Aspects cliniques et neurofonctionnels impliqués dans le cours évolutif de la dépression : l'expérience d'une cohorte en soins courants

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Aspects cliniques et neurofonctionnels impliqués dans le cours évolutif de la dépression – L'expérience d'une cohorte en soins courants.

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Liste des abréviations

AES : Apathy Evaluation Scale
ARS : Agence régionale de Santé
ASL : Arterial Spin Labeling
BDI : Beck Depression Inventory
CCA : Cortex Cingulaire Antérieur
CCP : Cortex Cingulaire postérieur
CGI : Clinical Global Impression
CNIL : Commission nationale de l'informatique et des libertés
CPP : Comité de Protection des Personnes
CPT: Continuous performance Test
CRP: C Reactive Protein
DGOS : Direction Générale de l'Offre de Soins
DSM : Diagnostic Statistical Manual of mental disorders - Manuel diagnostique et statistique des troubles mentaux
EC : Épaisseur Corticale
ECT : Électro Convulsivo Thérapie
EDM : Épisode Dépressif Majeur
ERD : Échelle de Ralentissement Dépressif
GIRCI : Groupement Interrégional de Recherche Clinique et d'Innovation
GSRD: Group for the Study of Resistant Depression
HAMA : Hamilton Anxiety rating scale
HAS : Haute Autorité de Santé
HDRS : Hamilton Depression Rating Scale
IRM : Imagerie par Résonance Magnétique
MADRS: Montgomery and Äsberg Depression Rating Scale
MCST: Modified Card Sorting Task
MG: Matière Grise
OMS : Organisation Mondiale de la Santé
PHRCi : Protocole Hospitalier de Recherche Clinique interrégional
RDoC : Research Domain Criteria
SDT : Soins à la Demande d'un Tiers
SDRE : Soins à la Demande d'un Représentant de l'Etat
SHAPS: Snaith Hamilton Pleasure Scale
STAI: State Trait Anxiety Inventory
TNF: Tumor Necrosis Factor – Facteur de nécrose tumorale
TMS: Transcranial Magnetic Stimulation / Stimulation magnétique transcrânienne
TMT: Trail Making Test
TRD: Treatment Resistant Depression
VBM: Voxel Based Morphometry
YMRS: Young Mania Rating Scale

Résumé

Introduction : Les enjeux actuels de la recherche sur la dépression sont alimentés par la volonté de mettre en évidence des marqueurs cliniques et radiologiques permettant de mieux caractériser le trouble dépressif récurrent et ainsi repérer, par des critères objectifs, sensibles, et reproductibles, des populations à risque de présenter une résistance thérapeutique. A ce jour, les dimensions sémiologiques, associées à la dépression résistante, sont peu explorées en neurosciences. Il existe un besoin de mieux repérer les profils cliniques de patients souffrant de dépression dont l'évolution sera péjorative, de mieux comprendre les mécanismes cérébraux associés à la dépression. Le but de ce travail est d'étudier, dans un cadre de recherche clairement établi mais en routine clinique, deux dimensions sémiologiques, identifiées dans la littérature comme associées au trouble dépressif résistant, l'anxiété et l'apathie. Ces marqueurs cliniques et leurs corrélats radiologiques seront ensuite testés dans une analyse longitudinale du pronostic à 6 mois d'une cohorte de patients souffrant de dépression.

Méthode : Les données originales de ce travail sont issues de la cohorte LONGIDEP. Cette étude prospective, naturalistique, a été menée chez 182 patients souffrant d'un épisode dépressif majeur qui bénéficiaient, dans le cadre des soins courants, d'une évaluation clinique, neuropsychologique et d'une imagerie par résonance magnétique (séquences morphologiques et de perfusion) à l'inclusion. Une nouvelle évaluation a été proposée à 6 mois de l'inclusion.

Résultats : 1) Les patients déprimés apathiques avaient un profil clinique et neuropsychologique spécifique. Ce profil était associé à des patterns physiopathologiques spécifiques à l'instar d'anomalies de la perfusion chez les déprimés apathiques. Nous n'avons pas démontré de valeur prédictive de l'apathie dans l'évolution de la dépression. 2) Les approches catégorielles versus sémiologiques/dimensionnelles dans l'étude de l'anxiété dans la dépression résistante étaient non concordantes. Les déprimés résistants présentaient une hyperperfusion amygdale centro-médiane. 3) L'anxiété trait et un pattern cognitif associé à la mémoire visuo-spatiale étaient prédictifs d'une évolution péjorative. Des anomalies structurales de régions clés, impliquées dans la régulation émotionnelle et plus précisément l'adaptation au danger/peur, étaient associées à une évolution péjorative de la dépression.

Conclusion : Des deux dimensions sémiologiques étudiées, l'anxiété apparaît être impliquées dans le pronostic de la dépression. L'étude des interrelations entre l'anxiété et les troubles de la motivation, et leur mécanismes cérébraux sous-jacents, est une perspective de recherche pour la dépression résistante. Ce travail a mis en avant la nécessité d développer la recherche sur la physiopathologie du symptôme afin d'améliorer notre compréhension des mécanismes biologiques de la dépression évoluant défavorablement.

1 Introduction

La dépression est une pathologie invalidante et récurrente (Corruble, Thuile, & Hardy, 2005). Cette maladie est la plus fréquente des pathologies mentales. La prévalence mondiale de la dépression évolue entre 10 et 15% en fonction des pays (Briley & Lépine, 2011). L'Organisation Mondiale de la santé (OMS) estime qu'elle touche environ 350 millions de personnes dans le monde (Smith, 2014). Par rapport aux autres maladies chroniques, elle augure, de loin, le plus fort taux d'handicap avec environ 76,4 millions d'années de vie vécue avec incapacité, soit 10,3% de la charge total d'handicap de l'ensemble des maladies invalidantes (à titre d'exemples : douleurs lombaires : 7,3% ; anémie : 5,9%, surdité :3%) (Smith, 2014). A l'échelle sociétale, les coûts directs (utilisation des soins) et indirects (liés au manque de productivité, absentéisme/présentéisme, non-emploi) sont conséquents et constituent un enjeu majeur de santé publique. En 2011, les dépenses ont été estimées à 36,6 milliards de dollar par an aux États-Unis d'Amérique (Briley & Lépine, 2011). La dépression expose à une surmortalité notamment cardio-vasculaire et par suicide (Briley & Lépine, 2011; Olchanski et al., 2013). Elle est largement sous diagnostiquée, souffrant de stigmatisation et de ressources de santé inadéquates (plus de 50% des pays dans le monde ont moins de 2 psychiatres pour 100000 habitants) (Smith, 2014).

Après un premier épisode dépressif caractérisé, le risque de rechute est estimé à 50%. Il s'élève à 70-80% après le second épisode (Corruble et al., 2005). La notion de « dépression résistante » a été proposée par Pierre Pichot en 1971 comme une « *dépression dont l'évolution n'est pas influencée par le traitement* » (Pichot, 1971). Depuis, plusieurs classification permettant de graduer le niveau de résistance ont été développées : Antidepressant Treatment History Form, Thase and Rush Model, European Staging Model, Massachusetts Staging Model, et le Maudsley Staging Model (Ruhé, van Rooijen, Spijker, Peeters, & Schene, 2012). Les enjeux actuels de la recherche sur la dépression sont alimentés par la volonté de mettre en évidence des marqueurs cliniques et radiologiques permettant de mieux caractériser le trouble dépressif récurrent et ainsi repérer, par des critères objectifs, sensibles, et reproductibles, des populations à risque de présenter une résistance thérapeutique. Le diagnostic actuel de la dépression se fait sur l'examen clinique et l'histoire du patient. Les formes cliniques étant hétérogènes, le diagnostic peut s'avérer parfois difficile à poser et avec des difficultés pour en apprécier le mode évolutif.

Plusieurs études se sont intéressées à identifier des facteurs cliniques associés à la dépression résistante (pour revue, (Bennabi et al., 2015)). Parmi ceux-ci, des éléments de sévérité de l'épisode dépressif prédisent la résistance thérapeutique de la dépression tels que : les éléments mélancoliques, les symptômes psychotiques, les caractéristiques

suicidaires (Balestri et al., 2016; Kautzky et al., 2018; Souery et al., 2007). De plus, certaines caractéristiques de la maladie telles que l'antécédent de non réponse au premier essai d'antidépresseur, la notion de bipolarité, le début précoce de la maladie, un nombre élevé de récurrences et la présence de symptômes résiduels, sont prédictifs d'une évolution péjorative (Dudek et al., 2010). Une étude récente, dans le cadre d'un consortium européen, le « *Group for the Study of Resistant Depression* » (GSRD), a permis de répliquer certains résultats en pointant la forte valeur prédictive de la sévérité symptomatique, du risque suicidaire, du nombre élevé d'épisodes dépressif antérieurs, et d'une comorbidité anxieuse. La valeur diagnostique de ces facteurs a été testée sur un échantillon indépendant avec un niveau de précision de 0,86 (Kautzky et al., 2018). La dimension émotionnelle de la dépression apparait donc centrale dans le pronostic de celle-ci.

Enfin, des éléments de personnalité tels que la faible dépendance à la récompense, un niveau élevé de neuroticisme (i.e. la tendance persistante à l'expérience des émotions négatives), les comportements introvertis, un moindre intérêt pour le monde environnant sont également des éléments péjorant le pronostic (Takahashi et al., 2013b, 2013a). Ces éléments de personnalité nous semblent mettre en évidence une dimension moins fréquemment étudiée dans la dépression, l'apathie. En effet, telle que définie par Marin, l'apathie est caractérisée par une diminution des cognitions, des émotions et des comportements orientés vers un but (R. S. Marin, 1991). Dans son concept originel, l'apathie s'exprime par une indifférence pour le monde environnant (R. S. Marin, 1991). Ainsi définie, l'apathie pourrait constituer un facteur de mauvais pronostic de la dépression.

Par ailleurs, plusieurs travaux se sont attachés à identifier des marqueurs radiologiques prédictifs de la réponse aux antidépresseurs ou caractéristiques du trouble dépressif résistant. L'ensemble des données d'imagerie s'intéresse aux boucles fonctionnelles impliquées dans la régulation des émotions et du système de récompense, s'inscrivant dans un réseau fronto-striato-limbique. Malgré des résultats hétérogènes, quelques données robustes émergent néanmoins. Tout d'abord, au niveau structural : l'atrophie de l'hippocampe a été décrite comme prédictive d'une moins bonne réponse au traitement antidépresseur (Fu, Steiner, & Costafreda, 2013; Gong et al., 2011). De récentes données sur l'épaisseur corticale (EC) ont montré que la diminution de l'EC au niveau du Cortex Cingulaire Postérieur (CCP) permettait de discriminer une population de patients non-en-rémission (HDRS (Hamilton Depression Rating Scale) > 7) de patients en rémission (Järnum et al., 2011). De plus, au niveau fonctionnel : une augmentation de l'activité du Cortex Cingulaire Antérieur (CCA) en phase dépressive serait prédictive d'une meilleure réponse à l'inverse de l'hyperactivité de l'insula et du striatum (Fu et al., 2013; Gong et al., 2011). Une hypoperfusion des aires frontales et du CCA, détectée en imagerie de perfusion Arterial Spin Labeling (ASL), a pu être décrite comme

caractérisant une population de patients non en rémission (Järnum et al., 2011). Le CCA, région d'intérêt dans la dépression a donc été décrite comme ayant un rôle clé dans la prédiction de la réponse au traitement antidépresseur. Il fait partie du réseau de mode par défaut (default mode network). Plusieurs auteurs ont pu évoquer le rôle central de ce réseau dans la physiopathologie de la dépression (B. Li et al., 2012; Liu et al., 2012). Une étude récente a même fait l'hypothèse que ce réseau de mode par défaut pouvait être découpé en deux sous-régions, le sous-réseau antérieur et le sous-réseau postérieur. L'activité fonctionnelle de ces deux réseaux est augmentée chez le patient en état dépressif caractérisé. La persistance d'une hyperactivité dans le réseau antérieur chez un patient déprimé en rémission serait un biomarqueur de dépression asymptomatique et d'une rechute potentielle (Liu et al., 2012). Les limites classiquement rencontrées dans les études de neuroimagerie sur la dépression sont la taille des échantillons, et le manque d'analyse longitudinale. Ces biais sont partiellement corrigés par des méta-analyses qui se heurtent la plupart du temps à l'hétérogénéité des échantillons inclus tant sur le plan clinique (dépression unipolaire vs bipolaire), que sur le plan méthodologique (modalités d'imagerie et paradigmes expérimentaux).

L'ensemble de ces données de la littérature met en exergue qu'il n'existe pas de consensus clair autour de la physiopathologie de la dépression, et ce, en partie lié à l'hétérogénéité sémiologique des patients souffrant d'un épisode dépressif. A ce jour, les dimensions sémiologiques, associées à la dépression résistante, sont peu explorées en neurosciences. En effet, les principales connaissances scientifiques sont issues de cohortes épidémiologiques rapportant des indicateurs, pour la plupart catégoriels, comme les comorbidités anxieuses. Les enjeux actuels sont donc de mieux repérer les profils cliniques de patients souffrant de dépression dont l'évolution sera péjorative, de mieux comprendre les mécanismes cérébraux associés à la dépression - dans toutes ces formes cliniques - et aider ainsi au développement de modèles physiopathologiques qui sous-tendent la résistance thérapeutique.

Le but de ce travail est d'étudier, dans un cadre de recherche clairement établi mais en routine clinique, deux dimensions sémiologiques, identifiées dans la littérature comme associées au trouble dépressif résistant, l'anxiété et l'apathie. Ces marqueurs cliniques et leurs corrélats radiologiques (basés sur l'analyse des anomalies volumétriques de la substance grise) seront ensuite testés dans une analyse longitudinale du pronostic à 6 mois d'une cohorte de patients souffrant de dépression.

Nous proposons d'étudier la dépression et son évolution selon deux dimensions sémiologiques :

- Les troubles de la motivation illustrés par l'apathie. Dans un premier temps, nous étudierons les spécificités cliniques et neuropsychologiques de l'apathie dans une population de patients souffrant d'un épisode dépressif. Ensuite, nous nous focaliserons sur les patterns de perfusion cérébrale de l'apathie dans la dépression.
- Les troubles émotionnels illustrés par l'anxiété. Nous nous intéresserons au lien entre l'anxiété, dans sa présentation sémiologique et catégorielle, et dépression résistante. Nous proposerons d'étudier les corrélats de perfusion amygdaliens chez les patients résistants.

Et une perspective longitudinale (figure 1) :

- Un suivi à 6 mois de la cohorte de patients ainsi créée nous permettra d'étudier les facteurs cliniques et volumétriques (par imagerie anatomique avec une analyse en Voxel Based Morphometry) associées à l'évolution péjorative de la dépression.

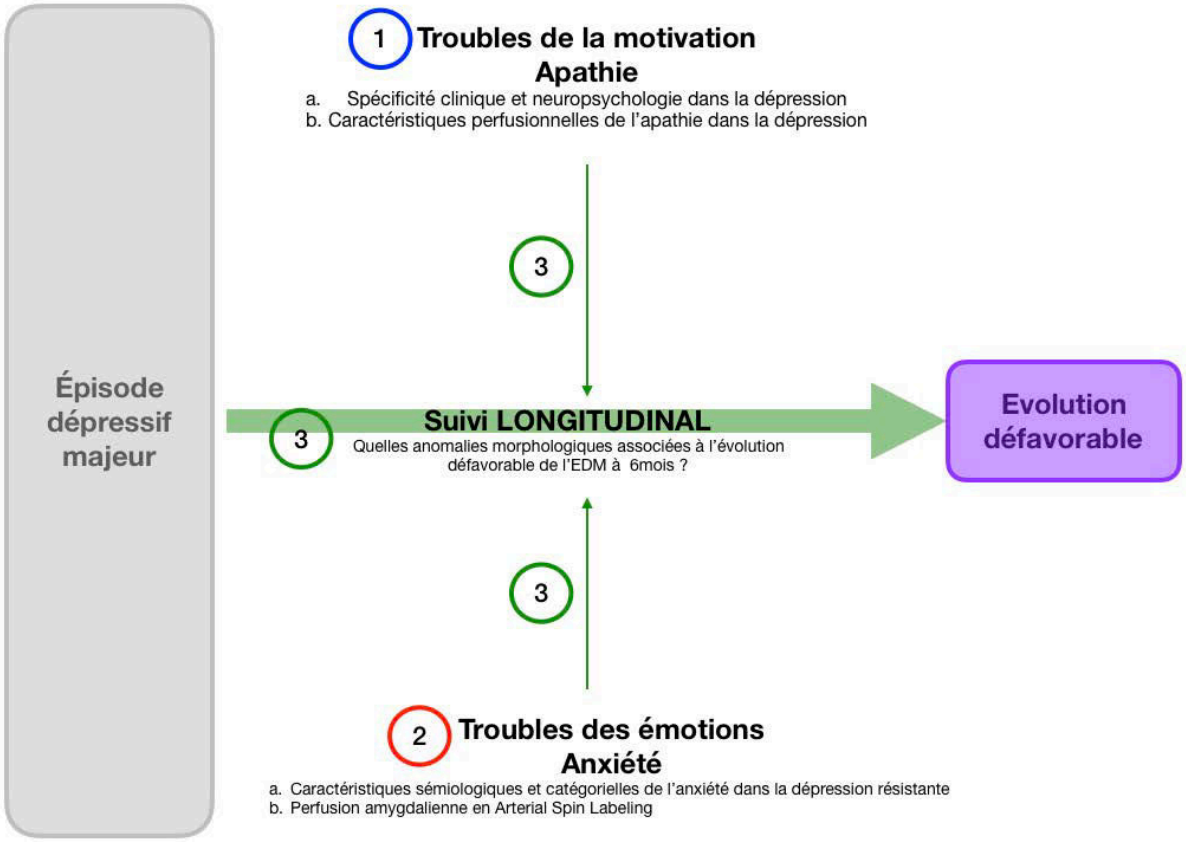

Figure 1 : Axes développés dans l'étude des mécanismes associés à l'évolution péjorative de la dépression.

2 Méthode : la cohorte de soins courant LONGIDEP

2.1 Méthodologie de la recherche

Il s'agit d'une étude prospective, naturalistique visant à explorer les modifications morphologiques et fonctionnelles impliquées dans la dépression et leur corrélation clinique notamment en termes d'évolution péjorative. Cette étude est non contrôlée, non randomisée, et ouverte.

2.2 Déroulement de la recherche

L'étude était expliquée à chaque patient répondant aux critères d'inclusion au sein du Pôle Hospitalo-Universitaire de Psychiatrie d'Adulte du Centre Hospitalier Guillaume Régnier. Une notice d'information et de non opposition leur a été remise.

Après signature de la notice d'information par l'investigateur confirmant la non opposition du patient pour participer à l'étude, chaque patient a bénéficié d'une Imagerie par Résonance Magnétique (IRM) contenant les séquences morphologiques classiquement réalisées en routine clinique ainsi que les séquences de perfusion (ASL). L'évaluation clinique et l'examen radiologique étaient réalisés dans un délai maximum de 5 jours.

Les critères d'inclusion étaient :

- Hommes et femmes âgés de plus de 18 ans ;
- Patient ayant un diagnostic (selon les critères du DSM 5) d'Episode Dépressif Majeur, et/ou de trouble dépressif récurrent unipolaire ou bipolaire, ou de dépression chronique et résistante (selon les critères de Thase et Rush). Les patients seront ainsi stratifiés selon les différents stades de la classification de Thase et Rush, échelle largement utilisée pour caractériser la résistance thérapeutique dans la dépression.
- Intensité de l'EDM avec un score minimum de 14 (MADRS) ;
- Patient en état de recevoir l'information sur le protocole ;
- Patient ayant reçu l'information sur le protocole et n'ayant pas manifesté son opposition à participer.

Les critères d'exclusion étaient :

Liés à l'IRM

- Stimulateur cardiaque ou défibrillateur implantable,
- Clips neurochirurgicaux,
- Implants cochléaires,
- Corps étrangers métalliques intra orbitaires ou encéphaliques,
- Endoprothèses posées depuis moins de 4 semaines et les matériels d'ostéosynthèse posés depuis moins de 6 semaines,
- Claustrophobie,
- Femme enceinte ou allaitante (principe de précaution),
- État hémodynamique instable, une insuffisance respiratoire aigüe, un état général précaire ou une nécessité d'une surveillance continue incompatible avec les contraintes de l'IRM,

Autres critères

- Personne majeure faisant l'objet d'une protection légale (sauvegarde de justice, curatelle, tutelle), personne privée de liberté et personne hospitalisée sous contrainte (SDT, SDRE),
- Personne souffrant d'une comorbidité psychiatrique (trouble schizophrénique, trouble schizo-affectif, trouble de la personnalité, dépendance actuelle à l'alcool ou toute substance psychoactive, troubles du comportement alimentaire, trouble obsessionnel compulsif) à l'exclusion des comorbidités anxieuses (trouble anxieux généralisé, trouble panique, état de stress post-traumatique, phobie sociale, phobie simple),
- Personne ayant une pathologie grave intercurrente au pronostic vital engagé,
- Personne souffrant d'une pathologie neurologique comorbide (toute pathologie neurodégénérative : maladie de Parkinson, maladie d'Alzheimer, maladie à corps de Lewi, démence autre, sclérose en plaque ; tout processus intracrânien expansif),
- Personne aux antécédents de traumatisme crânien grave (ayant occasionné un coma) et/ou avec lésion IRM décelable,
- Personne ayant un antécédent d'IRM cérébrale anormale.

2.2.1 Bilan clinique et neuropsychologique

L'évaluation clinique était conduite durant un temps de consultation habituelle avec un médecin psychiatre et un neuropsychologue avec les échelles suivantes :

Psychiatriques

- Apathy Evaluation Scale (AES)
- Échelle de ralentissement (ERD)
- Young Mania Rating Scale (YMRS)
- Montgomery Asberg Depression Rating Scale (MADRS)
- STAI (State Trait Anxiety Inventory) forme A et B
- Questionnaire abrégé de Beck
- SHAPS (Snaith-Hamilton Pleasure Scale)

Neuropsychologiques

- Test de latéralité dit Échelle d'Edinburgh
- Empan verbal direct et inversé
- Échelle de Mattis
- Fluences verbales
- Test Stroop
- Trail Making Test (TMT) part A et B
- Modified card sorting test (MCST)
- Continuous performance Test III (CPT III)

2.2.2 Bilan radiologique

L'IRM encéphalique dans le cadre du bilan de la maladie dépressive devient très fréquemment prescrite. Dans le cadre de ce protocole, elle était justifiée par trois indications principales :

- L'élimination d'une cause organique aux symptômes présentés par les patients devant le caractère chronique et récidivant de la dépression. Selon l'HAS, en 2009, dans son guide « Affections longue durée » sur les troubles dépressifs récurrents et résistants, l'indication d'imagerie cérébrale est argumentée comme suit : « bilan initial, suivi

(réévaluation d'une dépression chronique, aide au diagnostic étiologique d'une démence) » (Haute Autorité de Santé, 2009),

- L'utilisation croissante de la stimulation magnétique transcrânienne répétée (rTMS) comme thérapeutique des pathologies dépressives réfractaires. Depuis le début des années 2000, la littérature sur l'efficacité globale de la rTMS dans le traitement de la dépression récurrente et résistante converge vers sa promotion. Ainsi, en novembre 2009, la Food Drug Administration a donné son accord pour: « l'indication de la rTMS dans le traitement des épisodes dépressifs majeurs (EDM) ayant résisté à au moins un traitement médicamenteux antidépresseur » (Lefaucheur et al., 2011). Ces recommandations ont été également émises en France : « on peut proposer la rTMS en cas d'échec d'un traitement antidépresseur bien conduit en dehors des dépressions avec caractéristiques psychotiques pour lesquelles le recours à l'Electro-Convulsivo-Thérapie (ECT) est recommandé » (Lefaucheur et al., 2011) tout comme par la Canadian Network for Mood and Anxiety Treatment (Kennedy et al., 2009). En outre, de plus en plus d'études concernant l'optimisation des procédures de rTMS ont montré la supériorité du ciblage via la neuronavigation comparé à l'utilisation de la méthode empirique des 5 cm (Schönfeldt-Lecuona et al., 2010). L'indication de l'IRM cérébrale morphologique dans la pratique de la rTMS est double. D'une part dans le bilan pré-thérapeutique, d'autre part dans le cadre de la neuronavigation,
- Le substrat neurobiologique des pathologies psychiatriques pousse à la recherche d'anomalies morphologiques et fonctionnelles (Giacobbe, Mayberg, & Lozano, 2009; M. L. Phillips, Drevets, Rauch, & Lane, 2003a, 2003b).

Une IRM était pratiquée dans le service de radiologie du CHU de Rennes sur une IRM Siemens 3 Tesla Verio (Siemens HealthCare, Erlangen, Germany). Le patient était installé dans l'IRM, avec mise en place d'une antenne standard de type « HEAD ». L'examen se déroulait dans les mêmes conditions qu'un examen d'IRM standard.

L'ensemble de cet examen était composé des séquences suivantes :

- Séquences anatomiques : 3D T1, T2,
- Séquence de perfusion : ASL (pulsée et pseudo-continue).

La durée totale de l'examen était d'environ 30 minutes, installation du patient comprise.

La réalisation de l'IRM ne nécessitait pas de préparation particulière, si ce n'est de rassurer le patient et de lui expliquer le déroulement de l'examen, sa durée et le bruit produit

par la machine. C'est un examen pratiqué en routine clinique qui ne présente pas de risque particulier pour le patient si l'on tient compte des contre-indications.

Le compte rendu de l'examen était rédigé à partir des images du protocole standard et transmis au service prescripteur dans les délais habituels.

2.2.3 Suivi longitudinal

Chaque patient bénéficiait d'un suivi longitudinal avec 4 visites supplémentaires à la visite d'inclusion. A chacune de ces visites, le bilan clinique standardisé, réalisé à l'inclusion, était passé. Chacun de ces bilans se réalisait en consultation médicale et neuropsychologique. Un résumé de l'ensemble des phases d'évaluation est résumé en figure 2.

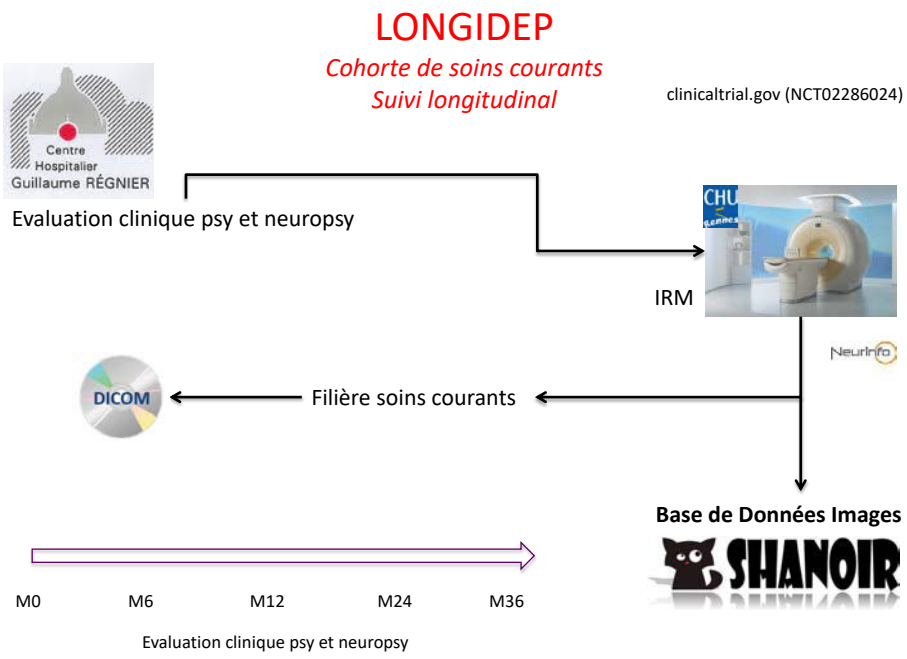

Figure 2: Procédure d'inclusion et de suivi de la cohorte LONGIDEP. M : mois.

2.3 Aspects réglementaires

Le projet LONGIDEP a bénéficié d'un accord du Comité de Protection des Personnes (CPP) Ouest VI (Brest) le 09 avril 2014. Cette étude a été déclarée à la Commission Nationale Informatique et Liberté (CNIL) le 16 juin 2014 (n° de déclaration : 1774329). L'étude est enregistrée sur clinicaltrial.gov (NCT02286024).

2.4 Aspects techniques

L'ensemble des données images est anonymisé et stocké sur le serveur Shanoir. Shanoir est un environnement de stockage et d'organisation (basé ontologie) de données d'imageries, ainsi que leurs métadonnées, destinées à la recherche (Barillot et al., 2016). Il s'agit d'un serveur accessible par navigateur web. L'acquisition des données, la validation des données, la supervision technique, l'anonymisation, le transfert et l'archivage des données sur le serveur Shanoir était réalisé par un investigateur de l'étude ou un membre de la plateforme d'imagerie Neurinfo.

2.5 État des lieux de la cohorte LONGIDEP

Les premières inclusions ont eu lieu en novembre 2014.

Visite	Nombre de patients
Initiale	182
A 6 mois	79
A 12 mois	41
A 24 mois	26
A 36 mois	4

Tableau 1: état des lieux de la cohorte LONGIDEP au 19/10/2018.

3 Résultats

3.1 Les troubles de la motivation dans la dépression, le cas de l'apathie :

Comme évoqué en introduction, les troubles de la motivation ont pu être identifiés dans la littérature comme prédictif d'une évolution péjorative de la dépression. Les données existantes ont pointé le lien entre traits de personnalité et pronostic de la dépression (Takahashi et al., 2013b, 2013a). Aucune donnée à ce jour ne s'est intéressée aux troubles de la motivation dans leur approche syndromique telle que l'apathie. Dans cette première partie de travail, nous proposons d'étudier l'apathie dans la dépression. En effet, l'apathie, dans sa description princeps faite par Marin, est caractérisée par une diminution des cognitions, émotions, comportements orientés vers un but. Il s'agit d'une entité transnosographique qui a été le plus étudiée dans les maladies neurodégénératives telles que la maladie d'Alzheimer, la maladie de Parkinson, ou le traumatisme crânien, ou psychiatriques comme la schizophrénie (Cathomas, Hartmann, Seifritz, Pryce, & Kaiser, 2015; Drapier et al., 2006; R. S. Marin, 1990; G. Robert et al., 2012; Starkstein & Leentjens, 2008).

Peu ou pas d'étude ne s'est intéressée à ce syndrome dans la dépression. Malgré tout, il existe un argument cliniquement significatif pointant l'apathie comme un syndrome permettant de différencier deux types de dépression ; les déprimés apathiques, indifférents à leur environnement, à faible expression émotionnelle et les non-apathiques se plaignant plus fréquemment d'angoisse, de souffrance morale. Nous formulons l'hypothèse que l'apathie, telle que définie par Marin, constitue un marqueur motivationnel permettant de distinguer deux profils de dépression avec comme hypothèse secondaire des pronostics évolutifs différents. Nous avons testé cette hypothèse au travers de deux études sur 1/ les aspects cliniques et neuropsychologiques caractéristiques de l'apathie dans la dépression (partie 3.1.1) et 2/ la comparaison du débit sanguin cérébral des patients déprimés apathiques et non-apathiques (partie 3.1.2).

3.1.1 Apathy and depression: Which clinical specificities?

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Apathy and depression: Which clinical specificities?

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ABSTRACT

Background: Ever since it was first defined, apathy has been described as a transnosographic entity, involved in many neuropsychiatric disorders not least depression. Owing to its impact on therapeutic outcomes and morbidity, this clinical dimension is of considerable interest in the pathophysiology of depression. However, the literature does not adequately emphasize the links between depression and apathy.

Methods: In a prospective open-cohort study of 70 depressed patients (from November 2014 to June 2015), we sought to compare the clinical and neuropsychological profiles of apathetic versus nonapathetic depressed patients.

Results: After controlling for confounding factors (age, duration of disease, Selective Serotonin Reuptake Inhibitor, Post Traumatic Stress Disorder comorbidity, Forward Span), we found negative link between apathy and anhedonia (t-value = −2.56; p = .014). Thus, we found a close to significance link between anxiety and apathy (t-value = −1.89; p = .065). Furthermore, apathetic depressed patients had cognitive deficits, notably in verbal working memory (F = 5.875, p = .04).

Conclusions: The link between anhedonia and apathy highlights the difference between the consumption and programming of pleasure. The cognitive impairments of apathetic depressed patients may have an impact on their ability to allocate resources appropriately. The relationship between anxiety and apathy has been discussed in light of lack of insight. Taken together, results indicate that the apathy dimension subtends two clinical profiles of depression, which can be viewed as different pathophysiological clusters, as they probably affect two distinct networks. Further studies are needed to test this clinical hypothesis in the light of neurobiology.

