attention, working memory, cognitive control, reward, mood, and emotion [1–4]. Accordingly, disruptions of NA functions have been associated with several disorders, with a potentially important role in neurodegenerative diseases [5–10]. This makes the NA system an important molecular target for drug development [11–15]. However, knowledge of the neurofunctional basis of the NA system on which such an endeavor is based is still incomplete and highly controversial. A major reason for the lack of knowledge is the lack of specific in vivo imaging tools in humans.

Detailed mapping of anatomical distribution of α_2 -adrenergic receptors (ARs) in the human brain is essential for understanding the neurochemistry of neurodegenerative and neuropsychiatric disorders. Until now, it has only been studied ex vivo using quantitative autoradiography [16–24]. Although these studies have provided important insights, they have

substantial limitations inherent to the technique. Findings obtained with autoradiography have highlighted dramatic species differences in the levels of α_2 -ARs [18] in several brain areas, making it difficult to extrapolate findings from animals to humans and complicating the interpretation of behavioral studies in rodents. The results obtained with autoradiography in humans are based on fragmentary analyses, and caveats are found in the restrictions of the tissue samples analyzed, such as samples of the human frontal cortex only related to Brodmann's area 10 [22] or Brodmann's area 9 [17,25]. Finally, autoradiography findings are limited by the sample size that can be used (ranging from 2 [26] to 22 [21] subjects).

In vivo imaging of the NA system has recently become feasible in humans with the development of a novel PET radiotracer: the [^{11}C]yohimbine [27,28]. [^{11}C]yohimbine binds with high selectivity to all α_2 -ARs subtypes [29]. This represents a great opportunity to fill in missing data in the living human brain by directly quantifying regional α_2 -AR availability. Here, for the first time, we use [^{11}C]yohimbine in a large sample of subjects to map the distribution of α_2 -ARs in the living human brain.

2. Materials and Methods

2.1. Participants

Forty-six healthy subjects (23 males (mean age \pm SD, 35.1 ± 9.4 ; range 20–50 y) and 23 females (mean age \pm SD, 35.5 ± 9 ; range 20–50 y)) were selected to participate in the study. Male and female subjects were recruited to achieve a homogeneous age distribution between 20 and 50 years old. Exclusion criteria were as follows: ferromagnetic implanted materials, claustrophobia, pregnancy, history of noradrenergic medications, history of dependence on alcohol or other drugs of abuse, diagnosis of other neurological or psychiatric disorders, and history of head trauma. None of the participants were smokers.

2.2. PET Procedures

[^{11}C]yohimbine was synthesized as previously described [29]. The radiochemical purities of syntheses used for the study were greater than 95%, with corresponding molar activities of 70 ± 29 GBq/ μmol at the end of synthesis. All subjects received an intravenous bolus injection of $370 \text{ MBq} \pm 10\%$ of [^{11}C]yohimbine. List-mode PET data were acquired, during the 90 min from the injection of the tracer, simultaneously with 3T MRI data (Dixon T1, anatomic MPRAGE T1) on a Siemens mMR Biograph system.

2.3. Image Processing

Raw PET data were motion corrected [30], and then rebinned into 24 time frame (variable length frames, 8×15 s, 3×60 s, 5×120 s, 1×300 s, 7×600 s) sinograms for dynamic reconstruction. Images were reconstructed using 3D ordinary Poisson-ordered subset expectation maximization (OP-OSEM 3D), incorporating the system point spread function using 3 iterations of 21 subsets. Sinograms were corrected for scatter, randoms, normalization, and attenuation [31]. Reconstructions were performed with a zoom of 2 in a matrix of 172×172 voxels, yielding a voxel size of $2.03 \times 2.03 \times 2.08 \text{ mm}^3$, with a 4 mm 3D post-reconstruction Gaussian filtering. Individual MRI T1 was normalized to the MNI space (Montreal Neurological Institute template of the International Consortium for Brain Mapping Project) using the Segment function of SPM 12 [32]. Labeling of the structural brain regions was performed using the multi-atlas propagation with enhanced registration (MAPER) methodology [33], and the 83-region Hammers atlas [34]. After segmentation, regional time–activity curves (TAC) were extracted, and the non-displaceable binding potential (BP_{ND}) obtained with the Simplified Reference Tissue Model (SRTM) was calculated in the different ROIs with the corpus callosum taken as the reference region [28].

