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Le développement de biomarqueurs et de la neuromodulation de précision dans la dépression : préciser les diagnostics, personnaliser les soins

Ludovic Dormegny-Jeanjean

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ÉCOLE DOCTORALE DES SCIENCES DE LA VIE ET DE LA SANTÉ (414)

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**Le développement de biomarqueurs et de la
neuromodulation de précision dans la dépression
préciser les diagnostics, personnaliser les soins**

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Liste des abréviations

CIM : Classification Internationale des Maladies

DSM : *Diagnostic and Statistical Manual of mental disorders*

ECT : électroconvulsivothérapie

RDoCs : *Research Domain Criteria*

NIMH : *National Institute of Mental Health*

EEG : électroencéphalogramme

SNT : *Stanford Neuromodulation Protocol*

rTMS : Stimulation Magnétique Transcrânienne répétitive

sgACC : Cortex Cingulaire Antérieur subgenua

DLPFC-G (ou -D) : Cortex Préfrontal Dorso-Latéral Gauche (ou Droit)

ASL : *Arterial Spin Labelling*

IRMf : Imagerie par Résonance Magnétique fonctionnelle

rCBF : *regional Cerebral Blood Flow*

KP : catatonie périodique

WKL : Wernicke-Kleist-Leonhard

iADAPT : *Imagery guided Anti-Depressive Adaptive Personalized TMS*

TRH : hormone thyroïdienne

1 Introduction

La psychiatrie vit aujourd'hui une crise diagnostique, symptôme des limites des classifications actuelles. Le développement des biomarqueurs et des soins personnalisés, en particulier en neuromodulation, pourrait constituer un moyen de sortir de cette crise.

1.1 La crise diagnostique en psychiatrie

Historiquement, la crise diagnostique en psychiatrie est la succession de deux crises – la nature de la solution apportée à la première engendrant finalement la seconde : la crise de l'hétérogénéité conceptuelle et celle de l'homogénéisation athéorique.

Initialement, la méthode utilisée pour poser les diagnostics était une méthode d'école : un maître, ou un groupe d'auteurs, élaboraient les théories et la méthode qui étaient appliquées et perfectionnées par leurs disciples. Ces écoles avaient un rayonnement souvent national ou régional, avec parfois des mouvements d'experts qui diffusaient les idées et les méthodes de leur école. Conséquence de ce morcellement des façons de faire : les praticiens et les scientifiques échangeaient des connaissances acquises sur des bases théoriques et méthodologiques parfois très variables ce qui provoquait un certain nombre de malentendus.

Les échanges scientifiques devenant progressivement plus intenses et plus internationaux, il devint crucial de disposer de critères connus de tous. Ainsi, en 1948 et 1952, parurent respectivement les deux classifications majeures qui seront le support de cette unification : la sixième version de la classification internationale des maladies (CIM), qui inclut pour la première fois les troubles mentaux, et le *diagnostic and statistical manual of mental disorders*

(DSM) américain^{8,9}. À partir de la parution de la CIM-8 (1968) et du DSM-III (1980), l'objectif d'homogénéisation fut encore plus clairement revendiqué : le DSM proposa alors des critères diagnostiques opérationnalisés et un parallélisme conceptuel entre CIM et DSM s'installa progressivement. Ces deux classifications s'imposèrent progressivement dans le domaine scientifique et clinique (en 2010, 83% des cliniciens utilisaient régulièrement une des deux)¹⁰. La première crise diagnostique, celle de l'hétérogénéité conceptuelle, était résolue.

La seconde crise naquit de la façon même dont ces classifications avaient été conçues : à savoir une élaboration fondée sur le consensus et l'athéorisme. Les deux premières versions du DSM ne firent pas immédiatement consensus, de même que les CIM 6 et 7. Le reproche ? un trop grand attachement aux concepts psychanalytiques, alors dominants. Ici encore, ce furent la CIM-8 et le DSM-III marquèrent la rupture. Sous l'impulsion de Lewis, la CIM-8 s'orienta vers une critériologie purement descriptive et dénuée de tout fondement théorique^{11,12}. Robert Spitzer, qui coordonnait la rédaction du DSM-III, emboîta le pas à la CIM : les critères diagnostiques ne reposeraient plus désormais sur des bases théoriques mais seraient définis par consensus¹³. Ils devraient être faciles à identifier, considérés fiables et, surtout, avoir la meilleure reproductibilité inter-cotateur possible, mettant de côté l'identification des symptômes subjectifs – considérés trop dépendants du sujet ou de l'évaluateur et donc peu fiables –, ceux qui nécessitent une expertise spécifique – trop peu accessibles à la majorité des praticiens – ou ceux qui sont rares.

Les diagnostics posés grâce à ces critères doivent, quant à eux, être suffisamment simples, neutres et inclusifs pour être utilisables par des cliniciens et des scientifiques de cultures différentes et ne pas provoquer de rejet. On parle alors de *troubles mentaux*, définis comme des "*syndromes caractérisés par une perturbation cliniquement significative [...] qui reflètent un dysfonctionnement des processus psychologiques, biologiques ou de développement qui sous-tendent le fonctionnement mental*"¹⁴, une définition inclusive, communément ramenée au concept encore plus large d'"*élément de préoccupation médicale chez un patient, une*

anomalie, une blessure, un handicap ou une aberration" ¹⁵. L'objectif affiché du "**modèle trouble**" est de rendre ces classifications plus scientifiques car moins sujettes à la subjectivité et à l'interprétation – argument dont le sens ne se mesure qu'en considérant le contexte historique d'opposition croissante contre la psychanalyse.

Pourquoi des *troubles* et non des *maladies* mentales ? Le **modèle "maladie"** repose sur deux principes : d'une part, l'hypothèse naturalistique catégorielle définit les maladies comme dues à des causes aux effets importants qui provoquent une rupture du continuum entre population normale et population malade (distribution bimodale) – et, d'autre part, l'association causale de la symptomatologie avec une étiologie biologique ou un processus physiopathologique spécifique, y compris si cette association est théorique¹⁶. Si la notion de troubles est également une classification catégorielle, l'athéorisme est par définition contradictoire avec l'hypothèse de causalité étiologique ou physiopathologique inhérente au concept de maladie.

Certes, l'uniformisation de critères diagnostiques a été un apport considérable : les études épidémiologiques faites dans différents pays ont pu être comparées entre elles, les échanges entre scientifiques et entre cliniciens ont été facilités par l'adoption d'un langage commun, etc. Cependant, la démarche consistant à combiner recherche du consensus et athéorisme a rendu les catégories diagnostiques polythétiques¹⁷. La description du trouble "épisode dépressif caractérisé" (voir **Tableau 1**) en est un bon exemple : certains patients peuvent avoir des présentations symptomatiques très différentes (p. ex. avec ou sans tristesse de l'humeur, avec des signes végétatifs typiques ou inversés, une prédominance de l'anhédonie/amotivation, etc.) et pourtant, s'ils satisfont un nombre suffisant de critères, se voir attribuer le même diagnostic. Les conséquences directes sont une hétérogénéité importante, tant au niveau clinique que biologique, et une reproductibilité des diagnostics dans le temps (à la fois en inter- et intra-cotateur) qui est

Tableau 1 : critères diagnostiques d'un épisode dépressif caractérisé (EDC) selon le DSM-5¹⁴

Deux points sont remarquables : 1) le grand nombre de combinaisons de symptômes qui permettent de poser le diagnostic, avec des profils symptomatiques parfois très différents et 2) l'absence de référence à une étiologie ou à un processus physiopathologique, signant le diagnostic de trouble et non de maladie. Tableau issu de Jeanjean, 2020 (thèse d'exercice)¹⁸.

A. Au moins 5 des symptômes suivants doivent être présents pendant une même période d'une durée de 2 semaines et avoir représenté un changement par rapport au fonctionnement antérieur ; au moins un des symptômes est soit 1) une humeur dépressive, soit 2) une perte d'intérêt ou de plaisir. *NB : Ne pas inclure les symptômes manifestement attribuables à une autre affection médicale.*

- 1) Humeur dépressive présente pratiquement toute la journée, presque tous les jours, signalée par le sujet (ex. : se sent vide ou triste ou désespéré) ou observée par les autres (ex. : pleure ou est au bord des larmes). *NB : Éventuellement irritabilité chez l'enfant ou l'adolescent.*
- 2) Diminution marquée du plaisir pour toutes ou presque toutes les activités pratiquement toute la journée, presque tous les jours (signalée par le sujet ou observée par les autres).
- 3) Perte ou gain de poids significatif en absence de régime (ex. : modification du poids corporel en 1 mois excédant 5 %) ou diminution ou augmentation de l'appétit presque tous les jours. *NB : Chez l'enfant, prendre en compte l'absence de l'augmentation de poids attendue.*
- 4) Insomnie ou hypersomnie presque tous les jours.
- 5) Agitation ou ralentissement psychomoteur presque tous les jours (constatés par les autres, non limités à un sentiment subjectif de fébrilité ou de ralentissement intérieur).
- 6) Fatigue ou perte d'énergie presque tous les jours.
- 7) Sentiment de dévalorisation ou de culpabilité excessive ou inappropriée (qui peut être délirante) presque tous les jours (pas seulement se faire grief ou se sentir coupable d'être malade).
- 8) Diminution de l'aptitude à penser ou à se concentrer ou indécision presque tous les jours (signalée par le sujet ou observée par les autres).
- 9) Pensées de mort récurrentes (pas seulement une peur de mourir), idées suicidaires récurrentes sans plan précis ou tentative de suicide ou plan précis pour se suicider.

B. Les symptômes induisent une souffrance cliniquement significative ou une altération du fonctionnement social, professionnel, ou dans d'autres domaines importants.

C. Les symptômes ne sont pas attribuables à l'effet physiologique d'une substance ou d'une autre affection médicale.

D. L'occurrence de l'EDC n'est pas mieux expliquée par un trouble schizo-affectif, une schizophrénie, un trouble schizophréniforme, un trouble délirant, ou un autre trouble psychotique.

E. Il n'y a jamais eu d'épisode maniaque ou hypomaniaque. N.B. cette exclusion ne s'applique pas si tous les épisodes de type maniaque ou hypomaniaque ont été induits par une substance ou sont imputables aux effets physiologiques d'une autre affection médicale.

limitée^{17,19}. L'absence de modèles physiopathologiques pour guider les traitements a conduit à la formulation de recommandations médicales "*one size fit all*" dont l'efficacité est, dans le meilleur des cas, partielle (p. ex. un tiers des patients entre en rémission grâce à un premier antidépresseur et un tiers demeurera résistant après plusieurs essais^{20,21}). Le modèle consensuel, prônant la standardisation à outrance, montre alors ses limites.