Introduction

The definition of apathy has been widely discussed over recent decades. In his initial description of it, Marin characterized apathy as a loss of motivation that is "not attributable to diminished levels of consciousness, cognitive impairment, or emotional distress" [1]. He used the terms *apathy syndrome* to refer to primary motivation loss and *apathy symptoms* when this loss is secondary to neurological or psychiatric disorders [1,2]. Several authors subsequently depicted apathy as a disorder of motivation characterized by diminished quantitative goal-oriented behaviors and cognitions [3–5]. More recently, Cathomas et al. suggested that apathy is a transdiagnostic clinical phenotype that affects motivation in 5 subdomains (self-care, exploration, social interaction, work/education, and recreation) [5]. In 2009, Robert et al. put forward diagnostic criteria for clinical practice that can be used in Alzheimer's disease and other neuropsychiatric disorders [6]. These criteria were inspired by Marin's definition. The core feature is reduced motivation over at least the 4 previous weeks, affecting at least two out of three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions), and resulting in functional impairment [6]. As reported in previous papers, apathy is a trans nosographic syndrome and can be seen in neurological disorders such as Parkinson's disease, Alzheimer's disease, traumatic brain injury, dementia, and psychiatric disorders including depression and schizophrenia [1,4,5,7,8]. We therefore suggest studying apathy as a dimension affecting different areas of mental equilibrium (i.e. affective,

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Abstract

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Introduction

The definition of apathy has been widely discussed over recent decades. In his initial description of it, Marin characterized apathy as a loss of motivation that is "not attributable to diminished levels of consciousness, cognitive impairment, or emotional distress"(R. S. Marin, 1990). He used the terms *apathy syndrome* to refer to primary motivation loss and *apathy symptoms* when this loss is secondary to neurological or psychiatric disorders (R. S. Marin, 1990, 1991). Several authors subsequently depicted apathy as a disorder of motivation characterized by diminished quantitative goal-oriented behaviors and cognitions (Cathomas et al., 2015; Levy, 2005; Starkstein & Leentjens, 2008). More recently, Cathomas et al. suggested that apathy is a transdiagnostic clinical phenotype that affects motivation in 5 subdomains (self-care, exploration, social interaction, work/education, and recreation) (Cathomas et al., 2015). In 2009, Robert et al. put forward diagnostic criteria for clinical practice that can be used in Alzheimer's disease and other neuropsychiatric disorders (P. Robert et al., 2009). These criteria were inspired by Marin's definition. The core feature is reduced motivation over at least the 4 previous weeks, affecting at least two out of three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions), and resulting in functional impairment (P. Robert et al., 2009). As reported in previous papers, apathy is a transnosographic syndrome and can be seen in neurological disorders such as Parkinson's disease, Alzheimer's disease, traumatic brain injury, dementia, and psychiatric disorders including depression and schizophrenia (Cathomas et al., 2015; Drapier et al., 2006; R. S. Marin, 1990; G. Robert et al., 2012; Starkstein & Leentjens, 2008). We therefore suggest studying apathy as a dimension affecting different areas of mental equilibrium (i.e. affective, cognitive, behavioral).

There is growing interest in studying motivation loss in depression because of its detrimental impact on therapeutic outcome (Bech et al., 2015; R. Uher et al., 2012) and mortality (Lavretsky et al., 2010). A number of studies have shown that there are considerable inconsistencies in the terminology used to define motivation deficits, including *apathy*, *amotivation*, *avolition*, *anhedonia*, *psychomotor retardation*, *fatigue*, and *anergy* (Calabrese et al., 2014). Ambiguities related to the categorical approach to apathy concern the relationship between apathy and depression. Although apathy can occur in the absence of depression, most studies show that a considerable proportion of patients exhibit both apathy and depression (Andersson, Krogstad, & Finset, 1999; Starkstein & Leentjens, 2008). This highlights the overlap between apathy and depression (Calabrese et al., 2014). In 1993, Marin et al. addressed this issue in a study exploring the intercorrelations between scores on the Apathy Evaluation Scale (AES) and the Hamilton Rating Scale for Depression (HamD) in 107 normal aging individuals and patients with neuropsychiatric disorders (stroke, Alzheimer's

disease or major depression) (R. S. Marin, Firinciogullari, & Biedrzycki, 1993). In this study, HamD and AES scores were correlated on motivational dimensions (R. S. Marin et al., 1993). Thus, there is still a debate about some other clinical features of depression, such as abulia, athymhormia, psychic akinesia, and the negative syndrome of schizophrenia. According to some authors, these can be used for the differential diagnosis of apathy (Starkstein & Leentjens, 2008), whereas Marin and Wilkosz hypothesized a continuum of diminished motivation from the less to the more severe: apathy – abulia – akinetic mutism (Robert S. Marin & Wilkosz, 2005). Taken together, results indicate that apathy and depression overlap to a considerable degree, although there is a lack of consensus as to exactly how far. Even though apathy and depression share many common features, such as the loss of interest or pleasure, loss of goal-directed cognitive activity, reduced emotions, and cognitive dysfunction (e.g. executive function deficits) (Bredemeier, Warren, Berenbaum, Miller, & Heller, 2016; Kirsch-Darrow, Marsiske, Okun, Bauer, & Bowers, 2011), depressive mood disorder is extremely heterogeneous, with a high disparity of expression across the emotional and motivational dimensions. Consequently, clinical data on apathy in depression remain weak in the psychiatric literature. The reported prevalence of apathy in patients with depression varies considerably across studies, ranging from 32% to 94% (R. S. Marin et al., 1993; Moayedoddin et al., 2013; Mulin et al., 2011; Starkstein, Petracca, Chemerinski, & Kremer, 2001), owing to methodological issues (scales, definitions) and differences in population characteristics (age, sample, comorbid neurodegenerative disorders or dementia) (R. S. Marin et al., 1993; Moayedoddin et al., 2013; Mulin et al., 2011; Starkstein et al., 2001). This highlights the difficulty of gaining a clear description of the apathy dimension of depression without examining the mechanisms behind each dimension of apathy, notably the emotional and motivational dimensions (Starkstein & Leentjens, 2008).

To our knowledge, no study has so far specifically sought to identify the clinical profiles of patients with depression and apathy. We set out to address this issue by comparing the clinical and neuropsychological characteristics of apathetic (Ap) versus nonapathetic (Nap) patients with depressive mood disorder. The aim of this study was to 1) determine the prevalence of apathy in a sample of currently depressed patients in routine care, and 2) compare the clinical profiles (establishing using a standardized assessment) of Ap versus NAp depressed patients. We predicted that the two groups would present significantly different profiles that could help to better define the boundary of apathy in depression without dementia or neurodegenerative disorders.

Methods

Patient population

We included 70 patients who were experiencing a depressive mood episode (DME) according to DSM-IV criteria. The inclusion criterion was a Montgomery and Äsberg Depressive Rating Scale (MADRS (22)) score ≥ 15, with or without a personal history of depressive mood disorder (unipolar or bipolar subtype). Exclusion criteria included other Axis-I disorders (except for anxious comorbidities such as posttraumatic stress disorder, social phobia, generalized anxiety disorder or panic disorder) which were explored using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Patients with severe chronic physical illness were not included. Other exclusion criteria were diagnosed neurodegenerative disorders (e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease) a history of significant head injury, or diagnosed dementia (according to DSM-IV criteria). All patients underwent a neurological examination by a trained physician. On the basis of this assessment, no patient had any clinical sign of dementia nor abnormal neurological examination.

Study design

We conducted a prospective open-cohort study between November 2014 and June 2015. Depressed patients were recruited from the adult psychiatry department of our hospital. A complete description of the study was given to the participants, and their written informed consent was obtained. The study was approved by an ethics committee and registered with www.clinicaltrial.gov (NCT02286024). After they had been recruited, patients underwent a structured clinical interview in a single session.

Psychopathological and neuropsychological assessment

Patients were assessed by a trained psychiatrist. Sociodemographic (age, sex, education) and disease characteristics (disease duration, duration of current episode, number of DMEs, previous suicide attempts) were collected. Patients were clinically assessed on the intensity of their depression (MADRS (Montgomery & Asberg, 1979) and Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)), apathy (AES Clinician Version (R. S. Marin, Biedrzycki, & Firinciogullari, 1991)), psychomotor retardation (ERD (Jouvent, Frechette, Binoux, Lancrenon, & des Lauriers, 1980), anxiety (State-Trait Anxiety Inventory – YA and YB form (STAI-YA, STAI-YB) (Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A., 1983)), manic/hypomanic symptomatology (Young Mania Rating Scale (R. C. Young, Biggs, Ziegler, & Meyer, 1978)), and anhedonia (Snaith Hamilton Pleasure Scale

(SHAPS) (Snaith et al., 1995)). The choice of these scales was dictated by the desire to address the relationship between apathy and other core dimensions of depression, such as sadness (MADRS), anhedonia (SHAPS), and anxiety (MADRS, STAI).

In order to assess the relationship between cognitive dysfunction and apathy, participants underwent a neuropsychological assessment by a trained neuropsychologist. This assessment lasted one hour. We used the Mattis Dementia Rating Scale (29) to assess overall cognitive functioning. The Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-III (Wechsler D., 1997)) was used to examine verbal short-term memory (Wechsler D., 1997), and the Digit Symbol Coding subtest to measure processing speed and attention. A separate set of tests was used to assess executive functions: the categorical and phonological fluency test (Cardebat, Doyon, Puel, Goulet, & Joanette, 1990), a version of the Stroop test (Stroop, 1935), the Trail Making Test (Reitan, 1958), and Nelson's modified version of the Wisconsin Card Sorting Test (MCST (Nelson, 1976).

Statistical analyses

Statistical analyses were performed on all included and assessed patients (intention-to-treat analysis) with R software (http://www.R-project.org/). All results are reported as means ± *SD* for continuous variables, and rates for discrete variables. In order to avoid type I error (in the context of multiple comparison), the significance threshold for all tests was set at 1% ($p < 0.01$). We have conducted our analysis in two-steps:

a. First level: inter-group comparisons,

b. Second level: whole group correlations between apathy (AES) and anhedonia (SHAPS) and anxiety (STAI-YA) corrected by confounding factors identified in the first level.

Intergroup comparisons

Patients were divided into two groups using an AES cut-off score of 42, as suggested by Marin et al. (Calabrese et al., 2014; R. S. Marin et al., 1991): AES ≥ 42 = Ap group ($n = 21$); AES < 42 = NAp group ($n = 49$). We then compared their sociodemographic and clinical variables. Owing to the different sizes of the groups, quantitative variables were compared using the Wilcoxon test, and qualitative variables were compared with either the Fisher test or a chi-squared test, where applicable.

Whole-group analyses

In a second-step analysis, we used Pearson's correlation coefficients to study the relationships between apathy (AES total score) and two variables of interest highlighted by intergroup comparisons: state anxiety (STAI-YA) and anhedonia (SHAPS). Using a linear model, the link between apathy and both anhedonia and anxiety was corrected by confounding factors identified in literature (age, duration of disease) and in the intergroup comparisons (SSRI treatment, PTSD comorbidity, Forward Span).

Results

A total of 70 patients were included in the study. The prevalence of apathy was 30% in our sample of depressed patients.

Whole group analyses

The sociodemographic and clinical characteristics of the whole sample are summarized in Table 1. The sample was predominantly represented by women and middle-aged individuals.

Intergroup comparisons

The results of the intergroup comparisons are set out in Tables 1 and 2. The two groups were comparable on sociodemographic. After comparing anxious comorbidities between groups, only Post-Traumatic Stress Disorder was significantly higher in apathetic group (Ap=33.33 % vs NAp=6.67%; Fisher's exact Test, p = 0.013). Significantly more apathetic patients were treated with Selective Serotonin Reuptake Inhibitors (SSRI) (Ap = 14% vs. NAp = 6%; Fisher's exact Test, p = 0.007).

Psychopathological assessment

Compared with NAp patients, Ap patients were less anxious (W = 739, p = 0.004) and less anhedonic (W = 412, p = 0.004).
When each item of the MADRS scale was considered separately, Ap patients were found to complain less of lassitude (W = 738.5, p = 0.002) than NAp patients.

Neuropsychological assessment

We included the anxiety (STAI-YA) variables in all intergroup comparisons as between-participant factors. Compared with NAp, Ap patients scored significantly lower on Forward span (F = 5.875, p = 0.004), and made more perseverative errors on the MCST (F = 3.954, p = 0.047) but this latter did not achieve statistical significance (Table 2).

Figure 1 illustrates the relationship between apathy (AES total score) and state anxiety (STAI-YA total score). We found a link between these two variables (Pearson's r = -0.27, p = 0.02, 95% CI [-0.48, -0.04]). However, this result did not survive to the second level analysis when taking account confounding factors such as age, duration of disease, Selective Serotonin Reuptake Inhibitor, Post-Traumatic Stress Disorder comorbidity, Forward Span (t-value=-1.89; p-value=0.065).

Figure 2 illustrates the relationship between apathy (AES total score) and anhedonia (SHAPS total score). We found a link between these two variables (Pearson's r = -0.45, p = 0.001, 95% CI [-0.65, -0.20]). This result remained robust to the correction of confounding factors (age, duration of disease, Selective Serotonin Reuptake Inhibitor, Post-Traumatic Stress Disorder comorbidity, Forward Span) (t-value= -2.56; p-value= 0.014).

Discussion

General considerations

To our knowledge, this was the first study to compare Ap and NAp depressed patients free of neurological disorders and dementia. We found a 30% prevalence of apathy in our sample, in line with Starkstein et al. (Starkstein et al., 2001), who found a prevalence of 36.8% in a group of 95 depressed non-demented patients, and with Groeneweg-Koolhoven et al., who reported an incidence of 36% in a population of older patients (≥ 60 years) (Groeneweg-Koolhoven, Comijs, Naarding, de Waal, & van der Mast, 2016). In addition, the two patient groups had comparable sociodemographic and disease characteristics. This had not previously been demonstrated in this population.

Apathy and depression

Ap patients were less severely depressed than NAp patients, according to their MADRS total scores. We notice that this result cannot be considered as significant regarding to the significance threshold chosen for this study ($p < 0.01$). Nevertheless, some points have to be discussed. In fact, analysis showed that Item 7 of MADRS (lassitude) was significantly higher in NAp patients. This result confirmed the overlap between apathy and some items in depression assessment scales (Calabrese et al., 2014; R. S. Marin et al., 1993). Counterintuitively, Ap patients responded more positively than NAp patients to the motivational item (Items 7). One explanation could be a deficit in insight. In their review, Mograbi and Morris

found that in Alzheimer's disease, apathy was associated with poorer introspective abilities (Mograbi & Morris, 2014). However, we have to notice that this latter study investigated patients with cognitive deficit which could be involved almost in part in deficit of insight. Further investigation could question the link between cognitive deficit, deficit of insight and apathy in both diseases (depressive and AD) in a translational approach. Furthermore, in a population of 37 patients with social anxiety disorder, Vigne et al. demonstrated that those with poor insight had less intense depression (Vigne, de Menezes, Harrison, & Fontenelle, 2014). Marin et al. had previously observed that one of the items of the HamD most closely correlated with the AES was *lack of insight* (R. S. Marin et al., 1993). In their study, lack of insight was exhibited by subsamples of patients with right-hemisphere stroke, probable Alzheimer's disease, and major depression (R. S. Marin et al., 1993). The authors hypothesized that the association of apathy with insight may be specific to neuropsychiatric disorders characterized by lack of motivation (R. S. Marin et al., 1993). We suggest that a deficit in insight can be interpreted as a deficit in introspective ability, a characteristic of cognitive apathy. As a consequence, apathetic depressed patients may have greater difficulty identifying and/or expressing feelings. An additional apathetic manifestation, emotional blunting, may result in a lack of interest, while a lack of interest may, in return, lead to a lack of emotional reactivity, meaning that direct relationships between the symptoms themselves may intensify apathetic manifestations. In summary, we can hypothesize that the apathy dimension leads patients to perceive their depressive state as less intense.

Relationship between apathy and anxiety

We found a significant negative relationship between the level of self-reported state anxiety and apathy. However, this result did not survive to the second level analysis when taken account for confounding factors. Following on from the previous section, there is some evidence in the literature that a lack of insight may explain the link between apathy and anxiety. In a population of 115 patients with a history of schizophrenia spectrum disorder, Sellwood et al. found that dysphoria (i.e. depression and anxiety) was positively correlated with insight, after controlling for cognition, treatments, duration of disease, and schizophrenic symptomatology (Sellwood et al., 2013). Horning et al. subsequently studied the relationship between insight, depression, anxiety and apathy in 107 patients with Alzheimer's disease (Horning, Melrose, & Sultzer, 2014). After controlling for cognitive skills, they found that impaired insight was linked to a higher level of apathy, whereas greater insight was linked to depressed mood and anxiety (Horning et al., 2014). We can hypothesize that patients with a lack of emotional concern are less sensitive to anxiety. The results of our study, the first to have replicated the above results in a population of non-demented depressed patients, could

therefore be partially explained by the emotional dimension of the apathy syndrome. Finally, the link between anxiety and apathy in depression can be questioned through pathophysiology. Which neurobiological process links apathy with anxiety? Apathy is supported by dopaminergic circuitry (striatum, nucleus accumbens, orbito-frontal cortex) and anxiety by affective circuits (amygdala, insula, ventro-median prefrontal cortex). Therefore, which dimension of apathy could be linked with emotional side of depression whereas both dimensions are mediated by different cerebral networks? One hypothesis could stand in the capacity to evaluate the affective impact of reward (involving affective network) which refers to hedonic abilities (Berridge, Robinson, & Aldridge, 2009; Treadway & Zald, 2011).

Relationship between apathy and anhedonia

After correction for confounding factors, we found a significant negative relationship between the level of self-reported anhedonia and apathy. This result has to be considered through one limitation regarding the fact that this correlation was found between one hetero-administered (AES) and self-administered scales (SHAPS). Furthermore, the hetero-administered clinical assessments have not been conducted by independent clinicians, this should have allowed to test the convergence of outcomes. But the design of this study (open) did not allow doing such analysis. Nevertheless, Ap patients had significantly lower SHAPS scores, meaning that their ability to feel pleasure was intact. This result confirms the hypothesis of Thomsen et al. who, in a reconceptualization of anhedonia, proposed that "some aspects of *conscious liking* can be seemingly intact in the psychiatric disorders traditionally associated with anhedonia, including depression and schizophrenia" (Rømer Thomsen, Whybrow, & Kringelbach, 2015). Since Robinson and Berridge carried out their studies in the field of addiction (Berridge & Robinson, 2003; Robinson & Berridge, 1993), anhedonia has been divided into two components: motivational anhedonia (*wanting*), and consummatory anhedonia (*liking*) (Gaillard, Gourion, & Llorca, 2013; Rømer Thomsen et al., 2015; Treadway & Zald, 2011). This dichotomy has been extensively discussed in the literature and applied to other psychiatric disorders, such as depression and schizophrenia (Berridge et al., 2009; Gaillard et al., 2013; Rømer Thomsen et al., 2015; J. J. Simon et al., 2010; Treadway & Zald, 2011). The first, motivational component (reduced willingness to work for a reward) can be associated with several dimensions of apathy (i.e. lack of cognitive/emotional/behavioral goal-directed skills). Our results showed that Ap depressed patients can maintain their ability to feel pleasure despite motivation deficits. This result is of considerable interest, because of its impact on the pathophysiological understanding of depression. In previous studies (Berridge et al., 2009; Rømer Thomsen et al., 2015; Treadway & Zald, 2011), the Ap and NAp depressed patients probably did not share the same neural deficits, and could consequently could be viewed as

constituting two different clusters. Motivational anhedonia (*wanting*) is linked to the meso-cortico-limbic dopamine system (Tibboel, De Houwer, & Van Bockstaele, 2015; Treadway & Zald, 2011), whereas consummatory anhedonia (*liking*) is linked to subcortical (ventromedial prefrontal cortex and amygdala) networks mediated by the opioid system (Tibboel et al., 2011; Treadway & Zald, 2011). These neurobiological arguments, which underline the heterogeneity of depression profiles and highlight the need to better characterize this disease, have considerable implications for the therapeutic approach.

Relationship between apathy and cognition

In our sample, Ap depressed patients were more impaired than NAp patients on verbal working memory and tend to be significantly impaired in executive functioning. From a transdiagnostic perspective, apathy appears to have several psychological components, including cognitive impairments-more especially executive ones (Konstantakopoulos et al., 2011), also implicated in depression (Arnould, Rochat, Azouvi, & Van der Linden, 2013). Therefore, it appears important to precisely examine the overlaps and differences between apathy, depression (Beck & Bredemeier, 2016), and executive function deficit associated with worse inhibition on the behavioral measure. Although they have sufficient resources, depressed individuals have difficulty initiating efficient cognitive strategies (Hertel & Gerstle, 2003) and/or appropriately allocating their resources (Levens, Muhtadie, & Gotlib, 2009). The relationship between effort mobilization and apathy in depressed persons influences their cognitive impairments. Apathetic individuals probably make more effortful responses to easy cognitive challenges, in order to compensate for their cognitive deficits, and disengage earlier when the tasks become more difficult. Hence the difficulty of engaging in the first assessment task (forward span) and the perseverative errors on the MCST, possibly reflecting a repeated response while failing to consider the actual task requirements.

Conclusion

The present study focused on the phenomenology of apathy in depression free of neurological and dementia comorbidities. Ap depressed patients were less anhedonic, less anxious and had more executive function deficits than NAp patients. Despite the weaker correlation between anxiety and apathy, this result has been discussed in terms of lack of insight or lack of concern. Moreover, the most striking result of our study is the relationship between consummatory anhedonia (*liking*) and apathy (*wanting*) in depression. This finding supports the hypothesis that Ap and NAp have distinct clinical profiles of depression. Taken together,

these results indicate that the apathy dimension subtends two different subtypes of depression, which can be viewed as different pathophysiological clusters, as they probably affect two distinct neural networks. Further studies are needed to test this clinical hypothesis in the light of neurobiology.

Variable	Apathetic (*n* = 21) mean (+- *SD*) or *n* (%)	Nonapathetic (*n* = 49) mean (+- *SD*) or *n* (%)	*p* value
AES	46.04 (4.03)	36.18 (3.89)	**< 0.001**
Actual MDE duration (weeks)	24.43 (30.33)	26.32 (30.84)	0.516
Duration of disease (years)	16.33 (1.33)	13.5 (10.23)	0.477
Number of DMEs	5.52 (6.51)	4.53 (4.20)	0.922
Number of suicide attempts	1.67 (2.59)	1.12 (3.01)	0.299
Number of anxious comorbidities (*n* = 63)	0.94 (1.16)	1.51 (1.47)	0.166
Actual Panic Disorder (*n* = 63)	2 (11.11%)	8 (17.78%)	0.710
Lifetime Panic Disorder (*n* = 63)	5 (27.8%)	13 (28.9%)	0.930
Social Phobia (*n* = 63)	1 (5.56%)	9 (20%)	0.257
Post-Traumatic Stress Disorder (*n* = 63)	6 (33.33%)	3 (6.67%)	**0.013**
Generalized Anxiety Disorder (*n* = 63)	4 (22.22%)	23 (51.11%)	0.050
MADRS (total score)	26.00 (4.14)	28.5(5.20)	0.044
BDI (total score)	16.09 (5.16)	18.46 (8.5)	0.089
ERD (total score)	17.52 (9.34)	22.34 (9.24)	0.066
STAI-YA (total score)	**53.19 (11.46)**	**61.83 (10.71)**	**0.004**
STAI-YB (total score)	58.33 (7.63)	58.59 (12.40)	0.658
YMRS (total score)	1.62 (1.69)	1.00 (1.48)	0.102
SHAPS (total score) (*n* = 50)	**2.62 (2.12)**	**6.38 (4.32)**	**0.004**
MATTIS	133.40 (7.63)	135.30 (7.29)	0.300
Forward span	**5.40 (1.43)**	**6.77 (1.52)**	**0.004**
Backward span	4.55 (1.64)	4.78 (1.40)	0.500
Forward – Backward span	0.85 (1.69)	1.98 (1.57)	0.059
Verbal fluency - phonological	19.80 (6.08)	18.47 (6.99)	0.247
Verbal fluency - semantic	27.80 (6.84)	26.72 (8.82)	0.532
STROOP den	64.35 (16.78)	63.83 (15.77)	0.843

STROOP lec	84.40 (20.39)	89.98 (13.80)	0.181
STROOP i	33.60 (11.55)	35.19 (12.28)	0.593
STROOP scinter	0.54 (6.47)	-0.21 (10.18)	0.696
TMT A	52.55 (26.43)	43.23 (13.58)	0.288
TMT B	126.47 (78.52)	115.59 (75.37)	0.665
TMT B-A	76.89 (61.36)	72.39 (68.92)	0.735
MCST time	204.05 (67.09)	196.51 (74.99)	0.464
MCST categories	4.50 (2.06)	5.36 (1.31)	0.167
MCST perseverative	5.75 (6.73)	2.68 (3.54)	0.047
WAIS-III (digit span subtest)	45.85 (15.86)	50.87 (16.98)	0.395

Table 1: Intergroup comparisons between apathetic depressed patients (Ap) and nonapathetic (NAp) depressed patients. AES: Apathy Evaluation Scale, MADRS: Montgomery and Äsberg Depressive Rating Scale, BDI: Beck Depression Inventory, ERD: Echelle de Ralentissement de la Dépression, STAI : State Trait Anxiety Inventory (YA and YB form), YMRS : Young Mania Rating Scale, SHAPS : Snaith Hamilton Pleasure Scale , MDRS: Mattis Dementia Rating Scale, TMT: Trail Making Test (A and B form), MCST: Modified version of the Wisconsin Card Sorting Test, WAIS: Wechsler Adult Intelligence Scale.

Variable	Apathetic (*n* = 21) or mean (+- *SD*)	Nonapathetic (*n* = 49) mean (+- *SD*)	*p* value
MADRS (total score)	26.00 (4.14)	28.51 (5.20)	0.044
1: apparent sadness	3.24 (0.99)	3.84 (0.94)	0.019
2: reported sadness	3.76 (0.99)	3.98 (1.01)	0.410
3: inner tension	3.10 (0.77)	2.86 (1.28)	0.673
4: reduced sleep	1.57 (1.60)	2.10 (1.85)	0.276
5: reduced appetite	1.33 (1.59)	1.35 (1.65)	0.994
6: concentration difficulties	2.71 (1.27)	3.78 (4.24)	0.132
7: lassitude	**2.38 (1.47)**	**3.38 (1.17)**	**0.002**
8: inability to feel	3.19 (0.93)	3.67 (0.63)	0.034
9: pessimistic thoughts	3.00 (0.78)	2.88 (1.07)	0.925
10: suicidal thoughts	1.57 (1.54)	1.28 (1.12)	0.628

Table 2: Intergroup comparisons (Ap vs. NAp) of MADRS total score and subscores.
MADRS: Montgomery and Äsberg Depressive Rating Scale.

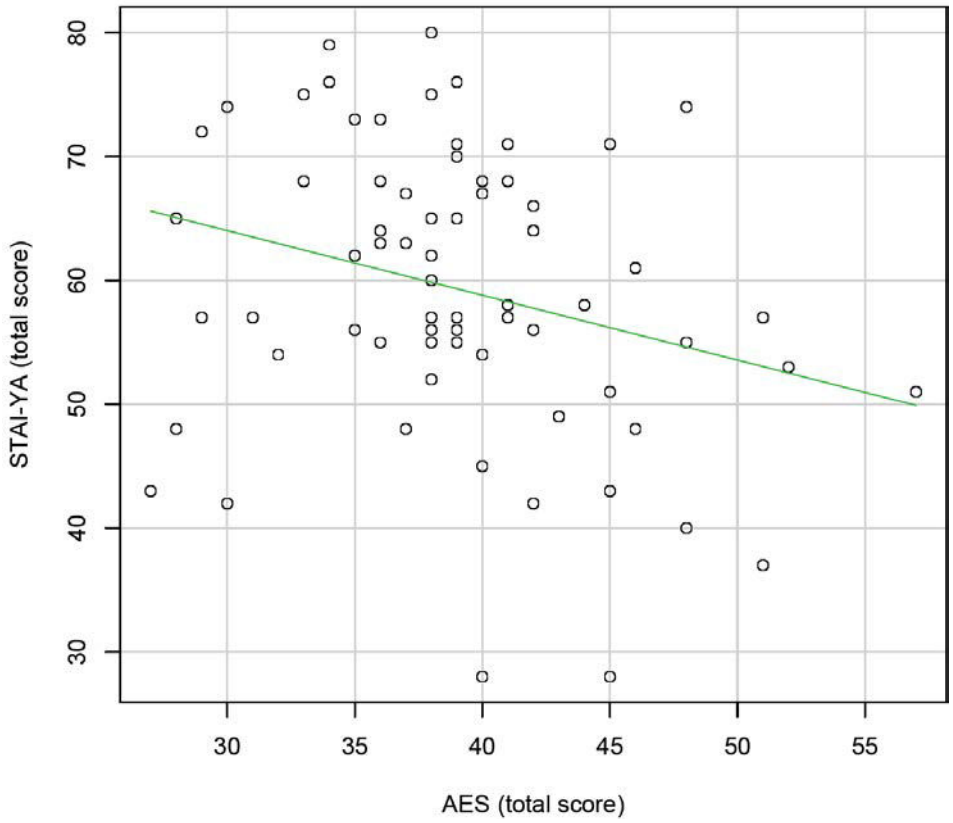

Figure 1: Relationship between apathy (AES total score) and state anxiety (STAI-YA total score). AES: Apathy Evaluation Scale, STAI : State Trait Anxiety Inventory (YA form).

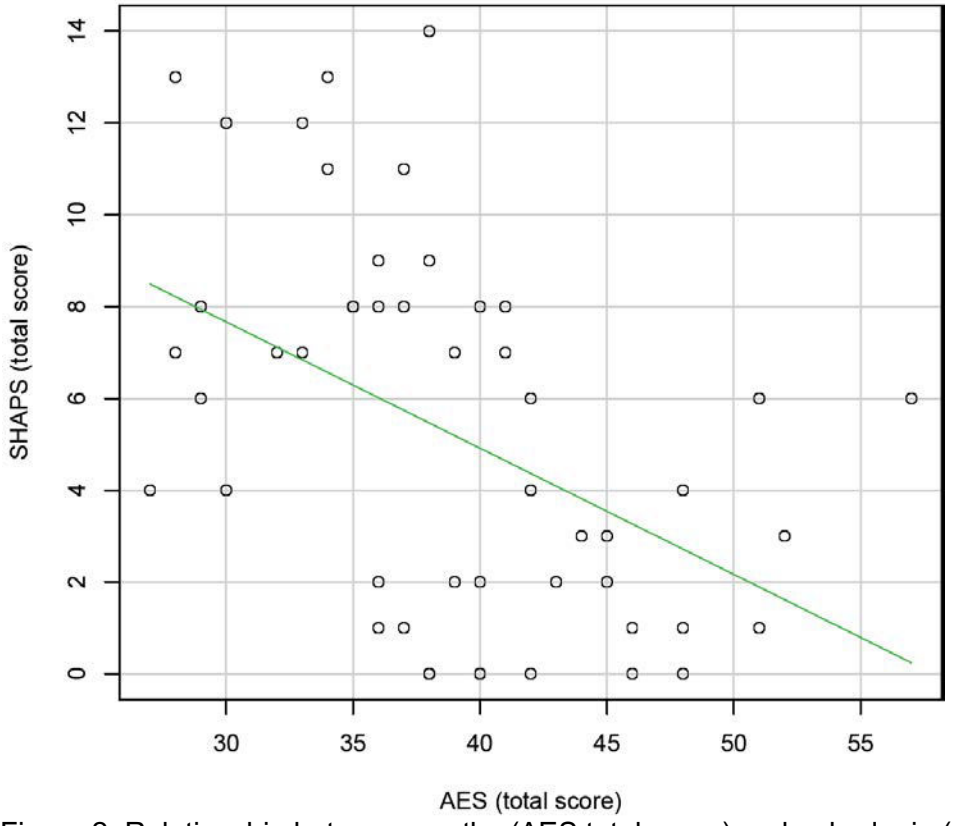

Figure 2: Relationship between apathy (AES total score) and anhedonia (SHAPS total score). AES: Apathy Evaluation Scale, SHAPS: Snaith Hamilton Pleasure Scale.

Points forts de la partie 3.1.1. Apathy and depression: Which clinical specificities?

Ce premier travail, sur les 70 premiers patients de la cohorte, nous a permis de montrer que l'apathie constituait une dimension sémiologique pertinente dans la dépression car associée à des caractéristiques cliniques et neuropsychologiques spécifiques. Les résultats principaux sont :

- La corrélation négative entre apathie et anhédonie et la tendance à la significativité pour une corrélation négative entre apathie et anxiété
- Les déprimés apathiques présentent des déficits cognitifs notamment sur la mémoire de travail verbale.

La dimension apathique permettrait de différencier deux phénotypes de dépression. Ces résultats nous ont conduits à tester l'hypothèse que l'apathie dans la dépression serait sous-tendue par une physiopathologie spécifique. Nous proposons de tester cette hypothèse au moyen d'une méthode d'imagerie de perfusion, l'ASL pseudo-continu. Ce travail est développé dans la partie 3.1.2.

3.1.2 Apathy in depression: An Arterial Spin Labeling perfusion MRI study

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Abstract: Introduction: Apathy is defined as a lack of goal-directed behavior. Neurovascular mechanisms underpinning apathy in depression remain little known. The aim of this study is to assess the perfusion correlates of apathy in depression by pseudo-continuous arterial spin labeling (pcASL) magnetic resonance imaging (MRI).
Methods: Perfusion imaging analysis was performed on 93 depressed patients included in a prospective study between November 2014 and February 2017, 30 of them were apathetic (Ap - AES ≥ 42), and 63 non-apathetic (NAp - AES < 42). Every patient underwent a psychiatric evaluation as well as a cerebral MRI. Imaging data included anatomical 3D T1-weighted and perfusion pcASL sequences. A statistical analysis was conducted on regions of interest, defined from the FreeSurfer atlas, to compare the cerebral blood flow between Ap and NAp groups.
Results: After correction for confounding factors, Ap patients perfused significantly more than NAp ones in bilateral accumbens and caudate nuclei, left middle frontal cortex, bilateral superior frontal cortex, right insula, and left putamen.
Conclusion: This study suggests the existence of abnormalities affecting key regions involved in the meso-cortico-limbic dopaminergic loop of reward system: the ventral and dorsal striatum and the frontal gyrus. Apathy appears to be a useful biomarker to characterize different phenotypes of depression. These findings are of high interest due to their impact on understanding motivational dimension in depression and its therapeutic issue.

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Highlights:

- An MRI perfusion ASL study of apathy in depression
- Apathetic and non-apathetic patients showed different brain perfusion patterns
- Perfusion differences were observed in key regions of reward system
- Apathy could be a critical biomarker of different phenotypes of depression
- A step forward understanding motivation in depression and its treatment

Introduction

Apathy is now well recognized as an important behavioral syndrome in several neuropsychiatric disorders (Marin, 1990, 1991). It is widely agreed that apathy is a transnosographic syndrome, found in various neurological disorders, such as Alzheimer's Disease (AD), Parkinson's Disease (PD) and other dementias, traumatic brain injury and stroke, but also in psychiatric disorders including schizophrenia and major depressive disorder (van Reekum et al., 2005). Apathy has a dramatic clinical as well as prognostic impact marked by impairment of activities of daily living (Freels et al., 1992), cognitive impairment with executive dysfunction (Zahodne and Tremont, 2013), increased risk of conversion to dementia (Vicini Chilovi et al., 2009), decreased response to treatment (Kos et al., 2016) and diminished quality of life (Prakash et al., 2016).