2.4. Statistical Analysis

Statistical analysis was performed using Rstudio (<https://github.com/rstudio/rstudio>, accessed on 1 September 2022). Results with $p < 0.05$ were considered statistically significant. First, we conducted a coarse-grained analysis by applying a 13 ROI (Hippocampus,

Occipital Lobe, Cingulate Gyrus, Frontal Lobe, Parietal Lobe, Thalamus, Parahippocampus, Insula, Temporal Lobe, Basal Ganglia, Amygdala, Cerebellum, Raphe nucleus) \times 2 side (left, right) \times 2 sex (male, female) ANOVA. Then, we performed fine-grained analyses by fractionating the 6 main ROIs according to the Hammers atlas [34]. For each one of these main ROIs (Occipital lobe, Cingulate gyrus, Frontal Lobe, Parietal Lobe, Temporal Lobe, Basal Ganglia), a n Subregion (varying from 2 to 9 according to the ROI) \times 2 side (left, right) \times 2 gender (male, female) ANOVA was performed.

For illustrative purposes only, SPM12 was used for whole brain voxel-based analysis on the spatially normalized and smoothed parametric BP images of the 46 control subjects. To assess sex-related variability, we applied a two-sample t test between males and females, with individual BP values taken as covariates for interindividual adjustment. Statistical parametric maps of the t statistic were computed with a threshold of $p = 0.005$ uncorrected at the voxel level.

3. Results

3.1. Regional ROI Analysis

Table 1 shows BP_{ND} values for the 13 anatomical regions. The results show a main effect of region ($F(11, 4090) = 118.53, p < 0.001$) (Table 2) as well as a main effect of sex ($F(1, 4090) = 29.11, p < 0.001$) without significant difference between sides ($p = 0.1$). An interaction between sex and region ($F(11, 4090) = 2.63, p < 0.005$) indicates that significant differences between females and males are observed in the cerebellum ($p = 0.01$), the frontal and parietal lobes ($p < 0.001$), and the hippocampus ($p < 0.001$). As there was no significant difference between left and right BP_{ND}, values were pooled to determine the mean BP_{ND} and the standard deviation (SD) within each ROI (Table 1).

Table 1. Regional distribution of α_2 -ARs in the human brain.

	¹¹ C]yohimbine BP _{ND}		
	Females	Males	All
Hippocampus	0.67 ± 0.23	0.55 ± 0.17	0.61 ± 0.21
Occipital Lobe	0.57 ± 0.21	0.60 ± 0.20	0.58 ± 0.20
Cingulate Gyrus	0.55 ± 0.14	0.56 ± 0.15	0.56 ± 0.14
Frontal Lobe	0.50 ± 0.17	0.54 ± 0.16	0.52 ± 0.17
Parietal Lobe	0.45 ± 0.13	0.51 ± 0.14	0.48 ± 0.14
Thalamus	0.46 ± 0.16	0.49 ± 0.13	0.48 ± 0.15
Parahippocampus	0.42 ± 0.12	0.44 ± 0.12	0.43 ± 0.12
Insula	0.42 ± 0.13	0.43 ± 0.15	0.42 ± 0.14
Temporal Lobe	0.36 ± 0.14	0.39 ± 0.15	0.38 ± 0.14
Basal Ganglia	0.30 ± 0.18	0.32 ± 0.18	0.31 ± 0.18
Amygdala	0.29 ± 0.10	0.30 ± 0.10	0.30 ± 0.10
Cerebellum	0.23 ± 0.18	0.31 ± 0.12	0.27 ± 0.16
Raphe	0.22 ± 0.16	0.26 ± 0.18	0.24 ± 0.17

Bold values indicate an effect of sex.

Table 2. Statistical differences in [¹¹C]yohimbine binding between regions.