1.2 La crise scientifique en psychiatrie

Le réalisme affirme que le monde extérieur est fait d'objets réels soulignés par et obéissant à des liens de causalité réguliers. Selon cette théorie métaphysique, objets et causalité sont réels, qu'ils soient ou non perçus ou compris par l'esprit humain. La façon dont nous percevons et appréhendons le monde est, quant à elle, limitée par nos capacités sensorielles et cognitives, par les outils dont nous disposons et par le filtre culturel par lequel nous interprétons nos perceptions. Par conséquent, nos représentations et notre compréhension sont par nature indirectes, biaisées et intrinsèquement faillibles. Le but de la recherche scientifique, en particulier de la recherche fondamentale, est d'optimiser l'adéquation de ces représentations avec la réalité. Cette optimisation repose sur l'approche hypothético-déductive que nous pouvons décomposer en deux éléments : **1) la boucle hypothético-déductive** qui suppose d'exprimer des conjectures de manière réfutable, c'est-à-dire des hypothèses et des modèles dont on peut déduire des prédictions testables, puis de les remettre en question de manière critique en les confrontant à la réalité²² ; et **2) l'évolutivité des modèles** qui correspond à la possibilité de modifier le modèle initial par les résultats de sa confrontation avec la réalité – par confirmation ou réfutation – et de répéter la boucle hypothético-déductive sur la base du nouveau modèle ainsi obtenu. La progression par l'approche hypothético-déductive,

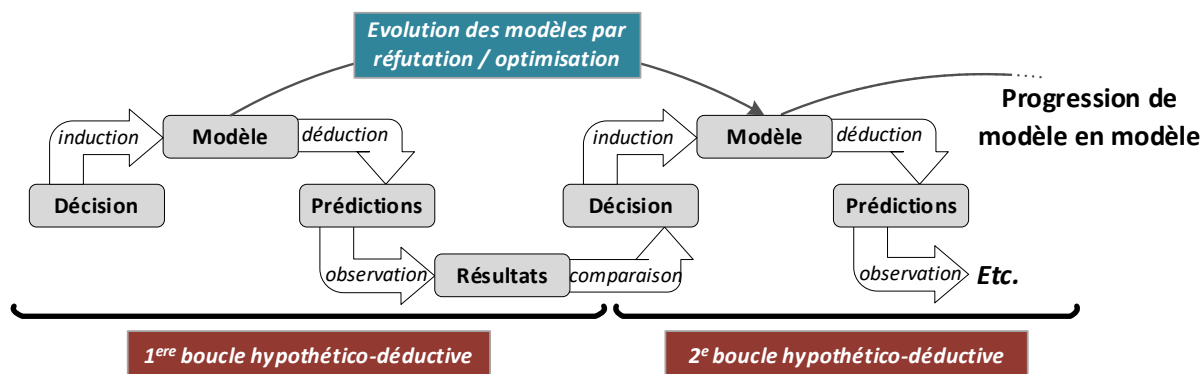


Figure 1 : Illustration schématique de l'approche hypothético-déductive

À chaque **boucle hypothético déductive**, les informations de base permettent d'induire un modèle à partir duquel un certain nombre de prédictions vont être déduites sous la forme d'hypothèses. Les prédictions du modèle sont confirmées, ou non, par l'observation dans un cadre naturel ou expérimental. Ces résultats sont comparés aux prédictions : les prédictions confirmées sont en faveur d'un maintien du modèle et les prédictions infirmées en faveur d'une réfutation. Si le **modèle est évolutif**, il peut être de nouveau évalué et optimisé grâce au déroulement d'une deuxième boucle hypothético-déductive, supposant de nouvelles prédictions, etc. Le cycle vertueux est alors amorcé, sa répétition permet une progression paradigmatique. Figure inspirée et modifiée de Foucher et al. 2010¹⁶.

résultante d'un cycle vertueux au fur et à mesure de l'optimisation des modèles (voir **Figure 1**), permet de tendre à la validation scientifique et à l'identification de phénomènes (c.à-d. qui est susceptible d'acquérir une valeur objective, universelle ou naturelle).

Cette démarche hypothético-déductive s'intègre presque naturellement dans les modèles médicaux habituels : les modèles "maladie". Les modèles à tester sont alors les maladies elles-mêmes, le plus souvent sous la forme d'hypothèses étiologiques et de liens de causalité physiopathologique. Malheureusement, cette intégration n'est pas chose aussi aisée dans un modèle "troubles". Contrairement aux objectifs initiaux, forcer l'athéorisme a éloigné la psychiatrie de cette démarche scientifique. En soit, comment mener une démarche hypothético-déductive sans théorie à confronter à la réalité ? Pire encore, leur caractère consensuel et imposé à tous, notamment pour obtenir des financements de recherche ou pour publier des articles scientifiques, a figé les modèles dans le temps^{23,24} – la seule possibilité

d'évolution étant la révision régulière du consensus, le plus souvent dans la continuité du modèle consensuel qui l'a précédé. Cette progressivité par renouvellement du consensus ne garantit pas non plus de faire appel à la réfutation ou à l'optimisation des modèles fondées sur des résultats. Comment optimiser un modèle de dépression si cette optimisation même doit disparaître par absence de financement du projet de recherche ou par refus de publication des résultats²³ ? En conséquence, ne pouvant s'appuyer sur aucun des deux piliers de l'approche scientifique hypothético-déductive, les modèles "troubles" en psychiatrie peinent à être validés^{16,25}.

1.2.1 L'impact de la crise scientifique en recherche appliquée

La crise scientifique en psychiatrie concerne-t-elle l'ensemble de la recherche sur la pathologie mentale ? Logiquement, elle affecte surtout la recherche fondamentale qui vise à mettre en évidence les phénomènes biologiques étiologiques ou qui participent à la pathophysiologie des pathologies mentales. La recherche appliquée, notamment en thérapeutique, est bien moins affectée. En effet, la pratique de la médecine fondée sur les preuves ne requiert pas nécessairement une compréhension exhaustive des phénomènes biologiques, ni une classification des maladies avec un haut niveau de validité. Au contraire, ces classifications consensuelles ont même été essentielles : l'élaboration de recommandations de bonnes pratiques fondées sur les preuves, compréhensibles et utilisables par tous, nécessite en premier lieu un haut niveau d'harmonisation des concepts et des outils ; cela, même si l'objet d'intérêt est mal défini.

La pratique de l'électroconvulsivothérapie (ECT) nous fournit un exemple de cet intérêt pratique : si l'on s'en tient aux preuves fournies par des études comparatives d'un bon niveau de qualité, nous savons que l'ECT est sûre et efficace pour améliorer la symptomatologie de plusieurs troubles mentaux (dont les troubles de l'humeur, les troubles psychotiques, etc.)^{26,27}. Des recommandations simples, qui permettent aux psychiatres de pratiquer l'ECT en

se basant sur ces preuves et avec un niveau acceptable de sécurité, ont donc été publiées²⁸⁻
³⁰. Pourtant, malgré une progression dans la compréhension des effets biologiques de l'ECT, nous ignorons toujours lequel de ces effets permet de soigner chaque trouble, si chaque patient que nous traitons présente une physiopathologie accessible aux effets de l'ECT, ni même si ce traitement est étiologique ou symptomatique³¹.

1.2.2 Les perspectives scientifiques actuelles

Ce cadre dans lequel évolue la recherche fondée sur les modèles "trouble", symbolisé par le programme de recherche centré sur le DSM, semble donc particulièrement inadapté à la recherche fondamentale sur les pathologies psychiatriques. Lors des travaux préliminaires à la révision 5 du DSM, la question d'une évolution du "programme de recherche DSM" a été soulevée, laissant espérer des changements fondamentaux³². Cependant, la publication du DSM-5 n'a révélé que relativement peu de changements et cette version est demeurée dans la continuité du modèle fondé sur les "troubles"¹⁴. Pourquoi cet immobilisme ? D'une part car l'influence de ce modèle ne se limite pas au monde scientifique et que ses autres utilisateurs (cliniciens, assureurs, décideurs en politique de santé etc.) ont besoin de pouvoir compter sur un cadre conceptuel stable²⁴ ; d'autre part, car, comme nous l'avons vu, ce modèle est adapté à la conduite d'une recherche appliquée. Il est probable qu'un changement radical et brusque risquerait de provoquer des effets contre-productifs. Alternative au changement radical : le développement d'un cadre de recherche alternatif et adapté aux besoins de la recherche fondamentale.

Les *Research Domain Criteria* (RDoCs) constituent l'alternative la plus connue, car développée au sein du *National Institute of Mental Health* (NIMH) des Etats-Unis³³. Les RDoCs se distinguent de deux façons : ils obéissent à une hypothèse normativiste et ils sont organisés en "*constructs*" dimensionnels. L'hypothèse normativiste suppose que les phénomènes, ainsi que leur expression clinique, sont le résultat de l'accumulation de nombreuses causes

mineures, fréquentes et sans interactions entre elles. Dans ce modèle, issu de la psychologie normale, il existe un continuum entre la population normale et les patients : les paramètres (ou dimensions) étudiés seraient distribués normalement et la population "patients" correspondrait aux extrêmes de la courbe de Gauss pour un ou plusieurs de ces paramètres³⁴. La distinction entre normal et anormal – c.à.d. considéré pathologique - est alors définie arbitrairement (typiquement, à 2 déviations standard de la moyenne). Les RDoCs proposent 25 *constructs* psychologiques, organisées selon six domaines sélectionnés par consensus à la fois pour leur pertinence en santé mentale et pour leurs corrélations neurobiologiques potentielles. Ces *constructs* s'inscrivent chacun dans une chaîne causale biologique hiérarchisée : gènes, molécules, cellules, circuits et physiologie. Comme le modèle "troubles", les RDoCs ne sont pas compatibles avec le concept de "maladie" ; non plus, cette fois-ci, par manque d'hypothèse biologique, mais par défaut de différenciation entre normal et pathologique selon un phénomène étiologique ou physiopathologique.

Les RDoCs ont été positivement accueillis par une partie des chercheurs, notamment grâce à la focalisation sur des chaînes de causalité biologiques, ainsi que la prise en compte de l'hétérogénéité au sein des populations non plus comme une limite mais comme un sujet d'étude (ce qui permet d'étudier un *construct* sur l'ensemble du spectre normal-anormal, une approche encore relativement rare)^{24,35}. Certaines limites du modèle troubles demeurent toutefois : si les *constructs* des RDoCs sont susceptibles d'être mis à jour c'est encore par le truchement du consensus et non d'une progressivité basée sur la réfutation ou l'optimisation des modèles eux-mêmes, ce qui en diminue la portée - les projets visant à valider ou réfuter ces *constructs* étant découragés ou non-financés par le NIMH^{36,37}.

1.3 Le rôle des biomarqueurs en psychiatrie

La notion de biomarqueur a été définie comme "une caractéristique qui est objectivement mesurée et évaluée comme un indicateur des processus biologiques normaux, des processus pathogènes ou des réponses [...] à une intervention thérapeutique"³⁸. Dans le domaine médical, on l'assimile couramment à son objectif clinique : il devient alors un biomarqueur diagnostic, de stadification, pronostic, de suivi, etc.^{38,39}. Selon s'il soit associé à l'étiologie, à la physiopathologie ou qu'il soit corrélé à la maladie mais indépendant de la chaîne de causalité physiopathologique, il sera considéré pathogénique primaire, secondaire, ou non-pathogénique⁴⁰.

1.3.1 L'impossible validation directe des diagnostics de troubles par des biomarqueurs

En tant que moyen d'observation des objets réels en pathologie, les biomarqueurs ont une place centrale dans l'application de l'approche hypothético-déductive en recherche biomédicale. Un de leur principaux rôles est de permettre la validation scientifique des modèles pathologiques et, indirectement, de la nosographie. Cette validation suppose deux étapes : **1) une étape corrélationnelle**, pour vérifier si le biomarqueur est effectivement associé au modèle testé (de façon plus ou moins forte, spécifique ou associée à sa sévérité)⁴¹; et **2) une étape de confirmation de la causalité** : s'assurer que l'existence du biomarqueur – reproduite par l'expérimentation – cause la survenue de l'expression clinique de la maladie, confirmant le lien de causalité entre le processus biologique révélé par le biomarqueur et la maladie.

Dans le paradigme biomédical classique, la validation complète d'un modèle diagnostic "maladie" par un biomarqueur n'est possible que si le processus biologique que ce dernier illustre est lié de façon causale au modèle physiopathologique étudié. Pour cela, deux

conditions doivent être remplies : le biomarqueur doit être pathogénique, et il doit exister une hypothèse physiopathologique qui correspond au diagnostic. L'application directe de la validation par les biomarqueurs en psychiatrie se heurte à une importante difficulté : la seconde condition préalable à cette validation n'est pas remplie, par définition, par les diagnostics de troubles¹⁶.

On note que ces contraintes concernent essentiellement les biomarqueurs diagnostics. L'utilisation des biomarqueurs en recherche appliquée, ici encore, moins affectée par ces limitations. En effet, ceux-ci peuvent n'être le reflet de processus biologiques qui n'impliquent pas nécessairement la physiopathologie. De nouveau, la pratique de l'ECT nous fournit un exemple de choix : la survenue d'une activité critique mesurée par un électroencéphalogramme (EEG) lors d'une séance d'ECT est un biomarqueur de l'action biologique de l'ECT qui n'implique pas, ou de façon minimale, la physiopathologie de la maladie traitée⁴². Il est d'ailleurs possible de confirmer à la fois qu'une activité EEG critique est un corrélat obligatoire de la stimulation avec une puissance suffisante et que cette activité EEG est causée par l'ECT. À noter que cet exemple ne nous révèle rien de l'effet thérapeutique de l'ECT : l'activité critique EEG ne serait qu'un corrélat de cet effet.

1.3.2 La place des biomarqueurs dans les classifications consensuelles

Pourtant, les biomarqueurs ont été volontiers mis en avant pour soutenir une validation scientifique des modèles consensuels en psychiatrie. Pour contourner le fait que les troubles mentaux ne remplissent les conditions préalables pour une validation directe par des biomarqueurs, le programme de recherche associé au DSM a proposé de les utiliser comme des validateurs externes⁴³.