Apathy has been extensively studied in neurodegenerative disorders using several imaging modalities assessing either cerebral metabolism or brain perfusion or with different image analyses such as morphometry or functional connectivity. Regarding apathy in Parkinson's disease (PD), neuroimaging positron emission tomography (PET) studies are contradictory, demonstrating either a negative correlation between apathy and cerebral metabolism in the striatum, cerebellum, and prefrontal, temporal, parietal and limbic lobes or a positive correlation between apathy and prefrontal, temporal, parietal and limbic areas (Robert et al., 2014, 2012; Wen et al., 2016). Functional magnetic resonance imaging (MRI) showed a decreased connectivity between the left striatal and frontal areas (Baggio et al., 2015) while T1 weighted imaging reported increased atrophy in the frontal and parietal lobes, insula and left nucleus accumbens in apathetic patients (Wen et al., 2016). In Alzheimer's disease, most studies linked apathy with the anterior cingulate cortex, the medial frontal cortex and some of them also involved the orbitofrontal cortex (Theleritis et al., 2014). So, apathy affects a large meso-cortico-limbic circuit including the striatum, the anterior cingulate, and the inferior prefrontal gyrus (Kos et al., 2016; Theleritis et al., 2014; Benoit and Robert, 2011; Kostić and Filippi, 2011; Wen et al., 2016).

Regarding to depression, the clinical specificity of apathy in depressed patients was described in a recent paper (Batail et al., 2017). The authors have found that apathetic depressed patients, although they had motivation deficit, had intact self-reported capacity to feel pleasure compared to non-apathetic ones. These findings suggest the existence of two subtypes of depression with different clinical profiles, in terms of motivational dimension and sensitivity to reward. Considering this result, depressed patients suffering from apathy should probably not share the same pathophysiological patterns than non-apathetic ones. Identifying perfusion

specificities of apathy in depression would provide a better understanding of its neurobiological mechanisms.

Arterial Spin Labeling (ASL) is a growing technique for perfusion brain imaging. This method is non-invasive and allows an absolute quantification of cerebral blood flow (CBF) (Detre et al., 1992). For these advantages, ASL has been described as a good alternative to nuclear medicine-based perfusion imaging techniques. Furthermore, ASL allows an accurate perfusion analysis and can be considered as a proxy for cerebral metabolic and synaptic function which is of high interest in studying pathophysiological patterns in neuropsychiatric disorders such as depression (Watts et al., 2013). Thus, it has shown a good correlation between measured perfusion abnormalities to microcirculatory deficits and clinical symptoms (Théberge, 2008). In addition, test-retest studies highlighted a reasonable reproducibility (Petersen et al., 2010; Ferré et al., 2013). Altogether, because of its sensitivity and discriminant power in specific disorders (Wolf and Detre, 2007), ASL is a useful modality which is suggested as a biomarker of pathological brain functions (Detre et al., 2012) and particularly in depression (Watts et al., 2013).

However, only few works have used the ASL technique to study depression as in adolescents (Ho et al., 2013), adults (Orosz et al., 2012), treatment resistance (Lui et al., 2009; Duhameau et al., 2010), or late-life depression (Colloby et al., 2012). As pointed out previously, ASL could be a useful marker for identifying specific patterns of CBF abnormalities associated with different subtypes of depression (Haller et al., 2016). To date, only one study has investigated CBF (using 99Tc-HMPAO single photon emission computed tomography) in a population of AD suffering from either depression or apathy. The authors have suggested that apathy and depression in AD involve distinct functional circuits (Kang et al., 2012). But no perfusion imaging study has yet investigated apathy in depression without neurodegenerative disorder.

The aim of this study is to assess the perfusion correlates of apathy in depression by arterial spin labeling MRI. We hypothesize that apathetic depressed patients will have different cerebral perfusion patterns compared to non-apathetic ones, particularly affecting key regions involved in emotional or reward processing.

Methods

Participants

A prospective cohort study was conducted. It was approved by a national ethic committee and registered in www.clinicaltrial.gov (NCT02286024). A complete description of the study was given to the subjects and their written informed consent was obtained. All patients were recruited between November 2014 and February 2017 from the adult psychiatry department of Rennes, France.

The study was proposed to patients suffering from a Mood Depressive Episode (MDE) under DSM 5 criterion with or without personal history of Mood Depressive Disorder (unipolar or bipolar subtype). Exclusion criteria included other Axis I disorder (except anxious comorbidities such as post-traumatic stress disorder, social phobia, generalized anxiety disorder, panic disorder) which were explored using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Patients with severe chronic physical illness were not included. Other exclusion criteria were potential safety contraindications for MRI (pacemakers, metal implants, pregnancy and lactation), neurological problems or a history of significant head injury and significant circulatory conditions that could affect cerebral circulation (i.e. non-controlled hypertension). All patients underwent a neurological examination by a trained physician to ensure that no included subject had any clinical sign of dementia or abnormal neurological examination.

After clinical assessment, patients underwent an imaging protocol by a maximum of three days. Out of the 124 screened patients, 12 had to be excluded for clinical reasons and 19 for radiological reasons, mostly because of dental material that caused large artifacts in the perfusion images, which results in a population sample of 93 patients. The image data were anonymously stored into Shanoir, a dedicated environment to manage brain imaging research repositories (Barillot et al., 2016).

The flowchart in Figure 1 synthesizes the recruitment process.

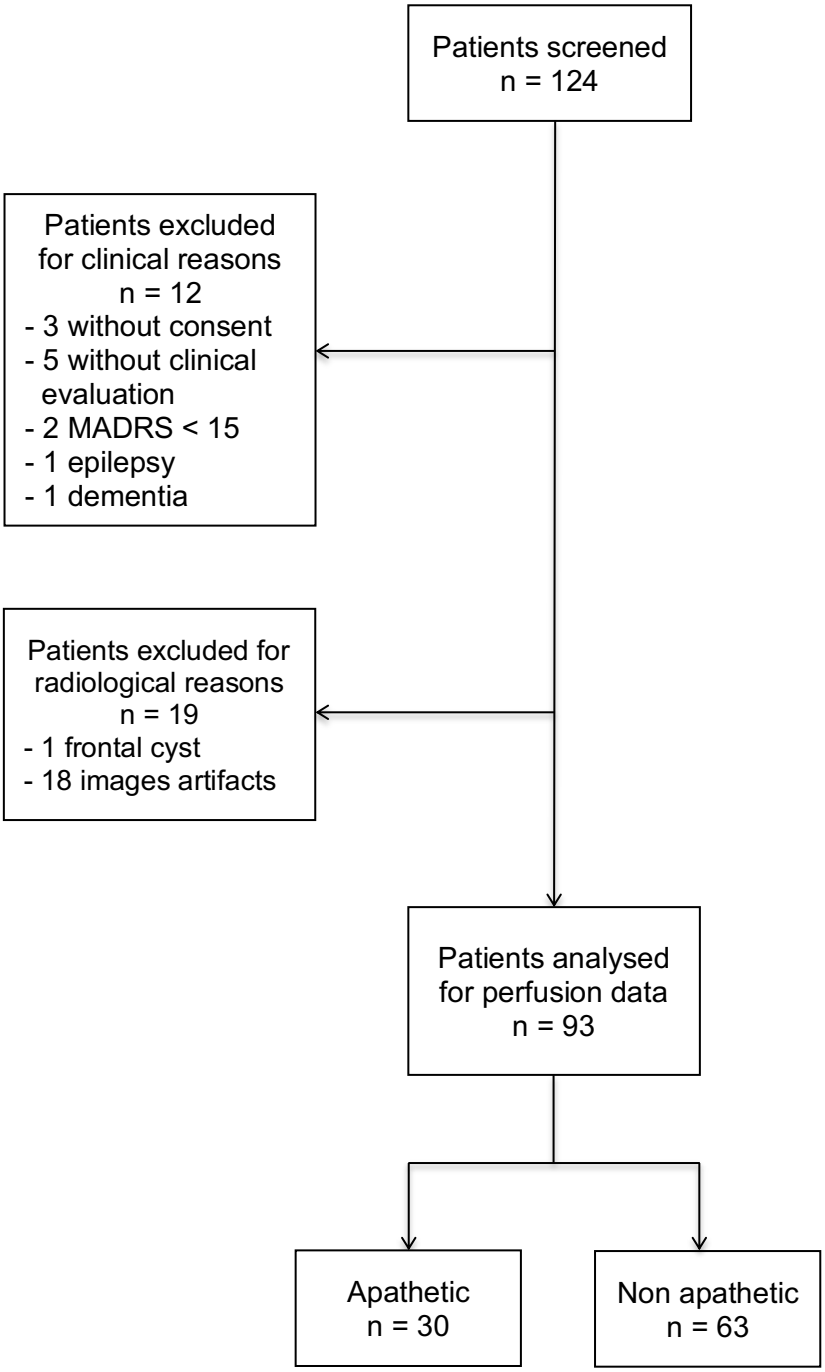


Figure 1 – Flow chart – Out of the 124 screened patients, 93 patients (30 apathetic and 63 non-apathetic) were included in the perfusion MRI data analysis.

Clinical assessment

Patients were assessed by a single structured clinical interview by a trained psychiatrist with the following scales:

Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998)

Apathy Evaluation Scale (AES) (Marin et al., 1991)

Beck Depression Inventory (BDI) (Beck et al., 1961)

Widlöcher Depressive Retardation Scale (WDRS) (Widlöcher, 1983)

Montgomery and Äsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979)

State Trait Anxiety Inventory (STAI) (Spielberger, C. D. et al., 1983)

Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)

Socio-demographic (age, gender, education) and disease characteristics (duration of disease, duration of episode, number of mood depressive episodes, medication status) were collected. Medication status of each patient was defined as the medication load score described in (Almeida et al., 2009). This is a composite score reflecting both the dose and the variety of treatment (antidepressant, mood stabilizer, antipsychotic, anxiolytic). It is obtained by summing all individual medication codes for each medication category for each patient.

The population sample was divided into two groups using a 42 – AES cut-off score, as suggested by (Calabrese et al., 2014; Marin et al., 1991) (AES ≥ 42 = apathetic group; AES < 42 = non-apathetic group). With this cut-off, 30 patients were apathetic and 63 non-apathetic. The prevalence of apathy was 32.26 % in our sample of depressed patients.

Socio-demographical information, disease and clinical characteristics for the whole sample and for the apathetic and non-apathetic groups are summarized in Table 1, with p-values referring to a t-test for quantitative variables and to a chi-squared test for qualitative variables. For all tests, the significance level was set at 5% ($p<0.05$).

The whole sample was characterized by a moderate depression intensity with middle-aged patients, predominantly women. Both apathetic and non-apathetic groups were comparable in regards to socio-demographic and disease characteristics.

Regarding the clinical characteristics, a close to significance difference was found for anhedonia with apathetic patient presenting a lower SHAPS score than NAp patients (Ap = 4.40 (± 3.41); NAp = 5.94 (± 4.15), $p=0.063$). Moreover, as far as psychomotor retardation is concerned, a WDRS total score significantly lower in Ap patients was observed (Ap = 18.80 (± 8.78); NAp = 23.38 (± 8.87), $p = 0.023$).

Variable n=93	Whole sample (n=93) Mean (± sd) or n (%)	Apathetic n=30 Mean (± sd) or n (%)	Non-apathetic n=63 Mean (± sd) or n (%)	p-value
AES	39.51 (7.72)	48.53 (5.39)	35.21 (4.10)	< 0.001**
Age	48.19 (15.06)	47.90 (15.74)	48.33 (14.85)	0.899
Gender (female)	64 (68.82)	23 (76.7)	41 (65.1)	0.260
Actual MDE duration (weeks)	29.48 (36.41)	27.47 (34.64)	30.44 (37.46)	0.707
Duration of disease (years)	15.04 (13.37)	14.57 (14.23)	15.27 (13.05)	0.820
Number of MDE	4.53 (4.71)	5.27 (6.18)	4.18 (3.82)	0.380
Medication load	3.07 (1.18)	2.97 (1.19)	3.13 (1.18)	0.541
MADRS (total score)	27.52 (5.37)	26.87 (5,25)	27.83 (5.45)	0.419
BDI (total score)	17.02 (7.94)	17.47 (7.40)	16.81 (8.24)	0.701
WDRS (total score)	21.90 (9.05)	18.80 (8.78)	23.38 (8.87)	0.023**
STAI YA (total score)	57.54 (12.67)	55.20 (12.47)	58.65(12.71)	0.220
STAI YB (total score)	59.09 (11.47)	61.10 (9.02)	58.13 (12.43)	0.195
SHAPS (total score)	5.44 (3.98)	4.40 (3.41)	5.94 (4.15)	0.063*

Table 1 – Population description (whole sample; n = 93): Socio-demographical information, disease and clinical characteristics are given for the whole sample and for the apathetic and non-apathetic groups. The p-value refers to a t-test for quantitative variables and to a chi-squared test for qualitative variables. For all tests, the significance level was set at 5% ($p<0.05$). ** for p-value < 0.05; * for p-value < 0.10.

Imaging protocol

Data acquisition

Patients were scanned on a 3T whole body Siemens MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. Anatomical data included a high-resolution 3D T1-weighted MPRAGE sequence (3D T1w) with the following imaging parameters: TR/TE/TI = 1900/2.26/900 ms, 256x256 mm2 FOV and 176 sagittal slices, 1x1x1 mm3 resolution, parallel imaging with GRAPPA factor 2. Perfusion data were acquired using a pseudo-continuous ASL sequence with total scan time of approximately 4 minutes (Wu et al., 2007). The imaging parameters were: TR/TE = 4000/12 ms, flip angle 90°, matrix size 64x64, labeling duration (LD)/post-labeling delay (PLD) = 1500/1500 ms, parallel imaging

SENSE factor 2. The labeling plane was placed 9 cm below the center of the acquisition volume. Twenty axial slices were acquired sequentially from inferior to superior in the AC-PC plane, with 3.5 x 3.5 mm2 in-plane resolution, 5 mm slice thickness and 1 mm gap. Thirty repetitions, i.e., label/control pairs, (60 volumes), finally composed the ASL data series. Additionally, M0 images were acquired at the same dimension and resolution as equilibrium magnetization maps (TR = 10 s, TE = 12 ms).

Data pre-processing

Pre-processing of the image data was performed with our AutoMRI[1] in-house pipeline using MATLAB (v. R2014a, The MathWorks Inc.) and the SPM8 toolbox (Wellcome Department of Imaging Neuroscience at University College London, UK). An overview of our data pre-processing is illustrated in Figure 2.

The anatomical 3D T1w was corrected for intensity inhomogeneity and segmented into grey matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) probability maps using the MNI ICBM152 template tissue probability as an a priori for brain tissue classification. Estimated by this same unified segmentation model SPM routine, spatial normalization parameters were applied to warp the 3D T1w volume to the MNI template.

The ASL data series was motion corrected by a rigid body transform minimizing the sum of squared differences cost function. A two-pass procedure first realigned all the control and label volumes onto the first volume of the series, then registered the series to the mean of the images aligned in the first pass. The motion-corrected ASL series was co-registered to the 3D T1w using a rigid transform. The latter was estimated by maximizing normalized mutual information between the mean control images, i.e., the average of all the realigned control volumes, and the 3D T1w GM map. The co-registered ASL images were then pairwise subtracted (control - label images) to produce a series of perfusion-weighted maps, which could be subsequently averaged by arithmetic sample mean to produce a perfusion weighted (PW) map. However, as the sample mean is very sensitive to outliers, we instead use Huber's M-estimator to robustly estimate the PW map (Maumet et al., 2014). This robust PW map was eventually quantified to a CBF map by applying the standard kinetic model (Buxton et al., 1998):

$$f = 6000.\frac{\lambda \Delta M \, e^{\frac{\mathrm{PLD}+idx_{sl}*\mathrm{TI}_{sl}}{\mathrm{T_{1b}}}}}{2\alpha \mathrm{T_{1b}} \left(1 - e^{\frac{-\tau}{\mathrm{T_{1b}}}}\right) M_0} \; [\mathrm{ml} \; / \; 100\mathrm{g} \; / \; \mathrm{min}]$$

[1] https://team.inria.fr/visages/software/

where f is the CBF map, ΔM is the perfusion weighted map, λ = 0.9 ml.g^{-1} is the blood/tissue water partition coefficient, α = 0.85 measures the labeling efficiency, T_{1b} = 1650 ms is the T_1 of blood (Alsop et al., 2015), M_0 represents the equilibrium magnetization of arterial blood, PLD = 1500 ms is the post-labeling delay of the ASL sequence, τ = 1500 ms is the labeling duration, idx_{sl} is the slice index, starting from 0 for the first acquired slice, TI_{sl} = 37 ms is the acquisition duration of one slice.

For subsequent region of interest (ROI) analysis, the mean CBF values were computed for each subject in the MNI space. The ROIs were extracted from the Desikan-Killiany Atlas (Desikan et al., 2006) using the FreeSurfer software[2] and were selected in light of the literature about apathy and neuroimaging (Gaillard et al., 2013; Kang et al., 2012; Treadway and Zald, 2011; Berridge et al., 2009). They were: thalamus, caudate, putamen, pallidum, amygdala, insula, accumbens area, posterior cingulate cortex, anterior cingulate cortex, orbitofrontal cortex, frontal cortex (superior, middle and inferior parts) for the left and right hemispheres. The anterior cingulate cortex was defined as the union of the Freesurfer ROIs "ctx-caudalanteriorcingulate" and "ctx- rostralanteriorcingulate", the orbitfrontal cortex as the union of "ctx-lateralorbitofrontal" and "ctx-medialorbitofrontal" and the middle frontal cortex as the union of "ctx-caudalmiddlefrontal" and "ctx-rostralmiddlefrontal", the inferior frontal cortex as the union of "ctx-parsopercularis" and "ctx-parsorbitalis" and "parstriangularis". To discard outliers that may be present in particular at GM/LCS interface due to the low resolution of ASL, we used the modified z-score proposed by Iglewicz and Hoaglin (Iglewicz and Hoaglin, 1993) before computing the average CBF value in a given ROI:

$$Z_i = \frac{0.6745(x_i - \tilde{x})}{\text{MAD}}$$

where $\tilde{x}$ denotes the median over the ROI and MAD the median absolute deviation[3]. Voxels x_i with a Z_i score greater than 3.5 were discarded.

[2] http://surfer.nmr.mgh.harvard.edu/fswiki/

[3] The median absolute deviation is defined as $\text{MAD} = \text{median}(|x_i - \tilde{x}|)$ where $\tilde{x}$ denotes the median of the data and $|x|$ the absolute value of x.

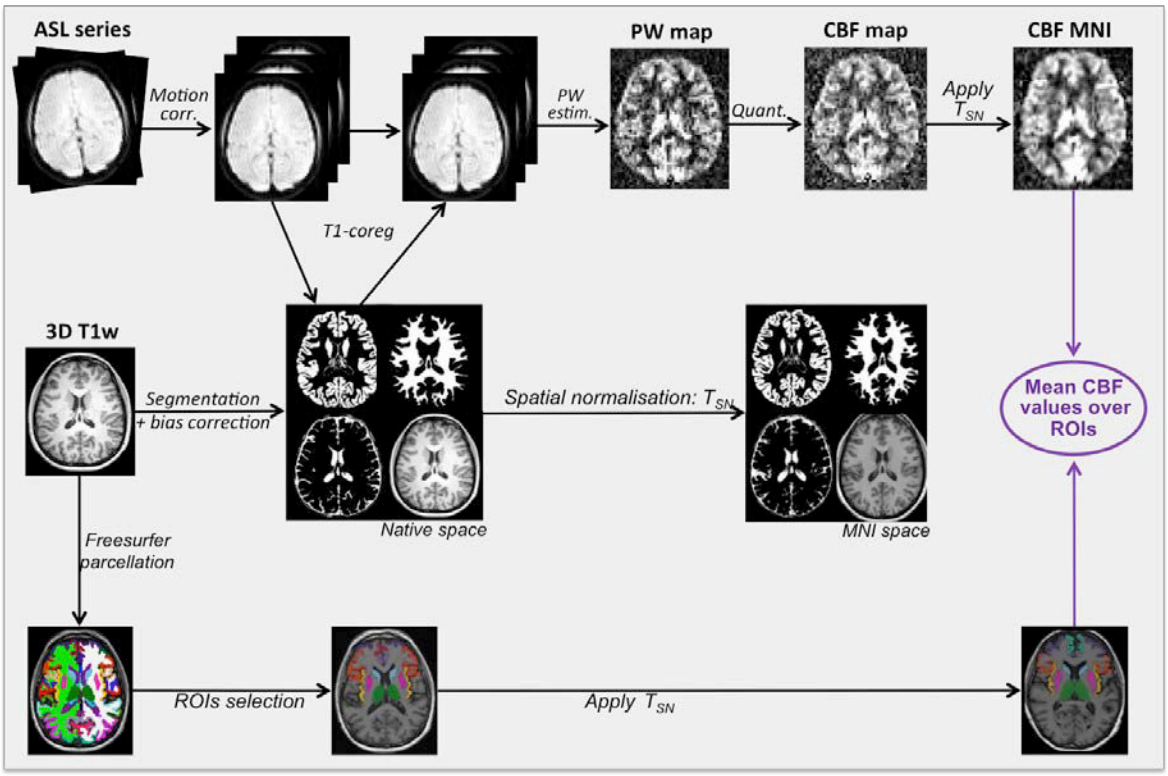


Figure 2: Overview of our data pre-processing pipeline.

Between group statistical analysis of perfusion MRI data

The statistical analysis was performed on the 93 patients included in this perfusion study (intention-to-treat analysis) with R software (http://www.R-project.org/). For each ROI, the mean CBF value over the ROI was compared between the Ap and NAp groups of depressed patients. This inter-group comparison of CBF of ROIs was conducted using a linear regression model in order to take into account confounding factors that could affect cerebral perfusion (age, gender, medication load, duration of disease). Considering between groups differences on clinical characteristics (see section 2.2), we integrated SHAPS and WDRS total scores in between group analyses of perfusional data as covariates. The statistical level of significance was set at alpha = 0.01.

Results

Significant differences of CBF between apathetic and non-apathetic patients were found in bilateral accumbens nuclei, bilateral caudate nucleus, left frontal middle gyrus, bilateral frontal superior gyri, right insula, and left putamen. Apathetic patients hyperperfused in these regions compared to NAp patients. These results are summarized in table 2 and illustrated in Figure 3.

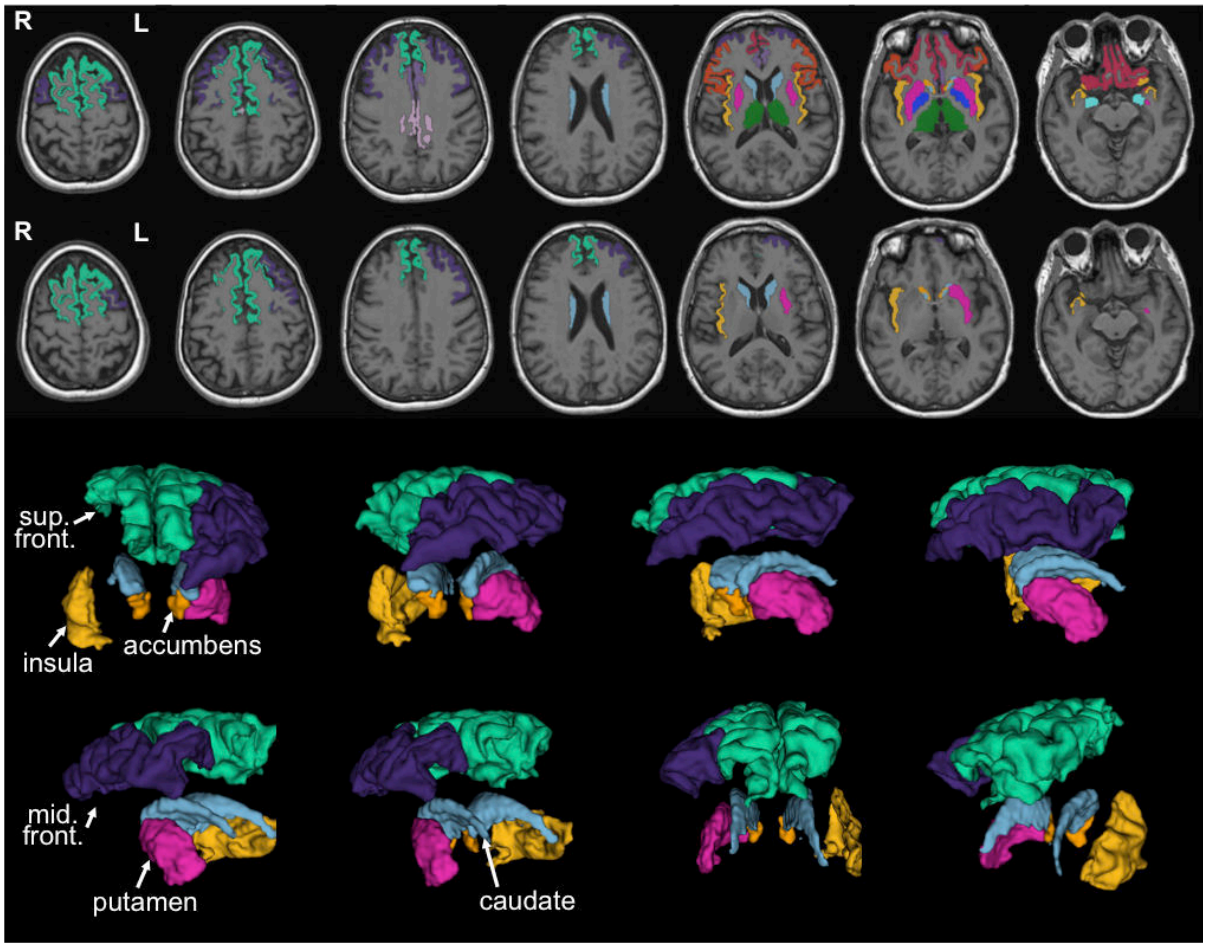


Figure 3: CBF ROI-based analysis between Ap and NAp groups illustrated on one subject. First row: analyzed ROIs (dark green: thalamus, light blue: caudate, pink: putamen, dark blue: pallidum, yellow: insula, turquoise blue: amygdala, old pink: posterior cingulate, anterior cingulate gyrus, red: orbitofrontal cortex, orange: inferior frontal cortex, purple: middle frontal cortex, green: superior frontal cortex, dark yellow: accumbens. Second row: ROIs showing a significant hyper-perfusion in the Ap group. Third and fourth rows: 3D views of these hyperperfused ROIs starting with an anterior view on the top left image.

Variable n=93	Apathetic (n=30) Mean (+/- SD)	Non-apathetic (n=63) Mean (+/- SD)	p-value
Accumbens left	38.60 (12.88)	32.16 (13.18)	**0.007**
Accumbens right	39.61 (14.85)	32.80 (11.43)	**0.007**
Caudate left	34.19 (11.22)	27.20 (11.16)	**0.003**
Caudate right	36.88 (13.32)	30.87 (10.63)	**0.009**
Frontal inferior gyrus left	44.77 (15.48)	38.23 (13.11)	0.015
Frontal inferior gyrus right	48.97 (15.63)	43.24 (11.88)	0.022
Frontal middle gyrus left	48.86 (16.40)	39.84 (13.85)	**0.001**
Frontal middle gyrus right	47.78 (15.46)	41.52 (12.65)	0.012
Frontal superior gyrus left	43.08 (14.27)	36.24 (12.13)	**0.005**
Frontal superior gyrus right	43.05 (13.59)	36.97 (11.07)	**0.007**
Insula left	42.43 (13.80)	36.52 (13.01)	0.014
Insula right	46.65 (14.77)	40.76 (10.81)	**0.008**
Putamen left	40.32 (9.83)	34.96 (11.13)	**0.006**
Putamen right	47.15 (12.94)	42.26 (10.19)	0.025
Pallidum left	38.49 (12.52)	34.27 (10.80)	0.036
Pallidum right	39.06 (13.86)	34.67 (8.41)	0.029
Thalamus left	38.73 (13.24)	35.18 (8.93)	0.077
Thalamus right	40.67 (14.44)	37.48 (8.80)	0.227
Amygdala left	33.23 (10.60)	28.25 (11.81)	0.013
Amygdala right	37.50 (11.72)	32.73 (11.03)	0.022
Anterior cingulate cortex left	44.92 (15.79)	39.93 (13.27)	0.057
Anterior cingulate cortex right	47.58 (15.11)	41.71 (12.11)	0.024
Posterior cingulate cortex left	49.27 (13.46)	44.09 (13.90)	0.052
Posterior cingulate cortex right	49.05 (13.18)	45.40 (12.59)	0.147
Orbito-frontal cortex left	44.81 (17.01)	39.46 (13.87)	0.053
Orbito-frontal cortex right	48.08 (17.37)	42.44 (12.59)	0.047

Table 2 – Intergroup comparisons of CBF in ROIs defined according to Freesurfer's atlas (n=93). Results are corrected for age, gender, medication load, duration of disease, WDRS total score, and SHAPS total score. The p-values in bold are significant (<0.01).

Discussion

General considerations

To our knowledge, this is the first study that aimed to compare cerebral perfusion, using pseudo continuous ASL, between apathetic and non-apathetic depressed patients with neither neurological disorder nor dementia. The prevalence of apathy in our sample (32.26 %) is in accordance with the literature as presented by Starkstein et al. (Starkstein et al., 2001) with a prevalence of 36.8 % in a population of 95 depressed non-demented patients. Besides, the SHAPS score tended to be lower in Ap patients than in Nap ones which is line with a previous study (Batail et al., 2017) where on a sample of 70 patients, Ap patients were shown to be less anhedonic. This suggests that Ap patients should have preserved self-reported capacity to feel pleasure. Therefore, apathy could be a dimension that dichotomizes two different phenotypes of depression. The literature strengthens this hypothesis by proposing a distinction between phenotypes (Tibboel et al., 2015; Treadway and Zald, 2011). On the one hand, an hedonic response to rewards or consummatory anhedonia « liking» seems to be associated with dysfunction in the subcortical network mediated by opioid system such as orbitofrontal cortex, anterior cingulate cortex and amygdala (Gaillard et al., 2013; Treadway and Zald, 2011; Berridge et al., 2009) On the other hand, a diminished motivation to pursue rewards or motivational anhedonia « wanting », which could be linked with apathy, is underlined by a dysfunction in the meso-cortico-limbic dopamine system such as prefrontal cortex, caudate/putamen nucleus, hippocampus (Tibboel et al., 2015; Berridge et al., 2009). Our perfusion results support this hypothesis as discussed below. Furthermore, apathetic depressed patients have a lower psychomotor retardation, assessed with Widlöcher Depressive Retardation Scale (WDRS). We can hypothesize that apathetic depressed patients have difficulties to initiate movement but not to perform it.

Perfusion patterns

The main result of this study was the confirmation of our hypothesis that Ap and NAp depressed patients do not share the same perfusion patterns.
The most striking results were an hyperperfusion, in Ap depressed patients, affecting several brain areas which belong to the dopaminergic (DAergic) circuitry including:

- the mesocortical pathway (MC): bilaterally the frontal superior and middle gyrus, and right insula,
- the mesolimbic pathway (ML): bilaterally the nucleus accumbens,
- the nigrostriatal pathway (NS): bilaterally caudate and left putamen nuclei.

This result is of high interest because it is the first study using arterial spin labeling which confirms the involvement of DA circuitry in mood depressive disorder described earlier in animal models, nuclear imaging studies, pharmacological studies (for review, see (Treadway and Zald, 2011)). DAergic system has been identified to have a critical role in motivation and some specific aspects such as reward prediction, motivational arousal, and incentive salience (Belujon and Grace, 2017; Berridge, 2007). Moreover, there is strong evidence that DA is much involved in motivation (i.e. motivational, ”wanting” dimension of reward processing) than hedonic impact of a stimulus (i.e. affective, “liking” dimension of reward processing) (Berridge, 2007; Treadway and Zald, 2011).
Three main DAergic pathways are involved in depression with different functions. First, the mesocortical pathway is linked with executive function (working memory), attentional process and inhibitory control in motivational context. The mesolimbic pathway is linked with associative learning of reward motivation and reinforcement of behavior linked with experience of pleasure. The nigrostriatal pathway is linked with motor planning, execution of movement and habit learning (Dunlop and Nemeroff, 2007; Treadway and Zald, 2011; Yadid and Friedman, 2008)

Mesocortical DAergic pathway

We found a significant hyperperfusion of the bilateral middle frontal cortex in apathetic depressed patients. The CBF in the right middle frontal cortical has been positively correlated with depressive symptoms in 43 depressed patients compared to 29 controls (Vasic et al., 2015). In addition, Nishi et al. found that the local CBF in the left superior and right middle frontal gyrus in depressed patients, at the resting state, was positively correlated with cognitive

impairment factor score (Nishi et al., 2010). These findings suggest that, among prefrontal regions, the middle and superior frontal gyri, are key regions related to cognitive function. Recently, Robert et al. found a positive correlation between the AES score and cerebral metabolism in the right middle frontal gyrus in a PET study in patients with Parkinson disease (Robert et al., 2012). Furthermore, there is some evidence that voluntary actions (i.e. goal directed behavior) in depressed patients suffering from apathy could be associated with more effortful cognitive control (Levy, 2005). Then, our results suggest that hyperperfusion of prefrontal cortex, in apathetic depressed patients, could be linked with higher cognitive activity in order to compensate deficit in initiating voluntary actions.