	Hippocampus	Occipital Lobe	Cingulate Gyrus	Frontal Lobe	Parietal Lobe	Thalamus	Parahippocampus	Insula	Temporal Lobe	Basal Ganglia	Amygdala	Cerebellum	Raphe
Hippocampus													
Occipital Lobe	ns												
Cingulate Gyrus	ns	ns											
Frontal Lobe	***	***	ns										
Parietal Lobe	***	***	***	***									
Thalamus	***	***	*	ns	ns								
Parahippocampus	***	***	***	***	ns	ns							
Insula	***	***	***	***	***	ns							
Temporal Lobe	***	***	***	***	***	***	ns						
Basal Ganglia	***	***	***	***	***	***	***	***	***				
Amygdala	***	***	***	***	***	***	***	***	**	ns			
Cerebellum	***	***	***	***	***	***	***	***	***	ns	ns		
Raphe	***	***	***	***	***	***	***	***	***	**	ns	ns	

ns: nonsignificant ($p > 0.1$), *** = $p < 0.0005$, ** = $p < 0.005$, * = $p < 0.05$.

3.2. Subregional ROI Analyses

Within the occipital lobe, a significant main effect of region is observed ($F(2, 264) = 87.5$; $p < 0.001$) showing that [¹¹C]yohimbine BP_{ND} is not different between the cuneus (0.69 ± 0.17) and the lingual gyrus (0.66 ± 0.17), two regions characterized by a stronger BP than the lateral parts of the occipital lobe (0.40 ± 0.14 , $ps < 0.001$).

Within the cingulate gyrus, a significant main effect of region is reported ($F(1, 176) = 24.6$; $p < 0.001$), showing that [¹¹C]yohimbine BP_{ND} is higher in its posterior part (PCC, 0.61 ± 0.14) than in its anterior part (ACC, 0.51 ± 0.13).

Within the frontal lobe, significant main effects of sex and regions are observed, without interaction. Males have overall higher [¹¹C]yohimbine BP_{ND} than females ($F(1, 1068) = 16.7$ $p < 0.001$). Among the frontal subregions, the highest [¹¹C]yohimbine BP_{ND} is found within the straight gyrus (0.65 ± 0.15), followed by the orbital gyrus (0.58 ± 0.16), the presubgenual ACC (0.57 ± 0.16), and the middle frontal gyrus (0.54 ± 0.15). Intermediate [¹¹C]yohimbine BP_{ND} is observed in the superior frontal gyrus (0.51 ± 0.15), the inferior frontal gyrus (0.49 ± 0.13), the precentral gyrus (0.43 ± 0.14), and the subgenual ACC (0.42 ± 0.13), while the lowest [¹¹C]yohimbine BP_{ND} is observed in the subcallosal area (0.36 ± 0.13). p -value thresholds are shown in Table 3.

Within the parietal lobe, only a significant effect of sex is observed ($F(1, 352) = 14.16$; $p < 0.001$), with males (0.51 ± 0.14) having overall higher [¹¹C]yohimbine BP_{ND} than females (0.45 ± 0.13).

Within the temporal lobe, significant main effects of sex ($F(1, 624) = 4.2$; $p = 0.04$), side ($F(1, 624) = 15.03$; $p < 0.001$), and region ($F(4, 624) = 22.2$; $p < 0.001$) are observed with no significant interaction between the three independent variables. Males (0.39 ± 0.15) have overall higher [¹¹C]yohimbine BP_{ND} than females (0.36 ± 0.14). BP_{ND} is higher on the right side (0.40 ± 0.14) than on the left side (0.36 ± 0.14). Finally, [¹¹C]yohimbine BP_{ND} is higher in the posterior temporal lobe (0.47 ± 0.13) than in a group of subregions composed of the fusiform gyrus (0.41 ± 0.13), the superior temporal gyrus (0.38 ± 0.15), and in the middle and inferior temporal gyrus (0.37 ± 0.12) which show intermediate binding levels. A lower [¹¹C]yohimbine BP_{ND} was reported in the anterior temporal lobe (0.32 ± 0.13).