La notion de validateurs externes englobe l'ensemble des marqueurs qui sont absents de la définition de plusieurs troubles mais qui, par une distribution différente, marquent la

différence entre ces troubles⁴³. Ces marqueurs peuvent être biologiques, cliniques, épidémiologiques ou associés à la réponse à une intervention thérapeutique.

Contrairement à ce que leur nom de validateur peut laisser entendre, les validateurs externes ne peuvent pas, par nature, valider les diagnostics car ils ne sont liés ni à la définition de la maladie ni à un modèle étiologique ou physiopathologique à tester. Leur rôle est en fait de renforcer la séparation entre des entités – en l'occurrence les troubles mentaux – en mettant en exergue les différences descriptives entre ces entités. Par nature, les biomarqueurs ne peuvent être que des validateurs externes dans le modèle "troubles" – dans la mesure où ils se rapportent à des mécanismes biologiques exclus de la définition desdits troubles.

La façon dont les diagnostics des différents troubles de l'humeur sont, encore récemment, mis en perspective entre eux est particulièrement illustrative : privés d'hypothèses physiopathologiques à tester, les travaux s'attachent à recenser des validateurs externes pour différencier les entités de la CIM ou du DSM⁴⁴⁻⁵⁰. En associant différents moyens d'exploration ou en recourant à l'intelligence artificielle, plusieurs études d'envergure ont même permis d'aller plus loin en soulignant l'hétérogénéité physiologique des patients à l'intérieur même de catégories diagnostiques réputées homogènes^{19,51,52}. Pourtant, malgré la multiplicité des hypothèses, en dépit parfois d'un haut niveau de qualité méthodologique des études, celles-ci ne peuvent aboutir à aucune validation car il s'agit d'une limite intrinsèque au cadre conceptuel.

1.3.3 L'utilisation des biomarqueurs comme vecteurs translationnels : vers la psychiatrie de précision et personnalisée

Dans le paradigme biomédical classique, l'idée maîtresse de la médecine de précision est de considérer les possibilités suivantes : que les patients soient singulièrement différents les uns des autres au sein de catégories consensuelles réputées homogènes, que leurs symptômes soient sous-tendus par des voies physiopathologiques diverses et que ces voies

physiopathologiques doivent être identifiées et traitées de façon ciblée. La psychiatrie de précision est l'application directe de ces principes dans le paradigme psychiatrique actuel, c.a.d. dans le modèle "trouble". La diversité physiopathologique expliquerait la fréquente résistance au traitement standard proposé dans les recommandations de bonne pratique et fondé sur la simple reconnaissance du tableau symptomatique – c.a.d. sur un diagnostic de trouble^{28,53-58}. La psychiatrie de précision s'appuie sur des marqueurs, principalement des biomarqueurs, qui différencient des sous-types de maladies psychiatriques et/ou de sous-population⁵⁹. La prise en charge est différente selon la présence ou non de ces marqueurs. Nous proposons de formuler les hypothèses qui sont faites lors de la pratique de la psychiatrie de précision ainsi : *"Dans une population considérée pathologique ou un sous-groupe au sein de cette population, nous faisons l'hypothèse que tel mécanisme physiopathologique est en jeu, en raison de la présence d'un (bio)marqueur, et nous supposons ce mécanisme pathogénique. Nous faisons aussi l'hypothèse qu'influencer ce mécanisme va avoir un effet sur l'intensité des symptômes ou sur le pronostic du patient"*. Comme les autres domaines en recherche appliquée, la psychiatrie de précision ne nécessite pas de modèle diagnostique validé dans la mesure où elle relève de la médecine basée sur les preuves.

Le terme de psychiatrie personnalisée est souvent considéré comme un synonyme de psychiatrie de précision⁵⁹. Pourtant, une définition alternative pourrait être proposée : l'adaptation d'une prise en charge de précision en considérant les caractéristiques individuelles comme des variables dont il faut aussi tenir compte. Ces caractéristiques peuvent être indépendantes de la pathologie (p.ex. la variabilité anatomique inter-individuelle) ou en relation avec elle (elles sont alors le reflet de la façon dont les processus physiopathologiques sont actifs chez chaque patient). Les identifier peut également faire appel à des biomarqueurs qui ne sont pas diagnostiques, mais physiologiques, et qui doivent nécessairement être mesurables à l'échelle individuelle (c.a.d. par une mesure fiable et reproductible chez chaque patient individuellement).

L'individualisation d'un traitement est également un processus d'adaptation aux caractéristiques individuelles de chaque patient. Cependant, elle peut ne pas reposer sur un modèle physiopathologique validé, mais sur les *a-priori*. Nous aimerions illustrer ce point de vue en faisant appel à un exemple récent : le Stanford Neuromodulation Protocol (SNT), qui vise à prendre en charge la dépression en stimulation magnétique transcrânienne répétitive (rTMS).

Le protocole SNT repose sur l'un des principaux marqueurs d'imagerie identifiés dans le champ de la dépression : l'hyperactivité du cortex cingulaire antérieur subgenuel (sgACC)⁶⁰. Ce biomarqueur a aussi été identifié comme marqueur thérapeutique de l'efficacité de la rTMS dans la dépression : la diminution de l'activité du sgACC est associée à une plus grande efficacité⁶¹. La procédure SNT suppose que la stimulation par rTMS (voir **Figure 2**) d'une région du cortex préfrontal dorso-latéral gauche (DLPFC-G) fortement connectée au sgACC, supposée exercer une influence négative sur l'activité du sgACC, va diminuer l'activité de ce dernier et permettre une réduction des symptômes⁶²⁻⁶⁴. Cette procédure ne relève pas de la psychiatrie de précision dans la mesure où les patients ne sont pas sélectionnés en fonction de l'hyperactivité du sgACC – ils sont supposés la présenter systématiquement. Cependant, elle relève de l'individualisation car la région du DLPFC-G la plus connectée au sgACC chez chaque patient est repérée individuellement et utilisée comme cible en rTMS^{63,65,66}. La distribution spatiale de ce lien de connectivité n'en demeure pas moins une caractéristique physiologique individuelle *a priori* non-pathogénique en elle-même.

Principes de base de la stimulation magnétique transcrânienne (rTMS)

La rTMS est une technique de neuromodulation non-invasive dont le principe est d'appliquer, grâce à une bobine, un champ magnétique variable sur une zone corticale de la taille d'une pièce de monnaie¹. Cette application induit un champ électrique selon le phénomène physique décrit par la loi de Lenz-Faraday.

S'il est suffisamment intense, ce champ électrique peut créer des zones de dépolarisation au niveau axonal et des potentiels d'action. La répétition de ces stimulations – ou *pulses* – va entraîner des phénomènes d'influence à distance, suivant les liens de connectivité fonctionnelle entre la région stimulée et des régions distantes, ainsi que des mécanismes de plasticité susceptibles d'inscrire l'effet de la rTMS dans la durée²⁻⁴.

La rTMS peut activer (ou stimuler) ou inhiber la région ciblée, en fonction de la fréquence de répétition des pulses. On considère qu'une stimulation à haute fréquence (>5 Hz) est activatrice, et qu'une stimulation à basse fréquence (1 Hz) est inhibitrice^{5,6}.

La pratique standard de la rTMS dans la dépression suppose de stimuler le cortex dorsolatéral préfrontal gauche ou d'inhiber la même région à droite. Ces protocoles de soin ont atteint respectivement un niveau de preuve A et B pour la prise en charge de la dépression⁷.

Figure 2 : informations générales sur la stimulation magnétique transcrânienne

1 Deng, Z.D et al. (2013) ; 2 Huang et al. (2017) ; 3 Lefaucheur et al. (2012) ; 4 Eldaief et al. (2011) ; 5 Maeda et al. (2000), 6 Noda et al. (2015) ; 7 Lefaucheur et al. (2020) ; les références sont détaillées dans la section "références".

1.4 Plan de thèse

Ce rapport de thèse est constitué de plusieurs articles rapportant les résultats de travaux locaux visant le développement de biomarqueurs en psychiatrie et leur utilisation pour optimiser les soins dans la dépression, moyennant le développement de solutions techniques dédiées. Ces travaux ont été réalisés entre 2019 et 2022 dans deux hôpitaux intimement liés à l'activité de recherche (le Centre Hospitalier de Rouffach et les Hôpitaux Universitaires de Strasbourg) et au sein du laboratoire ICUBE (UMR CNRS 7357) à Strasbourg. Ma participation à ces activités de recherche était initialement motivée par une question relativement générale et naïve : *quel est le substrat biologique de la maladie mentale, en particulier des troubles de l'humeur, dont souffre le patient en face de moi et comment puis-je m'appuyer dessus pour prodiguer des soins ?* Après les premières expériences (cf. articles 1 et 2), forcé de constater que la confrontation du cadre conceptuel usuel, le modèle "troubles", avec la réalité ne permettait pas d'obtenir de réponse évidente. Il fallait donc que je révise mon propre modèle et ma question. En fait, cette dernière a plutôt été complétée par une autre : *de quels outils conceptuels ou techniques ai-je besoin pour répondre au mieux à mes questions initiales ?* Bien entendu, je ne saurais prétendre pouvoir répondre définitivement à ces questions dans ce travail de thèse. Mes lecteurs, qui ne seront probablement pas surpris, devront me pardonner un sentiment de frustration que je partage (mais qui, et j'en suis persuadé, doit nous pousser à continuer chercher ces réponses). Toutefois, je pense que ces travaux, qui portent sur des thèmes variés, permettent d'apporter quelques éléments d'orientation : le rapprochement avec le paradigme biomédical classique, la validation de l'intérêt d'un biomarqueur par des soins qui ne s'appuient pas sur la notion de catégorisation des patients – introduisant la notion d'individualisation – et une modélisation de la neurophysiologie et de la pathophysiologie qui repose sur les neurosciences des systèmes.

Initialement, nous faisons l'hypothèse que certains biomarqueurs permettraient à la fois d'éclairer les mécanismes physiopathologiques des troubles mentaux et de faciliter le

diagnostic. Les pathologies psychiatriques, dont les troubles de l'humeur, sont régulièrement associées à des anomalies neuroendocrines, ce qui a permis le développement de la psychoneuroendocrinologie⁶⁷⁻⁷⁰. Parmi les outils que cette discipline nous offre, on trouve un panel de tests dits de stimulation neuroendocrinienne, réputés plus performants que de simples dosages plasmatiques. qui pourraient constituer des biomarqueurs diagnostiques et thérapeutiques⁶⁹. Chacun suppose la stimulation d'un axe neuroendocrinien spécifique et est associé à l'exploration d'un système biologique (les neurotransmissions dopaminergique et noradrénergique, les axes thyroïdien et hypothalamo-hypophysaire corticotrope, etc.)⁶⁹. Dans les deux premiers articles de ce corpus, nous présenterons les résultats d'études au cours desquelles nous avons utilisé les tests comme biomarqueurs diagnostiques. Au cours de ces études, nous avons cherché à différencier plusieurs troubles mentaux (à savoir les troubles dépressifs, psychotiques et schizo-affectifs, selon le DSM-IV-TR)^{71,72}, puis à caractériser profil neuroendocrinien d'une population réputée homogène (trouble dépressif selon le DSM-IV-TR)^{72,73}. Nos résultats ont montré que ces biomarqueurs neuroendocriniens transcendaient les limites établies par le modèle "trouble" : certaines caractéristiques étaient transdiagnostiques et l'étude de la population supposée homogène a révélé plusieurs profils différents.