We found a hyperperfusion of right insula in apathetic depressed patients. There is recent evidence that this brain structure is not only involved in emotion but plays a role in-between emotion and motivation (Menon and Uddin, 2010; Robert et al., 2012). Precisely, insula is described as a critical hub of "salience network" and monitors internal and external stimuli in order to guide behavior (Menon and Uddin, 2010). Our results agree with functional connectivity in late-life depression patterns. In fact, Alexopoulos et al. found an increase of resting state functional connectivity in apathetic late-life depressed patients compared non-apathetic patients and healthy volunteers (Alexopoulos et al., 2012). The same team has centered his work on functional connectivity of anterior insular cortex. They have pointed out that insula is a primary node in salience network and its central role in motivated behavior in late-life depression (Yuen et al., 2014). Our study is convergent with this latter result in a large sample of depressed patients with another MRI modality.

Mesolimbic DAergic pathway

In our study, apathetic depressed patients had a higher cerebral perfusion in both accumbens nuclei (Nacc). To date, there is little evidence of the involvement of Nacc in apathy (Levy, 2005). Emotional and affective dimension of motivation is supported by ventromedial areas of prefrontal cortex (such as Orbito-Medial Prefontal Cortex (OMPFC)) and limbic basal ganglia (ventral striatum within Nacc, ventral pallidum) (Levy, 2012). Taking into account that OMPFC has a role in motivation value of behavior and that accumbens nucleus is a part of ventral striatum with close anatomical and functional relationship with OMPFC and ventral areas of basal ganglia (Levy, 2005), we could hypothesize that Nacc could play a role in attribution of affective value of a stimulus. Our results suggest that this nucleus could be involved in the emotional-affective dimension of motivation.

Nigrostriatal DAergic pathway

Apathetic depressed patients showed a higher cerebral perfusion in the dorsal striatum (composed of left caudate nucleus and left putamen) which is involved in motor and cognitive aspects of motivation (Menon & Uddin, 2010; Gabriel Robert et al., 2012). Both caudate nuclei were found with a hyperperfusion. As far as we know, no study has focused on caudate nucleus perfusion in apathetic depressed patients without any neurodegenerative disorder. Thobois et al. have reviewed that apathy was linked to dopaminergic denervation regardless of disease stages in PD (Thobois et al., 2017). In a recent study, Maillet et al. found in PD depressed patients an alteration of serotoninergic transmission in bilateral caudate nucleus (Maillet et al., 2016). Severity of apathy was associated with specific serotoninergic lesions in right caudate while depression was linked to serotoninergic alterations in anterior cingulate cortex (ACC) (Maillet et al., 2016). This suggests that apathy is a motivational dimension that could affect caudate nucleus within the reward network whereas affective dimension (like in depression) could be supported by a network centered around Anterior Cingulate Cortex (ACC). Some evidence converges with the involvement of caudate nucleus in prefrontal-basal ganglia circuits underlying apathy (Alexopoulos et al., 2012; Levy, 2005; Paul et al., 2005; Tanner et al., 2015). In fact, this nucleus could play a critical role in a disruption of cognitive processes such as difficulties in elaborating plan of action (Levy, 2005). Paul et al. have pointed out that caudate nucleus could play a role in behavioral side of apathy associated with disruption of frontal cortex (Paul et al., 2005).

In addition, we found a significant hyperperfusion of left putamen. This area seems to be particularly involved in the control of many types of motor skills such as motor learning, motor preparation and performance, control of amplitude of movement (Marchand et al., 2008). The study of Turner et al. (Turner et al., 2003) has investigated movement extent using PET mapping of regional cerebral blood flow in 13 healthy subjects. It was found that increasing movement extent was associated with parallel increases of CBF in putamen and globus pallidus. Taniwaki et al. (Taniwaki et al., 2003) has completed these results by showing with fMRI that the signal intensity of the right posterior putamen increased in parallel with the movement speed during a self-initiated task. In our study, apathetic depressed patients tended to be less slow with a higher perfusion of putamen than non-apathetic ones. This latter analysis highlights a specific role of putamen in apathy and suggests an involvement in the cognitive and motor side of this dimension

To sum up, we have shown that some perfusion differences underline the clinical dichotomy between apathetic depressed patients and non-apathetic depressed patients, described from a clinical side in (Batail et al., 2017). Our results lead us to hypothesize that perfusion patterns in apathetic depressed patients affect key dimensions of apathy such as cognitive (middle and superior frontal cortex), affective (Nacc) and behavioral (caudate and putamen nuclei) ones.

These clinical and imaging results are in accordance with the recent literature which proposes a distinction between deficits in the hedonic response to rewards or consummatory anhedonia "liking" (which seems to concern non-apathetic depressed patients), and a diminished motivation to pursue them or motivational anhedonia "wanting" (which seems to concern apathetic depressed patients) (Tibboel et al., 2015; Treadway and Zald, 2011). "Liking" is linked to subcortical (ventromedial prefrontal cortex and amygdala) networks mediated by the opioid system, whereas "wanting" is linked to the meso-cortico-limbic dopamine system (Tibboel et al., 2015; Berridge et al., 2009)

Limitations

First, we have to note that our groups did not count the same number of patients. This is due to the prospective nature of our study which contributed to a lesser recruitment of apathetic patients. Second, the inherently low spatial resolution of ASL did not allow a fine parcellation of the brain and the analysis of sub-regions of interest such as dorsal or ventral part of striatum or pallidum. Third, the design of our study focused on the comparison between Ap patients versus NAp patients and did not include any control group. A group of healthy subjects would have helped us to determine the baseline perfusion of the analyzed regions. Further studies are necessary to overcome these limitations.

Conclusion

This study focused on perfusion patterns of apathetic depressed patients. We have shown that cerebral perfusion of apathetic depressed patients and non-apathetic ones differ. It suggests the existence of CBF abnormalities in apathetic depressed patients. Interestingly, these abnormalities affect key regions involved in the meso-cortico-limbic dopaminergic loop of reward system: the frontal cortex, the ventral and the dorsal striatum. Each region seems to underlie some key functions represented by respectively cognitive, affective, and behavioral dimensions of apathy. Apathy appears to be a useful biomarker to better characterize different phenotypes of depression, with abnormalities of the motivational network for apathetic patients instead of abnormalities of the emotional network for more anhedonic ones. Identifying the radiological and clinical specificities of apathy in depression would provide a better understanding of its underlying neurobiological mechanisms and would help to better adjust treatment. Numerous therapeutic issues may be studied such as dopaminergic targeted pharmacologic strategies such as pramipexole (Cusin et al., 2013) or new cerebral targets for non-pharmacological treatments like repetitive transcranial magnetic stimulation or Neurofeedback (Arns et al., 2017).

Les points forts de la partie 3.1.2. Apathy in depression: An Arterial Spin Labeling perfusion MRI study.

- Étude des bases neurovasculaires de l'apathie dans la dépression, en ASL pseudo-continue,
- Hyperperfusion chez déprimés apathiques vs non-apathiques affectant des régions clés du système de la récompense (boucles dopaminergiques méso-cortico-limbiques : striatum ventral et dorsal, gyrus frontal),
- Vérifie l'hypothèse de biomarqueurs spécifiques de l'apathie permettant de caractériser différents phénotypes de dépression.

La figure 3 synthétise les différentes étapes et les principaux résultats de l'étude de l'apathie dans la dépression. Nous proposons, pour la suite de notre travail (partie 3.2), de s'intéresser à notre deuxième dimension sémiologique d'intérêt, l'anxiété.

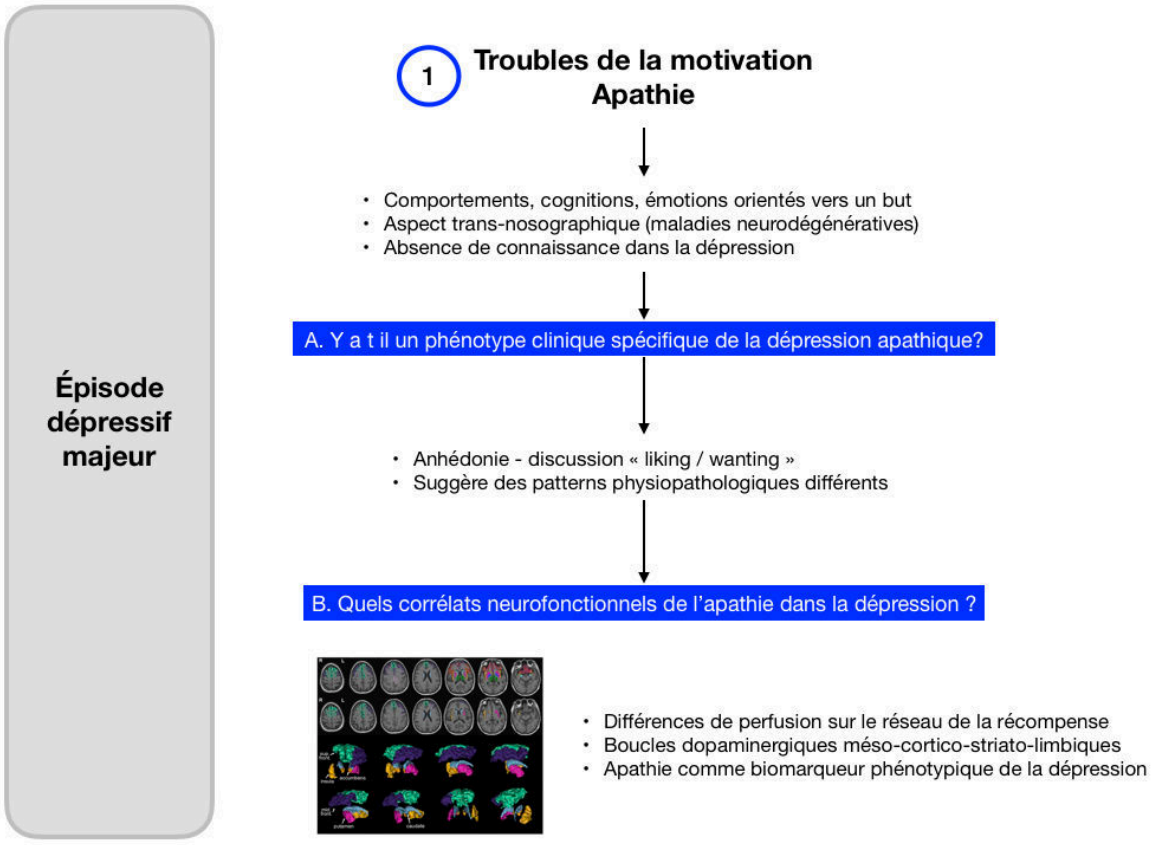


Figure 3: Synthèse des résultats de la partie troubles de la motivation dans la dépression.

3.2 Les troubles des émotions dans la dépression, l'exemple de l'anxiété et ses patterns de perfusion amygdalienne chez les patients déprimés résistants :

Le deuxième axe développé au cours de ce travail s'est concentré sur l'étude de l'anxiété dans une population de patients souffrant de dépression résistante. Les données de la littérature ont mis en évidence une cooccurrence de comorbidité anxieuses plus élevée chez les patients souffrant d'une forme résistante de dépression comparativement aux patients non-résistants. Aucune étude ne s'est intéressée aux caractéristiques sémiologiques des patients souffrant des formes résistantes de dépression. Nous avons proposé dans cette partie une étude en deux phases : 1) la comparaison des caractéristiques sémiologiques et catégorielles entre des patients déprimés résistants et non résistants 2) la comparaison de la perfusion amygdalienne, mesurée en ASL pulsée, entre ces deux populations de patients.

3.2.1 Anxiety and centro-medial amygdala perfusion in treatment resistant depression: An Arterial Spin Labeling perfusion MRI study

Ce travail a été mené dans le cadre d'une thèse de médecine (Dr Adrien Gothland) que j'ai encadré. L'article est en préparation et présenté tel qu'il sera soumis pour publication.

Abstract:

To date, only epidemiological studies have identified some comorbidities associated with treatment resistant depression (TRD) such as anxiety. On the neurobiological side, amygdala, a core nucleus involved in emotion regulation, is postulated to have a crucial role in the development of therapeutic resistance. In this study, we proposed a bed to bench approach which aimed to assess 1) clinical anxiety and depression associated with treatment resistant stage (according to Thase and Rush classification) with both categorical and dimensional/semiological approaches and 2) amygdala cerebral blood flow using arterial spin labeling (ASL) technique in patient suffering from TRD comparing to non TRD. We have conducted a two steps prospective open cohort study. A total of 83 patients for the first step clinical study, whom 45 of them underwent an ASL MRI acquisition have been included. Results have highlighted that categorical and dimensional/semiological features are not concordant. Categorical analysis exhibited significant differences between groups for actual panic anxiety patterns whereas dimensional analysis emphasized affective patterns (i.e. apparent sadness and pessimistic thoughts). Furthermore, TRD group had a significantly higher perfusion in centro-medial nucleus of amygdala compared to non TRD group. Our study highlighted that anxiety and its amygdala's ASL-CBF correlates are high of interest in the understanding of pathophysiology of TRD regarding the link between emotional and motivational cerebral networks which should be studied in further works.

Introduction

Depression is a debilitating illness which course is frequently recurrent. This disease affects more than 350 million people around world (World Health Organization, 2012) with a lifetime prevalence in the range of 10% to 15%. (Briley & Lépine, 2011). It is identified to be a leading cause of burden with high disability in everyday life (Ferrari et al., 2013). The risk of recurrence in specialized medical care after 15 years is estimated around 85% (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2009). Two major factors are involved in the risk of recurrence : the number of previous episode and the persistence of inter-critical residual symptoms (Hardeveld et al., 2009). The latter hits one third of people suffering from Mood Depressive Disorders (MDD) (Spadone & Corruble, 2010). The most identified are anxiety, severity of sadness, and psychiatric comorbities such as panic disorder (Fagiolini & Kupfer, 2003; Nierenberg et al., 2010; Taylor, Walters, Vittengl, Krebaum, & Jarrett, 2010). Recently, one European multi-centric project have studied clinical patterns associated with TRD in 702 subjects (Schosser et al., 2012). Four clinical variables were significantly associated with TRD as comorbid anxiety disorder, non-response to first line antidepressant, current suicidal risk, and melancholic features (Schosser et al., 2012).

During the last decade, the field of neuroscience has investigated the function and the morphology of the brain of patients suffering from depression and specifically TRD (Giacobbe et al., 2009; M. L. Phillips, Ladouceur, & Drevets, 2008). Amygdala has been identified of interest in most of TRD neuroimaging studies. It is a limbic structure localized in the anterior-internal part of temporal lobe (Dalgleish, 2004). It is one of the most important emotional region in brain, particularly in processing social signals of emotion (especially involving fear), in emotional conditioning and in consolidation of emotional memories (Dalgleish, 2004; LeDoux, 2007). During mood depressive episode (MDE), this structure have been identified with hyper-reactivity in both positive (Davey, Allen, Harrison, & Yücel, 2011) and negative (Arnone et al., 2012; Townsend et al., 2010; Victor, Furey, Fromm, Öhman, & Drevets, 2010; Zhong et al., 2011) emotional stimuli. As well as these findings, it has been demonstrated that abnormal reactivity or responsivity of amygdala is modulated by antidepressant treatment in patients suffering from MDE (Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012; Ruhé, Booij, Veltman, Michel, & Schene, 2012; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), as in healthy subjects with a single dose of citalopram (Y. Chen et al., 2011). In the therapeutic side, amygdala activity has been correlated with treatment response in depression (El-Hage, Leman, Camus, & Belzung, 2013). In fact, in a PET study, response to electro-convulsivotherapy in treatment resistant depression has been correlated with an enhancement of serotoninergic transmission in amygdala among others brain regions (Lanzenberger et al., 2012). Furthermore, lower pre-treatment metabolic activity of amygdala has been identified to

be predictive of response to antidepressant treatment (Saxena et al., 2003). Recently, Williams and colleagues have demonstrated with a fMRI-BOLD task that pre-treatment reactivity of amygdala to subliminal sadness was a moderator of non-response to a serotonin-norepinephrine reuptake inhibitor (Williams et al., 2015). Moreover, the authors have shown that pre-treatment amygdala hypo-reactivity to subliminal happy and threat was a general predictor of treatment response regardless of medication type (Williams et al., 2015). Finally, the involvement of pre-therapeutic amygdala activity linked with poorer response to antidepressant treatment have been replicated and synthetized in a meta-analysis work (Fu et al., 2013) and a review (El-Hage et al., 2013). Taken all together, these data indicate the central role of amygdala in reflecting treatment resistance.

To sum up, amygdala, anxiety, and melancholic symptoms seem to be closely linked to TRD. Concerning clinical features, most of the data associated with therapeutic outcomes are defined according to a categorical approach (i.e. DSM-related comorbities). There's not much studies who has investigated the reproducibility of these results using a dimensional/semiological approach. From the imaging side, to our knowledge, there are no study that focused on resting state perfusion characteristics of amygdala using arterial spin labeling in TRD patients. In fact, ASL is a growing technique that is non-invasive (endogenous tracer), accurate and reproducible comparing to other perfusion imaging modalities, which allow an absolute quantification of cerebral blood flow (Detre, Leigh, Williams, & Koretsky, 1992; J.-C. Ferré et al., 2013; Wintermark et al., 2005).

The aim of this study is to assess 1) clinical anxiety and melancholic associated with treatment resistant stage (according to Thase and Rush classification (M E Thase & Rush, 1997)) with both categorical and dimensional/semiological approaches and 2) amygdala cerebral blood flow using ASL technique in patient suffering from TRD comparing to non TRD. We hypothesize that 1) patients with a high level of resistance will have concordant categorical and dimensional/semiological characteristics and 2) patients suffering from TRD will have a higher resting state perfusion of amygdala using ASL technique. We propose to assess these hypotheses in a two steps prospective open cohort study.

Methods

Patient population

The study was proposed to patients suffering from a Mood Depressive Episode (MDE) under DSM 5 criterion with or without personal history of Mood Depressive Disorder (unipolar or bipolar subtype). Exclusion criteria included other Axis I disorders (except anxious comorbidities such as post-traumatic stress disorder, social phobia, generalized anxiety

disorder, panic disorder) which were explored using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Patients with severe chronic physical illness were not included. Other exclusion criteria were potential safety contraindications for MRI (pacemakers, metal implants, pregnancy and lactation), neurological problems or a history of significant head injury and significant circulatory conditions that could affect cerebral circulation (i.e. non-controlled hypertension). All patients underwent a neurological examination by a trained physician to ensure that no included subject had any clinical sign of dementia or abnormal neurological examination.

Study design

A prospective open cohort study was conducted. Depressed patients were recruited from the adult psychiatry department of Rennes, France. A complete description of the study had been given to the subjects, their written informed consent was obtained. The study was approved by an ethic committee. This study is a first analysis, focusing on amygdala perfusion in treatment resistant depression, of an ongoing cohort study which is registered in www.clinicaltrial.gov (NCT02286024). When recruited, patients underwent a structured clinical interview. After clinical assessment, patients had imaging protocol by a maximum of three days. Clinical data were anonymously retrieved in a notebook. Imaging data followed two different pathways, 1/ a routine care one, as usual and 2/ a research one where they were anonymously stored in a imaging data base (www.shanoir.org). All patients were recruited between November 2014 and November 2015.

Clinical assessment

Patients were assessed by a single interview by a trained psychiatrist with following scales:

- Montgomery and Äsberg Depression Rating Scale (Montgomery & Asberg, 1979),
- State Trait Anxiety Inventory (Spielberger, C. D. et al., 1983),
- Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998).

Socio-demographic (age, gender, education) and disease characteristics (diagnosis, duration of disease, duration of episode, number of mood depressive episodes, antecedent of suicidal attempts/ electroconvulsive therapy/ transcranial magnetic stimulation, treatment resistance stage according to Thase and Rush's classification) were retrieved.

Imaging protocol

Data acquisition

Patients were scanned on a 3T whole body Siemens MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. Anatomical data included a high resolution 3D T1-weighted MPRAGE sequence (3D T1) with the following imaging parameters: TR/TE/TI = 1900/2.27/900 ms, 256x256 mm^2 FOV and 176 sagittal slices, 1x1x1 mm^3 resolution, parallel imaging GRAPPA2 (Jean-Christophe Ferré, Petr, Bannier, Barillot, & Gauvrit, 2012). Perfusion data were acquired using a pulsed ASL PICORE Q2TIPS sequence with total scan time of approximately 6 minutes. The imaging parameters were: TR/TE = 3000/18 ms, flip angle 90°, matrix size 64_ 64, TI_1 /TI_{1s} /TI_2 = 700/1500/1700 ms, parallel imaging SENSE2. The labeling slice was 10 cm thick and was placed 3 cm below the acquisition volume. Crusher was set to achieve a cut-off velocity of 4 cm/s. Fourteen axial slices were acquired sequentially from inferior to superior in the AC-PC plane, with 3x3 mm^2 in-plane resolution, 7 mm slice thickness and 0.7 mm gap. One control volume plus 60 repetitions, i.e., label/control pairs, (121 volumes), finally composed the ASL data series.

Data pre-processing

Pre-processing of the image data was performed with an inhouse pipeline using MATLAB (v. R2014a, The MathWorks Inc.) and the SPM8 toolbox (Wellcome Department of Imaging Neuroscience at University College London, UK) as follows:

The anatomical 3D T1 was corrected for intensity inhomogeneity and segmented into grey matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) probability maps using the MNI template tissue probability as an a priori for brain tissue classification. Estimated by this same unified segmentation model SPM routine, spatial normalisation parameters were applied to warp the 3D T1 volume to the MNI space.

The ASL data series was motion corrected by a rigid body transform minimising the sum of squared differences cost function. A two-pass procedure first realigned all the control and label volumes onto the first volume of the series, then registered the series to the mean of the images aligned in the first pass. The motion-corrected ASL series was co-registered to the 3D T1 using a rigid transform. The latter was estimated by maximizing normalised mutual information between the mean control image, i.e., the average of all the realigned control volumes, and the 3D T1 GM map. Letting aside the first volume of the series, pM_0, the co-registered ASL images were pairwise subtracted (control - label images) to produce a series

of perfusion weighted maps, which was subsequently averaged to produce a perfusion weighted (PW) map. The PW map was quantified to a CBF map by applying the standard kinetic model (Buxton et al., 1998; Cavuşoğlu, Pfeuffer, Uğurbil, & Uludağ, 2009):

$$f = 6000.\frac{\lambda \Delta M}{2\alpha \mathrm{TI}_1 \exp\frac{-\mathrm{TI}_2 + idx_{sl} * \mathrm{TI}_{sl}}{\mathrm{T1}b} M0}$$

where f is the CBF map, ΔM is the perfusion weighted map, λ = 0.9 ml.g^{-1} is the blood/tissue water partition coefficient, M_0 represents the equilibrium magnetization of arterial blood and is approximated by the first volume of the series pM_0, α = 0.95 measures the labeling efficiency, TI_2 = 1700 ms is the inversion time of the ASL sequence, idx_{sl} is the slice index, starting from 0 for the first acquired slice, TI_{sl} = 45 ms is the acquisitionduration of one slice, TI_1 = 700 ms is the temporal width of the bolus, T_{1b} = 1500 ms is the T_1 of blood (Wang et al., 2011).

For subsequent region of interest (ROI) analysis, the mean CBF values over the amygdala and its subdivisions (centro-medial (CM), superficial (SF) and latero-basal (LB) nuclear groups) were computed for each subject in the MNI space (figure 2). These ROIs were extracted from the Juelich cytoarchitectonic atlas (Amunts et al., 2005) using the SPM Anatomy toolbox (v2.0, (Eickhoff et al., 2005)). To refine this segmentation and ensure that the CBF values were computed from grey matter, only the ROI voxels having a grey matter probability superior to 0.7 were retained.

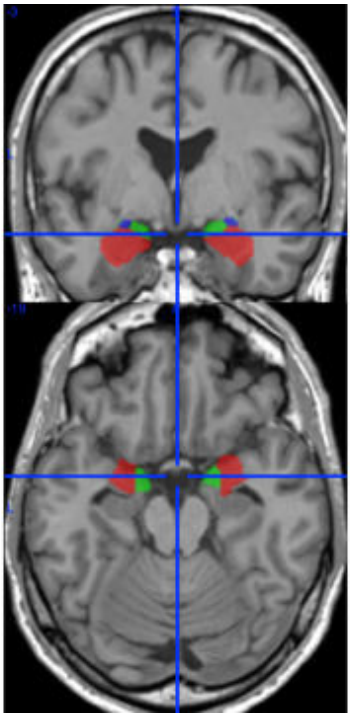


Figure 2 : Amygdala ROI extracted from Juelich cytoarchitectonic atalas (SPM Anatomy Toolbox v2.0 (39)). Red: Basolateral, Green: Centro-median, Blue: Superficial

Statistical analyses

Statistical analyses were performed on all included and assessed patients with R software (http://www.R-project.org/). All results are reported as means (± SD) for continuous variables and number (rates) for discrete variables. The significance threshold for all tests was set at 5% ($p < 0.05$).

Study 1 – Clinical comparison

In a first step, we compared clinical features of a group of 83 patients stratified in 5 groups according to their level of treatment-resistance assessed with Thase and Rush classification (M E Thase & Rush, 1997). Quantitative variables were compared using a Kruskall and Wallis test, and qualitative variable using a Fisher test.

Groups were compared for socio-demographic, disease characteristics, and clinical variables. The latter were analyzed according to a two-steps approach: 1/ categorical (comorbidities, frequencies and number) and 2/dimensional (severity of depression with total score and sub-scores of MADRS, anxiety with STAI auto-questionnaire).

Study 2 – Amygdala perfusion comparison

We compared cerebral blood flow (CBF) of amygdala, as described above, in 45 patients of the whole sample who underwent resting state MRI. The threshold used was the resistance of at least two lines of antidepressant treatment (i.e. stage 2 of Thase & Rush classification). CBF were compared using a Wilcoxon test.

Finally, a multivariate analysis was conducted in order to estimate the link between CBF in amygdala and clinical variables of interest such as:

- MADRS tot score insofar as amygdala perfusion can be linked with severity of depression (notably according to emotional dimension (Arnone et al., 2012; Victor et al., 2010)),
- STAI Y-A score (state anxiety) for the same reason described above (LeDoux, 2007),
- CBF of total gray matter of each patient in order to take into account the intersubject perfusion variability (Fan, Jahanian, Holdsworth, & Zaharchuk, 2016; Henriksen et al., 2012).

Results

Step 1 - Clinical comparison

General characteristics

Socio-demographic and disease characteristics are synthetized in table 1. Patients with a high degree of resistance had more severe disease characteristics (higher duration of actual MDE, chi-squared = 14.63, p = 0.006; longer duration of disease, chi-squared = 17.68, p = 0.001; more MDE, chi-squared = 10.04, p = 0.04) and were older (chi-squared = 18.41, p = 0.001).

Variable (N=83)	Mean (± sd) or n (%)
Age (year)	46.87 (14.68)
Gender (female)	53 (63.86%)
Education (year) (n=78)	12.86 (2.56)
Diagnosis (n=82)	
Unipolar disorder	52 (63.41%)
Bipolar disorder type 1	7 (8.54%)
Bipolar disorder type 2	12 (14.63%)
Bipolar disorder type 3	11 (13.42%)
Duration of disease (year)	15.40 (11.83)
Duration of episode (week)	28.82 (33.55)
Number of Mood Depressive Episodes	4.86 (4.73)
Antecedent	
Suicidal Attempt	41 (49.40%)
Electroconvulsive therapy	14 (16.87%)
Transcranial Magnetic Stimulation	13 (15.66%)
Resistance Stage (Thase & Rush) (n=79)	
Stage 1	9 (11.39%)
Stage 2	29 (36.71%)
Stage 3	29 (36.71%)
Stage 4	9 (11.39%)
Stage 5	3 (3.80%)
Number of anxious comorbidities (n=76)	1.26 (1.32)
MADRS (total score)	27.96 (5.09)

STAI-YA (total score) (n=82)	59.71 (12.02)
STAI-YB (total score) (n=82)	58.71 (10.94)

Table 1: Sociodemographic and disease characteristics of whole sample.

Categorical approach

Results of Fisher test and Kruskall and Wallis test are summarized in table 2. Groups were significantly different according to actual Panic Disorder comorbidity.

Variable (n=72)	Stage 1 (n=8)	Stage 2 (n=26)	Stage 3 (n=28)	Stage 4 (n=8)	Stage 5 (n=2)	p
Actual PD	0 (0%)	3 (11.5%)	5 (17.9%)	1 (12.5%)	2 (100%)	0.05
Lifetime PD	1 (12.5%)	8 (30.8%)	7 (30.8%)	1 (12.5%)	2 (100%)	0.18
Social Phobia	2 (25%)	3 (11.5%)	3 (10.7%)	2 (12.5%)	1 (50%)	0.41
GAD	1 (12.5%)	14 (53.8%)	12 (42.9%)	4 (50%)	1 (50%)	0.32
PTSD	0 (0%)	7 (26.9%)	1 (3.6%)	1 (12.5%)	0 (0%)	0.09

Table 2: Comparison of frequency/sum of anxious comorbidities. Categorical approach (MINI – DSMIV-TR). PD: Panic Disorder ; GAD : General Anxiety Disorder ; PTSD : Post Traumatic Stress Disorder.

Dimensional approach

Results of comparison of different scores and sub-scores at MADRS and STAI (state-YA; trait-YB) are summarized in table 3. Groups were significantly different according to affective dimensions (i.e. apparent sadness and pessimistic thoughts) but not anxiety sub-scores.

Variable (n=79)	Stage 1 (n=9)	Stage 2 (n=29)	Stage 3 (n=29)	Stage 4 (n=9)	Stage 5 (n=3)	p
MADRS (total score)	26.89 (5.30)	27.21 (4.75)	28.21 (5.18)	28.67 (5.92)	32.33 (1.15)	0.48
1 : apparent sadness	3.33 (1)	3.48 (0.95)	3.93 (0.84)	3.33 (1)	5 (0)	**0.03**
2 : reported sadness	4.33 (0.71)	3.83 (1.04)	4 (0.96)	3.78 (0.97)	5.33 (0.58)	0.12
3 : inner tension	2.56 (1.42)	2.72 (1.44)	2.93 (1.19)	3.78 (0.83)	4 (0)	0.09
4 : reduced sleep	1.56 (1.67)	2.35 (1.72)	1.83 (1.81)	2.22 (1.79)	1.33 (2.31)	0.67
5 : reduced appetite	1.11 (1.36)	1.45 (1.57)	1.17 (1.71)	1.44 (1.81)	0.33 (0.57)	0.84
6 : concentration diff.	3.33 (1.22)	2.83 (1.07)	3.38 (1.18)	3.11 (0.93)	2.33 (1.16)	0.13
7 : lassitude	2.33 (1.73)	3.28 (1)	3.10 (1.50)	3.56 (0.53)	4 (0)	0.23
8 : inability to feel	3.44 (0.88)	3.66 (0.67)	3.66 (0.77)	3 (0.87)	3.66 (0.58)	0.25
9 : pessimistic thoughts	2.56 (1.33)	2.59 (1.02)	3.10 (0.94)	3.22 (1.09)	4 (0)	**0.03**
10 : suicidal thoughts	2 (1.80)	1.17 (0.97)	1.21 (1.21)	1.22 (1.20)	2.33 (1.53)	0.47
STAI-YA (state anxiety)	48.13 (11.22)	61.03 (11.93)	60.76 (11.33	60.22 (14.92)	58 (10.82)	0.09
STAI-YB (trait anxiety)	55.38 (10.54)	59.72 (10.88)	59.19 (11.26)	54.98 (11.72)	60.02 (8.97)	0.68

Table 3: Comparison of MADRS scores/subscores and STAI according to a dimensionnal approach. (concentration diff. = concentration difficulties)

Step 2 - Amygdala perfusion comparison

Comparison of CBF in total amygdala and sub-regions

Table 4 synthetizes cerebral blood flows of both TRD and non TRD groups. TRD group had a significantly higher perfusion assessed using ASL technique in centro-medial nucleus of amygdala compared to non TRD group.

Variable n = 45	Mean	Standard deviation	TRD mean (sd) n = 19	Non TRD mean (sd) n = 26	p-value
Total amygdala					
Bilateral	36.66	14.28	37.69 (16.60)	35.91 (12.60)	0.70
Left	38.59	13.94	38.82 (14.98)	38.41 (13.43)	0.93
Right	34.77	16.70	36.54 (19.52)	33.47 (14.57)	0.57
Baso-lateral nucleus of amygdala					
Bilateral	33.58	15.60	34.39 (16.99)	33.00 (14.83)	0.78
Left	34.45	15.24	34.63 (16.22)	34.32 (14.81)	0.95
Right	32.88	17.86	34.22 (19.59)	31.90 (16.81)	0.68
Centro-medial nucleus of amygdala					
Bilateral	34.60	13.98	39.78 (16.84)	30.82 (10.22)	**0.05**
Left	35.50	15.93	41.05 (18.13)	31.44 (13.02)	0.06
Right	33.60	14.95	38.09 (18.86)	30.31 (10.53)	0.12

Table 4: Cerebral Blood Flow in amygdala (whole nucleus and sub-regions described according to ANAT template). Comparison between Treatment Resistant Depression (TRD) group and Non TRD group (Wilcoxon test).

Multivariate analysis

The linear model is summed up in table 5. The result of univariate analysis (see 3.2.1.) is robust to the correction of proposed confounding factors such as severity of depression, level of anxiety and CBF of grey mater of each patient.

Variable (n=45)	Estimate	Standard Error	t value	p
MADRS score	0.69	0.36	1.92	0.06
STAI-A score	-0.12	0.19	-0.63	0.53
TRD group	7.86	3.88	2.03	0.05
CBF GM patient	0.21	0.15	1.41	0.17

Table 5: Multivariate analysis (linear model) assessing mean cerebral blood flow (CBF) of centro-medial amygdala.

Discussion

Clinical aspects

Our study highlighted that in a clinical point of view, categorical and dimensional/semiological features aren't totally concordant. Categorical analysis exhibited more actual panic anxiety patterns whereas dimensional analysis emphasized more affective patterns (i.e. apparent sadness and pessimistic thoughts).

In line with the literature actual panic disorder is a more frequent comorbidity in patients with a high degree of therapeutic resistance (Fagiolini & Kupfer, 2003; Souery et al., 2007). On the other hand, there were no higher frequency of social phobia nor other anxious disorder in our population.