Within the basal ganglia, a significant main effect of region is reported ($F(4, 440) = 60.54$; $p < 0.001$) showing that [¹¹C]yohimbine BP_{ND} is higher in the nucleus accumbens (0.41 ± 0.14), the putamen (0.40 ± 0.17), and the pallidum (0.39 ± 0.15) than in the substantia nigra (0.19 ± 0.14) and the caudate (0.17 ± 0.12).

We summarized all the BP_{ND} values in Table 4.

Table 3. Differences in [¹¹C]yohimbine binding between subregions of the frontal lobe.

	Inferior Frontal Gyrus	Middle Frontal Gyrus	Orbital Gyrus	Precentral Gyrus	Presubgenual ACC	Straight Gyrus	Subcallosal Area	Subgenual ACC	Superior Frontal Gyrus
Inferior Frontal Gyrus									
Middle Frontal Gyrus	ns								
Orbital Gyrus	****	ns							
Precentral Gyrus	ns	****	****						
Presubgenual ACC	*	ns	ns	****					
Straight Gyrus	****	****	***	****	**				
Subcallosal Area	****	****	****	*	****	****			
Subgenual ACC	ns	****	****	ns	****	****	ns		
Superior Frontal Gyrus	ns	ns	**	*	ns	****	****	***	

(ns: nonsignificant, **** = $p < 0.001$, *** = $p < 0.005$, ** = $p < 0.01$, * = $p < 0.05$).

Table 4. Subregional distribution of α₂-ARs in the human brain in fractionated ROIs. Bold values indicate an effect of sex.

	[¹¹ C]yohimbine BP _{ND}		
	Females	Males	All
Cuneus	0.67 ± 0.17	0.71 ± 0.16	0.68 ± 0.17
Lingual Gyrus	0.65 ± 0.18	0.67 ± 0.16	0.66 ± 0.17
Straight Gyrus	0.65 ± 0.15	0.65 ± 0.14	0.65 ± 0.14
Posterior Cingulate Cortex	0.60 ± 0.15	0.62 ± 0.14	0.61 ± 0.14
Hippocampus	0.67 ± 0.23	0.55 ± 0.17	0.61 ± 0.21
Orbital Gyrus	0.55 ± 0.17	0.60 ± 0.14	0.58 ± 0.16
Presubgenual ACC	0.56 ± 0.18	0.57 ± 0.15	0.57 ± 0.16
Middle Frontal Gyrus	0.49 ± 0.14	0.58 ± 0.16	0.54 ± 0.15
Anterior Cingulate Cortex	0.51 ± 0.12	0.51 ± 0.14	0.51 ± 0.13
Superior Frontal Gyrus	0.49 ± 0.15	0.53 ± 0.15	0.51 ± 0.15
Superior Parietal Gyrus	0.47 ± 0.13	0.52 ± 0.14	0.50 ± 0.14
Inferior Frontal Gyrus	0.46 ± 0.11	0.51 ± 0.14	0.49 ± 0.13
Supramarginal Gyrus	0.46 ± 0.13	0.50 ± 0.14	0.48 ± 0.14
Angular Gyrus	0.44 ± 0.14	0.51 ± 0.15	0.48 ± 0.15
Thalamus	0.46 ± 0.16	0.49 ± 0.13	0.48 ± 0.15
Posterior Temporal Lobe	0.46 ± 0.13	0.48 ± 0.13	0.47 ± 0.13
Postcentral Gyrus	0.43 ± 0.13	0.49 ± 0.14	0.46 ± 0.14
Parahippocampus	0.42 ± 0.12	0.44 ± 0.12	0.43 ± 0.12
Precentral Gyrus	0.40 ± 0.13	0.46 ± 0.14	0.43 ± 0.14
Subgenual ACC	0.42 ± 0.13	0.41 ± 0.12	0.42 ± 0.13
Insula	0.42 ± 0.13	0.43 ± 0.15	0.42 ± 0.14
Fusiform gyrus	0.41 ± 0.12	0.41 ± 0.14	0.41 ± 0.13
Nucleus Accumbens	0.40 ± 0.16	0.41 ± 0.13	0.41 ± 0.14
Lateral Occipital Lobe	0.39 ± 0.13	0.42 ± 0.14	0.40 ± 0.14
Putamen	0.37 ± 0.18	0.43 ± 0.17	0.40 ± 0.17
Pallidum	0.37 ± 0.14	0.41 ± 0.16	0.39 ± 0.15
Superior Temporal Gyrus	0.36 ± 0.14	0.39 ± 0.16	0.38 ± 0.15
Middle and Inferior Temporal Gyrus	0.37 ± 0.12	0.36 ± 0.13	0.37 ± 0.12

Table 4. Cont.