La troisième étude a marqué une évolution conceptuelle significative par rapport aux précédentes. Cette évolution s'associe à une modification de l'hypothèse : nous supposons alors que faire appel à un cadre conceptuel proche du paradigme biomédical classique permettrait de mettre en évidence un biomarqueur diagnostique individuel en imagerie. En effet, nous avons fait le choix de nous émanciper du modèle consensuel pour nous approcher d'une autre classification catégorielle qui nous a semblé plus proche du modèle "maladie" : la classification de Wernicke-Kleist-Leonhard (WKL)⁷⁴. L'objectif de cette étude était d'explorer les performances de l'*arterial spin labelling* (ASL) en tant que biomarqueur diagnostique de la catatonie périodique (KP). La KP est un phénotype de psychose dont la présentation initiale

peut se confondre avec celle de la dépression et dont la physiopathologie était supposée être une atteinte du système psychomoteur. Dans cette étude, nous proposons d'utiliser l'ASL, une technique d'imagerie par résonance magnétique fonctionnelle (IRMf) qui permet l'estimation du débit sanguin régional cérébral (*regional cerebral blood flow*, rCBF), comme biomarqueur⁴⁰. Le protocole d'imagerie développé au sein de notre laboratoire a permis de confirmer que les modifications de rCBF en lien avec la pathologie étaient mesurables de façon fiable et à l'échelle du patient unique. De plus, ces modifications se trouvaient dans une région connue pour son implication dans le système psychomoteur, offrant un argument en faveur de la définition de la KP comme "maladie". En sus de ses résultats directs, cette étude a montré que notre protocole d'imagerie pouvait fournir une information spatiale précise qui tient compte à la fois de caractéristiques propres au patient (anatomie structurelle et fonctionnelle) et de la maladie. Ce faisant, elle confirmait la possibilité d'identifier, grâce à l'ASL, des cibles potentiellement accessibles en rTMS.

La rTMS est une technique de stimulation par nature focale, mais sa précision est limitée par la méthode de réalisation. En effet, les protocoles de soins actuels utilisent des repères externes pour positionner la bobine, tenant peu compte de la variabilité inter-individuelle anatomique et fonctionnelle. De plus, les mouvements du patient lors d'une session de rTMS facilitent la dispersion de la stimulation. Les progrès que nous avons obtenus en imagerie laissaient entrevoir la possibilité de guider précisément la rTMS. Encore fallait-il s'assurer que la stimulation fût bien délivrée à l'endroit désigné. La combinaison d'un neuronavigateur et d'une assistance robotique offrait la possibilité de placer précisément la bobine de stimulation en regard d'une cible identifiée en imagerie et de la maintenir en place pendant la séance^{75,76}. Le quatrième article de ce corpus a pour objectif d'évaluer les performances de cet outil grâce à un modèle basé sur la cartographie du cortex moteur et l'estimation des champs électriques induits par la rTMS⁷⁷. Recourir à une assistance robotique pour le placement de la bobine a permis d'améliorer sensiblement la précision et la fiabilité de la rTMS, mais les simulations ont

montré des corrélations inattendues entre les champs induits quand la rTMS était robotisée. Ces connaissances nous ont permis d'améliorer notre connaissance de l'outil, en identifiant un possible biais lié à la robotisation. Cette étude nous a offert le socle de connaissances non seulement pour réaliser des soins en rTMS de précision mais aussi pour préparer des études de neurophysiologie utilisant la cartographie pour étudier l'inhibition intercorticale au sein certains systèmes neurologiques, en particulier psychomoteurs.

Déterminer un biomarqueur en ASL dans une population que nous supposions déjà très hétérogène, la population dépressive, nous a obligé à effectuer une démarche différente que pour la KP. Les mesures individuelles en ASL ont montré une hétérogénéité encore plus importante que celle à laquelle nous nous attendions. Nous faisons l'hypothèse qu'il s'agissait tout de même d'un biomarqueur impliqué dans la physiopathologie des différents types de dépression. Mais comment s'en assurer ? Grâce au développement parallèle de la rTMS de précision, il devenait possible d'optimiser la rTMS en utilisant l'estimation du rCBF de chaque patient individuellement. Nous avons proposé d'utiliser comme cibles les anomalies de rCBF repérées chez chaque patient individuellement grâce à l'ASL, et de les "rééquilibrer" – soit en stimulant les régions hypoperfusées ou en inhibant les régions hyperperfusées. L'étude *iADAPT (Imagery guided Anti-Depressive Adaptive Personalized TMS, NCT02863380)*, objet du cinquième article de ce corpus, constitue l'application de cette approche dans le champ de la dépression⁷⁸. Les résultats ont montré qu'optimiser la rTMS à partir d'images ASL et en utilisant la précision offerte par la robotisation permet d'obtenir un effet spécifique et qui est observable à la fois en imagerie et au niveau clinique. Ces résultats étaient en faveur d'un lien entre le biomarqueur et la physiologie dépressive, malgré l'apparente hétérogénéité et le risque qu'il ne puisse s'agir que de bruit. Cette approche thérapeutique individualisée était différente de l'approche de précision et de la personnalisation dans la mesure où la notion de classification selon le biomarqueur n'intervenait pas. Pour comprendre ce biomarqueur, et peut être un jour valider des modèles diagnostiques grâce à lui, il nous reste encore à effectuer

une démarche de phénotypage inverse : analyser les données individuelles pour identifier des regroupements qui peuvent être intégrés dans un modèle maladie.

2 Articles

2.1 Article 1 : Dopaminergic, Noradrenergic, Adrenal, and Thyroid Abnormalities in Psychotic and Affective Disorders



Dopaminergic, Noradrenergic, Adrenal, and Thyroid Abnormalities in Psychotic and Affective Disorders

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Background: This study aimed to assess hypothalamic-pituitary dopaminergic (DA), noradrenergic (NA), thyroid (HPT), and adrenal (HPA) activity in schizophrenia, in schizoaffective disorder, and in bipolar disorder.

Method: We investigated a combined approach of hormone responses to (1) apomorphine (APO), a short-acting DA receptor agonist which decreases prolactin secretion (PRL), and stimulates secretion of growth hormone (GH), adrenocorticotropin (ACTH), and cortisol; (2) clonidine (CLO), an alpha 2-adrenoceptor agonist which stimulates GH secretion; (3) 8 AM and 11 PM protirelin (TRH) which stimulates thyrotropin (TSH) secretion; and (4) dexamethasone which suppresses cortisol secretion, in 13 hospitalized healthy male controls and 39 untreated male inpatients: 13 with DSM-IV paranoid schizophrenia, 13 with DSM-IV schizoaffective disorder (bipolar subtype, depressed at the time of the study), and 13 with DSM-IV bipolar disorder (depressed).

Results: Compared to controls, paranoid schizophrenic patients showed (1) lower APO-induced ACTH and cortisol stimulation, and (2) higher post-dexamethasone cortisol values. Compared to controls, schizoaffective and bipolar patients showed (1) lower $\Delta\Delta$ TSH values (i.e., difference between 11 PM and 8 AM TRH-TSH responses), (2) lower APO-induced PRL suppression, (3) lower CLO-induced GH stimulation, and (4) higher post-dexamethasone cortisol values.

Conclusions: Although results must be interpreted with caution because of the small sample, this preliminary study suggests that depressed bipolar and schizoaffective patients share common biological dysregulations, distinct from that of paranoid schizophrenic patients. From a pathophysiological viewpoint, paranoid schizophrenic patients can be characterized by hyposensitivity of the hypothalamic DA receptors (possibly resulting from an increase in presynaptic DA release) associated with increased HPA axis activity, while depressed bipolar and schizoaffective patients can be characterized by hyposensitivity of the pituitary TRH and DA-D₂ receptors (possibly linked

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to the activation of the hypothalamic TRH and tuberoinfundibular DA neurons, respectively), together with subsensitive postsynaptic α_2 -adrenoreceptors at the hypothalamic level (possibly secondary to an erratic release of NA) and increased HPA axis activity.

Keywords: schizophrenia, bipolar disorder, schizoaffective disorder, apomorphine challenge, clonidine challenge, TRH test, dexamethasone suppression test

INTRODUCTION

It is now well established that the secretion of the hypothalamic hypophysiotropic hormones is controlled by neurotransmitters posited to play a preeminent role in the pathophysiology of major psychiatric disorders such as schizophrenia (SCH), schizoaffective disorder (SAD), and bipolar disorder (BD) (1, 2). Moreover, significant progress over the last decades has also demonstrated that neuropeptides and neurohormones may be directly involved in numerous mental illnesses [for a review, see (3)]. Thus, the neuroendocrine strategy can characterize the hypothalamic-pituitary dysfunction of affective and psychotic diseases, and assess the functionality of some neurotransmitter systems by using suitable pharmacological stimuli. To evaluate the DA function in psychiatric patients, several studies have used subcutaneous administration of apomorphine (APO), a non-selective short acting dopamine (DA) agonist (4). APO inhibits prolactin (PRL) secretion and stimulates adrenocorticotrophic hormone (ACTH), cortisol, and growth hormone (GH) release (4–6). In drug-free SCHs, it has been consistently found blunted hypothalamic-pituitary-adrenal (HPA) axis responses to APO compared to controls (5–8); this blunting may reflect a hyposensitivity of the hypothalamic DA receptors in SCHs. Lower responsiveness of cortisol to APO has also been found in SADs (5); but not in depressed BDs (9). Regarding GH and PRL responses to APO, contradictory results have been reported in SCHs and SADs (4–11). However, some studies found lower APO induced-PRL suppression in depressed BDs compared to healthy controls and unipolar depressed patients (9, 12). Interestingly, it has been reported in patients with major unipolar depressive disorder with HPA axis overactivity and melancholic and psychotic features altered ACTH/cortisol and GH responses to APO (13). These latter findings are in line with the hypothesis that hypercortisolemia by increasing DA release may induce a hyposensitivity of hypothalamic DA receptors (14).

Measurement of GH levels following administration of clonidine (CLO)—a partial α_2 -adrenoceptor agonist—has been widely used in the evaluation of noradrenergic (NA) α_2 -receptor function in psychiatric patients (15). In depressed patients and in SADs, GH response to CLO is often blunted (9, 15, 16)

Abbreviations: ACTH, adrenocorticotrophic hormone; APO, apomorphine; BD, bipolar disorder; CLO, clonidine; DA, dopamine; DST, dexamethasone suppression test; GH, growth hormone; HPA, hypothalamic-pituitary adrenal (axis); HPT, hypothalamic-pituitary thyroid (axis); 5-HT, serotonin (5-hydroxytryptamine); NA, noradrenaline; PRL, prolactin; SAD, schizoaffective disorder; SCH, schizophrenia; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

suggesting a hyposensitivity of hypothalamic α_2 -adrenoceptors (15). In SCH, GH response to CLO differs from study to study: increased, decreased, or unchanged responses have been reported [for review, see (3)].

Overactivity of the HPA axis, and increased levels of cortisol, is one of the most replicated biological findings in severe depressed patients (17). However, hyperactivity of the HPA axis is not specific to depression since it has also been found in SCH and SAD (18, 19). Although, the mechanisms underlying this abnormality are not fully understood, the most striking feature is that type II glucocorticoid receptor (GR)-mediated feed back inhibition is impaired—as reflected by a nonsuppression or an early escape of serum cortisol levels in response to the dexamethasone suppression test (DST) (20).

Many euthyroid major depressed inpatients display a chronobiological HPT axis dysregulation (i.e., loss of the nocturnal surge of thyrotropin [TSH], blunted 11 PM TSH response to protirelin [TRH] test, and reduced difference between 11 PM and 8 AM TRH-TSH responses [$\Delta\Delta$ TSH] (21), possibly associated with abnormal morning TRH-TSH response and/or alterations in total and/or free thyroxine (T_4) and triiodothyronine (T_3) serum concentrations (22). Chronobiological dysregulation of the HPT axis (as reflected by reduced $\Delta\Delta$ TSH values) has rarely been found in SCHs, while it has been reported quite comparable rates of reduced $\Delta\Delta$ TSH values in SADs, unipolar, and BD depressed patients (9).

In the present study, we used a series of five neuroendocrine challenges (APO test, CLO test, 8 AM and 11 PM TRH tests, overnight DST) and examined nine hormonal responses in a population of 52 male drug-free hospitalized subjects. Our aim was to identify response patterns in order to provide some indication of altered central nervous system function in patients with psychotic and affective diseases.

MATERIAL AND METHODS

Participants

Thirty-nine drug-free male inpatients, without a history of suicidal behavior, and 13 healthy male hospitalized control (HC) subjects participated in this study. Patients were recruited from the inpatient units of the Pole 8/9 of the Centre Hospitalier of Rouffach (France). All subjects underwent a standard clinical interview and a semi-structured diagnostic interview [Schedule for Affective Disorder and Schizophrenia-Lifetime Version (23)]. Patients were independently classified according to the Diagnostic and Statistical Manual of Mental

Disorders (DSM-IV) (24) criteria by two psychiatrists, blind to the results of neuroendocrine investigations. The patient group consisted of 13 paranoid SCHs, 13 SADs (bipolar subtype, depressed at the time of the study), and 13 BDs (type II, depressed at the time of the study). Before testing, inpatients were medication-free for at least 2 weeks. The intensity of clinical symptoms was evaluated with the Brief Psychiatric Rating Scale (BPRS, 18-item). The control group consisted of 13 hospitalized normal male volunteers without a personal or family history of major psychiatric illness; none of them met criteria for Axis I diagnostic or had been previously treated with psychotropic medications. This study was approved by the local ethical committee (Rouffach Hospital Review Board), and was conducted in accordance with the Declaration of Helsinki. All subjects gave their informed consent prior to participation.