Dimensional analysis emphasized more affective patterns (i.e. apparent sadness and pessimistic thoughts) than anxious ones (such as item 3 of MADRS (inner tension) or STAI-YA (state anxiety)). Our results are in accordance with categorical data of the literature which illustrates that melancholic subtypes are associated with TRD (Kornstein & Schneider, 2001; Mendlewicz et al., 2010; Schosser et al., 2012; Sherbourne, Schoenbaum, Wells, & Croghan, 2004). Taken all together, the most stringent dimension associated with TRD is the severity of depressive thoughts/emotions. We could postulate that the concept of "psychic pain" is more effective in defining TRD clinical profile. This dimension should integrate pessimistic thoughts, depreciation ideas, and resultant anxiety/inner tension.

Neuroimaging aspects

From the imaging point of view, CBF of centro-medial nucleus of amygdala is more important in patients with TRD. This result is robust to the correction with some confounding factors.

To our knowledge, this is the first cohort study that used arterial spin labeling perfusion MRI in patients suffering from TRD.

We have confirmed our hypothesis of a higher ASL-CBF in the centro-medial nucleus of amygdala. The central amygdala have been described to be involved in patients suffering from co-occuring anxiety-related and alcohol-related behaviors (Gilpin, Herman, & Roberto, 2015). In addition, some works on animal models have demonstrated that more central than basolateral amygdala is implicated in controlling motivation for food consumption during aversive conditioned stimulus (Petrovich, Ross, Mody, Holland, & Gallagher, 2009). This nucleus seems to be at the interface between emotional integration and control of goal-directed behaviors. Some authors have suggested that there is a link between anxiety dimensions and

modulations of goal-directed behaviors (Admon et al., 2014; Sterpenich, Schwartz, Maquet, & Desseilles, 2014). Anxiety and depression moderate motivation-related brain networks during goal maintenance (Spielberg et al., 2014). These studies illustrated this using fMRI or functional connectivity paradigms (Admon et al., 2014; Gold, Morey, & McCarthy, 2015; Spielberg et al., 2014; Sterpenich et al., 2014). Brains regions involved in these processes were amygdala, prefrontal cortex and striatum (Admon et al., 2014; Gold et al., 2015; Spielberg et al., 2014; Sterpenich et al., 2014).

In our study, there were no significant difference between groups according to perfusion of latero-basal nucleus of amygdala. This part is largely involved in processing emotional valence of stimulus (Hartley & Phelps, 2009). It has a more integrative role and is closely linked to centro-medial amygdala through a high density of projections (Hartley & Phelps, 2009).

In an overall point of view, we can hypothesize that central amygdala is implicated in both positive (i.e. anxiety) and negative (i.e. loss of motivation) residual dimensions that bolster treatment resistance. This area could be the seed of a "TRD network" including projections to regions involved in motivations and goal-directed behavior such as prefrontal cortex (inferior frontal gyrus, orbitofrontal cortex, and ventromedial prefrontal cortex) and striatum. Central amygdala and its projections to motivational brain regions could be a biomarker of TRD. A further study could emphasize this hypothesis using resting state ASL and connectivity analysis.

Methodological and conceptual discussion

First, it must be pointed out that our sample was composed of patients with a global high level of severity of disease. In fact, 51.9% of the population had a degree of resistance at stage 3 (i.e. resistance to tricyclic antidepressant) or above. Moreover, MADRS and STAI Y-A/Y-B scores were in favor of high severity of actual depressive episode which illustrates the naturalistic design of this study. So, our sample had an overall high-level treatment resistance which can affect the generalizability of our results.

From the clinical step of this study, besides statistical limitations mentioned above, some other methodological aspects have to be pointed out. First, the Thase & Rush classification can be discussed. Indeed, it is one of the most used in studies on TRD but its use doesn't make consensus regarding to the lack of dose and duration criteria (Berlim & Turecki, 2007; Fava, 2003; Ruhé, van Rooijen, et al., 2012; Souery, Papakostas, & Trivedi, 2006), or the implicit across-class hierarchy (Fava, 2003; Mace & Taylor, 2000; Ruhé, van Rooijen, et al., 2012; Michael E. Thase et al., 2002). Second, the choice of a STAI (Y-A, Y-B) auto-questionnaires in order to assess anxiety can be discussed. In fact, some previous works have demonstrated that these subjective scales doesn't only rate anxiety dimension but also depression and self-

esteem (Bieling, Antony, & Swinson, 1998; Caci, Baylé, Dossios, Robert, & Boyer, 2003). For further analysis, we could get round this by using an hetero-questionnaire such as the Hamilton Anxiety Scale (Hamilton M., 1959).

From the imaging step, the higher perfusion of centro-medial amygdala in TRD group was statistically significant but with a small effect size ($t = 2$, $p = 0.05$). This has to be replicated in a larger sample. Furthermore, we have made the choice of an amygdala-ROI analysis because amygdala is high of interest in the field of emotion processing which activity (metabolic, perfusion, functional) have been linked with treatment resistance. We assume that this approach remains restrictive. Further study should explore a whole brain analysis in order to reproduce these results.

Conclusion

Our study has highlighted that anxiety and its amygdala's ASL-CBF correlates are high of interest in the understanding of pathophysiology of TRD. One of the most important challenge lie in the definition of clinical anxiety and its link with other emotional patterns such as affective ones. Such cohort study which associates clinical features and innovative imaging techniques is a promising bed to bench approach. Despite some methodological and statistical constraints, the naturalistic dimension remains strong point of this design. This work opens onto some perspectives such as 1) a longitudinal study in order to assess how amygdala-ASL-perfusion can predict therapeutic outcome? and 2) work on the hypothesis of a "TRD network" involving emotional (i.e. central amygdala) and motivational (i.e. prefrontal cortex and striatum) regions.

Points forts de la partie 3.2.1. Anxiety and centro-medial amygdala perfusion in treatment resistant depression: An Arterial Spin Labeling perfusion MRI study

- Étude en 2 phases avec une approche basée « bed to bench » : 1) caractéristiques sémiologiques et catégorielles de patients déprimés résistants et 2) comparaison de la perfusion amygdalienne (et de ses sous-régions) entre patients déprimés résistants et non-résistants.
- Phase 1 - clinique : 83 patients / phase 2 - imagerie : 45 patients ASL
- Phase 1 : les approches sémiologiques et catégorielles non concordantes : patients TRD présentent plus de comorbidité trouble panique (donc sur versant anxiété) et plus de patterns sémiologiques affectifs (intensité de la tristesse et des pensées pessimistes). Les résultats cliniques nous ont amené à réaliser une analyse factorielle complémentaire afin de mieux comprendre cette non concordance (partie 3.2.2.).
- Phase 2 : nous retrouvons une hyperperfusion amygdale centro-médiane chez les TRD : discussion du rôle de cette sous-région amygdalienne dont certaines de ses projections se font vers le réseau de la récompense (striatum). Ce dernier résultat est à souligner dans la mesure où il ouvre la question de l'interaction de régions cérébrales impliquées dans la régulation émotionnelle avec d'autres impliquées dans la régulation de la motivation.

3.2.2 Analyse complémentaire – analyse factorielle de l'échelle State Trait Anxiety Inventory (A et B)

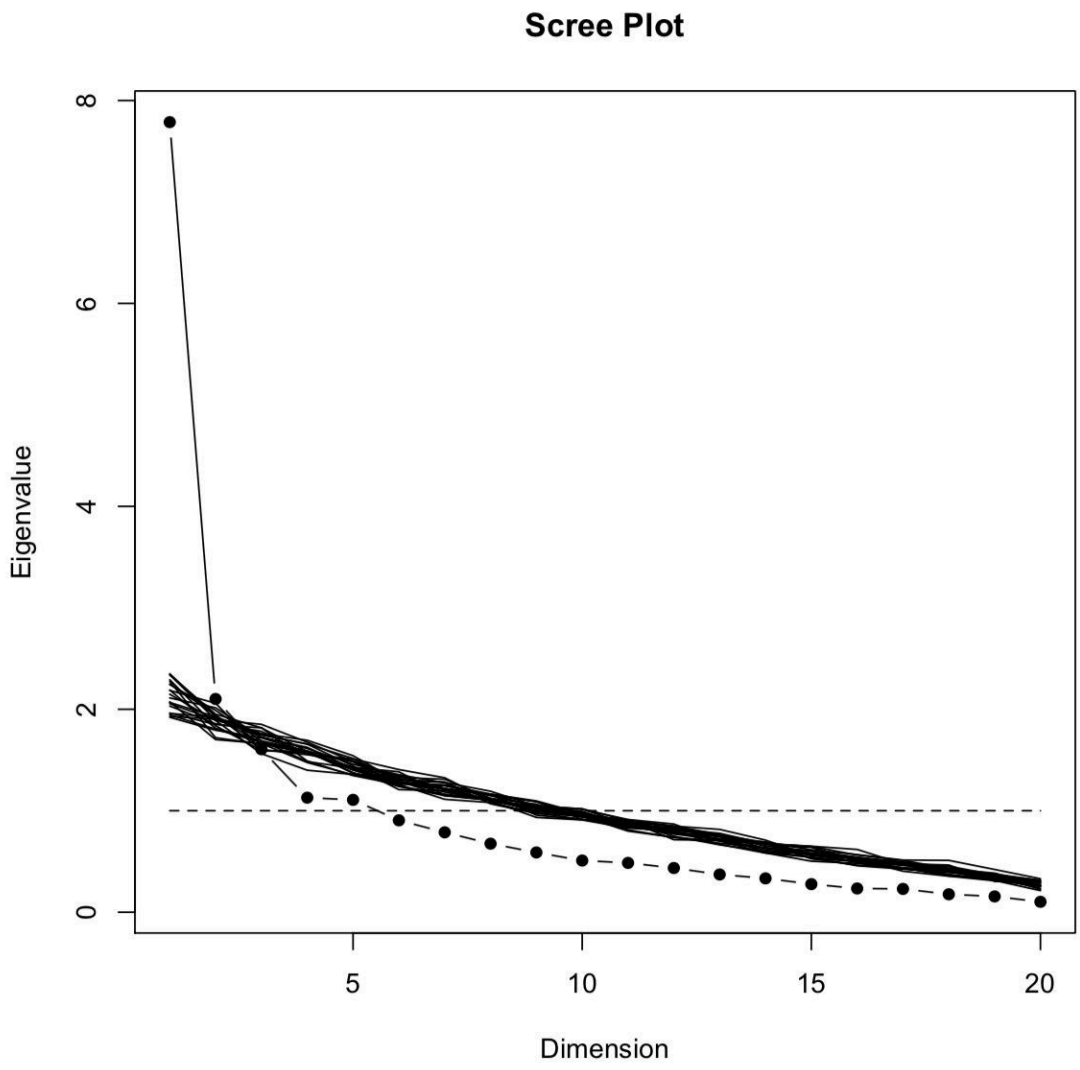
Dans cette dernière étude, les aspects dimensionnels correspondaient eux à la comparaison par ANOVA des échelles cliniques MADRS, STAI-Y A et STAI-Y B. Les items de la MADRS étaient eux aussi comparés individuellement afin d'évaluer les composantes anxieuses de cette échelle.

Plusieurs articles soutiennent que les STAI-Y ne mesureraient pas seulement l'anxiété, mais également des valences dépressives et d'estime de soi (Bieling et al., 1998; Caci et al., 2003). De fait, nous avons réalisé des analyses factorielles exploratoires des échelles STAI-Y A et B afin de discriminer des facteurs plus spécifiques de l'anxiété pour notre échantillon de patients déprimés résistants. Le nombre de facteurs était déterminé en calculant les valeurs propres, en dessinant leur scree plot, et en générant 20 simulations.

Le Scree Plot de l'échelle STAI-Y A indiquait 2 facteurs (figure 4). Ces 2 facteurs étaient les valeurs propres au-dessus de ce qui pouvait être attendu par chance sur les 20 simulations. Ces facteurs comptaient pour 44.60% (27.10% pour le facteur 1 et 17.60% pour le facteur 2) de la variance totale des items de la STAI-Y A. La structure factorielle de cette échelle est détaillée dans le tableau 2.

- Le facteur 1 de la STAI-YA semble rassembler à la fois des items ayant attrait à l'anxiété état (2, 12, 13, 15 et 17) et d'autres avec des caractéristiques plus thymiques et d'estime de soi (5, 8, 11, 16 et 20), et d'instabilité psychique (14, 18 et 19).
- Le facteur 2 semble plus spécifique de l'anxiété et constituait donc une variable d'intérêt (tension interne, ruminations, débordement émotionnel, inquiétude, peur) : 1, 3, 4, 6, 7 et 9.

Le Scree Plot de la STAI-Y B en revanche n'indiquait qu'un seul facteur.



Le Scree plot est le graphique de la progression des valeurs propres (eigenvalue, en ordonnée) en fonction des items (en abscisse). Ces valeurs propres ont été obtenues par l'analyse factorielle des items de l'échelle. Afin de déterminer le nombre de facteurs nécessaires, nous effectuons une analyse parallèle qui consiste à comparer la progression des valeurs propres de l'échantillon empirique avec celle d'un échantillon aléatoire simulé, comptant le même nombre de répondants et le même nombre d'items. Le nombre de facteurs conservés correspond alors au nombre de valeurs propres empiriques supérieures aux valeurs propres simulées lorsqu'elles sont comparées une à une, de la plus élevée à la plus faible. ***Ici, nous retenons donc 2 facteurs.***

Figure 4: Scree plot illustrant l'analyse factorielle de l'échelle STAI-YA.

	Items	Facteur 1	Facteur 2
1	Je me sens calme.	0.287	0.512
2	Je me sens en sécurité, sans inquiétude, en sûreté	0.453	0.297
3	Je suis tendu(e), crispé(e)	0.152	0.938
4	Je me sens surmené(e).	0.271	0.440
5	Je me sens tranquille, bien dans ma peau.	0.677	0.214
6	Je me sens ému(e), bouleversé(e), contrarié(e).	0.128	0.567
7	L'idée de malheurs éventuels me tracasse en ce moment.	0.321	0.471
8	Je me sens content(e)	0.704	0.294
9	Je me sens effrayé(e).	0.293	0.456
10	Je me sens à mon aise.	0.872	0.153
11	Je sens que j'ai confiance en moi.	0.752	0.180
12	Je me sens nerveux (nerveuse), irritable.	0.760	
13	J'ai la frousse, la trouille (j'ai peur).	0.354	0.172
14	Je me sens indécis(e).	0.224	0.192
15	Je suis décontracté(e), détendu(e).	0.574	0.445
16	Je suis satisfait(e).	0.662	0.217
17	Je suis inquiet, soucieux (inquiète, soucieuse).	0.555	0.418
18	Je ne sais plus où j'en suis, je me sens déconcerté(e), dérouté(e).	0.697	0.122
19	Je me sens solide, posé(e), pondéré(e), réfléchi(e).	0.708	0.147
20	Je me sens de bonne humeur, aimable.	0.541	0.240

*Ce tableau examine la relation entre les variables (items originaux de la STAI-Y A) et les facteurs retenus sur le scree plot. Plus cette relation est forte, plus la variable est expliquée par le facteur. Cette relation, qui peut s'exprimer par un chiffre variant de -1 à +1 s'appelle la « **saturation** » (factor loading) de la variable sur le facteur. Typiquement, on considère qu'une variable n'est associée à un facteur que si sa saturation dépasse 0,30 en valeur absolue.*

Tableau 2: Synthèse des facteurs identifiés à l'issue de l'analyse factorielle de l'échelle STAI-YA.

L'analyse factorielle de la STAI-Y A – anxiété état – nous a permis de décomposer les items de cette échelle en deux facteurs : STAI-Y A1 et STAI-Y A2. Selon nous, le facteur STAI-Y A2 circonscrivait plus particulièrement l'exacerbation anxieuse aigue. Cela est cohérent avec le fait que ce soit le trouble panique actuel qui ressortait associé aux patients les plus résistants, tant les items de ce facteur STAI-Y A2 décrivent des dimensions similaires : « effrayé », « tendu », « crispé », « bouleversé », « surmené », « malheurs éventuels ». Ce type d'approche permet d'illustrer une limite des échelles utilisées pour mesurer l'anxiété. En effet, l'analyse factorielle réalisée sur notre échantillon montre que l'échelle STAI-YA mesure des patterns de troubles émotionnels plus complexes que l'anxiété. Il pourrait être intéressant de procéder à ce type d'analyse d'affiner notre approche centrée sur l'anxiété.

La figure 5 synthétise les différentes étapes et les principaux résultats de l'étude de l'anxiété dans la dépression (partie 3.2.). Nous proposons, pour la suite de notre travail (partie 3.3), de s'intéresser au suivi longitudinal de la cohorte LONGIDEP à 6 mois.

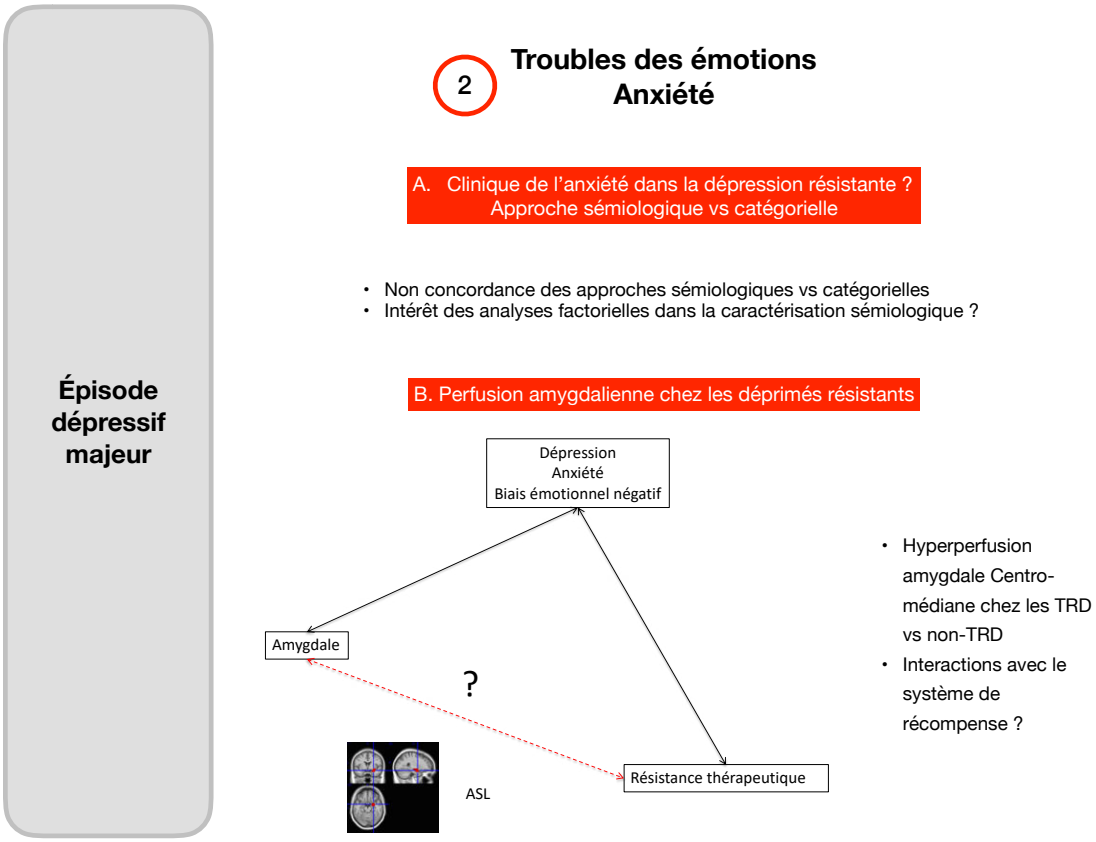


Figure 5: Synthèse des résultats de la partie anxiété et patterns de perfusion amygdalienne dans la dépression résistante.

3.3 Approche longitudinale : étude des facteurs prédictifs d'une évolution péjorative à 6 mois de suivi des patients déprimés

Dans la dernière partie de notre travail, nous avons suivi les patients inclus à 6 mois. Cette visite, réalisée dans le cadre des soins courants, permettait d'évaluer l'évolution clinique. Le critère de jugement principal était le score CGI amélioration. L'objectif est d'étudier de manière prospective les déterminants de l'évolution péjorative de l'épisode dépressif. Dans ce dernier volet de notre travail nous avons intégré les dimensions apathie et anxiété dans les analyses. L'approche longitudinale a été déclinée en deux temps :

- L'étude des facteurs cliniques et neuropsychologiques chez les 50 premiers patients revus à 6 mois (partie 3.3.1.),
- L'étude des différences de volume de la substance grise, chez 57 patients, séparés en patients déprimés répondeurs et non-répondeurs, revus à 6 mois (partie 3.3.2.).

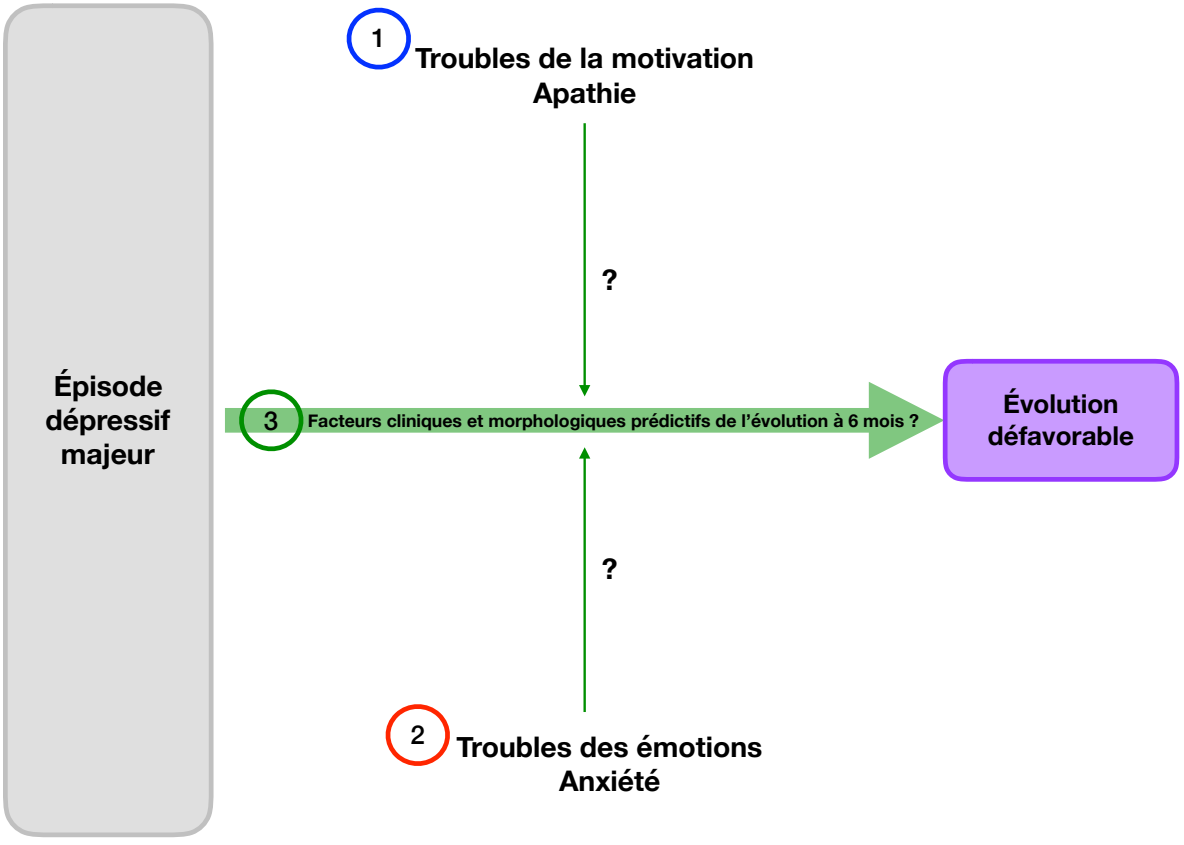


Figure 6: Schéma illustrant la dernière partie de notre travail : l'analyse longitudinale à 6 mois.

3.3.1 Clinical and neuropsychological predictors of pejorative outcome in depression: a 6 months follow-up study.

Dans une étude préliminaire, réalisée sur 44 patients revus à 6 mois de l'inclusion, nous avons recherché les facteurs cliniques et neuropsychologiques prédictifs d'une évolution péjorative de la dépression. Nous avons postulé qu'un profil d'anxiété serait prédictif d'une évolution péjorative à 6 mois. Nous avons porté une attention particulière à la valeur prédictive du score d'apathie (AES). En effet, au regard de la corrélation négative entre l'apathie et l'anxiété état dans notre première étude, nous avons émis l'hypothèse que l'apathie pourrait être un facteur protecteur de l'évolution de la maladie dépressive. Nous avons proposé également d'étudier la valeur prédictive de variables neuropsychologiques (réalisées dans le cadre d'un bilan de soins courant). Ce dernier point constitue l'originalité de ce travail car il projetait d'affiner la caractérisation clinique des patients souffrant d'une dépression au pronostic défavorable. **Cette étude a été menée dans le cadre d'une thèse de médecine (Dr Margaux Dolan) que j'ai dirigée. L'article est en préparation et est présenté telle qu'il est prévu de le soumettre pour publication.**

Abstract

Background: Finding predictors of Treatment Resistant Depression (TRD) is a key topic in individual clinical management of patients. Our objective was to define the phenotype of depressed patients with poor evolution, using simultaneously socio demographic, clinical and neuropsychological factors. Our hypothesis was that an anxious profile would be associated with non-response at 6 months.

Methods: All patients with depressive disorder were included in a single-center prospective study. They underwent clinical and neuropsychological assessments by a psychiatrist and a neuropsychologist at baseline and 6 months. Response was defined by Clinical Global Impression (CGI)-Improvement score ≤ 2 at the 6 months' assessment. Univariate and multiple logistic regression analysis were performed to determine factors associated with treatment response.

Results: 107 patients were included, among them, 50 completed both assessments. CGI-I was performed on 44 patients. The overall response rate was 48%. Socio-demographic and clinical factors associated with response at 6 months in the univariate analysis were an increased age (OR=1.08; p=0.01) and a higher WDRS (Widlöcher Depressive Retardation Scale) score (OR=1.08; p=0.04) whereas some professional status (p=0.04) and a higher STAI-YB (State Trait Anxiety Inventory – YB form) score (OR=0.94; p=0.04), reflecting high trait anxiety, were predictive of non-response. Among neuropsychological factors, higher scores at the semantic fluency test (OR=0.89; p=0.03) and Digit Symbol Test (OR=0.94; p=0.02), evaluating executive functions and visuo-spatial memory, were predictive of non-response. In a multivariate analysis, higher trait anxiety (OR=0.93; p=0.03) and higher score at the Digit Symbol Test (OR=0.93; p=0.02) were independent predictors of non-response.

Conclusion: Higher trait anxiety and higher score at the Digit Symbol test are predictors of pejorative evolution of depression. Our study demonstrates the role of anxiety in depression clinical course and improved our understanding of its influence on depressed patients' cognitive processes.

Introduction

Despite the range of available treatments, Treatment Resistant Depression (TRD) appears to be a common problem in clinical practice. About 30 to 50% of Major Depressive Disorder (MDD) patients do not respond to a first line antidepressant treatment (Rush et al., 2006; Souery et al., 2007), and about 10% to 20% of all patients do not respond at all (Balestri et al., 2016). Considering remission, antidepressant treatment studies demonstrated high rates of non-remitters, with two third of non-remitters following a first line treatment and one third after four acute treatments (Rush et al., 2006). TRD and partial remission have severe consequences : significant occupational and psychosocial dysfunction, early relapse and increased recurrence rates (Paykel, 2008). Therefore, the ability to predict poor clinical evolution appears as a main research objective.
Several studies aimed to identify factors associated with non-response and/or non-remission, investigating socio demographic characteristics and illness related variables. Among them we focused on three significant studies.

In a multicenter study, Souery et al included a total of 702 patients with DSM IV major depressive disorder (Souery et al., 2007). After retrospective assessment, 346 patients were considered as nonresistant (HAM-D-17 < 17 after a single antidepressant treatment or at the second trial after the failure), and 356 were considered resistant (HAM-D-17 > 17 after two adequate consecutive treatments). Souery found 11 variables associated with TRD: anxiety comorbidity, comorbid panic disorder, social phobia, personality disorder, suicidal risk, severity, melancholia, a number of hospitalizations > 1, recurrent episodes, early age at onset, and non-response to first antidepressant lifetime. Comorbid anxiety was the most powerful clinical factor associated with TRD.

In 2016, Balestri et al conducted the first study evaluating predictors of treatment resistance after three adequate antidepressant treatments (Balestri et al., 2016). 407 major depressive disorder (MDD) patients were recruited for a two-stage trial, after the failure of at least one adequate antidepressant treatment. Patients firstly received venlafaxine and then, in case of non-response, escitalopram. The definition of non-response was an improvement < 50% on the MADRS. 27,61% of the subjects were considered resistant to the three lines of treatments. Clinical predictors were: longer duration and higher severity of the current episode, outpatient status, higher suicidal risk level, higher rate of psychiatric antecedents and side effects during treatments. Among them the severity of the illness was identified as the most discriminative one.
Min et al highlighted the roles of baseline trait anxiety and resilience, considering that individual differences in stress response might be important in predicting depression outcome (Min, Lee,

Lee, Lee, & Chae, 2012). 178 patients with depressive disorders were recruited and completed measures of trauma experiences, psychological symptoms and resilience at baseline. Response was defined by a score ≤2 on the Clinical Global Impression-Improvement (CGI-I). Univariate analyses and multiple logistic regression analysis were performed. The results showed that low trait anxiety, high resilience, and their interactions predicted treatment response after adjusting for age and treatment duration.

The biggest issues with these studies are the lack of consensus to characterize TRD and the variety of main outcomes, making it difficult to draw conclusions from literature (Berlim & Turecki, 2007; Conway, George, & Sackeim, 2017). Some authors consider as main outcome the non-response to one, two or three treatments, some others consider only non-remission, or both, non-response and non-remission (Balestri et al., 2016; Souery et al., 2007). Another challenge lies in the heterogeneity of psychometric scales used to evaluate the main outcome and the large variety of thresholds or percentage decrease to define response and remission.

Regarding the design of the studies, retrospective assessments represent an important limitation. Prospective studies and the capture of clinical characteristics at each stage of the depressive episode are clearly needed. Furthermore, the short followed-up period in some studies is questionable. The duration of four to eight weeks after treatment may be considered insufficient to ascertain a lack of response. Despite the numerous variables analyzed, we found mostly categorical data coming from the MINI, but relatively few dimensional data, except for anxiety. The role of apathy, anhedonia, psychomotor retardation on the depression outcome would be interesting to evaluate. Finally, it is essential to integrate neuropsychological data, because depression is no more seen as an exclusive affective disorder, but also as a disorder associated with cognitive impairment.

The primary objective of this study was to investigate socio-demographic, clinical and neuropsychological predictors of poor evolution in a naturalistic follow up study of depressed patients. In other words, we proposed to identify the phenotype of depressed patients associated with non-response. In view of the literature, one of our hypotheses was that an anxious clinical and neuropsychological profile would be a significant predictor of poor evolution.

Methods

Patient population

Patients suffering from Major Depressive Disorder (MDD) were included according to DSM 5. Exclusion criteria included other axis I disorders (except for anxious comorbidities such as post-traumatic stress disorder, social phobia, generalized anxiety disorder, panic disorder) and patients with severe physical illness which could have interfered with the clinical and neuropsychological assessments.

Study design

Patients were recruited from routine care units in the psychiatric university hospital in Rennes between November 2014 and December 2016, and were enrolled in a naturalistic prospective open cohort study. Psychiatric follow-up was maintained independently of the study and all decisions regarding clinical management were made by their referring doctor. The level of resistance of each patient was evaluated using the Thase and Rush Staging Model (M E Thase & Rush, 1997). We have chosen two assessments at baseline and at 6 months because treatment response at 3 to 6 months was found to be a strong predictor of long term prognosis of depression (G. E. Simon, 2000). Our main outcome was the response at 6 months, assessed by the CGI-I (Clinical Global Impression- Improvement) (Guy, 1976). Written informed consent was obtained from all participants prior to their inclusion. The study protocol was approved by an Ethical Committee and registered with www.clinicaltrial.gov (NCT02286024).

Clinical assessments

Assessments were done by a trained psychiatrist and a trained neuropsychologist. Socio demographic data and disease characteristics were collected. Current and lifetime diagnoses were obtained using a semi structured interview, The Mini International Neuropsychiatric Interview version 5.0.0 (Sheehan et al., 1998).The severity of the MDD was evaluated using MADRS (Montgomery & Asberg, 1979), the Beck Depression Inventory (Beck et al., 1961), the Clinical Global Impression-Severity (CGI-S) (Guy, 1976), and the Young Mania Rating Scale (YMRS) (R. C. Young et al., 1978).

Our main endpoint was determined with the CGI-I. The CGI is a well-established research rating tool, applicable to all psychiatric disorder, and has been shown to correlate well with standard scales across a wide range of psychiatric indications. It provides a global rating of illness severity and improvement, taking into account the patient's history, social circumstances, symptoms and the impact of the illness on the patient's ability to function

(Busner & Targum, 2007). Searching for corresponding points on different depression scales to define response, Leucht reported that a CGI-I score of 2 corresponded to a reduction from baseline on the HAMD-17 of 50 to 60% and a CGI-I score of 1 corresponded to a reduction of 75 to 85% on the HAMD-17 (Leucht et al., 2013). Min and Schneider also used the endpoint of two on the CGI-I and assimilated a score of 1 or 2 to treatment response and a score ≥3 to non-response (Min et al., 2012; Schneider et al., 2003). Thus, in our study, the cut off of 2 on the CGI-I was used to distinguish two groups: patients scoring 1 or 2 with a "good evolution" (*ie*, very much improved or much improved) or respondent patients, and patients scoring from 3 to 7 with a "poor evolution" (*ie*, minimally improved to very much worse) or non-respondent patients.