	¹¹ C]yohimbine BP _{ND}		
	Females	Males	All
Subcallosal Area	0.36 ± 0.14	0.35 ± 0.12	0.35 ± 0.13
Anterior Temporal Lobe	0.30 ± 0.13	0.33 ± 0.13	0.32 ± 0.13
Amygdala	0.29 ± 0.10	0.30 ± 0.10	0.30 ± 0.10
Cerebellum	0.23 ± 0.18	0.31 ± 0.12	0.27 ± 0.16
Raphe	0.22 ± 0.16	0.26 ± 0.18	0.24 ± 0.17
Substantia Nigra	0.20 ± 0.14	0.19 ± 0.14	0.19 ± 0.14
Caudate Nucleus	0.15 ± 0.14	0.19 ± 0.09	0.17 ± 0.12

3.3. Whole Brain Illustrations

The distribution of α₂-ARs in the living human brain can be illustrated using the average parametric images of [¹¹C]yohimbine BP_{ND} values overlaid on an average T1-weighted image of the 46 subjects (Figure 1).

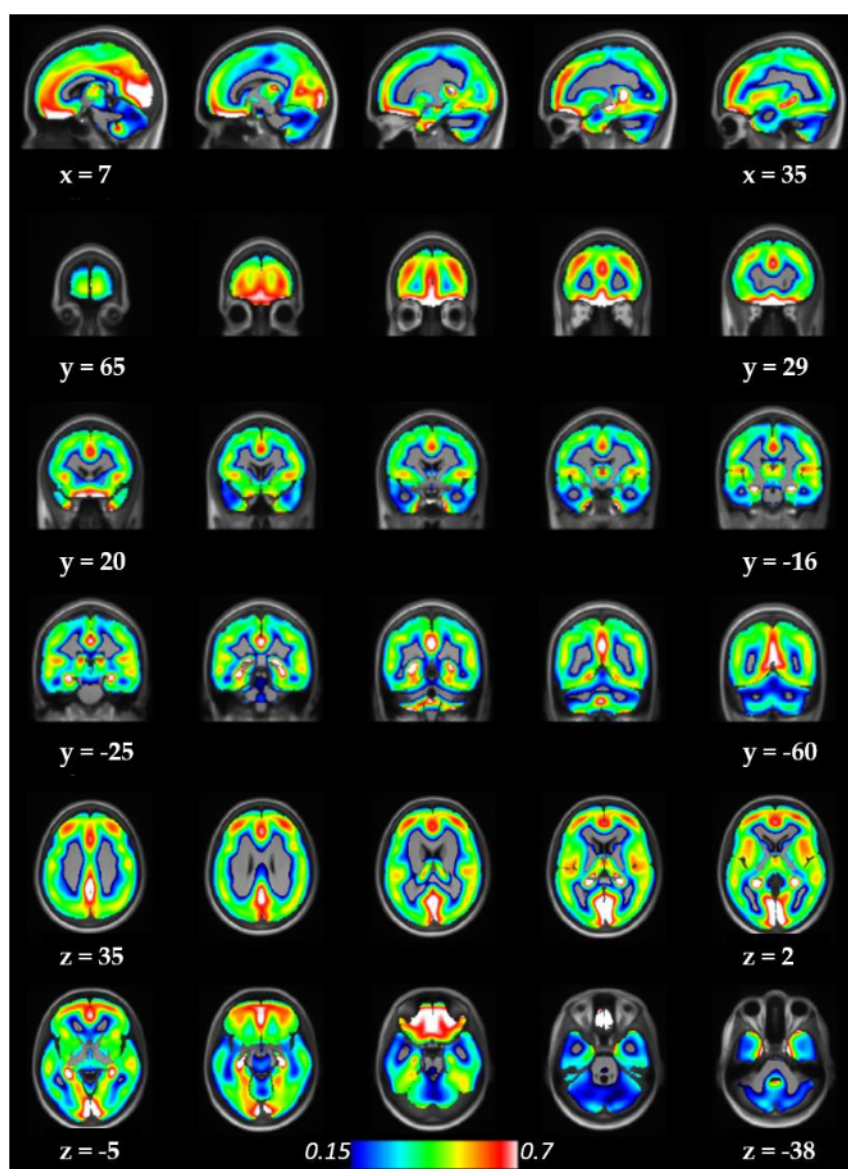


Figure 1. Widespread distribution of α₂-ARs in the living human brain. Color bar gives estimates of BP_{ND} in units of mL·cm⁻³. In order to facilitate the use of this map, the average parametric image of

BP_{ND} values of this dataset can be downloaded and used for any purpose with a simple request to the corresponding author.

The gender effect found in the main coarse-grained and fine-grained statistical analyses can be illustrated using the statistical parametric maps comparing females to males (Figure 2).