Routine physical examination and laboratory tests were performed in all subjects. None had a history of endocrinopathy, major medical illness, acute weight change (all were within 15% of ideal body weight), alcohol, or substance abuse. All subjects had basal PRL, TSH, FT₄, and FT₃ values within the normal range. No patient had received long-acting neuroleptics, electroconvulsive therapy, lithium salts, fluoxetine, or monoamine oxidase inhibitor antidepressants within 2 years of testing. All subjects were on a caffeine-restricted diet for at least three days before testing and their environment was synchronized, with diurnal activity from 8 AM to 11 PM, and nocturnal rest (sleep).

Procedures

To reduce bias due to interferences between the tests, the order of the tests was carefully determined. Two TRH-TSH stimulation tests were carried out at 8 AM and 11 PM (day 1), using 200 µg of synthetic TRH IV (Stimu-TSH, Laboratoires Roussel, Paris, France) (25). This procedure has the advantage to take into account the circadian activity of the HPT axis, which is maximal during night. After an overnight fast, subjects were awoken at 7 AM. An indwelling cannula was inserted into an antecubital arm vein and kept open with a slow infusion of 0.9% saline. Baseline blood samples for levels of TSH were collected at -15 and 0 min. The first TRH-TSH stimulation test was carried out at 8 AM, and blood samples were taken after 15, 30, and 60 min. The second TRH-TSH test was performed at 11 PM, on the same day, using the same procedure; subjects were awake during the sampling and fasting from 6 PM. The DST was carried out at midnight with oral ingestion of 1 mg of dexamethasone (Dectancyl, Laboratoires Roussel, Paris, France), followed by blood samples drawn for the assay of serum cortisol at 8 AM, 4 PM, and 11 PM the next day (day 2) (26).

On day 4, an APO test (SC injection of 0.75 mg Apokinon, Laboratoires Aguettant, France) (10) and on day 8, a CLO test (0.375 mg of Catapressan[®], given orally, Laboratoires Boehringer Ingelheim, France) (27) were carried out at 9 AM, after an overnight fasting, according to the same sampling procedure. Subjects were awoken at 7 AM, and a cannula was inserted into an anterior forearm vein. Blood was drawn at -30, -15, and 0 min before APO or CLO administration and further samples for the assay of GH (following APO and CLO), and PRL, ACTH,

cortisol (following APO) were collected at 15, 30, 60, 90, 120, and 150 min. Throughout the tests subjects were in bed and did not smoke.

Assays

Blood samples were centrifuged at 3,000 rpm and 4°C, and the serum separated and stored at -20°C until assay. All hormone concentrations were determined by immunoassay techniques based on enhanced luminescence (13). The ACTH assay (Nichols Advantage[®] ACTH, Nichols Institute Diagnostics, San Juan Capistrano, CA) had intra-assay and inter-assay coefficients of variation of 2.7%–7.9% respectively; the sensitivity was 1 ng/l. The GH assay (Nichols Advantage[®] hGH, same supplier) had intra-assay and inter-assay coefficients of variation of 3.9%–7.5% respectively; the sensitivity was 0.1 µg/l. The TSH assay (Amerlite TSH-60 Assay, Amersham International plc, Amersham, UK) had intra-assay and inter-assay coefficients of variation of 5.1%–7% respectively; the sensitivity was less than 0.04 mU/l. The FT₄ assay (Amerlite FT₄ Assay, same supplier) had intra-assay and inter-assay coefficients of variation of 5.1%–5.3% respectively; the sensitivity was 0.5 pmol/l. The FT₃ assay (Amerlite FT₃ Assay, same supplier) had intra-assay and inter-assay coefficients of variation of 6.0%–8.0% respectively; the sensitivity was less than 0.5 pmol/l. The prolactin assay (Amerlite Prolactin Assay, same supplier) had intra-assay and inter-assay coefficients of variation of 5.5%–6%, respectively; the sensitivity was less than 1.3 µg/l.

The cortisol assay (Amerlite Cortisol Assay, same supplier) had intra-assay and inter-assay coefficients of variation of 6.2%–8.9%; the sensitivity was less than 3 nmol/l.

Statistical Analysis

Hormonal concentrations at 0 min, immediately before SC injection of APO, were used to define baseline values of PRL, ACTH, and cortisol (i.e., PRL_{BL}, ACTH_{BL}, and cortisol_{BL}) (5). ACTH and cortisol responses were determined for each subject by subtracting the baseline level from the peak level after APO (i.e., ΔACTH and Δcortisol). The PRL response to APO was expressed as percentage of change from baseline according to the formula: $PRL_S = (PRL_S AUC / PRL_{BL} AUC) \times 100$ (10) in which PRL_{BL}AUC is the basal PRL area under the curve (calculated as follows: PRL_{BL} × 150 min), and PRL_SAUC is the PRL suppression area (defined as the difference between PRL_{BL}AUC and PRL_{AUC} after APO). GH values from time points -30, -15, and 0 min were averaged to obtain a single baseline value before APO (GH_{APO}BL) and CLO (GH_{CLO}BL) stimulation tests. To be included in this research, subjects had to have, before APO and CLO, a GH_{BL} value < 2 µg/l. The maximum GH responses to APO and CLO (ΔGH_{APO} and ΔGH_{CLO}, respectively) were determined for each subject by subtracting the baseline GH level from the peak GH level. The mean of the two TSH values, at -15 and 0 min, was calculated to give baseline TSH (TSH_{BL}) value. The maximum TSH response (ΔTSH) was determined by subtracting TSH_{BL} level from the peak TSH level after TRH injection; ΔΔTSH was defined as the difference between 11 PM-ΔTSH and 8 AM-ΔTSH values. To evaluate the cortisol response to DST we used the maximum

cortisol level after DST in any blood sample obtained at 8 AM, 4 PM, and 11 PM on day 2 (26).

Analyses were performed using StatView software version 5.0 (SAS Institute Inc, Cary NC, USA). Given the small sample size, non-parametric statistical methods were employed. The comparisons between different patient groups and the control group were performed using the Mann-Whitney two-tailed test (U test)—formal corrections for multiple comparisons were not needed since we made planned comparisons. Within-group differences were tested by the Wilcoxon two-tailed signed rank test (T test) for paired data. Correlations between quantitative variables were estimated using the Spearman rank coefficient (Δ). We used receiver operating characteristic (ROC) curves to determine thresholds of abnormal results (28). Categorical data were analyzed with either Fisher’s exact test (two-tailed) or Yates’ χ^2 -test. Results were considered significant when $p \leq 0.05$.

Results

Table 1 displays the demographic data and the main results of the DST, TRH, APO, and CLO tests for patients and HCs. Patients and HCs were comparable for age. Basal hormone values were not different across diagnostic groups of subjects. BDs had lower BPRS scores (mean \pm SD, 44.6 ± 12.1) than SCHs (54.9 ± 14.9) and SADs (52.7 ± 15.6) ($p < 0.05$ by U test).

Apomorphine Test

PRL Levels

There was no age effect for PRLBL and PRLs values. Compared with HCs, PRLs values were lower in SADs and BDs, while in

SCHs the difference was not significant. PRLs values were neither influenced by PRLBL levels nor by HPA axis activity (i.e., cortisol at baseline and following DST). As illustrated in **Figure 1A**, 3 SCHs (23%), 7 SADs (54%), 8 BDs (61%), and 1 HC (8%) exhibited a PRLs value below 25%. SADs and BDs showed more frequently blunted PRLs values than HCs ($p = 0.03$ and $p = 0.01$, respectively, by Fisher’s exact test). The distribution was not significantly different between SCHs and HCs ($p > 0.30$ by Fisher’s exact test).

ACTH Levels

ACTH values were not related to age. The ACTH response to APO was not correlated with ACTHBL levels. Compared with HCs, Δ ACTH values (**Figure 1B**) were lower in SCHs, while in SADs and BDs Δ ACTH values were not significantly different. Owing to a wide variation of Δ ACTH values, no meaningful threshold for a blunted response could be defined.

Cortisol Levels

CortisolBL and Δ Cortisol values were not influenced by age. Δ Cortisol values were lower in SCHs than in HCs. In SADs and BDs, Δ Cortisol levels were not significantly altered. Cortisol response to APO was unrelated to the HPA axis activity, as evaluated by cortisol values at baseline and following DST. We found a positive correlation between Δ Cortisol and Δ ACTH values in the overall population ($\rho = 0.75$; $n = 52$; $p < 0.00001$), in SCHs ($\rho = 0.78$; $n = 13$; $p = 0.006$), in SADs ($\rho = 0.68$; $n = 13$; $p = 0.01$), in BDs ($\rho = 0.69$; $n = 13$; $p = 0.01$), and in HCs ($\rho = 0.88$; $n = 13$; $p = 0.002$). As shown in **Figure 1C**, 7

TABLE 1 | Demographic characteristics and biological data for normal controls and patients.

	Control subjects(n =13)	Schizophrenic patients(paranoid subtype)(n=13)	Schizoaffective patients(bipolar subtype)(n=13)	Bipolar patients (depressed)(n=13)
Age, years ^a	33.2 \pm 9.2	31.1 \pm 10.3	32.3 \pm 10.8	34.3 \pm 10.8
Apomorphine test				
PRLBL (μ g/l)	9.2 \pm 5.2	7.0 \pm 3.5	8.7 \pm 4.4	7.7 \pm 3.3
PRLs (%)	40 \pm 16	35 \pm 15	24 \pm 18*	19 \pm 10**
ACTHBL (ng/l)	27.5 \pm 18.9	25.7 \pm 16.1	28.1 \pm 15.5	27.2 \pm 11.2
Δ ACTH (ng/l)	50 \pm 74	12.5 \pm 26*	51 \pm 50	23 \pm 38
CortisolBL (nmol/l)	257 \pm 75	343 \pm 150	332 \pm 103	243 \pm 81
Δ Cortisol (nmol/l)	154 \pm 160	26 \pm 112*	126 \pm 155	107 \pm 106
GHBL (μ g/l)	0.4 \pm 0.3	0.7 \pm 0.5	1.0 \pm 0.8	0.5 \pm 0.4
Δ GH (μ g/l)	16.6 \pm 9.4	15.9 \pm 21.0	20.2 \pm 17.0	14.3 \pm 8.7
Clonidine test				
GHBL (μ g/l)	0.4 \pm 0.3	0.6 \pm 0.3	0.5 \pm 0.4	0.4 \pm 0.3
Δ GH (μ g/l)	17.4 \pm 7.8	15.5 \pm 19.4	7.5 \pm 10.3**	9.2 \pm 8.3*
TRH tests				
8 AM-FT4BL (pmol/l)	14.9 \pm 3.9	15.1 \pm 4.2	14.6 \pm 4.0	14.3 \pm 4.1
8 AM-FT3BL (pmol/l)	5.1 \pm 0.8	5.2 \pm 0.9	5.3 \pm 0.8	5.5 \pm 0.7
8 AM-TSHBL (mU/l)	1.13 \pm 0.45	1.30 \pm 0.69	1.27 \pm 0.50	1.25 \pm 0.58
8 AM- Δ TSH (mU/l)	6.6 \pm 3.3	6.6 \pm 3.8	5.7 \pm 2.5	7.4 \pm 3.2
11PM-TSHBL (mU/l)	1.23 \pm 0.72	1.39 \pm 0.80	1.18 \pm 0.52	0.99 \pm 0.55
11 PM- Δ TSH (mU/l)	10.4 \pm 4.1	10.4 \pm 4.8	7.2 \pm 2.4*	8.2 \pm 3.4
$\Delta\Delta$ TSH (mU/l)	3.8 \pm 1.4	3.8 \pm 2.3	1.4 \pm 1.3**	0.7 \pm 1.4***
Post-dexamethasone				
Maximum Cortisol (nmol/l)	26 \pm 15	86 \pm 124*	64 \pm 67*	71 \pm 91**

^aValues are mean \pm SD. PRL indicates, prolactin; ACTH, adrenocorticotropin hormone; GH, growth hormone; TSH, thyrotropin; BL, basal concentration; PRLs, prolactin suppression; Δ , peak concentration minus basal concentration; $\Delta\Delta$ TSH, 11- Δ TSH minus 8 AM- Δ TSH.