Dimensional characteristics were assessed: apathy with the Apathy Evaluation Scale (AES) Clinician Version (R. S. Marin et al., 1991), psychomotor retardation with the WDRS scale (Widlöcher Depressive Retardation Scale) (Widlöcher, 1983), anhedonia with the Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995). For the anxiety dimension, two scales were used: the Hamilton Anxiety Rating Scale (HAM-A) (HAMILTON, 1959) to measure both psychic anxiety and somatic anxiety and the State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970), consisting on two different subscales measuring the state (STAI-YA) and the trait anxiety (STAI-YB).

Neuropsychological assessments

In order to integrate neuropsychological data and to investigate the relationship between neurocognitive performance and treatment outcome, subjects underwent several tests.
The Mattis Dementia Rating Scale (MDRS)[24] was used to assess overall cognitive functioning. A separate set of tasks was done to evaluate executive functions. In the semantic and phonemic tasks (Marson, Dymek, Duke, & Harrell, 1997), subjects were asked to generate in two minutes as many words as possible, with words nominating animals and words starting with the "p" letter. These tests require to retrieve from long term storage, to selectively focus attention on a semantic or phonemic category, to do strategic search of words with clusters for the semantic task and to continuously update the words that have been used. For the Digit Symbol (or Coding), subtest of the Wechsler Adult Intelligence Scale (WAIS) (David, 1981), the instruction was to write down the symbols with their matching digit. The test requires processing speed, sustained attention, visual spatial skills and provides an assessment of the working memory. In the Digit Span, subtest of the WAIS evaluating short term memory, patients heard a sequence of numerical digits and were tasked to recall the sequence correctly forwards and backwards. The Stroop test (Stroop, 1935) is a three steps test in which patients finally need to name the ink color, inhibiting the reading of the word. It assesses the selective

attention, cognitive flexibility, cognitive inhibition, and information processing speed. The Trail Making Test (TMT) (Reitan, 1958) consisted of two parts in which the subject were instructed to connect a set of 25 dots as quickly as possible, first with numbers, then with numbers and letters. The test provides information about visual search speed, scanning, speed of processing, mental flexibility. In the Modified Wisconsin Card Sorting Test (MCST) (Nelson, 1976), a number of stimulus cards were presented to the patient who was told to match the cards, but not how to match them; however, he was told whether a particular match was right or wrong. It's a neuropsychological test of set shifting, evaluating the ability to display flexibility in the face of changing schedules of reinforcement. Finally, the Conners Continuous Performance Test -III (CPTIII) (Keith Conners, Sitarenios, & Ayearst, 2017) is a computer administered test that is designed to assess problems with attention. Respondents were instructed to press the spacebar or the appropriate key on the mouse for any letter that appeared, except the letter X.

Statistical analyses

Statistical analyses were only performed on patients who underwent both baseline and 6 months' assessments. Since socio demographic, clinical and neuropsychological data were not available for each patient, the number of patients varied slightly for each variable. Descriptive analyses were used to determine patient's demographic and diagnostic characteristic, according to their respondent or non-respondent status. Quantitative variables are expressed as total number (missing data), mean ± standard deviation (min; Q1; median; Q3; max). Categorical variables are expressed as total number (missing data), number (%) for each category. Univariate logistic regression with respondent status at 6 months as the dependent variable was performed on complete cases for each variable. Variables with a p-value <0.20 in univariate analysis were entered in a multivariate stepwise logistic regression model to derive adjusted odds-ratio (OR) with 95% confidence intervals (95% CI). Model adequacy was assessed using Hosmer-Lemeshow goodness-of-fit test. Data were analyzed using SAS, v.9.4 software (SAS Institute, Cary, NC, USA).

Results

117 patients were included in the study, among them, 50 underwent the second evaluation at 6 months. We restricted analyses to 44 patients because of missing data for 6 patients regarding the CGI-I at 6 months (see Flow Chart in Figures).

Whole group analyses at baseline

The socio-demographic and clinical characteristics of the whole sample at baseline are summarized in Table 1.

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
SOCIO-DEMOGRAPHICAL VARIABLES			
Age	44 (0) 51.3 ± 15.3	21 (0) 58.4 ± 15.1	23 (0) 44.8 ± 12.6
Sex	44 (0)	21 (0)	23 (0)
Man	9 (20.5%)	4 (19.0%)	5 (21.7%)
Woman	35 (79.5%)	17 (81.0%)	18 (78.3%)
Laterality	43 (1)	21 (0)	22 (1)
Right	40 (93.0%)	20 (95.2%)	20 (90.9%)
Marital Status –recoded variable	44 (0)	21 (0)	23 (0)
Single	7 (15.9%)	3 (14.3%)	4 (17.4%)
Married	19 (43.2%)	10 (47.6%)	9 (39.1%)
Cohabitation	8 (18.2%)	3 (14.3%)	5 (21.7%)
Widowed/Divorced	10 (22.7%)	5 (23.8%)	5 (21.7%)
Number of children	44 (0)	21 (0)	23 (0)
0	9 (20.5%)	2 (9.5%)	7 (30.4%)
1	8 (18.2%)	3 (14.3%)	5 (21.7%)
2	18 (40.9%)	10 (47.6%)	8 (34.8%)
3	9 (20.5%)	6 (28.6%)	3 (13.0%)
Number of years of study (years) – recoded variable	41 (3)	19 (2)	22 (1)
<10	7 (17.1%)	4 (21.1%)	3 (13.6%)
[10-13[	19 (46.3%)	6 (31.6%)	13 (59.1%)
>=13	15 (36.6%)	9 (47.4%)	6 (27.3%)
Professional status – recoded variable	43 (1)	21 (0)	22 (1)
None/Unemployed	3 (7.0%)	1 (4.8%)	2 (9.1%)
Employee/student	7 (16.3%)	1 (4.8%)	6 (27.3%)

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
Retired	13 (30.2%)	11 (52.4%)	2 (9.1%)
Work stoppage/Long term illness	20 (46.5%)	8 (38.1%)	12 (54.5%)
DISEASE CHARACTERISTICS			
Number of depressive episodes	44 (0) 5 ± 5	21 (0) 5 ± 3	23 (0) 5 ± 6
Illness duration (years)	44 (0) 17 ± 16	21 (0) 20 ± 19	23 (0) 14 ± 11
Level of resistance Thase and Rush	40 (4)	17 (4)	23 (0)
Stage 1	7 (17.5%)	2 (11.8%)	5 (21.7%)
Stage 2	14 (35.0%)	6 (35.3%)	8 (34.8%)
Stage 3	15 (37.5%)	6 (35.3%)	9 (39.1%)
Stage 4	4 (10.0%)	3 (17.6%)	1 (4.3%)
Duration of the depressive episode (weeks)	44 (0) 31 ± 38	21 (0) 23 ± 30	23 (0) 38 ± 43
Depressive disorder	43 (1)	20 (1)	23 (0)
Unipolar disorder	29 (67.4%)	15 (75.0%)	14 (60.9%)
Bipolar disorder	14 (32.6%)	5 (25.0%)	9 (39.1%)
Bipolar disorder type 3	43 (1)	20 (1)	23 (0)
Yes	5 (11.6%)	3 (15.0%)	2 (8.7%)
Bipolar disorder type 2	43 (1)	20 (1)	23 (0)
Yes	7 (16.3%)	1 (5.0%)	6 (26.1%)
Bipolar disorder type 1	43 (1)	20 (1)	23 (0)
Yes	2 (4.7%)	1 (5.0%)	1 (4.3%)
Number of maniac or hypomanic episodes	43 (1) 1 ± 3	20 (1) 0 ± 1	23 (0) 2 ± 3

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
History of suicide attempt	42 (2)	20 (1)	22 (1)
Yes	20 (47.6%)	8 (40.0%)	12 (54.5%)
Number of suicide attempts	42 (2)	20 (1)	22 (1)
0	23 (54.8%)	13 (65.0%)	10 (45.5%)
1	9 (21.4%)	4 (20.0%)	5 (22.7%)
2 and more	10 (23.8%)	3 (15.0%)	7 (31.8%)
Suicidal risk	44 (0)	21 (0)	23 (0)
Yes	19 (43.2%)	8 (38.1%)	11 (47.8%)
Mild suicidal risk	44 (0)	21 (0)	23 (0)
Yes	14 (31.8%)	6 (28.6%)	8 (34.8%)
Moderate suicidal risk	44 (0)	21 (0)	23 (0)
Yes	5 (11.4%)	2 (9.5%)	3 (13.0%)
Melancholia	44 (0)	21 (0)	23 (0)
Yes	4 (9.1%)	3 (14.3%)	1 (4.3%)
Psychotic symptoms	44 (0)	21 (0)	23 (0)
Yes	1 (2.3%)	1 (4.8%)	0 (0.0%)
Panic disorder lifetime	44 (0)	21 (0)	23 (0)
Yes	14 (31.8%)	7 (33.3%)	7 (30.4%)
Current panic disorder	44 (0)	21 (0)	23 (0)
Yes	6 (13.6%)	3 (14.3%)	3 (13.0%)
Generalized Anxiety Disorder	44 (0)	21 (0)	23 (0)
Yes	22 (50.0%)	11 (52.4%)	11 (47.8%)
Social Phobia	44 (0)	21 (0)	23 (0)

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
Yes	3 (6.8%)	1 (4.8%)	2 (8.7%)
Post traumatic syndrome disorder	44 (0)	21 (0)	23 (0)
Yes	4 (9.1%)	1 (4.8%)	3 (13.0%)
CLINICAL VARIABLES			
AES	44 (0) 39 ± 7	21 (0) 39 ± 7	23 (0) 40 ± 8
WDRS	44 (0) 22 ± 9	21 (0) 25 ± 10	23 (0) 19 ± 9
YMRS	44 (0) 2 ± 1	21 (0) 2 ± 2	23 (0) 2 ± 1
MADRS total score	44 (0) 28 ± 5	21 (0) 28 ± 5	23 (0) 27 ± 5
BDI	43 (1) 17 ± 8	21 (0) 15 ± 8	22 (1) 19 ± 8
CGI S	29 (15) 4 ± 1	14 (7) 5 ± 1	15 (8) 4 ± 1
HAMA total score	29 (15) 26 ± 10	14 (7) 22 ± 7	15 (8) 29 ± 11
SHAPS	44 (0) 5 ± 4	21 (0) 5 ± 4	23 (0) 6 ± 4
NEUROPSYCHOLOGICAL VARIABLES			
Digit Span: Direct	44 (0)	21 (0)	23 (0)

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
	6 ± 2	6 ± 2	6 ± 2
Digit Span: Indirect	44 (0) 5 ± 2	21 (0) 4 ± 2	23 (0) 5 ± 1
MATTIS attention	44 (0) 36 ± 1	21 (0) 36 ± 1	23 (0) 36 ± 1
MATTIS initiation	44 (0) 35 ± 3	21 (0) 34 ± 4	23 (0) 36 ± 3
MATTIS construction	44 (0) 6 ± 0	21 (0) 6 ± 0	23 (0) 6 ± 0
MATTIS conceptualization	44 (0) 36 ± 3	21 (0) 36 ± 3	23 (0) 36 ± 2
MATTIS memory	44 (0) 22 ± 3	21 (0) 22 ± 3	23 (0) 22 ± 3
MATTIS total score	44 (0) 135 ± 7	21 (0) 134 ± 8	23 (0) 136 ± 7
Phonemic fluency	44 (0) 26 ± 8	21 (0) 25 ± 8	23 (0) 28 ± 8
Semantic fluency	44 (0) 19 ± 7	21 (0) 16 ± 6	23 (0) 21 ± 7
STROOP denomination	43 (1) 63 ± 13	20 (1) 59 ± 15	23 (0) 66 ± 10
STROOP reading	43 (1) 87 ± 20	20 (1) 85 ± 16	23 (0) 89 ± 24

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
STROOP interference	43 (1) 30 ± 12	20 (1) 27 ± 12	23 (0) 33 ± 11
STROOP interference score	43 (1) -2.85 ± 8.46	20 (1) -3.83 ± 9.06	23 (0) -2.00 ± 8.00
TMT A	44 (0) 48 ± 18	21 (0) 52 ± 22	23 (0) 44 ± 14
TMT B	39 (5) 111 ± 73	17 (4) 134 ± 101	22 (1) 94 ± 33
TMT B-A	39 (5) 67 ± 70	17 (4) 88 ± 98	22 (1) 50 ± 31
TMT B-A errors	39 (5) 1 ± 1	17 (4) 1 ± 1	22 (1) 0 ± 1
WCST number of correct categories	41 (3) 5 ± 1	18 (3) 5 ± 1	23 (0) 5 ± 2
WCST number of errors	41 (3) 11 ± 6	18 (3) 12 ± 6	23 (0) 10 ± 5
WCST number of perseverations	41 (3) 4 ± 3	18 (3) 5 ± 4	23 (0) 3 ± 2
Code WAIS III	44 (0) 48 ± 15	21 (0) 42 ± 12	23 (0) 54 ± 16
CPT III correct detection	32 (12) 55 ± 12	14 (7) 60 ± 13	18 (5) 52 ± 11
CPT omission errors	32 (12) 54 ± 12	14 (7) 57 ± 12	18 (5) 52 ± 12

Variable(s)*	Global (n=44) N (NA) Mean ± sd or n(%)	Respondent patients (n=21) N Mean ± sd or n(%)	Non respondent patients (n=23) N Mean ± sd or n(%)
CPT commission errors	32 (12) 53 ± 12	14 (7) 56 ± 15	18 (5) 51 ± 10
CPT perseverations	32 (12) 58 ± 14	14 (7) 60 ± 16	18 (5) 57 ± 12
CPT HRT	32 (12) 55 ± 9	14 (7) 56 ± 8	18 (5) 54 ± 10
CPT HRT SD	32 (12) 54 ± 10	14 (7) 58 ± 9	18 (5) 51 ± 11
CPT variability	31 (13) 55 ± 13	13 (8) 59 ± 14	18 (5) 53 ± 12
CPT III Hit SE block change	32 (12) 54 ± 11	14 (7) 59 ± 13	18 (5) 51 ± 9
CPT ISI change	32 (12) 44 ± 11	14 (7) 44 ± 13	18 (5) 43 ± 10

Table 1: Baseline variables for the whole group and according to the respondent status.

The sample was predominantly represented by women (79,5%) and the mean age was 51,3 years old. The mean number of depressive episodes including the current depressive episode was 5 and the mean duration of the current episode at baseline was 31 weeks (with 29,5% of the depressive episodes > 25weeks).

Baseline symptom severity assessed by the MADRS and the self-rated scale BDI showed respectively a score of 28 and a score of 17. The mean score of the CGI-S was 4 (among the 29 patients with complete data for the CGI at baseline).

Comorbid anxiety disorders were present in 70,5% of patients, comprising generalized anxiety disorders in 50% of patients, lifetime panic disorders in 31,8%, current panic disorder in 13,6%, post-traumatic stress disorder in 9,1% and social anxiety disorder in 6,8% of patients. The mean total score at the HAMA scale was 26,17 at the HAMA psychic subscale and 9 at the HAMA physical subscale. The mean state anxiety score was 55 and the mean trait anxiety score was 59. There was a mean score of 22 on the WDRS, 39 on the AES and 5 on the SHAPS.

Baseline characteristics according to treatment outcome

The overall response rate was 47,7%. 21 patients were considered responders and 23 patients were non-responders. Socio demographic, clinical and neuropsychological of each group are summarized in table 1.

Univariate logistic regression

Results of the univariate analysis were reported in table 2. Including only variables with a p ≤0,2 which were later entered in the multivariate logistic regressions.

Response was related to an increased age (OR=1,08; p=0,01), a higher score on the WDRS (OR=1,08 p=0,04). Non-response was associated to certain professional status (p=0,04), a higher score on the STAI YB (OR=0,94; p=0,04), a higher score at the semantic fluency test (OR=0,89; p=0,03) and a higher score at the Digit Symbol Test (OR=0,94; p=0,02).

Focusing on anxiety, a lower score on the HAMA-psychic was found for the respondent patients; however, this association did not reach the statistical significance (p=0,051).

Variable	N	OR [IC95%]	P
Age	44	1.08 [1.02 ; 1.13]	p = 0.0070
Socio professional status – recoded variable (ref = retired)	43		p = 0.0345
None/Unemployed		0.09 [0.01 ; 1.55]	
Worker/Student		0.03 [0.00 ; 0.41]	
Work stoppage/Long term illness		0.12 [0.02 ; 0.70]	
Duration of the disease (years)	44	1.03 [0.99 ; 1.07]	p = 0.1806
Duration of the depressive episode (weeks) – (ref = <=5)	44		p = 0.1157
]5-25]		3.50 [0.68 ; 17.96]	
>25		0.89 [0.14 ; 5.48]	
Bipolar disorder type 2 (ref = no)	43	0.15 [0.02 ; 1.37]	p = 0.0924
WDRS	44	1.08 [1.00 ; 1.16]	p = 0.0423
STAI YB	44	0.94 [0.89 ; 1.00]	p = 0.0407
HAMA psychic score	29	0.85 [0.72 ; 1.00]	p = 0.0510
HAMA physic score	29	0.90 [0.78 ; 1.05]	p = 0.1853
HAMA total	29	0.92 [0.83 ; 1.01]	p = 0.0643
BDI	43	0.94 [0.87 ; 1.02]	p = 0.1218

Variable	N	OR [IC95%]	P
CGI S	29	1.65 [0.78 ; 3.50]	p = 0.1879
MATTIS attention	44	0.59 [0.28 ; 1.23]	p = 0.1570
MATTIS initiation	44	0.86 [0.71 ; 1.05]	p = 0.1392
Semantic fluency	44	0.89 [0.80 ; 0.99]	p = 0.0256
STROOP denomination	43	0.95 [0.90 ; 1.01]	p = 0.0769
STROOP interference	43	0.95 [0.90 ; 1.01]	p = 0.0822
TMT A	44	1.02 [0.99 ; 1.06]	p = 0.1944
TMT B	39	1.01 [1.00 ; 1.03]	p = 0.1422
TMT B-A	39	1.01 [1.00 ; 1.03]	p = 0.1584
WCST number of perseverations	41	1.19 [0.94 ; 1.50]	p = 0.1483
Code WAIS III	44	0.94 [0.90 ; 0.99]	p = 0.0153
CPT III correct detectability	32	1.06 [0.99 ; 1.13]	p = 0.1033
CPT HRT SD	32	1.07 [0.99 ; 1.16]	p = 0.0758
CPT variability	31	1.04 [0.98 ; 1.11]	p = 0.1927
CPT III Hit SE block change	32	1.08 [1.00 ; 1.17]	p = 0.0626

Table 2: Univariate analysis – clinical and neuropsychological baseline variables predictive of CGI-I rated response at 6 months.

Multivariate logistic regressions

In multivariate analysis, reported in table 3, higher trait anxiety (OR=0,93; p=0,03) and higher score at the Digit Symbol Test (OR=0,93; p=0,02) were independent predictors of non-response. The model was validated, with a p of 0,83 at the Hosmer and Lemeshow test.

Variable	**N**	**OR [IC95%]**	**P**
STAI YB	44	0.93 [0.87 - 0.99]	p = 0.0298
Code WAIS III	44	0.93 [0.88 - 0.99]	p = 0.0150

* Hosmer-Lemeshow test, p=0.8272

Table 3: Multivariate analysis – clinical and neuropsychological baseline variables predictive of CGI-I rated response at 6 months

Discussion

To our knowledge, this is the first study evaluating simultaneously clinical and neuropsychological predictors of depression outcome. One of the strengths of the study was its realization in prospective and naturalistic conditions.

Clinical predictors

Trait anxiety

The most significant clinical predictor of non-response at 6 months was trait anxiety assessed with the STAI YB. Trait anxiety is a stable personality trait describing one's tendency to respond fearfully to a wide variety of stimuli (Spielberger et al., 1970) and experience negative emotions as fears, worries and anxiety. It is part of the personality dimension of neuroticism. Highly trait-anxious people modify their perception of reality because of a cognitive-perceptual bias. There is an over attentional bias to threatening stimuli and a distorted negative interpretation of information, with negative valence attributed to a variety of stimuli.

Our finding is consistent with previous studies who found an association between trait anxiety and poor treatment outcome in depressed patients. In a two-year prospective study, Szádóczky found anxious personality traits to predict non remission at the end of the two year follow up (Szádóczky, Rózsa, Zámbori, & Füredi, 2004). Min concluded that low trait anxiety might contribute to better treatment outcome at 6 months in depressed patients, as well as high resilience (Min et al., 2012).

Beyond the issue of anxiety trait, several studies highlighted the role of anxiety symptom or anxiety syndrome in depression outcome. For Souery, comorbid anxiety was the most powerful clinical factor associated with TRD (Souery et al., 2007). This result has not been confirmed in our study, one explanation can be the high percentage of comorbid anxiety found in the sample (70,8%). In a STAR*D study, Fava defined anxious depression as a major depressive disorder with high levels of anxiety symptoms (HAM-D anxiety/somatization factor score ≥7), and concluded it was associated with non-remission (Fava et al., 2008). Wu had similar findings (Z. Wu et al., 2013). More recently, Gaspersz focused on another dimension of anxiety, the distress specifier introduced in DSM-5 and evaluated its ability to predict treatment response in depressed patients (Gaspersz et al., 2017). The anxious distress specifier was found to predict poorer treatment outcomes as shown by higher depression severity at 1 year and 2 years and lower remission rates at 2 years. In contrast, the presence of comorbid anxiety disorders did not predict these treatment outcomes.

These results emphasize the role of anxiety, either from a dimensional or a categorical aspect, in the evolution of depression.

Other clinical predictors

In the univariate analysis age was associated with response at 6 months. Referring to Min who found a negative correlation between age and anxiety, our hypothesis is that age is significant only in the univariate because older patients have lower scores of anxiety trait[6]. However, there are contrasting results. In a recent review, Vera de Carlo concluded that older age could be associated with lower rate of response in TRD patients but that age seemed to not affect remission (De Carlo, Calati, & Serretti, 2016). Only one parameter received a broad consensus: the early age at onset found as a predictor of non-response (Bennabi et al., 2015; Souery et al., 2007).

The professional status was associated with non-response for two categories: students/workers and patients on work stoppage or with a long-term illness, in comparison with retired patients. We wonder about the role of professional stressors, what retired people are protected from. There is little literature regarding occupational status. In one study, higher executives had an increased risk to be non-responders unlike manual employees (Souery et al., 2007). However, there was no significant difference in the group of patients without occupation or invalids.

The score on the WDRS was associated with response, that is when the score increases by one point there is more chance for a favorable outcome. The WDRS scale assesses psychomotor retardation by focusing on its motor and cognitive aspects. A number of studies have investigated the predictive role of psychomotor retardation on response, thus, these studies were fairly divided for which types of antidepressants psychomotor retardation is a successful predictor of response (Buyukdura, McClintock, & Croarkin, 2011). Some hypothesized that SNRIs, TCAs would be more effective than SSRIs because patients with psychomotor retardation are likely to have a dopamine and/or norepinephrine imbalance. It would be interesting to adjust psychomotor retardation with patients' treatments.

Neuropsychological predictors

There are meaningful results for two tests: the semantic fluency task and Coding. For both tests when scores increase by one point, there is less chance for a favorable outcome. These results are quite intriguing. In fact, we expected on the contrary to find non-responders subjects less performing. In order to discuss this issue, we will first do an overview of the cognitive functions in depressive subjects, then draw attention on the influence of anxiety on depressed patient's cognitive performances.

There are firm evidences of global cognitive impairment in the acute phase of depression. Hammar reported cognitive dysfunctions in different domains: executive functions, attention and memory tasks (Hammar & Ardal, 2009). Focusing on verbal fluency in depressed patients, Fossati found that only semantic fluency was impaired in comparison with normal control subjects (Fossati, Guillaume, Ergis, & Allilaire, 2003). The deficit was related to a reduced number of switches with normal cluster sizes. For the coding test, Bierman found a negative linear relationship with depression severity, which underlined the impaired information-processing speed in depressive disorders (Bierman, Comijs, Jonker, & Beekman, 2005). Moreover, considering prediction, the few longitudinal studies only identified impaired cognitive functions as predictors of non-response. Kalayam and Alexopoulos found that, in elderly depressed patients, executive deficits (with lower initiation and perseveration scores on tests assessed with the MATTIS) could predict poor response (Kalayam & Alexopoulos, 1999). Majer concluded that impaired divided attention was associated with non-response (Majer et al., 2004).

One of the particularities of our study is the high level of anxiety. Indeed, for the whole sample, the mean total score on the HAMA was 26 (*i.e.,* corresponding to a moderate to severe anxiety), the mean scores on the STAI were 55 for the STAI YA (*i.e.,* corresponding to a moderate state anxiety) and 59 for the STAI YB (*i.e.,* corresponding to a severe trait anxiety) and 70,5% of the patients had at least one anxious comorbidity. Moreover, the finding of anxiety trait, seen as a predictor of poor evolution, led us to study the implication of anxiety in the evolution of depression.

Yet explanatory models are known to assume a relation between anxiety and cognitive functioning (Bierman et al., 2005). Eysenck posited that anxiety produces intrusive negative thoughts which interfere in the phonological loop of working memory (Eysenck & Calvo, 1992). The study of Gawda showed no significant differences with low anxiety and high anxiety in terms of number of words in the fluency tests, but the within-group comparisons for the high trait anxiety group showed significant differences between scores in more difficult tasks and easier tasks (Gawda & Szepietowska, 2016). It is in line with theories arguing that trait anxiety impairs processing efficiency more than performance effectiveness (Eysenck & Calvo, 1992). Mendl provided a second possible explanatory model for the association between anxiety and cognitive functioning, citing the Yerkes and Dodson law (Mendl, 1999; Yerkes & Dodson, 1908). Anxiety has a curvilinear relation with performance, suggesting that cognitive performance is best when an individual is at an optimal level or stress and drops below or above that state.

This latter hypothesis was explored in two studies. In 2005, Bierman investigated how anxiety affects cognitive performance in elderly subjects, taking account of comorbid depression or not (Bierman et al., 2005). While depressive symptoms showed significant impairments on

almost all cognitive tests, a curvilinear relationship was found between anxiety and cognitive performance: mild anxiety symptoms were associated with better cognitive performance. In addition, the impact of anxiety on cognitive functioning seemed to be strongly influenced by depressive symptoms. Correcting for depressive symptoms changed the effect on cognitive performance from negative to positive in most cognitive-performance tests, indicating a beneficial effect on cognition, especially for mild anxiety symptoms. More recently, the relation between anxiety and cognitive performance was also examined in elderly patients (Potvin et al., 2013). Mild and moderate state anxiety levels were associated with better performance on verbal fluency and general cognitive functioning tests. Moderate and high state anxiety levels were beneficial for the speed of information processing-visuomotor coordination in participants using medications: indeed, high anxiety was positively associated with better performance on Digit Symbol Coding in participants using 4 medications.

According to these findings, our hypothesis to explain the predictive role for the semantic fluency and the code in non-response is the positive influence of anxiety on neuropsychological performance in our population of depressed patients. In other words, such higher performance could illustrate a neuropsychological phenotype of anxiety which is predictive of non-response. It highlights the fact that performance is not always a good sign of evolution, and can be on the contrary predictive of poor evolution. Further studies should expand on a qualitative evaluation to define deeply the neuropsychological profile and evaluate other indicators of anxious phenotype on cognitive tasks such as the numbers of errors, the number of perseverations.

Limitations

First, the sample size is small. It would be important to increase the statistical power with more included patients and less lost to follow-up after the first assessment. Nevertheless, our design includes all at once a clinical assessment and a neuropsychological assessment.

Second, all patients were recruited from the university psychiatric department in Rennes, a potential selection bias related to participants may limit the generalization of our findings. The rating scales show moderate depression scores, a mean duration of the depressive episode of 31 weeks, an illness evolving for 17 years, and a heavy burden of anxiety symptoms. Further studies should focus on patients at the beginning of their mood depressive disorder.

Concerning the neuropsychological data, few points need to be considered. Age is an important factor to consider when evaluating depression and cognitive functions, with an age-related decline especially for coding scores (Joy, Kaplan, & Fein, 2004). The mean age is 51,3 but there is a significant proportion of elderly patients: among the 50 patients, 18 are older than

60, of which 7 are more than 70 years old. However, the variable was entered in the multivariate analysis and its effect on coding was considered. The level of education was evaluated for each patient at baseline and was not entered in the multivariate analysis, but there was no significant difference between responders and non-responders.

Finally, because it was a naturalistic study, drug therapy was not controlled in our study, which explain the treatment heterogeneity for each patient. There is in particular a high percentage of benzodiazepines (50%) and antipsychotics (42,5%) that can distort the neuropsychological assessment, but in the same way there was no significant difference between responders and non-responders.

Conclusion

Predictive factors associated with poor evolution of depression are clearly needed to help clinicians to identify certain « red flags » and closely monitor their patients and adjust their treatment. In the present study, we identified two predictive factors of a poor evolution of depression at 6 months: a high trait anxiety and a high score at the Digit Symbol Test, which would be influenced by the level of anxiety. According to our theory, the clinical and neuropsychological phenotype predictive of non-response would be an anxious phenotype. These results underline the key role of anxiety in depression outcome. One issue of understanding could be the interaction between trait anxiety and resilience. Patients with high anxiety trait would not be affected by the resilience levels in overall response rate, whereas patients with low trait anxiety would be affected by levels of resilience in their prognosis (Min et al., 2012). In this perspective, anxiety trait could interrupt the cognitive and behavioral processes such as positive coping strategies implicated in resilience. Future research should narrow the predictive phenotype of a poor evolution of depression with, in particular, neurobiological markers. The rise of the research domain criteria (RDoC), by integrating many other levels of information as genes, molecules, cells, circuits, physiology will help to seek an integrative understanding of depression and the role of anxiety on its evolution.

Points forts de l'étude partie 3.3.1. Clinical and neuropsychological predictors of pejorative outcome in depression: a 6 months follow-up study

- Étude qui se focalise sur les facteurs sociodémographiques, cliniques, neuropsychologiques prédictifs d'une évolution péjorative de la dépression.
- Critère de jugement principal : score CGI improvement (>2 = non répondeur)
- 44 patients inclus dans l'analyse statistique (régression logistique uni et multivariée)
- Un haut niveau d'anxiété trait (STAI-YB) et de bonnes performances au code (code) sont des prédicteurs de mauvaise évolution.
- Hypothèse d'un phénotype anxieux (clinique et neuropsychologique) sous tendant l'évolution péjorative. Ce résultat nous a amené à étudier, dans la partie 3.2.2, les corrélats morphologiques du phénotype anxieux prédictif de l'évolution péjorative.

3.3.2 Structural abnormalities predictive of pejorative outcome of depression: the role of thalamus and cerebellum

Dans une dernière partie de notre travail, nous proposons d'étudier les anomalies morphométriques, analysées par la technique Voxel Based Morphometry, et associées à l'évolution péjorative de la dépression à 6 mois. Nous avons choisi cette technique d'analyse car elle présente l'avantage de nécessiter une technique d'acquisition d'IRM réalisable en soins courant, la séquence morphologique 3D T1. Cette séquence anatomique est la plus utilisée en routine clinique. Elle a donc la qualité de l'accessibilité. Les méthodes d'IRM structurelle - en particulier la VBM - permettent une étude non invasive du volume de la matière grise (MG) avec des résultats automatisés, reproductibles et précis (Whitwell, 2009). Une étude récente, en machine learning, sur les marqueurs pronostiques de la dépression a pu montrer que les anomalies morphométriques analysées en VBM avaient un meilleur pouvoir pronostique que les variables cliniques (Johnston, Steele, Tolomeo, Christmas, & Matthews, 2015). Au total, l'analyse VBM est une technique d'intérêt dans l'étude des processus physiopathologiques de la dépression résistante (Kim, 2018).

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Structural abnormalities associated with pejorative outcome in depression: the role of thalamus and cerebellum.

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Keywords:	mood disorders, Depression, Treatment Resistance, neuroimaging, Anxiety/Anxiety disorders

Abstract

Objective: The aim of this work is to identify gray matter (GM) volume abnormalities associated with pejorative outcome of depression, in a homogeneous cohort, using a whole brain structural analysis.

Method: In this 6-month follow-up study, we compared baseline gray matter volumes between 2 groups based on illness improvement: 27 MDD patients in the “responder” (R) group (Clinical Global Impression- Improvement (CGI-I) score ≤ 2) and 30 in the “non-responder” (NR) group (CGI-I > 2). A Voxel Based-Morphometry analysis was performed with multiple comparison correction.

Results: The NR group had higher baseline anxiety scores in comparison with the R group. Moreover, significant GM volume decreases in the bilateral thalami, in precentral gyrus, middle temporal gyrus, precuneus and middle cingulum were found for the NR patients. Thus, they exhibited significant GM volume increase in the left anterior lobe of cerebellum and posterior cingulate cortex.

Conclusion: In addition to prior knowledge, our study has pointed out the role of thalamus and cerebellum in prognosis of MDD. These findings suggest the involvement if thalamus and cerebellum in emotion regulation and precisely anxious dimension in depression. The present study provides a step towards the understanding of neurobiological processes involved in treatment resistant depression.

Keywords: Mood disorders, Depressive Disorder, Treatment-Resistant, Neuroimaging, Cerebellar Grey Matter, Grey Matter, Thalamus.

Introduction

Major Depressive Disorder (MDD) is a very common mental disorder with a lifetime prevalence of 16% (Kessler et al., 2003) and is the leading cause of disability worldwide (Vasic, Walter, Höse, & Wolf, 2008). Only 50% of patients respond to their first treatment and remission rate with standard antidepressant treatments is only 30-40% (Murray et al., 2012; Rush et al., 2006). Despite an important variability of treatment response, reliable predictors of outcome in patient with MDD are lacking (Nathan & Gorman, 2007).