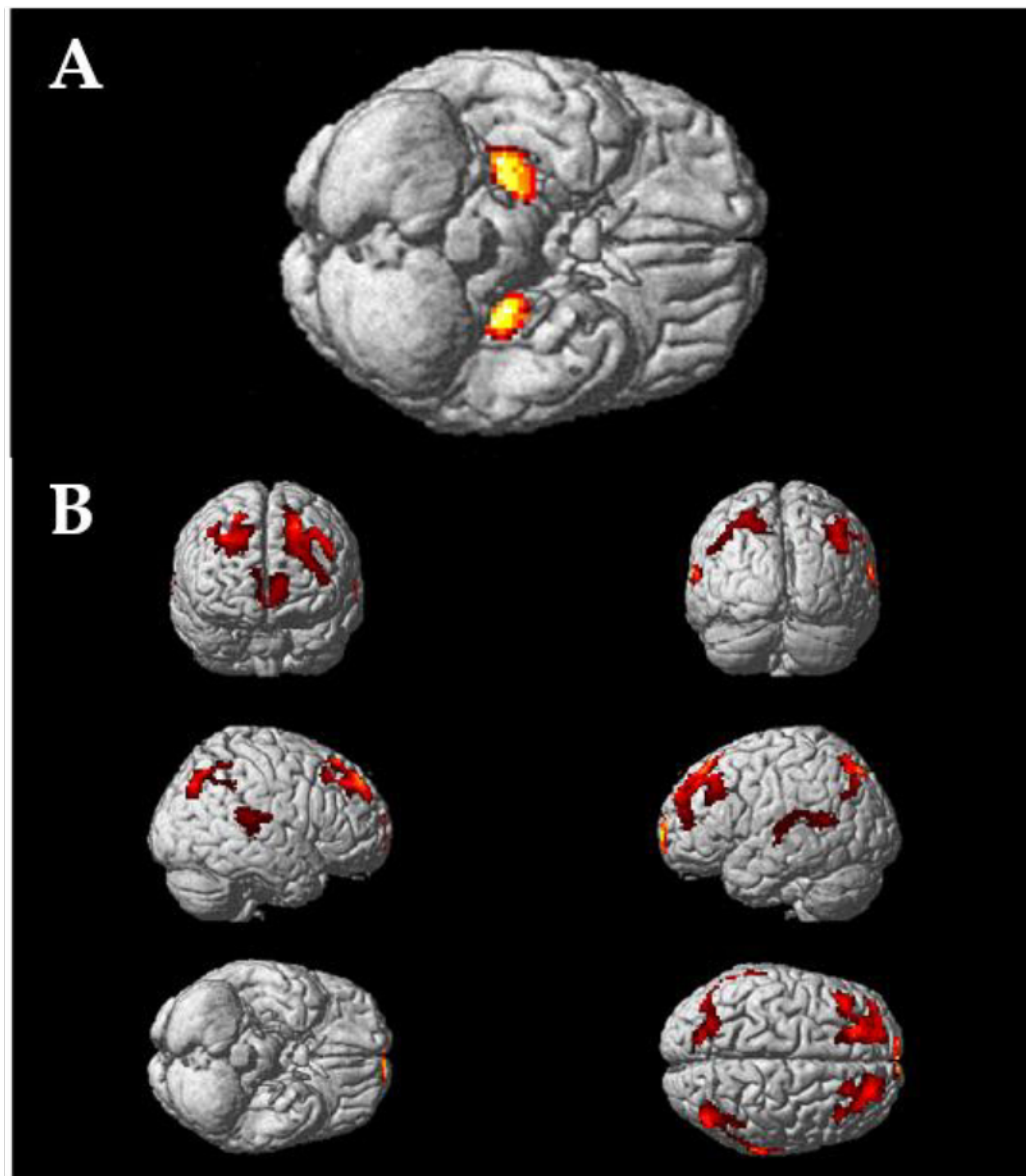


Figure 2. Statistical parametric maps comparing females to males. Data are surface-rendered onto the T1-weighted average reference brain provided by SPM12 using a voxel threshold of $p < 0.005$ (uncorrected) without cluster correction ($k = 100$ voxels). (A) Increase in [¹¹C]yohimbine binding in female compared with male subjects is observed bilaterally in the hippocampus. (B) Increase in [¹¹C]yohimbine binding in male compared with female subjects is observed in the orbital gyrus, superior frontal gyrus, and the middle and superior temporal gyrus, as well as the superior parietal and angular gyrus.

4. Discussion

In this paper, we present for the first time a complete human brain mapping of the α_2 -ARs in vivo. Our data confirm the widespread distribution of these receptors throughout the human brain. The regional distribution of [¹¹C]yohimbine binding is broadly consistent with the major findings of post-mortem human brain studies [17,19–22], further validating

the use of the radiotracer. More specifically, the present dataset provides a complete and refined picture of subregional variations in α_2 -ARs based on 35 anatomical subdivisions of the Hammers' probabilistic atlas [34,35]. This statistical mapping is intended to provide a tool for interpreting current issues on the physiological bases of NA functions in the human brain and for conducting future investigations of the role of α_2 -ARs in regulating NA neurotransmission in healthy and clinical conditions. Furthermore, this statistical mapping also raises new issues such as gender effects.

4.1. Regional Distribution of [^{11}C]yohimbine