Comparisons between control and patient groups were tested by U test (two-tailed): * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

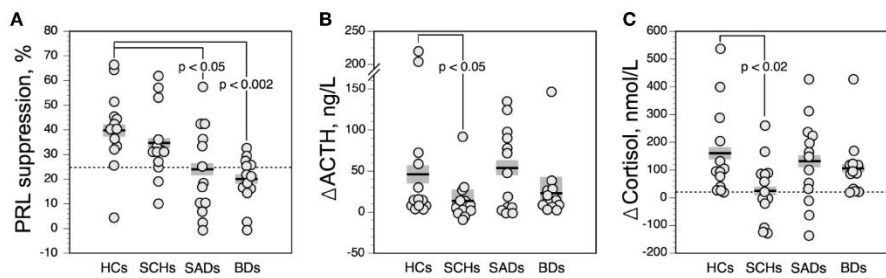


FIGURE 1 | Prolactin suppression (A), and maximum increment in serum adrenocorticotrophic hormone (ACTH) (B), and cortisol (C) above baseline after 0.75 mg SC of apomorphine in controls and patients. The solid horizontal lines indicate the group mean; the shaded areas represent \pm SEM. HCs, healthy control subjects; SCHs, patients with paranoid schizophrenia; SADs, patients with schizoaffective disorder; BDs, patients with bipolar depression.

SCHs (54%), 3 SADs (23%), 3 BDs (23%), and 1 HC (8%) exhibited a Δ Cortisol value below 20 nmol/l. While the distribution of blunted cortisol responses was similar in SADs and BDs and did not differ significantly from HCs, blunted cortisol responses were more frequent in SCHs than in HCs ($p = 0.03$ by Fisher’s exact test).

GH Levels

Δ GH_{APO} values did not differ across patients and controls, and were unrelated to age. APO-GH responses were not significantly correlated with GHBL levels. Interestingly, Δ GH_{APO} values were positively correlated with Δ ACTH and Δ Cortisol values in the whole population ($\rho = 0.44$; $n = 52$; $p = 0.001$ and $\rho = 0.31$; $n = 52$; $p = 0.02$, respectively), whereas such a correlation was not found significantly in HCs or in patients. When using a Δ GH_{APO} value of less than 6 μ g/l to define a blunted response, 6 SCH (46%), 4 SADs (31%), 2 BDs (15%), and 1 HC (8%) showed blunted responses. Compared to HCs, there was a trend towards increased frequency of blunted GH_{APO} response in SCHs ($p = 0.07$ by Fisher’s exact test).

Clonidine Test

The GH responses to CLO were not influenced by GHBL values. GHBL and Δ GH_{CLO} values were not significantly correlated with age in our population. **Figure 2A** shows the time courses of serum GH in the 4 diagnostic groups. Δ GH_{CLO} values were lower in SADs and BDs than in HCs (**Figure 2B**). No such difference was observed between SCHs and HCs. Δ GH_{CLO} and Δ GH_{APO} values were not significantly correlated in the total sample, in patients and in HCs. When using a value of less than 8 μ g/l to define a blunted Δ GH_{CLO}, 4 SCH (31%), 8 SADs (61%) and 7 BDs (54%) had blunted responses; none were noted in HCs. Blunted GH_{CLO} response was more frequent in SADs and BDs than in HCs ($p = 0.01$ and $p = 0.03$ respectively, by Fisher’s exact test), in SCHs the frequency did not reach statistical significance ($p = 0.09$ by Fisher’s exact test).

Protirelin (TRH) Tests

The effect of age was not significant for FT4, FT3, and TSH values (TSHBL, Δ TSH, $\Delta\Delta$ TSH). As illustrated in **Figure 3A**, Δ TSH values were higher in the evening than in the morning in

HCs, SCHs and SADs (all $p < 0.005$ by T test). In BDs, this increment was not significant ($p = 0.09$ by T test). TRH-TSH responses (i.e., 8 AM- Δ TSH and 11 PM- Δ TSH), when compared with HCs, were not different in SCHs and BDs. In SADs, however, 11PM- Δ TSH values were lower than in HCs. When using an 11PM- Δ TSH value below 6.5 mU/l to define a blunted response, 6 SADs (46%) and 6 BDs (46%) (both $p = 0.07$ by Fisher’s exact test, when compared with HCs); 3 SCHs (23%) and 1 HC (8%) exhibited a blunted response. As shown in **Figure 3B**, $\Delta\Delta$ TSH values were reduced in SADs and BDs, while SCH showed similar $\Delta\Delta$ TSH values than HCs. Moreover, 12 SADs (92%) and 13 BDs (100%)—while only 2 SCHs (15%) and 1 HC (8%)—exhibited a $\Delta\Delta$ TSH value below 2,5 mU/l. Rates of reduced $\Delta\Delta$ TSH values were comparable in SADs and BDs and were higher than in HCs and SCHs (all $p < 0.0003$ by Fisher’s exact test).

Dexamethasone Suppression Test

Post-DST cortisol values were not influenced by age. Compared with HCs, post-DST cortisol levels were higher in patients. However the incidence of nonsuppression of cortisol after dexamethasone [i.e., highest post-DST cortisol level > 130 nmol/l (13)] was rather low: DST nonsuppression was

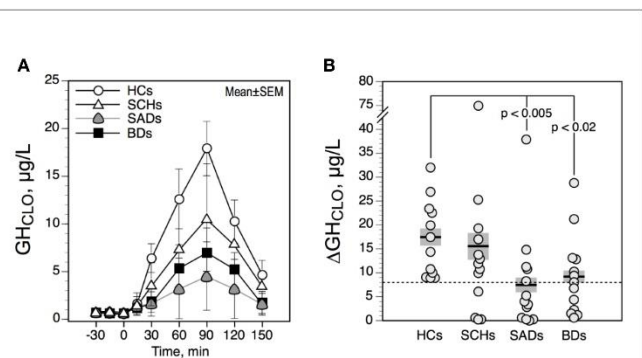


FIGURE 2 | Time course (A) and maximum increment (B) in serum growth hormone (GH) above baseline after 0.375 mg of clonidine PO in controls and patients. The solid horizontal lines indicate the group mean; the shaded areas represent \pm SEM. HCs, healthy control subjects; SCHs, patients with paranoid schizophrenia; SADs, patients with schizoaffective disorder; BDs, patients with bipolar depression.

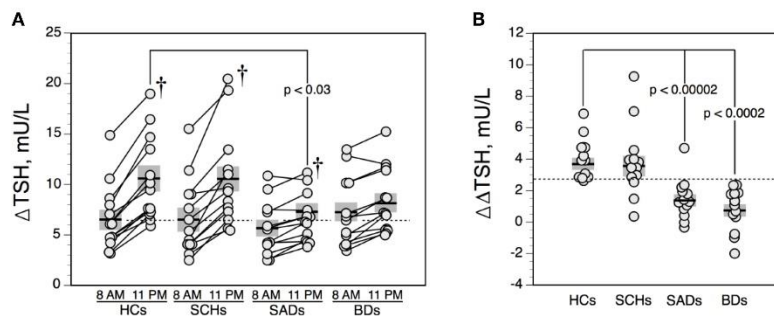


FIGURE 3 | Maximum increment in serum thyrotropin (TSH) level above baseline (Δ TSH) after 200 μ g IV of protirelin (TRH) (A), and difference between 11 PM- Δ TSH and 8 AM- Δ TSH ($\Delta\Delta$ TSH) (B) in controls and patients. The solid horizontal lines indicate the group mean; the shaded areas represent \pm SEM. HCs, healthy control subjects; SCHs, patients with paranoid schizophrenia; SADs, patients with schizoaffective disorder; BDs, patients with bipolar depression. $\dagger p < 0.005$ by T test (comparison between 8 AM- Δ TSH and 11 PM- Δ TSH values).

observed in 2 SCHs and 2 BDs (both 15%); 1 SAD (8%); and none HC (Figure 4).

Frequency of Abnormal Test Responses Among Patients and Control Subjects

Figure 5 summarizes the number of abnormal test responses in patients and HCs. When analyzing the frequency of normal/abnormal test responses (i.e., APO-PRLs, APO- Δ Cortisol, CLO- Δ GH, TRH- $\Delta\Delta$ TSH), SADs and BDs displayed a similar pattern of abnormalities, significantly different from SCHs (Yates' $\chi^2 = 28.43$, $df = 7$, $p < 0.0002$).

DISCUSSION

Our study clearly demonstrates that multihormonal responses to a series of neuroendocrine test battery (APO test, CLO test, 8 AM

and 11 PM TRH tests, and DST) vary according to diagnostic categories. In unmedicated paranoid SCH inpatients, pituitary-adrenal response to APO (i.e., Δ ACTH and Δ Cortisol) was reduced, while hormone responses to CLO and TRH tests were not significantly altered. The patterns of abnormality of hormonal responses of unmedicated depressed SAD and BD inpatients were very close and were characterized by a reduced APO-induced PRL suppression, a reduced CLO-induced GH stimulation, and a chronobiological alteration of the HPT axis (as reflected by reduced $\Delta\Delta$ TSH values). It should be noted that in the affective groups, BDs showed weaker psychotic symptoms than SADs (as reflected by lower BPRS scores), while their hormonal profile was quite comparable. Hence, this would suggest that the biological correlates of psychotic symptoms depend on the nosographical context. Increased HPA axis activity (as evidenced by higher post-DST cortisol values compared to HCs) was observed in SCHs as well as SADs and BDs—although overt hyperactivity of this axis (i.e., DST non-suppression) was rather infrequent in patients of our sample. In addition, the differences observed in test responses between patients and HCs did not seem to be an artifact of factors known to influence serum hormone levels (such as age, gender, medication) since we investigated a population of middle-aged male drug-free subjects.

Apomorphine Test

Confirming our previous studies (5, 7, 8), ACTH and cortisol responses to APO are strongly correlated. This suggests that cortisol stimulation by APO, despite localization of DA- D_2 receptors in the adrenal gland (29), is secondary to that of ACTH. Blunted ACTH/cortisol to APO response has consistently been found in schizophrenia (5–8). This blunting appears independent of HPA axis activity (6) and DST status (7, 8). Moreover, it seems unlikely that decrease APO-induced ACTH/cortisol stimulation is due to decreased reserve of pituitary ACTH (8) or residual antipsychotic effect, given that, in our study, baseline PRL levels are similar between SCHs and HC (antipsychotics *via* a D_2 blocking effect can increase prolactinemia). From a pathophysiological viewpoint, the mechanisms underlying a reduced ACTH/cortisol response to

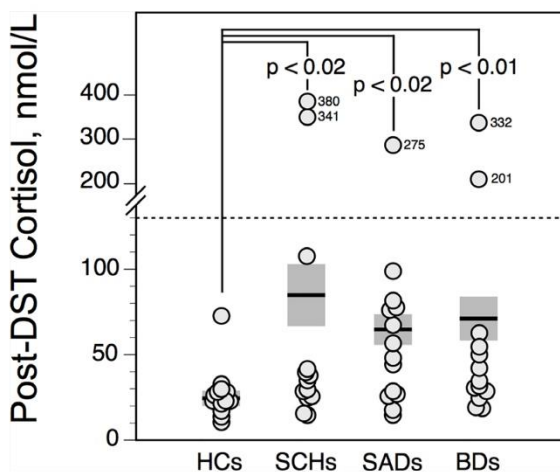


FIGURE 4 | Highest serum cortisol value following dexamethasone suppression test (DST) in controls and patients. The solid horizontal lines indicate the group mean; the shaded areas represent \pm SEM. HCs, healthy control subjects; SCHs, patients with paranoid schizophrenia; SADs, patients with schizoaffective disorder; BDs, patients with bipolar depression.