Over the past decade, the use of neuroimaging techniques has enabled significant advances toward understanding the pathophysiology of mood disorders. Structural MRI (sMRI) methods – especially voxel-based morphometry (VBM) – allow non-invasive and accessible investigations of the distribution of grey matter (GM) with automated, repeatable and accurate results (Whitwell, 2009). They provided cumulative evidence of GM abnormalities in emotion and mood regulation key regions in patients with MDD compared to healthy controls (HC). Across recent VBM studies, the most consistent findings reported were that subjects with MDD under treatment had reduced GM volume in the anterior cingulate cortex (ACC), hippocampus, amygdala, thalamus and orbitofrontal cortex relative to those without MDD (Bora, Fornito, Pantelis, & Yücel, 2012; Du et al., 2012). A recent meta-analysis comparing medication naive patients on first episode to healthy controls has revealed interesting results such as increased GM volume in the bilateral thalamus, cuneus, left paracentral lobule and medial superior frontal gyrus in MDD patients (W. Peng, Chen, Yin, Jia, & Gong, 2016). However, the neural process of treatment resistance remains poorly understood. Some authors have studied the association of treatment response in depression (TRD) with gray matter (GM) volume variation. GM volume abnormalities have been reported including regions involved in cognitive functioning such as deficit in left (Furtado et al., 2012), right (Fu et al., 2013), or both (J. L. Phillips, Batten, Tremblay, Aldosary, & Blier, 2015) hippocampus volume (Sämann et al., 2013) and dorsolateral prefrontal cortex (DLPFC) (Fu et al., 2013; C.-T. Li et al., 2010). Other key regions involved in emotional processing has been found in TRD such as anterior cingulate gyrus (Fujino et al., 2015; Machino et al., 2014), amygdala (Sandu et al., 2017), temporal gyrus (Liu et al., 2012; Ma et al., 2012; Machino et al., 2014; Sämann et al., 2013), insula (Johnston et al., 2015), and cerebellum (Liu et al., 2012; Machino et al., 2014). A meta-analysis have highlighted that in studies using manual region of interest analysis, only right hippocampal deficit GM was associated with lack of improvement after antidepressant trial (ATD) and in whole brain VBM studies, only left DLPFC was associated with poor response (Fu et al., 2013). Finally, we have to notice that all these studies used heterogeneous designs, which could limit the generalizability of the current literature. In fact, the main difference remains in the type of

cohort, which may be prospective (Abbott et al., 2014; Fujino et al., 2015; Furtado et al., 2012; Korgaonkar et al., 2015; C.-T. Li et al., 2010; J. L. Phillips et al., 2015; Sämann et al., 2013; Schmaal et al., 2015) or retrospective (Johnston et al., 2015; Liu et al., 2012; Machino et al., 2014; Sandu et al., 2017). Moreover, the duration of the follow up was also variable from 5 weeks (Sämann et al., 2013) to two years (Schmaal et al., 2015) and the imaging analyses were also different varying from ROI approaches (Abbott et al., 2014; Furtado et al., 2012; J. L. Phillips et al., 2015; Sandu et al., 2017) to whole brain analysis (Fujino et al., 2015; C.-T. Li et al., 2010; Ma et al., 2012; Machino et al., 2014; Sämann et al., 2013), as well as machine learning techniques (Johnston et al., 2015; Korgaonkar et al., 2015; Liu et al., 2012; Schmaal et al., 2015). But, the variable results could also be attributed to methodological issues : some studies assessed the response to different therapeutic modalities such as transcranial magnetic stimulation (Furtado et al., 2012), electroconvulsive therapy (Abbott et al., 2014), ATD (Korgaonkar et al., 2015; C.-T. Li et al., 2010; Sämann et al., 2013), or cognitive behavioral therapy (Fujino et al., 2015), whereas in other patients received personalized therapeutic strategies (J. L. Phillips et al., 2015). Thus, these studies did not use consensual definitions of treatment resistance such as resistance to at least two different ATD trial or criteria from Massachusetts General Hospital staging or according to depression rating scales decrease. Taken together, all these data used heterogenous experimental designs which could impact the generalizability of previous results.

In this study, we compare whole brain volume differences between two groups of depressed patients – responders / non-responders – followed during six months. The aim of this work is to identify gray matter volume abnormalities associated with pejorative outcome of depression, in a homogeneous cohort, using a whole brain structural analysis. Regarding to the current literature, we hypothesized that patients who do not achieve remission will have baseline abnormal brain structures affecting key regions involved in emotional and cognitive processes.

Methods

Patient population

Patients included suffered from a depressive mood episode according to DSM-5 criteria with or without a personal history of depressive mood disorder (unipolar or bipolar subtype). Exclusion criteria included other Axis-I disorders (except for anxious comorbidities such as post-traumatic stress disorder, social phobia, generalized anxiety disorder or panic disorder), which were explored using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Patients with severe chronic physical illness were not included. Other exclusion criteria

were potential safety contraindications for MRI (pacemakers, metal implants, pregnancy and lactation), diagnosed neurodegenerative disorders (e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease), a history of significant head injury, or diagnosed dementia (according to DSM-5 criteria).

Study design

Depressed patients were recruited from routine care units in the psychiatric university hospital in Rennes between November 2014 and January 2017 and were enrolled in a naturalistic prospective open cohort study. A complete description of the study has been given to the subjects, and their written informed consent was obtained. The study was approved by an ethic committee and is registered in www.clinicaltrial.gov (NCT02286024). When recruited, patients underwent a first structured clinical interview at baseline. By a maximum of three days after clinical assessment patients had an imaging protocol. They received personalized care according to therapeutic guidelines described elsewhere (J. L. Phillips et al., 2015). Clinical data were anonymously retrieved in a notebook. At 6 months follow-up patients underwent a second structured clinical interview.

Clinical assessment

Patients were assessed at baseline and at 6 months by a trained clinician (psychiatrist or psychiatry resident). Sociodemographic (age, gender) and disease characteristics (diagnosis, disease duration, number of mood depressive episodes, actual medication, antecedent of suicidal attempts, treatment resistance stage according to Thase and Rush's classification) were collected.
In addition, these following scales were assessed:

- Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998)
- Montgomery and Äsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) and Beck Depression Inventory (BDI) (Beck et al., 1961)
- Widlöcher Depressive Retardation Scale (WDRS) (Widlöcher, 1983)
- State Trait Anxiety Inventory A and B (STAI) (Spielberger, C. D. et al., 1983) and Hamilton Anxiety Scale (HAMA) (Hamilton M., 1959)
- Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)
- Apathy Evaluation Scale (AES) (R. S. Marin et al., 1991)
- Clinical Global Impression – Severity (CGI-S) and the Clinical Global Impression - Improvement (CGI-I), (Guy, 1976).

The Clinical Global Impression – improvement subscale (CGI-I) scale was used after a 6-months period to measure the treatment response. The CGI-I measure is rated from 1 (very much improved) to 7. This measure is indeed a well-established research brief rating tool applicable to all psychiatric disorders and well correlated with other standard scales (Busner & Targum, 2007). It provides a global rating of illness severity and improvement, taking into accounts the patient's history, social circumstances, symptoms and the impact of the illness on the patient's ability to function (Busner & Targum, 2007). Leucht also demonstrated that a CGI-I score of 2 corresponded to a 50-60% reduction in the HAMD-17 score, while a score of 1 reflected a decrease from 75 to 85 % of the same scale within the 6-months longitudinal follow-up of depressive patients (Leucht et al., 2013). Min also used this threshold of a score ≤ 2 after a 6 months' follow-up to define a favorable clinical course and a therapeutic response (Min et al., 2012).

Imaging procedure

Data acquisition

Patients were scanned on a 3T whole body Siemens MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. Anatomical data included a high-resolution 3D T1-weighted MPRAGE sequence (3D T1w) with the following imaging parameters: TR/TE/TI = 1900/2.26/900 ms, 256x256 mm2 FOV and 176 sagittal slices, 1x1x1 mm3 resolution, parallel imaging GRAPPA2.

Data processing

Imaging data were analyzed by optimized voxel-based morphometry (VBM), using Statistical Parametric Mapping software (SPM) (http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (MathWorks, Natick, Massachusetts). First, MRI scans were segmented into GM, white matter and cerebrospinal fluid using a unified tissue-segmentation module, after correcting for image-intensity non-uniformity. These linearly transformed and segmented images were nonlinearly transformed by the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration method (Ashburner, 2007) and then modulated to the customized template for DARTEL followed by smoothing using an 8-mm full width at half-maximum kernel.

Statistical analyses

Statistical analyses were performed with R software (http://www.R-project.org/) only on patients who had undergone both baseline and 6 months assessments. All results are reported as means ± standard derivation (SD) for continuous variables, and rates for discrete variables. The significance threshold for all tests was set at 5%.

Statistical analysis of clinical data

The whole sample was divided into two groups using a 2-CGI-I cut-off score at the 6 months assessment, as suggested by Min et al. (Min et al., 2012) (CGI-I ≤ 2 : R group; CGI-I > 2 : NR group). Socio-demographic and clinical variables were then compared between these 2 groups.

Shapiro Wilk test was used for each variable to determine if the data set is well-modeled by a normal distribution. Quantitative variables were then compared using either the Student's test or the Wilcoxon test, when needed. Owing to the different sizes of the groups, qualitative variables were compared with either the Chi-squared test or a Fisher test, when needed.

Morphometric data analysis

A whole-brain voxelwise analysis was performed in SPM to detect differences in GM between the NR and R groups with the 2- CGI-I cut-off score. Age, gender, total intracranial volume (TIV), and medication load were included as covariates in each comparison. A composite measure of medication load for each patient was assessed using a previously established method (Sackeim, 2001). The two-sample t-tests were conducted within a group GM mask obtained by selecting a threshold of 0.2 on the mean GM map of all subjects. Thresholds were set at a corrected $p < 0.01$, with multiple comparison correction using the AlphaSim program in AFNI, determined by Monte Carlo simulation (Parameters were: single voxel p-value = 0.01, a minimum cluster size of 7.3 mm^3, FWHM = 8 mm, within a gray matter mask corresponding to the MNI atlas). The student *t*-value reported in the result section corresponds to the maximum value of each cluster.

Results

Demographics and clinical measures

Initially, 120 patients were included at baseline. The 57 patients were present at follow up. Of these patients, 2 did not have an imaging protocol and CGI-I score was missing for 5 of them. In total, 57 patients were analyzed. According to the 2-CGI-I cut off score, 27 were responder patients and 30 non-responder ones. The study's flowchart is shown on Figure 1. Socio-demographical and clinical characteristics at baseline and at 6 months of all analyzed patients are summarized in Table 1. The sample was predominantly represented by women, middle-aged and suffering from moderate depression.

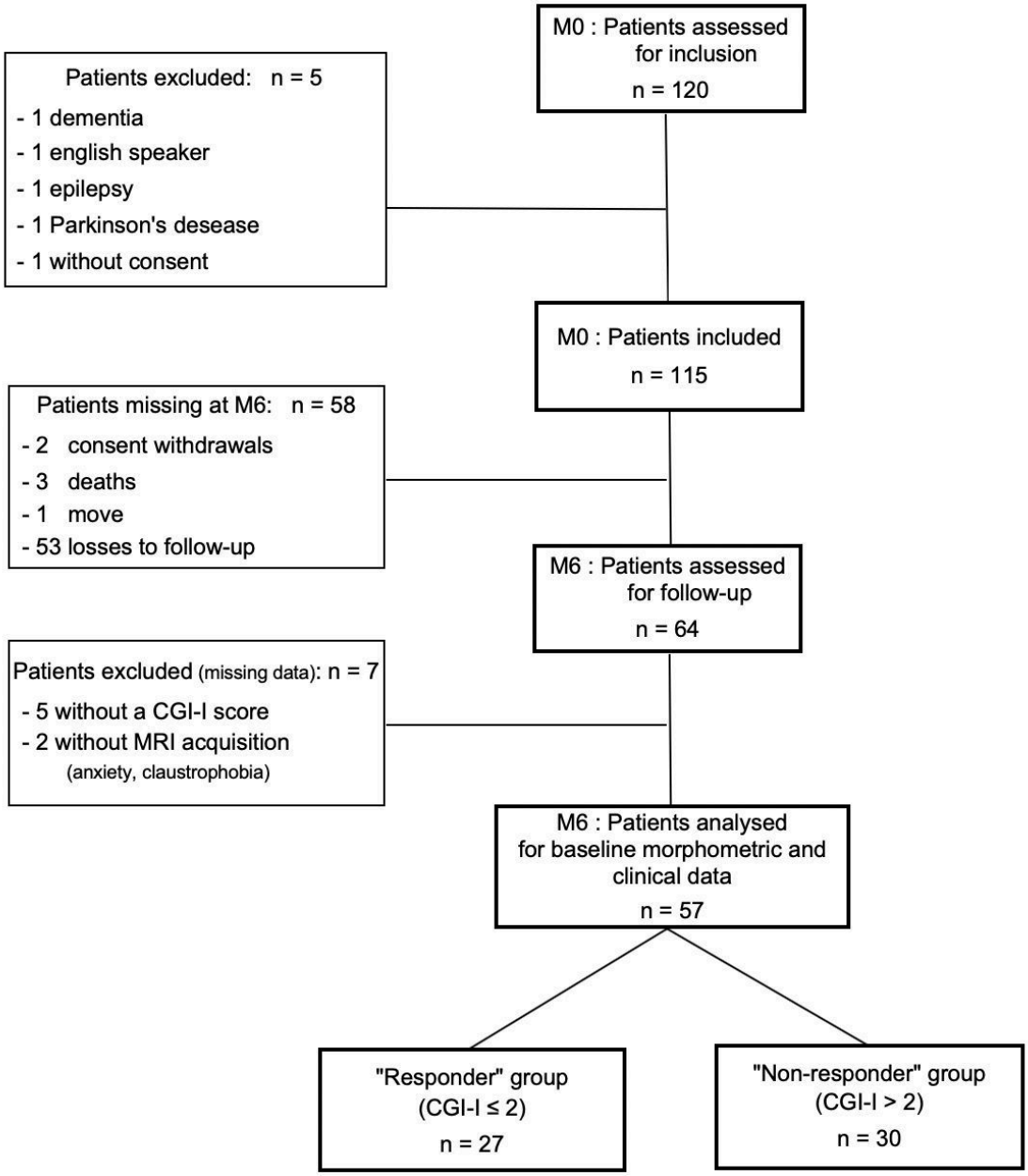

Figure 1 : Flow chart

Variables (N=57)	M0				M6			
	Mean/n	sd / %	N	Range	Mean/n	sd / %	N	Range
Sociodemagraphic								
Age (years)	50.95	14.52	57	18 - 76				
Gender (female)	43,00	75.44%	57	-	43,00	75.44%	57	-
Disease duration (years)	16.92	15.37	57	0 - 57	17.21	14.63	57	0.67 - 57
Number of episodes	4.56	4.52	55	0 - 30	4.90	4.63	52	1 - 31
Number of suicidal attempts	1.22	2.11	55	0 - 10	1.20	2.18	54	0 - 10
Thase and Rush score > 2	24,00	47.10%	51	1 - 4	28,00	50.91%	55	1 - 5
Comorbidities								
Bipolar disorder :	20	35.71%	56	-	20	35.71%	56	-
type 1	3	5.26%	56	-	3	5.36%	56	-
type 2	10	17.54%	56	-	9	16.07%	56	-
type 3	7	12.28%	56	-	8	14.29%	56	-
Panic disorder	8	14.04%	57	-	9	15.79%	57	-
Generalized anxiety disorder	23	40.35%	57	-	19	33.33%	57	-
Social phobia	7	12.28%	57	-	8	14.04%	57	-
PTSD	5	8.77%	57	-	6	10.53%	57	-
Medication								
Antidepressant :								
- SSRI	8	14.04%	56	-	13	24.07%	54	-
- NSRI	22	38.60%	56	-	12	22.22%	54	-
- TCA	9	15.79%	56	-	15	27.78%	54	-
- others	13	22.81%	56	-	12	22.22%	54	-
Mood stabilizer :								
- Lithium	6	10.53%	56	-	10	18.52%	54	-
- Anticonvulsant	22	38.60%	56	-	20	37.04%	54	-
- Antipsychotic	23	40.35%	56	-	21	38.89%	54	-
Benzodiazepine	30	52.63%	56	-	23	42.59%	54	-
Clinical variables								
MADRS	26.67	5.65	57	14 - 43	15.11	10.50	57	0 - 40
BDI	17.00	7.46	52	4 - 33	11.80	8.95	55	0 - 35
CGI-S	4.48	2.25	42	0 - 7	3.05	1.59	56	1 - 6
HAMA	25.49	14.18	42	10 - 46	16.98	10.53	57	1 - 45
STAI-YB	61.54	11.49	56	34 - 79	54.40	13.83	53	24 - 78
SHAPS	5.28	3.87	57	0 - 14	3.56	3.92	55	0 - 14
WDRS	22.07	9.35	57	3 - 40	12.29	9.08	56	0 - 32
AES	40.65	8.66	57	24 - 69	38.61	11.74	57	18 - 63
YMRS	1.93	1.80	57	0 - 7	1.37	2.28	57	0 - 10

sd: standard derivation; PTSD: Posttraumatic stress disorde; SSRI: Selective serotonin reuptake inhibitors; NSRI: Serotonin–norepinephrine reuptake inhibitors; TCA: Tricyclic antidepressants; MADRS: Montgomery-Åsberg Depression Rating Scale; BDI: Beck Depression Inventory; CGI-S: Clinical Global Impression-Severity; HAMA: Hamilton Anxiety Rating Scale; STAI : State-Trait Anxiety Inventory; SHAPS: Snaith Hamilton Pleasure Scale; WDRS: Widlöcher Depressive Retardation Scale; AES: Apathy Evaluation Scale: YMRS : Young Maniac Rating Scale

Table 1: Population description at baseline and at 6 months

Baseline demographic data and clinical characteristics from 27 responder patients and 30 non-responder patients were compared. Results are shown in Table 2. The non-responder group was significantly younger in comparison with the responder group. No significant difference was found between the two groups on gender, education level, age of onset, comorbidities, medication load, illness duration and number of depressive episodes. In addition, severity of depression (measured by MADRS and BDI scores) was not significantly different between the responder group and non-responder group. Non-responders were more anxious at baseline (HAMA).

Variables at baseline (N=57)	Responder (N=27)			Non-responder (N=30)			
	Mean/n	sd / %	N	Mean	sd / %	N	p-Value
Sociodemagraphic variables							
Age (years)	54.33	15.98	27	47.90	12.57	30	0.049b
Gender (female)	19	70.37%	27	24	80%%	30	0.399c
Education (years)	12.88	4.30	25	11.93	2.12	29	0.559b
Duration of illness (years)	20.90	18.60	27	13.33	10.87	30	0.221b
Comorbidities							
Bipolar disorder :	8	29.63%	27	12	41.37%	29	0.359c
type 1	1	3.70%	27	2	6.89%	29	1d
type 2	3	11.11%	27	7	24.14%	29	0.299d
type 3	4	14.82%	27	3	10.34%	29	0.700d
Panic disorder	2	9.09%	22	3	10.71%	28	1[d]
Generalized anxiety	11	40.74%	27	12	40.00%	28	0.955c
Social phobia	3	11.11%	27	4	13.79%	30	1d
PTSD	1	3.70%	27	4	13.33%	28	0.356d
Psychotic symptoms	2	7.41%	27	2	6.67%	30	1d
Medication							
Antidepressant :							
- SSRI	5	18.52%	27	3	10.34%	29	0.462d
- NSRI	13	48.15%	27	9	31.03%	29	0.190c
- TCA	5	18.51%	27	4	13.79%	29	0.725d
- others	6	22.22%	27	7	24.14%	29	0.865c
Mood stabilizer :							
- Lithium	4	15.39%	26	2	5.13%	29	0.406d
- Anticonvulsant	11	40.74%	27	11	37.93%	29	0.830c
- Antipsychotic	11	40.74%	27	12	41.38%	29	0.961c
Benzodiazepine	17	62.96%	27	13	44.83%	29	0.174c
Medication Load	3.41	1.05	27	3.00	1.19	30	0.198b
Clinical variables							
MADRS	26.86	5.74	22	26.50	4.94	28	0.815a
BDI	15.76	7.45	25	18.15	7.43	27	0.253a
HAMA	21.30	8.89	20	28.14	10.74	22	0.029a
STAI-YA	56.42	12.09	26	57.14	12.88	29	0.833a
STAI-YB	59.15	11.25	26	63.60	11.47	30	0.115b
SHAPS	4.37	3.53	27	6.10	4.03	30	0.100b
WDRS	24.00	9.84	27	20.33	8.70	30	0.144a
AES	39.04	6.32	27	42.10	10.21	30	0.175b

sd: standard derivation; PTSD: Posttraumatic stress disorde; SSRI: Selective serotonin reuptake inhibitors; NSRI: Serotonin–norepinephrine reuptake inhibitors; TCA: Tricyclic antidepressants; MADRS: Montgomery-Åsberg Depression Rating Scale; BDI: Beck Depression Inventory; CGI-S: Clinical Global Impression-Severity; HAMA: Hamilton Anxiety Rating Scale; STAI : State-Trait Anxiety Inventory; SHAPS: Snaith Hamilton Pleasure Scale; WDRS: Widlöcher Depressive Retardation Scale; AES: Apathy Evaluation Scale; a: Student test; b: Wilcoxon test ; c: Chi2 test ; d: Fisher test

Table 2: Intergroup comparison: demographic and clinical characteristics at baseline between responder and non-responder patients

Morphometric results: group comparisons of GM volume using VBM

Group comparison was controlled for age, gender, TIV, and medication load. The detailed t-test results, including the coordinates of the clusters are presented in table 3.

Anatomic regions		Side	Cluster size	Coordinates of peak voxel in MNI space (mm)			Tmax score
				x	y	z	
NR < R							
Thalamus	Ventral Lateral Nucleus	L	300	-19	-26	16	3.3405
		R	574	9	-14	10	3.6938
	Medial Dorsal Nucleus	R	647	9	-15	10	3.6938
Frontal Lobe	Precentral gyrus	R	1995	67	-12	33	5.0364
Temporal Lobe	Middle Temporal Gyrus	R	729	70	-8	-18	3.2892
Parietal Lobe	Precuneus	L	1456	-36	-81	33	4.1393
	Middle Cingulum	R	493	6	-35	45	3.0970
NR > R							
Cerebellum	Anterior lobe	L	97	-7	-46	0	3.4653
Limbic Lobe	Posterior Cingulate Cortex	L	1206	-5	-55	10	3.4653

VBM: Voxel-Based Morphometry; L: Left; R: Right; MNI: Montreal Neurological Institute coordinate system or template;Tmax: maximal statistical value of peak voxel showing differences of gray matter volume beetween two groups

Table 3: Regions of statistically significant differences of volume at baseline between responder (R) and non-responder (NR) patients according to VBM analyses.

Reduced GM in the non-responder group

The comparison between R and NR revealed a significant reduction of GM volume in several clusters, including: bilateral thalami, right frontal lobe (precentral gyrus), parietal lobes (precuneus and mid cingulum), and temporal lobe (mid temporal gyrus). Images are presented in figure 2.

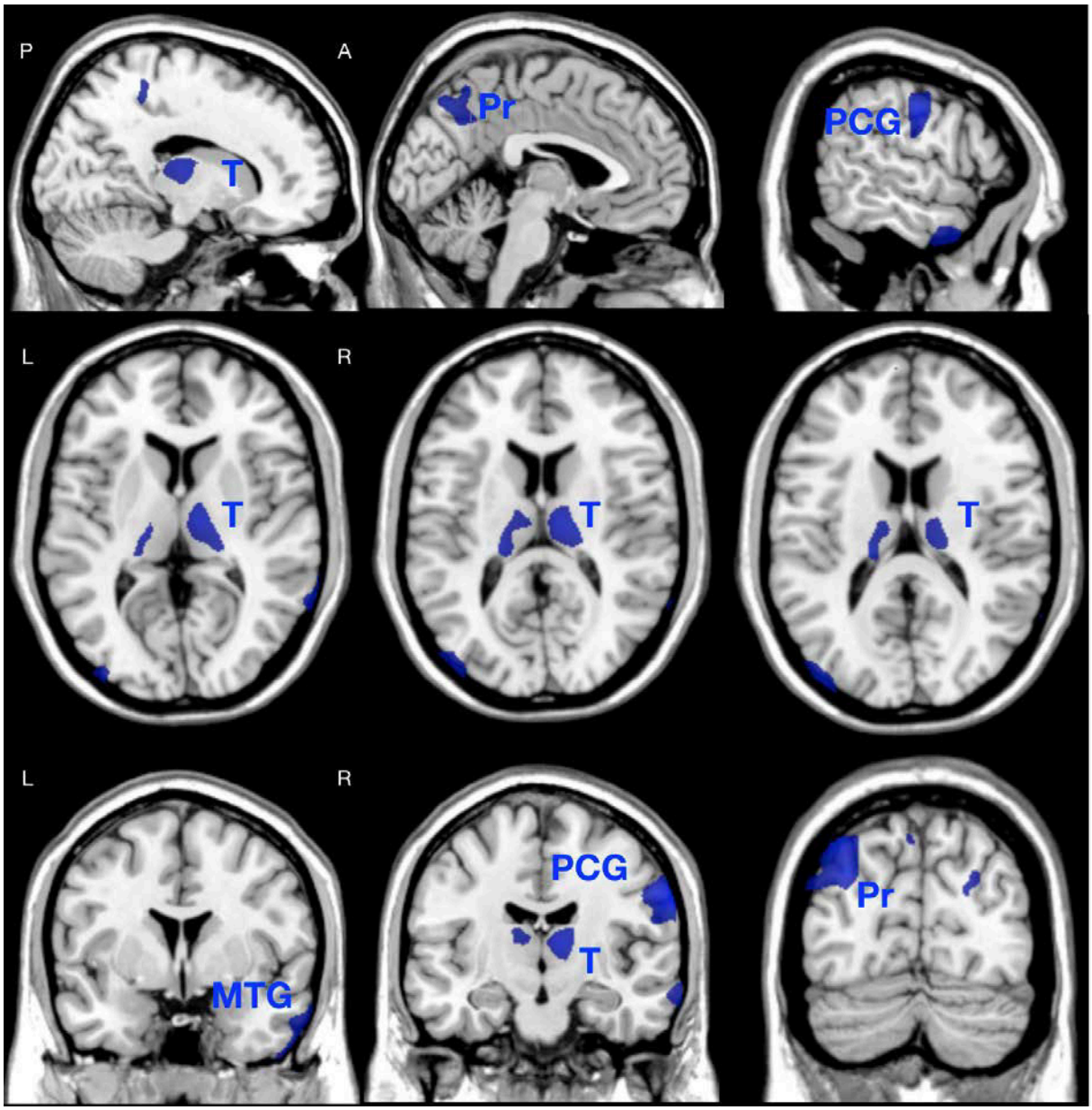

Figure 2: Regions showing significantly decreased GM volume in non-responder (NR) patients compared to responder (R) patients. P: posterior, A: anterior, L: left, R: right. T: thalamus, Pr: precuneus, PCG: posterior central gyrus, MTG: middle temporal gyrus.

Increase GM in the non-responder group

In comparison with R patients, NR patients showed significant increased GM volume cluster in left anterior cerebellum and left posterior cingulate cortex. Images are presented in figure 3.

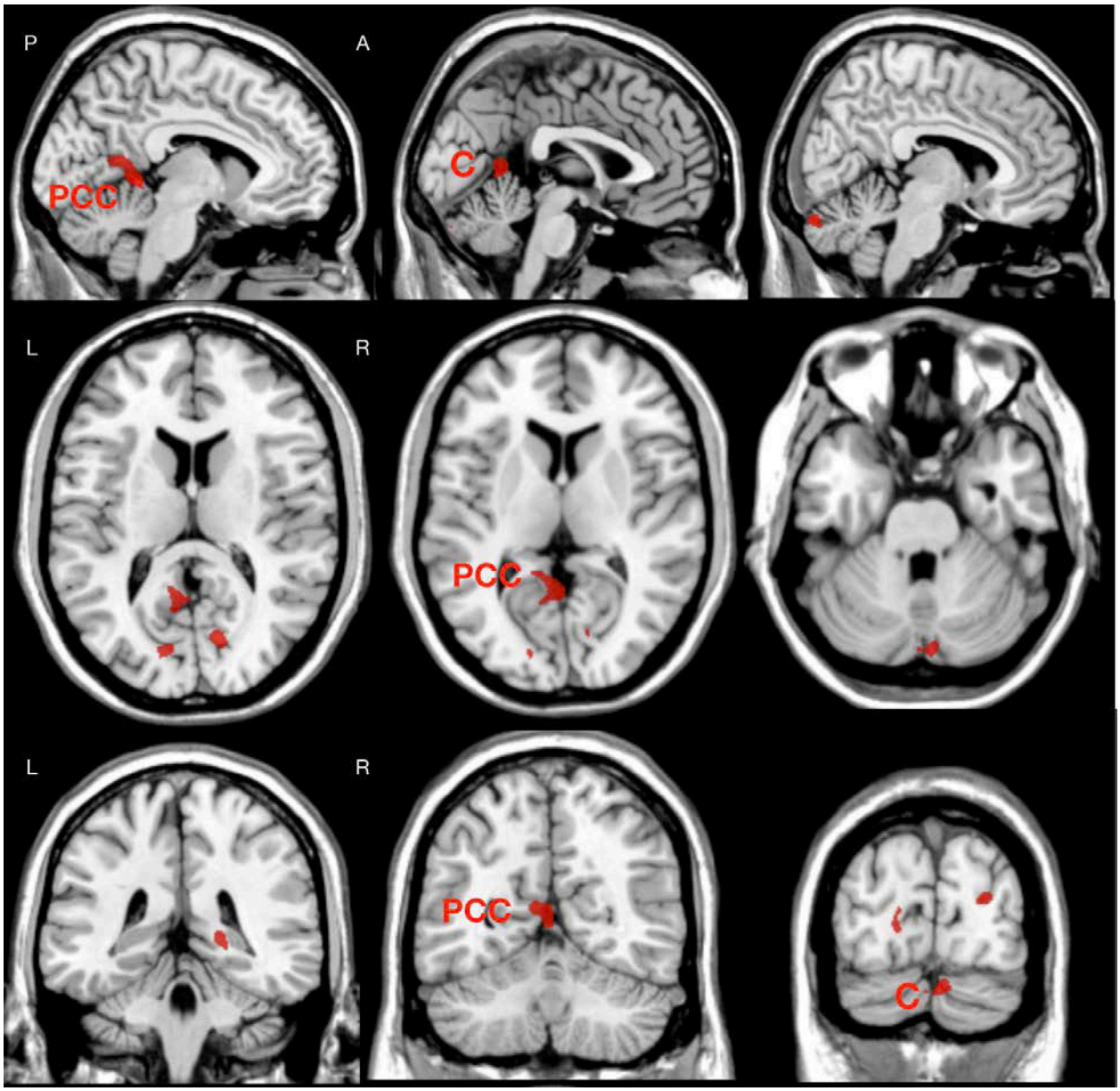

Figure 3: Regions showing significantly increased GM volume in non-responder (NR) patients compared to responder (R) patients. P: posterior, A: anterior, L: left, R: right. C: Cerebellum, PCC: Posterior Cingulate Cortex.

Discussion

General considerations

In addition to prior knowledge on that topic, the major findings of our study were a significant GM volume reduction in bilateral thalamus and an increase in cerebellum at baseline in MDD patients with a poor depression outcome at 6 months. Our results appeared in line with our hypothesis and previous findings from structural neuroimaging studies (C.-H. Chen et al., 2007). Altogether, there is converging evidence that pejorative outcome of depression is associated with gray matter abnormalities affecting key regions involved in emotional and cognitive processes.

Cortical gray matter volume reductions

In our NR group, we observed structural abnormalities including reduced GM volume over the frontal (precentral gyrus), the temporal (middle temporal gyrus), and the parietal lobes (precuneus and middle cingulum). These results were consistent with Peng et al who reported that the frontal-limbic circuit abnormality is implicated in the pathogenesis of MDD and are closely associated with clinical manifestations, including emotional bias, rumination and cognitive deficit (J. Peng et al., 2011). A recent meta-analysis of VBM studies in adults with MDD (Fu et al., 2013) revealed an association between a decrease in gray matter volume in the left DLPFC and reduced likelihood of antidepressant response (C.-H. Chen et al., 2007; Costafreda, Chu, Ashburner, & Fu, 2009; C.-T. Li et al., 2010). Another structural MRI study using machine learning approach also reported association between reduced GM volume in right DLPFC and poor response after a 6 weeks period of treatment (Gong et al., 2011). According to Li, structural deficits in the left DLPFC might predict poor or delayed antidepressant responses in adult patients with recurrent MDD (C.-T. Li et al., 2010). Furthermore, the same authors have highlighted the volume variation of some small regions within parietal lobe (postcentral gyrus) correlated with depressive symptoms or visual/acoustic attention (C.-T. Li et al., 2010).

Thalamic volume reduction

The thalamus is a pair mass of gray matter in the dorsal part of the diencephalon which has mainly a function of relay and integration of sensory and motor signals to the cerebral cortex and a function of regulation of consciousness, sleep, and alertness (Taber, Wen, Khan, &

Hurley, 2004). It is also a key structure in memory and emotion and is only recently known to be involved in the pathophysiology of mood disorders (Taber et al., 2004). In early 1980s, Angelini et al. characterized a depressive syndrome as a very frequent side effect after stereotaxic thalamotomy in patients with abnormal movements (Angelini, Nardocci, Bono, & Broggi, 1982). Later, Young et al. pointed out the role of the anterior and mediodorsal thalamus in the expression and experience of emotion (K. A. Young, Holcomb, Yazdani, Hicks, & German, 2004).

Our findings exhibited a GM volume reduction in ventral lateral nucleus and medial dorsal nucleus. In contrast with the large number of studies (Bora et al., 2012), only two recent analyses have revealed volumetric reductions in this regions in MDD (Nugent, Davis, Zarate, & Drevets, 2013; Webb, Weber, Mundy, & Killgore, 2014).

Besides, a recent study suggested a significant correlation between severity of depression and anxiety symptoms and thalamic reductions in GM volume in an adolescent MDD group compared to healthy controls in a whole-brain VBM analysis (Hagan et al., 2015). This study is in accordance with our clinical results in which non-responder patients had significant higher anxiety score on the HAMA scale at baseline. This result suggests that thalamic volume reduction plays a role in the outcome of depression via its involvement in the pathophysiology of emotion such as anxiety. It could be interesting to explore the proper role of the thalamus in anxious dimension and prediction of evolution of MDD.