Important regional variations of α_2 -ARs availability are observed. The highest [^{11}C]yohimbine binding was seen in the hippocampus followed by the occipital lobe, the cingulate gyrus, and the frontal lobe. Regions with moderate levels of specific binding included the parietal lobe, the thalamus, the parahippocampus, the insula, and the temporal lobe. Low [^{11}C]yohimbine binding was found in the basal ganglia, amygdala, cerebellum, and raphe nucleus. This broad overview does not contradict quantitative autoradiographic studies [16,18,20,21,24].

4.2. Subregional Variations in α_2 -ARs Availability

With the exception of the parietal lobe showing remarkable homogeneity (with intermediate to high levels of binding), parcellating the brain into anatomical subregions pinpoints important variations of [^{11}C]yohimbine binding within each structure.

The occipital lobe presents a substantial variation of specific binding ranging from very high to intermediate/low, with the medial structures of the visual cortex (cuneus and lingual gyrus) showing the highest binding of all ROIs, whereas the lateral parts of the occipital lobe are characterized by a binding level comparable to structures of the basal ganglia. This strong heterogeneity has been ignored in previous studies, either because only medial regions were examined (e.g., primary visual cortex) [20,21,23] or because global indexes of occipital binding were calculated [24].

The frontal lobe is also characterized by high heterogeneity (Table 3 and Figure 2). A high level of binding was found in the presubgenual ACC and in the straight, orbital, and middle frontal gyri. A medium level of binding was found in the subgenual ACC and in the inferior, superior, and prefrontal gyri. A low level of binding was found in the subcallosal area. These variations were not detected, or even taken in account, in previous autoradiographic studies of the frontal cortex with only a few numbers of subregions of interest (e.g., BA 9 in [17,36,37]; BA 8–9 in [38]; BA 10 in [22]). This observation may prove crucial for understanding the complex and controversial roles of the NA system in the many functions supported by the frontal lobe [39–43].