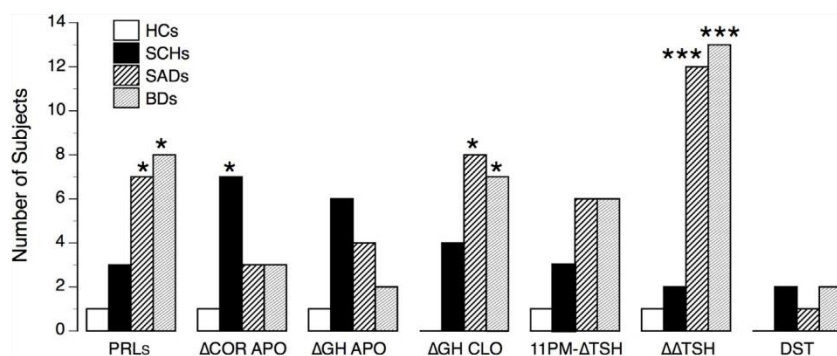


FIGURE 5 | Number of abnormal test responses in controls and patients. HCs, healthy control subjects; SCHs, patients with paranoid schizophrenia; SADs, patients with schizoaffective disorder; BDs, patients with bipolar depression. PRLs, prolactin suppression following apomorphine (APO); ΔCOR APO, maximum increment in serum cortisol level above baseline after APO; ΔGH APO, maximum increment in serum growth hormone (GH) level above baseline after APO; ΔGH CLO, maximum increment in serum growth hormone (GH) level above baseline after clonidine (CLO); 11 PM-ΔTSH, maximum increment in serum thyrotropin level above baseline (ΔTSH) after protirelin (TRH); ΔΔTSH, difference between 11 PM-ΔTSH and 8 A-ΔTSH values. Comparisons between HCs and patients: * $p < 0.05$; *** $p < 0.001$ (by Fisher's exact test).

APO are not completely understood. It is known that APO binds the D_2 -like (D_2 , D_3 , D_4) receptor and the D_1 -like receptor (D_1 , D_5) subtypes (30). Since D_2 and D_1 receptors are involved in the regulation of CRH (31, 32)—and therefore ACTH release—one may hypothesize that the blunted ACTH/cortisol response to APO reflects reduced hypothalamic DA receptor sensitivity. Interestingly, D_2 receptors are also expressed in the pituitary corticotroph cells but their role is thought to be inhibitory on ACTH secretion (33). Therefore, the blunted ACTH/cortisol response to APO in paranoid SCHs is compatible with a hyposensitivity (or persistent down-regulation) of the DA- D_2 and/or D_1 receptors connected with the regulation of HPA axis possibly secondary to increased presynaptic DA activity at the hypothalamic level. Given the DA abnormality in SCH is thought to primarily involve synthesis and release activity (34), our results are in line with the hypothesis of an increased DA activity in the mesolimbic-hypothalamic pathway in paranoid SCHs. However, APO has also affinity for serotonin receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), and α -adrenergic receptors (α_{1B} , α_{1D} , α_{2A} , α_{2B} , and α_{2C}) (30, 35). Most of these receptors have been involved to different degrees in the regulation of CRH activity [for a review, see (3)]. Consequently, the blunted APO-induced ACTH/cortisol stimulation might also reflect in part 5-HT and α -adrenergic receptor dysfunction, although this hypothesis needs further investigation in schizophrenic patients.

The GH and ACTH/cortisol responses to APO are correlated in the whole sample, but not in the diagnostic groups of subjects. Despite there is a trend towards blunting in SCHs, ΔGH_{APO} values are not significantly different across patients and HCs. This latter result is in agreement with previous published reports (5–7, 36, 37) but not all (38, 39). As previously discussed (8), the effect of APO on GH involves different pathways from those mediating ACTH/cortisol response, since this response requires the participation of GH-releasing-hormone (GHRH) neurons and acetylcholine, and other neurotransmitters/hormones such as NA, 5-HT, GABA, ghrelin, and cholecystokinin are probably

involved in the GH response to APO. These confounding factors consequently may limit the value of the GH response to APO in the investigation of DA function in psychiatry.

In agreement with several studies (5, 9, 12, 40) APO induced-PRL suppression is altered in our population of BDs and SADs. The lack of significant difference in the PRL response to APO between SCHs and HCs is also consistent with prior reports (5, 7, 9) but not all (41). The release of PRL is inhibited by the tuberoinfundibular (TI) DA neurons *via* D_2 receptors (4). Our findings suggest hyposensitivity of the D_2 receptors of the lactotrophs in BDs and SADs, possibly secondary to the activation of the TIDA neurons. However, it is also possible that PRLs blunting might be due to functional alteration of lactotrophs cells. This hypothesis is not confirmed by a previous study (40), in which 8 AM and 11 PM PRL responses to TRH stimulation tests were comparable between unipolar (UP) and bipolar depressed patients, while BDs, unlike UPs, exhibited blunted APO-induced PRLs values (12).

Clonidine Test

CLO induces a robust GH response *via* activation of postsynaptic α_2 -adrenoceptors, which increase the secretion of GHRH and inhibit the secretion of somatostatin (42). The blunted GH response to CLO is well documented in depression (16, 26, 43) and in SAD (9, 16). Such a response may be due to decreased postsynaptic α_2 -receptor responsiveness linked to an erratic release of presynaptic NA (43). Thus, the comparable ΔGH values found in depressed BDs and SADs suggest a possible biological link between these two diseases (i.e., NA dysregulation). In agreement with a previous study of our group (16), ΔGH_{CLO} values in paranoid SCHs are not altered (suggesting normal sensitivity of hypothalamic α_2 -adrenoceptors in these patients), although in disorganized SCHs it has been found greater CLO-induced GH responses (37) (suggesting hypersensitivity of α_2 -adrenoceptors in these patients). However, this latter finding has not been replicated (16).

Protirelin (TRH) Tests

Results obtained from the morning TRH-TSH challenge agree with those of previous published reports [for review, see (21)]. Morning TRH-TSH responses are not significantly different across the patient and control groups. In the evening, TRH-TSH responses at 11 PM are higher than at 8 AM (albeit not significant in BDs). Consistent with a previous study, $\Delta\Delta\text{TSH}$ values are reduced in depressed SADs and BDs, while they are unaltered in SCHs (9). We have already discussed that the $\Delta\Delta\text{TSH}$ test is a chronobiological refinement of the TRH test (25, 44). Pathophysiological components involved in an abnormal $\Delta\Delta\text{TSH}$ test may be synthesized as follows (21):

1. A chronobiological component involving the determinants of circadian TSH secretion [i.e., a weaker output of the hypothalamic suprachiasmatic nuclei (45)], since reduced $\Delta\Delta\text{TSH}$ values are associated with decreased 24-h TSH mesor and amplitude levels in depression (25).
2. A chronesthetic component involving TRH receptor sensitivity, since altered sensitivity of TRH receptors is more evidenced at 11 PM than at 8 AM (25). TRH receptor hyposensitivity may be adaptive to prolonged hypersecretion of endogenous TRH (46).
3. A self-regulating component, since the $\Delta\Delta\text{TSH}$ test takes into account the negative feedback of thyroid hormones on TSH secretion. Indeed, the TRH test performed at 8 AM stimulates thyroid hormone secretion, increasing, therefore, the negative feedback of thyroid hormones on TSH secretion in the evening (44).
4. A dynamic component, since 11 PM- $\Delta\Delta\text{TSH}$ blunting could also be related to a reduced TSH resynthesis in the thyrotrophs during the hours following the 8 AM TRH test (given that TRH stimulates preformed TSH). Decreased TSH synthesis could involve a hyposensitivity of the pituitary TRH receptors and/or an increased negative feedback of thyroid hormones, or a decreased central TRH activity [especially in recent suicide attempters in whom FT_4 levels are also reduced (44)]. In our population, no patient had a history of suicidal behavior; therefore reduced $\Delta\Delta\text{TSH}$ values in SADs and BDs are unlikely to be due to a decrease in the central activity of TRH.

Dexamethasone Suppression Test

In our sample, SCHs, SADs and BDs exhibit significant higher post-DST cortisol values than HCs, indicating a weaker suppressing effect of dexamethasone. This finding, which could reflect decreased type II GR function, converges with the growing literature on HPA axis dysregulation in psychotic and affective diseases (18, 19, 47). However in our study, DST nonsuppression occurs only in a low proportion of patients. This non-expected low incidence—especially in depressed SADs and BDs—is nonetheless in accordance with some previous but not all reports [for review, see (3)]. We could presume that the sensitivity in detecting HPA axis overactivity would be better using the combined dexamethasone/corticotropin-releasing hormone (DEX/CRH) test (48–50), although all studies do not

agree (51, 52). It has been hypothesized that the hyperactivity of the HPA axis is primarily a reflection of abnormal limbic-hypothalamic activation, with increased secretion of hypothalamic CRH and consequent excessive adrenal cortisol secretion (17). Given the high rate of reduced $\Delta\Delta\text{TSH}$ values in BDs and SADs—possibly reflecting endogenous TRH hypersecretion—one may hypothesize that increased TRH secretion (both from hypophysiotropic and non-hypophysiotropic neurons) could decrease glucocorticoid secretion by impairing the last steps of 11β -hydroxylation without affecting the earlier steps (53). In such case, the GR function would be only partially attenuated, despite CRH overdrive, explaining therefore why SAD and BD patients with reduced $\Delta\Delta\text{TSH}$ values are often DST suppressors.

Limitations

Some shortcomings in this present study require discussion. First, our results concern only a specific group of drug-free male inpatients; they do not appear at present transposable to outpatients, and consequently they cannot be generalizable to affective and psychotic patients. Second, given the exploratory nature of our research, and the drastic inclusion criteria, we studied a rather small sample of psychiatric inpatients. This may have reduced the statistical power of our analyses (performed with nonparametric methods). Thus, our findings must be considered preliminary until replicated in a larger patient population. Third, among the confounding factors in assessing neurotransmitter function, insufficient washout period could be a major bias. However, our exclusion criteria and the length of the wash-out period (minimum 2 weeks for the APO test and 3 weeks for the CLO test) seem sufficient to avoid biases induced by drugs on the systems studied (5, 54). Finally, we did not measure serum dexamethasone. However, it has been argued that the concentration of dexamethasone bound to the receptors in the pituitary is the relevant physiologic parameter rather than the dexamethasone concentration in plasma (55, 56).

In conclusion, the multivariate neuroendocrine approach used in this study was able to identify patterns of hormonal response abnormalities in drug-free hospitalized patients with psychotic and affective symptoms. From a pathophysiological viewpoint, our results suggest that depressed bipolar and schizoaffective patients share common biological dysregulations, clearly distinct from that of paranoid schizophrenic patients. Future studies are needed to determine whether these findings could be relevant in managing psychiatric treatments.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Centre Hospitalier Rouffach. The patients/

participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FD designed the study, wrote the protocol, and wrote the first draft of the manuscript. M-CM undertook the statistical analysis and interpreted the results. AE made clinical assessments. FG made clinical assessments. VD made clinical assessments. LJ managed the literature searches. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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2.2 Article 2 : Thyroid axis and dopamine function in depression

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2.3 Article 3 : A Brain Imaging-Based Diagnostic Biomarker for Periodic Catatonia: Preliminary Evidence Using a Bayesian Approach

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2.4 Article 4 : 3D-mapping of TMS effects with automatic robotic placement improved reliability and the risk of spurious correlation

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2.5 Article 5 : Individualizing rTMS in treatment-resistant depression from patient-specific perfusion abnormalities : a proof-of-concept superiority study in comparison to standard rTMS and tDCS

Individualizing rTMS in treatment-resistant depression from patient-specific perfusion abnormalities

a proof-of-concept superiority study in comparison to standard rTMS and tDCS

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Abstract

Background

Studies examining treatment resistant depression (TRD) as a group implicitly assume that they have similar pathophysiology and should respond to the same treatment, e.g. standard rTMS (S-rTMS) and tDCS aimed at correcting left prefrontal hypoactivity. However new advance in ASL-fMRI (arterial spin labeling), revealed more heterogeneous subject-specific perfusion anomalies than expected. Some even presenting with hyper-perfusion of the left prefrontal cortices.

Objective

To establish the relevance of these patients-specific perfusion anomalies, individualized rTMS protocols (I-rTMS) were designed to 'correct' them and compared to S-rTMS and tDCS.

Methods

iADAPT was randomized, cross-over trial comparing I-rTMS to active comparators on brain perfusion and single blind evaluation of clinical symptoms. At baseline, patient's specific anomalies were determined from 3 ASL-fMRI sessions. I-rTMS multi-target protocols aimed at correcting all reachable bi-frontal anomalies, i.e. up-regulating hypoperfusions and down-regulating hyperperfusion. S-rTMS and tDCS were placed on F3. The use of a robotic device under neuronavigation control ensured compliance with the designed rTMS protocols. Each treatment arm consisted in 20 sessions delivered in two weeks and was evaluated on pre/post ASL-fMRI and clinical assessments.