Cerebellum

In our study, we found a significant GM volume increase in cerebellum in the non-responder group. In contrast to the large number of imaging studies exploring cerebral cortex in MDD, fewer morphometric MRI studies have assessed this region in MDD. Given its well-described role in motor control; particularly in coordination, precision, and accurate timing, cerebellum was recently well-recognized to participate in the organization of higher order functions; in both cognitive and affective processing control (Adamaszek et al., 2017; J. R. Phillips, Hewedi, Eissa, & Moustafa, 2015). More precisely, prior studies showed cerebellar involvement in elaborating negative emotions (Turner et al., 2007; Xu et al., 2017). Impairments in subjective experiences of pleasant emotions in response to positive stimuli have been reported in patients with cerebellar lesions (Adamaszek et al., 2017; Turner et al., 2007). According to Clausi et al., this region has a role in modulating the unconscious and conscious levels of emotional processing (Clausi et al., 2017).

However, previous whole brain structural MRI studies investigating on GM volumes abnormalities in MDD have reported different observations in this area ranging from a volumic

decrease (Fossati, 2015; T. S. Frodl et al., 2008; J. Peng et al., 2011) to no significant difference (Guo et al., 2013) in MDD patients compared to healthy controls. Then, Depping et al. showed that cerebellar volume increase following ECT was associated with HAMD score reduction (Depping et al., 2017). This latter study was in contradiction with our results. One explanation could be drawn in the link between neuroplasticity and clinical severity. In fact, in a previous study, significant volume increase of amygdala has been found in currently depressed patients and positively linked with severity of depression (van Eijndhoven et al., 2009). Bansal et al. indeed found evidence for compensatory and neuroplastic thickening of the cortex that attenuates symptoms and suggests that the severity and clinical course of depressive illness may depend upon whether an individual is able to engender in the brain an adaptive neuroplastic response (Bansal, Hellerstein, & Peterson, 2017). In addition to this hypothesis of neuroplasticity, there is a core of evidence that inflammatory processes, known to be involved in pejorative outcome of depression (Strawbridge et al., 2015), could modulate morphologic alteration in the brain (T. Frodl & Amico, 2014). The underlying mechanism of increase in GM volume is not completely explained but might possibly be due to chronic neuronal damage such as an inflammatory process leading to an increase of synaptic connections (C.-T. Li et al., 2010; Stoll, 1998; L.-M. Wu et al., 2007). In light of our results, we assume that cerebellum could be involved in pejorative outcome and a marker of the severity of depression, like amygdala volume variation. Since the non-responder patients showed significant higher anxiety score than responder ones in this cohort, it would be interesting to explore the association between anxious dimension and cerebellar volume. Indeed, a recent review has highlighted the potential role of cerebellum in the physiological mechanism of fear regulation, in anxiety-related disorders and treatment resistance in disorders such as MDD (Moreno-Rius, 2018).

Limitations

Our results have to be discussed through some limitations. First, the small sample-size may have affected statistical power of our analyses. The second, comorbid psychiatric conditions should be taken into consideration when interpreting our results; however, there was no statistically significant difference in comorbid conditions between groups. Third, patients recruited were not drug-free but all were treated with antidepressants, antipsychotics or mood stabilizers. Nevertheless, this latter point has been corrected in our analysis using medication load score.

Conclusion

The present study focused on structural abnormalities associated with pejorative outcome at 6 months in patients with MDD. In addition to their role in the physiopathology of MDD, our results have highlighted the implication of thalamic-frontocortical-cerebellar circuit in the prognosis of MDD. The most striking results were that non-responder patients were characterized by GM volume decrease in thalamus and increase in cerebellum. These patients were also more anxious than responder patients at baseline. Consistent with our clinical results and prior findings, the implication of these regions in outcome of depression could be linked with the severity of the depressive state through their involvement in anxious dimension. Future studies could go further on that point by focusing on anxiety dimension in order to identify the proper role of the thalamus and cerebellum. The present findings provided a step towards the understanding of physiological mechanisms which underlie pejorative outcome of depression.

Points forts de la partie 3.3.2. Structural abnormalities predictive of pejorative outcome of depression: the role of thalamus and cerebellum.

- Étude en voxel-based-morphometry sur les 57 premiers patients revus à 6 mois
- Les patients non-répondeurs étaient significativement plus anxieux (HAM-A :27.2 vs 20.53 ; p=0.039)
- Non-répondeurs : hypotrophie bilatérale thalamus / hypertrophie cérébelleuse
- Résultats corrigés par âge, sexe, volume total intracrânien, traitements pharmacologiques
- Discussion du rôle du thalamus et du cervelet dans la physiopathologie de la dépression résistante en lien avec la dimension anxiété.
- Hypothèse de l'implication des boucles cérébello-thalamiques dans la régulation émotionnelle et son implication dans la dimension anxieuse prédictive de la résistance de la dépression.

La figure 7 synthétise les différentes étapes et les principaux résultats de l'analyse longitudinale des facteurs cliniques, neuropsychologiques, et morphométriques, associés à l'évolution péjorative de la dépression.

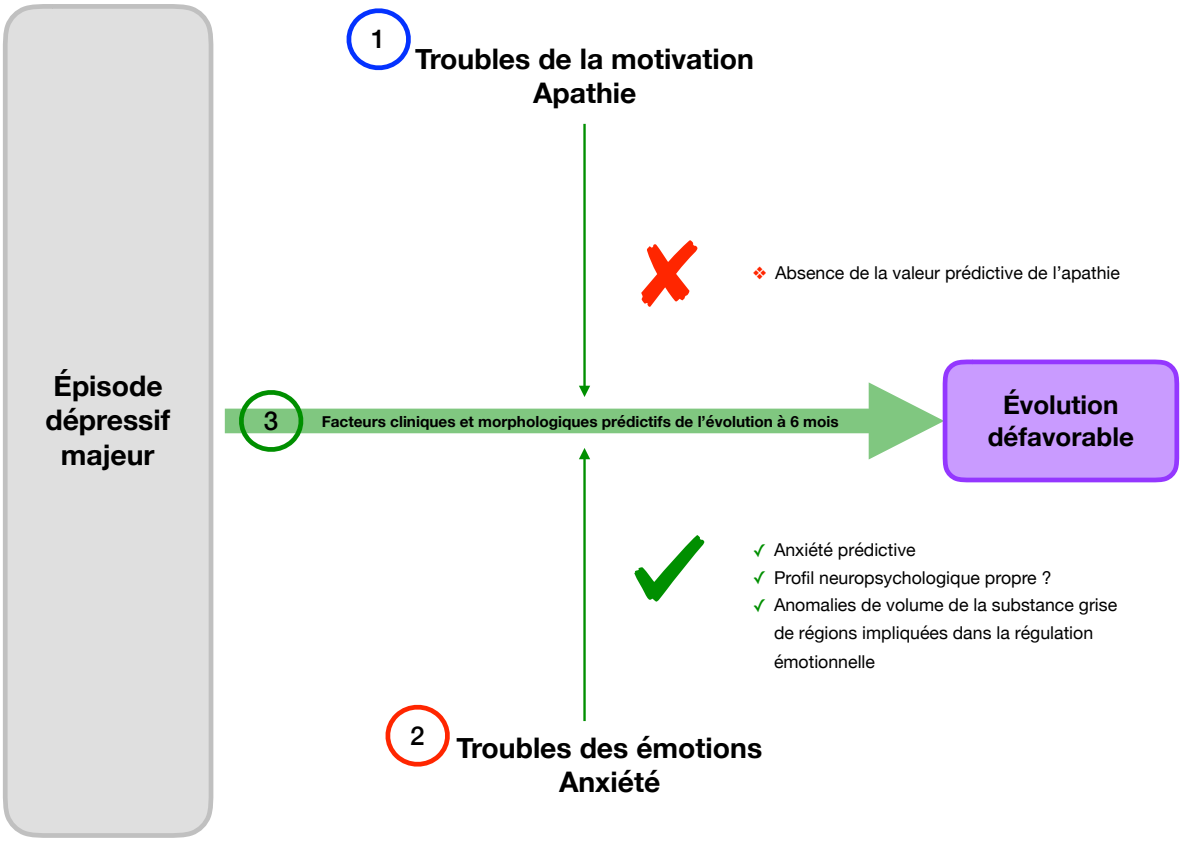

Figure 7: Synthèse des résultats de l'analyse longitudinale des facteurs cliniques et morphologiques associés à l'évolution défavorable de la dépression.

4 Discussion

4.1 Principaux résultats

4.1.1 L'apathie dans la dépression résistante – quelle est la place des troubles de la motivation dans la prédiction de l'évolution de la dépression ?

Synthèse des résultats (figure 3 et 7) :

- Les patients déprimés apathiques ont un profil clinique et neuropsychologique spécifique.
- Patterns physiopathologiques spécifiques à l'instar d'anomalies de la perfusion chez les déprimés apathiques. Réseau dopaminergique mis en exergue.
- Pas de valeur prédictive de l'évolution de la dépression à 6 mois.

Nos travaux nous ont permis de montrer que l'apathie est un syndrome pertinent cliniquement dans la dépression. Le résultat principal de l'étude décrite en partie 3.1 est la corrélation négative entre l'apathie et l'anhédonie. Celui-ci nous amené à disséquer les aspects motivationnels en perte d'intérêt – ou déficit de motivation « de programmation » - et perte de plaisir – ou déficit de motivation « de consommation ». Le lien avec l'anxiété, bien qu'il soit moins robuste dans notre étude, souligne la question de l'interaction entre émotion et motivation et prédiction de l'évolution de la dépression. Partant du postulat que l'anxiété est un fort prédicteur de résistance thérapeutique, que l'apathie et l'anxiété sont corrélés négativement, nous pourrions poser l'hypothèse d'un rôle protecteur de l'apathie dans l'évolution de la dépression. L'apathie serait alors décrite comme une indifférence à ses émotions, une mise à distance de la souffrance morale.

Concernant le lien entre apathie et l'évolution péjorative de la dépression, nous n'avons pas montré de valeur prédictive de cette dimension. Ce résultat négatif nous amène à poser la question du lien entre l'apathie et la dépression résistante. En effet, aucune donnée de la littérature n'a interrogé ce lien. Afin de discuter cet aspect nous proposons de décrire le lien, plus étayé, entre anhédonie et dépression résistante. Uher et al., ont démontré que la dimension « interest- activity » – résultat d'une analyse factorielle d'échelles cotant l'intensité dépressive (Rudolf Uher et al., 2009) – était un fort prédicteur de dépression résistante (R. Uher et al., 2012). D'autres études ont pu mettre en évidence un lien entre l'anhédonie et un délai plus important à atteindre la rémission chez des jeunes patients (McMakin et al., 2012), ou un effet anti-anhédonique – indépendamment de l'effet sur la score total de la dépression – dans la réponse à la kétamine dans une population de patients souffrant de trouble bipolaire résistant (Lally et al., 2014). Ainsi, dans le champ des troubles de la motivation, l'anhédonie semble être un prédicteur plus pertinent que l'apathie.

La deuxième partie de nos travaux sur l'apathie concernait l'étude des caractéristiques de perfusion cérébrales en utilisant une technique innovante, l'ASL. Cette étude a permis de montrer que les patients déprimés apathiques présentaient des patterns de perfusion spécifiques et affectant des régions clés du réseau dopaminergique. Ce résultat confirme notre hypothèse principale de l'existence d'une physiopathologie propre de l'apathie dans la dépression. L'implication du réseau dopaminergique est pertinente au regard du lien avec le système de la récompense. Cette étude nous semble apporter des arguments physiopathologiques robuste à des stratégies thérapeutiques ciblées de la dimension apathique dans la dépression ; les agonistes dopaminergiques tel que le pramipexole ou des techniques non pharmacologiques telles que la stimulation magnétique transcrânienne du cortex préfrontal dorsolatéral.

4.1.2 L'anxiété dans la dépression résistante – une question phénotypique

Synthèse des résultats (figure 5 et 7) :

- Non concordance des approches catégorielles versus sémiologiques/dimensionnelles.
- Hyperperfusion amygdale centro-médiane chez les déprimés résistants.
- Anxiété trait et profil neuropsychologique prédictifs d'une évolution péjorative.
- Anomalies structurales de régions clés, impliquées dans la régulation émotionnelle et plus précisément l'adaptation au danger/peur, associées à une évolution péjorative de la dépression.

Notre étude sur l'anxiété (partie 3.2) dans la population de patient souffrant d'un degré élevé de résistance thérapeutique nous a permis de mettre en évidence que cette population présentait plus fréquemment une comorbidité anxieuse de type panique alors qu'elle semblait présenter des patterns sémiologiques associés à la tristesse et les pensées pessimistes. Malgré les limites de cette étude, il apparait intéressant de pointer que les approches catégorielles et dimensionnelles des troubles émotionnels divergent. Cet aspect est central dans l'étude des facteurs cliniques associés à la dépression résistante. Les travaux de Uher et collègues mettent bien exergue cette problématique. En effet, ils soulignent que l'hétérogénéité des tableaux cliniques de dépression est mieux caractérisée par des approches dimensionnelles (i.e. basées sémiologie) que par des approches catégorielles. Ils ont proposé d'étudier, au sein d'une cohorte de 811 patients, par une analyse factorielle, la contribution de chaque item des échelles classiquement utilisées dans la dépression : la MADRS, la BDI, l'Hamilton Depressive Rating Scale (HDRS), soit 47 items au total. Trois facteurs ont été identifiés : l'humeur observée, le facteur cognitif, le facteur neurovégétatif. Deux d'entre eux nous semblent intéressant définis par une dimension anxiété pour le facteur

humeur observée et d'une dimension pessimisme pour le facteur cognitif (R. Uher et al., 2012). Les analyses factorielles – basées sémiologie – nous semblent plus pertinentes afin de proposer une caractérisation clinique plus précise des troubles émotionnels et permettre ainsi d'identifier des dimensions plus spécifiques et au plus fort pouvoir prédictif. Ces approches sont décrites dans la littérature comme fiables et valides (Rudolf Uher et al., 2009; Rudolf Uher & Rutter, 2012) dans leur applications en neurosciences (Veen et al., 2011; Wardenaar et al., 2011). Il existe donc un enjeu fort autour de la définition des construits sémiologiques permettant d'étudier ainsi les éléments physiopathologiques sous tendus. Nous avons mené ces réflexions au sein d'une revue de la littérature discutant des spécificités inhérentes à la psychiatrie dans les construits théoriques sous-tendant nos nosographies. Dans le champ plus large de la médecine, la psychiatrie illustre la problématique d'imposer des constructions de schémas cognitifs à l'information médicale – clinique et scientifique – pour élaborer les classifications et augmenter leur compréhension et leur utilité. Il existe un besoin de mieux définir et classer les signes et symptômes basé sur une double perspective biologique et psychologique mutuellement interactive (Micoulaud-Franchi et al., 2018). Nous proposons d'approfondir cette discussion en partie 4.1.4.

Concernant les analyses longitudinales (parties 3.3.1 et 3.3.2), nous avons montré que l'anxiété trait (mesurée par l'échelle STAI-YB) était prédictive de l'évolution péjorative, que la performance au code de la WAIS III était un prédicteur d'évolution favorable, et que l'évolution défavorable était associée à des anomalies structurales de régions clés impliquées dans la régulation des émotions – la peur. Ces résultats sont convergents avec l'hypothèse forte mettant l'anxiété comme facteur pronostique de la dépression.

4.1.3 Interaction entre anxiété et troubles de la motivation et pronostic de la dépression

L'étude présentée en partie 3.2 a rapporté une hyperperfusion des noyaux centro-médians de l'amygdale. Cette sous-région entretient des rapports anatomiques électifs avec des régions cérébrales comme le striatum, ayant un rôle clé dans le système de récompense. Ce dernier résultat nous invite à interroger l'interaction entre l'anxiété, les troubles de la motivation et le pronostic de la dépression. Une étude récente réalisée en imagerie nucléaire et a testé les corrélats d'occupation des récepteurs dopaminergiques $D_{2/3}$ (R $D_{2/3}$) striataux avec l'anxiété, l'anhédonie, et la réponse thérapeutique au traitement antidépresseur. Il s'agissait d'un essai thérapeutique randomisé, simple aveugle contre placebo, réalisée chez 33 patients déprimés et 16 sujets contrôles. Chez les patients souffrant de dépression, une plus grande disponibilité des R $D_{2/3}$ de la partie caudale du striatum ventral était corrélée à des symptômes anxieux plus intenses. A l'inverse, la disponibilité des R $D_{2/3}$ de la partie rostrale du striatum ventral corrélait négativement avec la sévérité de l'anhédonie. Les patients déprimés qui ne rencontraient pas les critères de rémission à l'issu de l'essai avaient une plus

grande disponibilité des R $D_{2/3}$ du striatum ventral. Les auteurs de conclure qu'une plus forte disponibilité des R $D_{2/3}$ du striatum ventral est associée à la comorbidité anxieuse de la dépression et une évolution péjorative de celle-ci (Peciña et al., 2017).

En synthèse de nos travaux et cette dernière étude, il existe des arguments cliniques et physiopathologiques plaidant pour une interaction des dimensions « positives », à l'instar de l'anxiété et des dimensions « négatives » à l'instar des troubles de la motivation, qui serait impliquée dans les mécanismes de résistance de la dépression. Des projets futurs pourraient étudier ces interrelations ainsi que les aspects neuronaux les supportant.

4.1.4 Commentaire général : la place de la sémiologie dans l'étude des facteurs pronostiques de la dépression

Ce travail s'intègre plus généralement dans les enjeux méthodologiques actuels de la recherche dans le champ des neurosciences ouvert par le récent projet Research Domain Criteria (RDoC). L'objectif des RDoC est de proposer une nouvelle méthodologie qui permettrait de classer les troubles mentaux selon des mécanismes biologiques. Cette classification a pour but de développer des modèles physiopathologiques fidèles et reproductibles des maladies psychiatriques (Cuthbert, 2014; Cuthbert & Insel, 2013). A travers une approche translationnelle (i.e. gènes → cellules → cerveau → comportement), les RDoC proposent des construits physiologiques permettant comprendre le fonctionnement cérébral.

Une des grandes limites des RDoC est de ne pas intégrer la notion de symptômes dans leur approche (Kozak & Cuthbert, 2016). Selon Maj, « *si le problème avec les catégories du DSM est qu'elles sont distantes du niveau des neurosciences, le problème de certains construits des RDoC est qu'ils sont quelque peu éloignés des phénomènes cliniques* » (Maj, 2014). Certains auteurs pointent le besoin de lier les symptômes aux construits des RDoC pour compléter l'approche translationnelle développée (Kozak & Cuthbert, 2016).

Notre travail s'inscrit dans ce hiatus constaté dans le domaine de la recherche en neurosciences et met en avant la nécessité de développer la recherche sur la physiopathologie des symptômes afin d'inférer les processus biologiques sous-jacents (Micoulaud-Franchi et al., 2018). Ce hiatus est avant tout conceptuel car questionne la place du symptôme dans la physiologie des troubles psychiques. L'intégration de la sémiologie comme centrale dans l'étude de la physiopathologie de la dépression est une approche qui épouse le raisonnement médical. Tristram Engelhardt écrivait à ce sujet que l'objectif de la médecine est de *« fournir une structure nomologique permettant de lier les signes et symptômes de manière à fournir un modèle d'explication* » (Giroux & Lemoine, 2012) … par conséquent, « *l'adoption d'un modèle médical ou psychologique est un choix pragmatique consistant à se focaliser sur une*

combinaison particulière de variables et sur leurs corrélations afin de réaliser des démarches assurées d'explication, de prédiction et de contrôle » (Giroux & Lemoine, 2012).

Ainsi, la sémiologie, au sens variable d'intérêt perturbant le fonctionnement du patient, offre cette perspective de recherche en neuroscience où l'on n'étudie pas seulement le fonctionnement du cerveau (i.e. approche RDoC) mais le fonctionnement du cerveau en fonction d'enjeux cliniques tel que le pronostic par exemple.

4.2 **Principales limites**

Ce travail doit être interpréter à la lumière de quelques limites. Tout d'abord, un biais d'attrition avec un taux de perdus de vue à 6 mois de 46%. Il faut préciser que certains patients revus à 6 mois ont été revus aux visites ultérieures. De plus, plusieurs caractéristiques spécifiques de notre population sont à prendre en compte telle que la variabilité de l'âge (18 – 76 ans), le fort niveau d'anxiété de l'échantillon, et le degré de résistance pharmacologique à l'inclusion. Ce dernier point constitue un biais de sélection inhérent à la spécificité du centre dont l'activité est centrée par une expertise et la coordination de soins de pathologies dépressives résistantes. Enfin, les patients recrutés étaient tous sous traitement pharmacologique et constitue une variable confondante qui a été prise en compte dans les analyses statistiques. Précisons que les patients qui ont été évalués ne bénéficiaient pas concomitamment d'un traitement par stimulation cérébrale. L'ensemble de ces limites est à mettre en perspective du caractère naturalistique du projet LONGIDEP. Cette spécificité représente des contraintes statistiques inhérentes à la variabilité de l'échantillon mais nous apparait être une force de notre étude car elle nous a permis de tester des hypothèses en population de soins courant sur un nombre important de patients.

4.3 **Perspectives de recherche : le projet DEPREDICT (PHRCi 2017)**

A la lumière des résultats de LONGIDEP et des réflexions méthodologiques, l'objectif de ce projet est de travailler sur l'anxiété trait selon une approche basée sémiologie. Nous testerons l'hypothèse selon laquelle l'anxiété trait – étudiée dans toutes ses dimensions : clinique, neuropsychologique, corrélats neurofonctionnels, corrélats immuno-inflammatoires – est hautement prédictif de l'évolution de la pathologie dépressive à 3 ans. Le projet DEPREDICT a été retenu pour un financement dans le cadre du PHRCi 2017 à hauteur de 249 257€.

4.3.1 Présentation de l'étude

Les résultats de cette étude préliminaire ont démontré que nos hypothèses cliniques et physiopathologiques étaient solides et méritaient d'être confortées en incluant un grand nombre de patients. Le projet actuel financé par la DGOS a pour objet d'étendre cette recherche à plusieurs centres de recherche en psychiatrie dans le cadre de réseaux financés par le GIRCI Grand Ouest (réseau HUGOPSY) et l'ARS (réseau recherche breton). Au-delà des résultats préliminaires, ce travail a pour objectif principal de mieux comprendre les facteurs péjoratifs d'évolution de la dépression. L'idée première est de tester, selon une approche dimensionnelle (Insel et al., 2010), l'hypothèse selon laquelle l'anxiété trait est un facteur prédictif puissant de la résistance thérapeutique. Ainsi, la résilience, définie comme la capacité d'un individu à s'adapter au stress (Russo, Murrough, Han, Charney, & Nestler, 2012) serait, à l'inverse, un facteur protecteur. La dépression résistante serait alors décrite comme une maladie de la résilience au stress (Min et al., 2012; Russo, Murrough, Han, Charney, & Nestler, 2012).

Le caractère innovant réside dans le fait que cette dimension soit investiguée selon un continuum clinico-biologique permettant de souligner sa cohérence physiopathologique (Insel et al., 2010). Aussi, ce projet propose de tester l'hypothèse selon laquelle l'anxiété, explorée selon une approche translationnelle, serait hautement prédictive d'une évolution péjorative de la maladie avec pour déterminants :

- Clinique : une anxiété trait et état plus sévère,
- Neuropsychologique : un profil cognitif sensible à l'interférence émotionnelle ;
- Radiologique : des anomalies morphologiques et fonctionnelles du système limbique et motivationnel ;
- Biologique: des anomalies immuno-inflammatoires (CRP, Il-1/6, TNF, leucocytose) (Russo et al., 2012).

L'objectif principal est de montrer que l'anxiété est prédictive de l'évolution péjorative de la maladie dépressive.

Les objectifs secondaires sont de montrer que l'anxiété est prédictive de l'évolution péjorative de la maladie dépressive. Cette dimension sera évaluée selon :

- Sa composante clinique (et sociodémographique),
- Sa composante neuropsychologique : des patterns cognitifs tels qu'un déficit des fonctions exécutives, illustrant une difficulté dans la prise de la décision, un profil cognitif sensible à l'interférence émotionnelle,
- Sa composante radiologique (IRM) : des anomalies morphologiques et fonctionnelles du système limbique caractérisées par une hypertrophie et une hyperperfusion amygdalienne. L'amygdale serait une région clé d'un réseau plus large impliquant le réseau de la motivation,
- Sa composante biologique: en accord avec les données de la littérature sur la neurobiologie de la résilience (Russo et al., 2012), des anomalies immuno-inflammatoires (CRP, Il-1/6, TNF, leucocytose) seraient associées à cette dimension sus décrite.

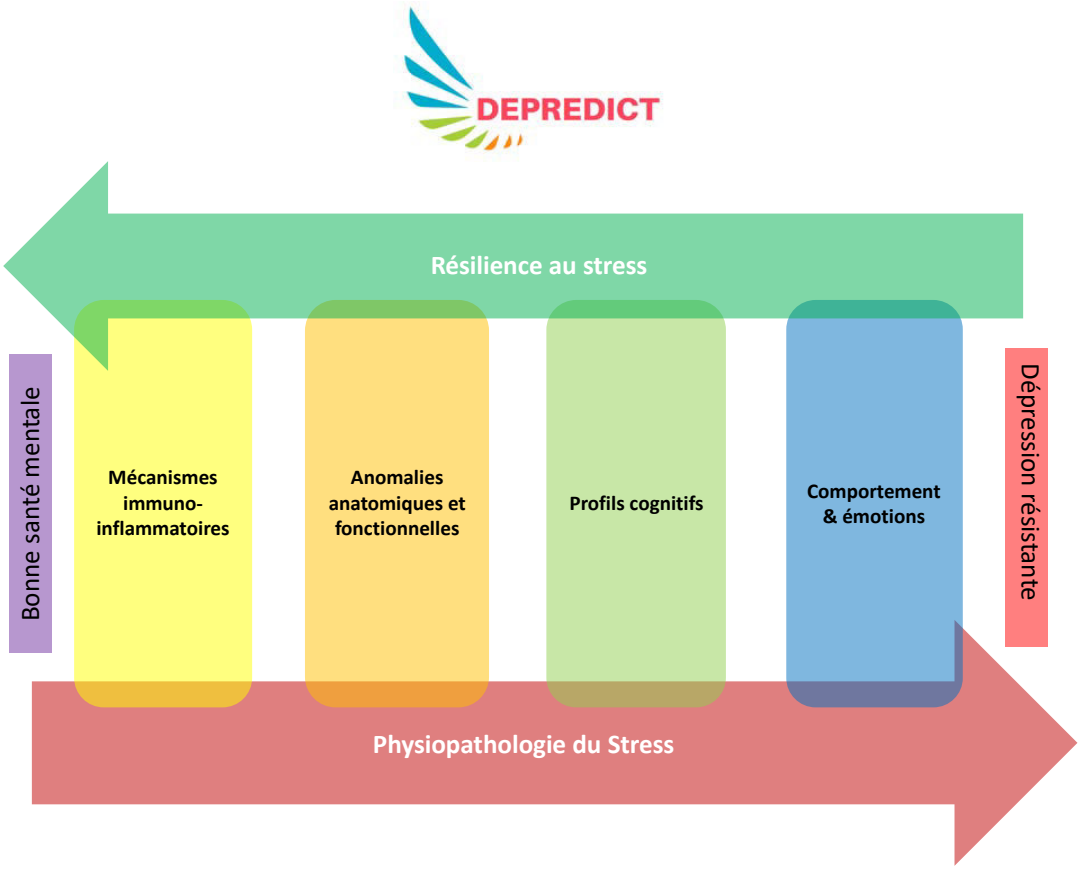

Figure 8 : Schéma résumant l'approche dimensionnelle du PHRCi DEPREDICT

4.3.2 Plan expérimental et apports de la cohorte LONGIDEP

Cette étude prospective, multicentrique, sera menée dans 8 centres du grand ouest. L'objectif est d'inclure 150 patients au total et les suivre selon les mêmes modalités que dans LONGIDEP (figure 9).

L'expérience de la cohorte LONGIDEP nous a permis de modifier le protocole en ayant une hypothèse centrée sur l'anxiété et la résilience au stress avec une approche dimensionnelle. L'étude DEPREDICT n'est plus un protocole de soins courants mais une étude de recherche à risque et contraintes minimes. Les principales modifications sont :

- Des critères d'inclusion plus restrictifs : âge de 18 à 55 ans, exclusion des patients ayant un grade de résistance élevée (stade Thase & Rush ≥ 3) ;
- Dosage de marqueurs biologiques immuno-inflammatoire à l'inclusion à 36 mois
- Politique de suivi strict, dans le cadre de la recherche médicale, visant à lutter contre le biais d'attrition ;
- Réalisation d'une imagerie longitudinale avec deux examens à l'inclusion et à 36 mois ;
- Protocole d'imagerie multimodale : morphologique, tenseur de diffusion, imagerie fonctionnelle BOLD de repos, imagerie de perfusion en ASL. La combinaison des modalités d'imagerie permettra de tester des hypothèses à l'échelle de réseaux neuronaux centrés sur les interactions entre structures impliquées dans la régulation des émotions et de la motivation.

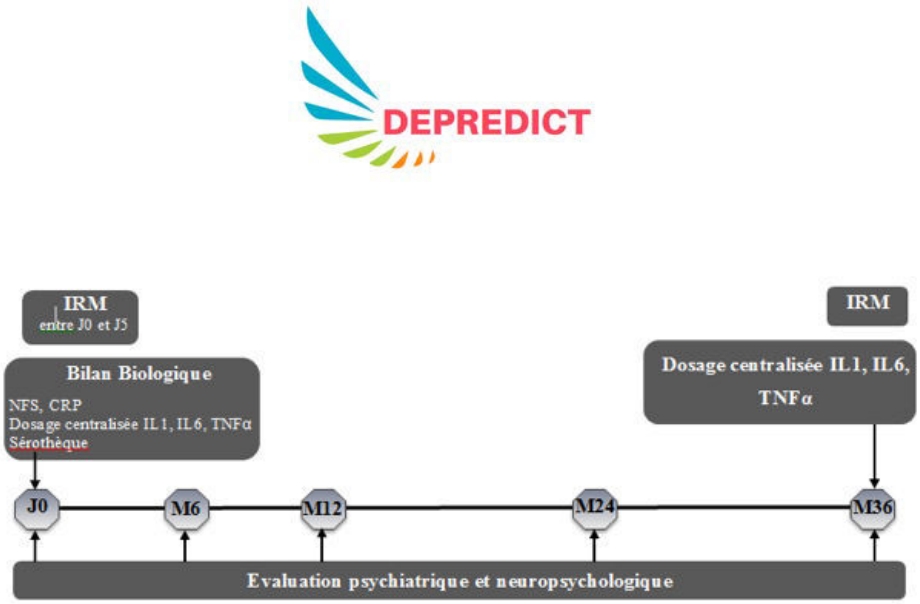

Figure 9 : Plan expérimental du projet DEPREDICT.

5 Liste des tableaux et figures

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Titre : Aspects cliniques et neurofonctionnels impliqués dans le cours évolutif de la dépression - L'expérience d'une cohorte en soins courants.

Mots clés : dépression, anxiété, apathie, imagerie cérébrale, pronostic, substance grise.

Résumé :

Le but de ce travail est d'étudier deux dimensions sémiologiques, identifiées dans la littérature comme associées au trouble dépressif résistant, l'anxiété et l'apathie. Ces marqueurs cliniques et leurs corrélats radiologiques seront ensuite testés dans une analyse longitudinale du pronostic à 6 mois d'une cohorte de patients souffrant de dépression.

Les données originales de ce travail sont issues de la cohorte LONGIDEP. Cette étude prospective, naturalistique, a été menée chez des patients souffrant d'un épisode dépressif majeur qui bénéficiaient, dans le cadre des soins courants, d'une évaluation clinique, neuropsychologique et d'une imagerie cérébrale à l'inclusion. Une nouvelle évaluation a été proposée à 6 mois de l'inclusion.

Cette étude nous a permis de montrer que 1) l'apathie dans la dépression est associée à un profil clinique et physiopathologique spécifique, 2) l'analyse catégorielle et sémiologique de l'anxiété dans une population de sujet déprimés résistants n'étaient pas concordantes. Les déprimés résistants présentaient une hyperperfusion amygdale centro-médiane, 3) l'anxiété trait, un pattern cognitif associé à la mémoire visuo-spatiale étaient prédictifs d'une évolution péjorative de la dépression. Des anomalies structurales de régions impliquées dans la régulation émotionnelle et plus précisément l'adaptation au danger/peur, étaient associées à une évolution péjorative de la dépression.

Des deux dimensions sémiologiques étudiées, l'anxiété apparaît être impliquées dans le pronostic de la dépression. L'étude des liens entre l'anxiété et les troubles de la motivation est une perspective de recherche pour la dépression résistante.

Title: Clinical and neurofunctional patterns associated with pejorative outcome of depression - Results from a routine care cohort

Keywords: depressive disorder, anxiety, apathy, brain imaging, prognosis, grey matter.

Abstract:

The aim of this work is to study anxiety and apathy in treatment resistant depression. These clinical factors and its imaging correlates will be tested in prediction of outcome in a 6-months follow-up.

Original data were retrieved in LONGIDEP cohort. This is a prospective study conducted in routine care. Patients suffering from a mood depressive episode benefited from a clinical, neuropsychological and brain imaging. They were assessed once again at 6 months.

Our study has shown that 1) apathy in depression is associated with specific clinical and pathophysiological patterns, 2) categorical and dimensional approach of anxiety in treatment resistant depression are not convergent. This latter population exhibited higher brain perfusion of centro-medial amygdala, 3) trait anxiety, cognitive patterns of visuospatial memory were predictive of pejorative outcome. Structural abnormalities in key regions involved in emotion regulation were associated with pejorative outcome of depression.

Only anxiety was involved in outcome of depression. The link between anxiety and motivation should be studied in further works.