Interestingly, while the basal ganglia as a whole shows [^{11}C]yohimbine binding lying in the low range (Table 1), it is worth mentioning that there are important regional variations between the different nuclei. While the nucleus accumbens, the putamen and pallidum show intermediate binding, and the caudate and the substantia nigra exhibit almost negligible binding (Table 4). This complements the former observation obtained with experimental animal studies, which revealed higher levels of the α_{2A} -ARs in the nucleus accumbens than in the caudate [44].

Finally, subregions of the thalamus could not be assessed with the Hammers atlas. However, in contrast to the above data, heterogeneous distribution of α_2 -ARs is expected from human [21] and animal literature [45,46], with concentrations in the midline, pulvinar, and posterior (intralaminar) nuclei as well as in visual and auditory relay nuclei (geniculate nuclei).

4.3. New Issues

Our consistent sample of subjects allowed for statistical comparisons between women and men. For the first, differences were found in the hippocampus, cerebellum, and frontal and parietal lobes. Interestingly, while the [^{11}C]yohimbine binding in the hippocampus was higher for females than males, the opposite pattern was observed in the other regions.

The higher BP_{ND} could reflect changes in both pre- and postsynaptic receptors. On the one hand, it can be interpreted as reflecting a higher density of α_2 -ARs, but on the other hand, higher BP_{ND} values can also be interpreted as reflecting a higher availability of α_2 -ARs sites due to a lower concentration of NA (given that [^{11}C]yohimbine is sensitive to endogenous variations of NA concentration [47]). This effect could be explained by the fact that central α_2 -ARs function would be attenuated by estrogen concentration and, as a consequence, would be relatively “blunted” in females. Some arguments come from animal studies showing that hypothalamic α_2 -ARs decrease following estrogen treatment in ovariectomized rats [48,49], leading α_2 -AR-mediated inhibition of NA release [50,51]. Further arguments come from clinical studies showing a gender effect in the prevalence of α_2 -AR-related disorders, such as mood and anxiety [52], which are almost twice as high in females than in males [53]. Our results highlight the need to consider this gender effect in all types of studies of the NA system.

4.4. Limitations

The main limitation of the present study, and by extension of the use of [^{11}C]yohimbine PET, is the fact that it does not differentiate between the different subtypes of α_2 -ARs that have been characterized pharmacologically (α_{2A} , α_{2B} , α_{2C}) [54]. The physiological relevance of these subtypes cannot be fully elucidated without specific radioligands, but the differences that have already been identified between the different α_2 receptor subtypes must be acknowledged for interpreting [^{11}C]yohimbine PET data. In particular, the α_{2A} -subtype is known to be the main inhibitory presynaptic feedback receptor [55–57] with α_{2C} to a less extent. These two subtypes are also known as heteroreceptors that inhibit the release of dopamine and serotonin [58,59] making the problem even more complex. In addition, there are α_2 -ARs both at the pre- and postsynaptic sites, which always makes interpretation of the results difficult. Nevertheless, it is broadly considered that the presynaptic inhibitory autoreceptors located on noradrenergic neurons in the locus coeruleus play a crucial role in the regulation of the release and synthesis of noradrenaline, while the postsynaptic α_2 -ARs located in the widely distributed projection areas of the neurons throughout the cortex modulate the signaling pathways [60,61]. Finally, it must be acknowledged that we did not apply partial volume correction, meaning that these data must be interpreted with caution, in particular with regard to the relative low binding in small structures or to the absence of differences between nearby regions due to the spillover effect.

5. Conclusions

The α_2 -ARs play a key role in regulating NA neurotransmission [62,63], but their *in vivo* imaging in humans was not possible until now. Providing a technical solution, [^{11}C]yohimbine PET allowed for the mapping of their distribution in the living human brain, which will help interpreting past and future investigations on the role of the NA system in numerous brain functions in healthy as well as in various clinical conditions. This is all the more important as altered NA transmission with specific loss of α_2 -ARs is currently suspected to play a critical role in both the symptoms and progression of some neurodegenerative and mood disorders [9,22].

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