Results

Twenty-two patients with TRD were included. They had heterogeneous abnormalities, with the most frequent pattern consisting in bilateral hypoperfusions (59%). I-rTMS was significantly superior to S-rTMS and tDCS on symptom reduction and the only treatment to have specific effects on brain perfusion showing the disengagement of negative emotional systems, e.g. subgenual cingulate, anterior insula.

Conclusion

These results suggest that patient-specific abnormalities contribute to their depression despite their heterogeneity. This questions the traditional way to study depression as a homogeneous entity and calls for the identification of more homogeneous pheno-biotypes.

Keywords

Repetitive transcranial magnetic stimulation, transcranial direct current stimulation, depression, individualization, perfusion imaging, robotization, arterial pin labeling, neuronavigation

Introduction

By lumping all depressions together under the same label, international classifications have conveyed the assumption that they were homogeneous in nature. Studies that include patients with major depressive episodes as a single group hence implicitly assume that they have the same pathophysiology, which should therefore respond to the same therapeutic strategy [1]. Accordingly, current therapeutic guidelines propose sequential trials of increasingly powerful yet also riskier drugs, doses, associations, and combinations [2]. The concept of treatment-resistant depression (TRD) emerged from the failure of this trial-and-error strategy and is generally defined by more than 2 unsuccessful attempts. By ascribing these failures to shortcomings of existing therapies, the concept of TRD does not call into question the ‘single-depression hypothesis’ but rather encourages the development of new therapeutic approaches. It is in this very spirit that repetitive transcranial magnetic stimulation or rTMS has been essentially developed [3].

rTMS provides a non-invasive way to modulate the activity of selective cortical areas or networks. It allows to achieve their up- or down-regulation, over days to months by adjusting stimulation frequencies, patterns, intensity and quantity [4]. The rationale of standard rTMS (S-rTMS) in TRD is mostly based on group studies showing a decrease in the perfusion of left dorsolateral prefrontal cortices (L-DLPFC) in (retarded) depressions [5][6]. S-rTMS consists in the stimulation of a single L-DLPFC target mostly using 10Hz trains in order to up-regulate its activity. S-rTMS is now widely acknowledged to be effective in TRD with a grade A level of evidence [3][7]. However, even though S-rTMS is safer, better tolerated, and cost-effective relative to other third therapeutic lines, it does not yield better than the most efficient ones, with only 16% of the patients in remission at 6 weeks [8][9].

TRD resistance to S-rTMS did not further call into question the ‘single-depression hypothesis’, and treatment failures are rather attributed to technical limitations mainly related to targeting. The first issue was the use of external landmark leading to off-target coil positioning [10]. Frameless neuronavigation was introduced to ensure proper targeting of L-DLPFC [11], but this did not result in significant improvements of S-rTMS in comparison studies [12]. The second issue was the size of L-DLPFC relative to the spatial accuracy of conventional figure-of-eight coils. These may not be able to modulate more than a tenth of all reachable parts of these cortices, not to mention the issue of coil orientation. A first way to work around this problem was to decrease focalization, either by using so-called H-coils, or by switching to anodal transcranial direct current stimulation (tDCS) [13][14]. Preliminary results are encouraging but we are not aware of a head-to-head comparative study supporting the superiority of unfocussed approaches [15]. The second way to address the accuracy issue was to improve the definition of the target by figuring out which part of the L-DLPFC had to be

up-regulated in each patient, i.e. to customize S-rTMS. The first idea was to use the same measure as in original group analysis in targeting the most hypo-perfused region in each patient. However, this did not lead to significant improvement in S-rTMS efficacy [16][17][18]. This failure has mostly been interpreted as a matter of poor signal-to-noise ratio. At the time, absolute brain perfusion could only be measured by injecting a radiotracer, resulting in a cumulative exposure to ionizing radiation limiting the number of measurements per patient. Being non-ionizing, BOLD-fMRI does not have this constraint and hundreds to thousands of scans could be done on the same patient. Yet, as these measures are only relative and not absolute, they cannot be used to map hypo-perfusions. But resting BOLD-fMRI allows for robust co-variation or correlation maps at the subject-level [19] which can be used to customize S-rTMS by targeting the part of the L-DLPFC that is the most involved in the inhibition of negative emotional systems. The latter are deeper brain regions shown to be hyperactive in group studies of depression. The most popular ones are the subgenual cingulate [20] and the right anterior insula [21]. These are out of reach of rTMS, but under the control of the L-DLPFC part that is most negatively correlated with their activity. Primary results of connectivity-based L-DLPFC targeting are encouraging [22][23][24], but superiority comparison studies are needed to conclude about the added value of the customization.

Thus, not only have almost all rTMS studies been performed under the ‘single-depression hypothesis’ but most of them are just optimization of the same ‘standard model’ of L-DLPFC hypoactivity (the downregulation of the right DLPFC being just a variation involving transcallosal inhibition). Challenging the ‘single-depression hypothesis’, requires leaving the atheoretic comfort zone of international classifications and take the chance of opting for the paradigmatic framework of systems neuropsychiatry [25][26]. This shift in perspective enables to re-interpret the all-too-frequent occurrence of TRD not as a technical artifact, but as the inadequacy of the ‘single-depression hypothesis’. The alternative hypothesis would be that major depressive disorders are a catch-all for many different natural entities, i.e. diseases and/or syndromes which would only respond to the treatment adapted to their specific pathophysiology and/or etiology. From this reversal of perspective, resistance to treatment is not a matter of biological inefficiency, but rather a matter of inappropriate therapeutic target. This is nothing but putting in plain biomedical words what is meant by ‘precision medicine’ [25][26]. The problem in neuropsychiatry is that we do not know what these entities actually are. Hopefully, advances in another non-ionizing fMRI technique, i.e. ASL-fMRI (arterial spin labeling), now makes it possible to repeat the measurement of absolute perfusion so that brain activity changes can be reliably mapped in every single patient [27][28]. The preliminary analysis of 14 patients with TRD showed that not only were there different patterns of abnormalities, but that they could go both directions in the same region. The L-DLPFC offered the most troublesome example displaying the

expected hypo-perfusion in 8 patients, their normo-perfusion in 4 and their hyper-perfusion in 2 [29]. Four years ago, the technique was too young, and we lacked sufficient data on reproducibility to convince us of the reality of results that went strongly against the standard model [30]. But the versatility of rTMS offered a way to challenge our disbelief in designing multi-target ‘corrective’ protocols adapted to patients’ specific anomalies, i.e. up-regulating hypo-active regions and down-regulating hyper-active regions. The iADAPT study aimed to establish the feasibility of such ‘individualized rTMS’ (I-rTMS) and to compare it to S-rTMS and tDCS in the same patient (cross-over). This article presents the results of the first-level analysis carried out at the population level. By showing that I-rTMS induced specific changes in brain perfusion with better therapeutic outcomes, this study provides support for the heterogeneous nature of TRD.

Methods

Study design

The iADAPT study (Figure 1, NCT02863380) is a monocentric, single blind, randomized, cross-over, superiority augmentation trial comparing individualized rTMS (I-rTMS) to two classical neuromodulation procedures: S-rTMS and tDCS (Figure 1). The cross-over design made it possible to deal with the heterogeneities of the TRD but entailed a risk of carry-over effect. To mitigate this effect, brain perfusion was chosen as surrogate endpoint biomarker for clinical efficacy [31][32]. The study was conducted in accordance with the principles of the Declaration of Helsinki [33] and was approved by the local ethic committee (CPP Est IV). All patients signed an informed consent.

[Figure 1](#)

Imaging procedures

All MRI examinations were performed on a VERIO® 3 Tesla scanner with a 32-channel head antenna (Siemens®, Erlangen, Germany) dedicated to research (IRIS platform, iCUBE lab).

Pre-stimulation MRI. Three MRI sessions were needed to determine patients’ specific anomalies. These were performed under the same conditions than the controls of our MRI database (morning sessions spaced at least one week apart) [30][34]. Sessions started by an automatic alignment of brain using MR scout scans in order to maximize both within and between subjects reproducibility. Anatomical images included MP-RAGE 3D-T1 for morphometry and neuronavigation ($0.7 \times 0.7 \times 0.7$ mm). Whole brain ASL-fMRI perfusion measurements were repeated twice at different TE during each MRI session (QUIPSS-II sequence, TE = 9.7 and 21 msec, TR/ TI1/ TI2 = 3000/ 600/ 1325 msec, $4 \times 4 \times 4$ mm) [35]. ASL-fMRI sequences were performed under different conditions: 5 min during rest or

passive video viewing (101 volumes) and 20 min while performing various tasks ('localizer', 401 volumes) [28].

Evaluation MRI. Each neuromodulation protocol was flanked by pre- and post-scanning sessions to measure brain perfusion. Similar ASL-fMRI sequences were used, one during 5 min looking at a video (ASL-9.7 ms, 101 vol) and the other during 10 min rest (ASL-21 msec, 201 vol).

Clinical assessments

Patients were assessed by the same psychiatrist, blinded to treatment arm/order, at inclusion, before and after each treatment. The severity of depression was assessed using the quick inventory of depressive symptoms, clinician rated version (QIDS-C) [36] while social, professional, familial or personal consequences of symptoms were assessed with the global assessment of functioning (GAF) [37].

Though unblind to treatment arm, patients contributed to their evaluation by filling self-questionnaires on depression (inventory of depressive symptoms, self-rated version – IDS-SR) [36], and ruminative thoughts (rumination response scale – RRS; rumination-reflection questionnaire – RRQ) [38][39].

Interventions

Neuromodulation was performed by trained personal in a day-hospital (CEMNIS – IRIS joint platform). The same devices were used for S- and I-rTMS sessions sharing most of standard procedures [40]. TMS stimulator was a MagPro R30 with MagOption® (MagVenture, Farum, Denmark) equipped with 65 mm figure-of-8 coil dedicated to TMS-robot® (Cool-B65 RO®, MagVenture, Farum, Denmark). The latter was fitted with specific navigation trackers and pressure sensor (Axilum Robotics, Strasbourg, France). rTMS protocols were planned on a neuronavigation system controlling the stimulator and robotic coil placement (Localite GmbH, Sankt Augustin, Germany). Sessions started by adjusting a tracker on the patient's head, calibrating the navigator to align it with his MRI and by finding the active motor threshold (AMT). Stimulator output was set at 160% of the AMT, i.e. about 130% of resting motor threshold.

S-rTMS: To remain close to the most validated procedure, F3 position was determined on the first day of treatment on patient's own external landmarks and recorded in the navigator. Stimulation parameters were 10Hz, 4 sec train, 75 repetitions, 26 sec interval (3000 pulses), 160% of the AMT.

I-rTMS: Pre-stimulation mapping was done according to previous publications. Measures from ASL-9.7 and ASL-21 sequences were analyzed in parallel. Cerebral blood flow (CBF) volumes were corrected for the effect of TE [27]. Each individual patient was compared to a group of controls for every 'brain state'

using both parametric and non-parametric statistical procedures [28]. Changes had to be significant in both measurements to be considered as an anomaly (conjunction of the parametric and non-parametric statistical maps computed from ASL-9.7 and ASL-21 sequences). Significant perfusion anomalies ($z > 3.2$ – unilateral; $k > 1 \text{ cm}^3$), were superimposed on brain anatomy to guide the planning of the protocol by the clinician. To be considered, anomalies had to be located in a reachable region of the frontal lobes (distance $< 35 \text{ mm}$ from the hot spot). Regions with reduced perfusion were stimulated in the same way as for S-rTMS, except that trains were distributed on the different targets (10Hz, 4 sec train, 75 repetitions for a total of 3000 pulses). Regions with perfusion increases were stimulated at 1 Hz, 160% of the AMT in trains of 200 to 400 pulses depending on the number of targets for a total of 1800 pulses. When the two protocols had to be mixed, i.e. in case of both hyper- and hypo-active targets, the number of pulses was adapted in order to keep the duration of the session identical between subjects. Accordingly, the number of pulses delivered during I-rTMS could only be equal to or less than that of S-rTMS.

tDCS: Direct currents were delivered by the DC-Stimulator plus (neuroConn GmbH, Ilmenau, Germany, EU) equipped with 35 cm^2 rubber electrodes. These were wrapped in saline-soaked sponge pads and held in place with rubber straps. The anode was placed on F3 and the cathode on the right arm, as close to the shoulder as possible. Stimulation parameters: 2 mA, 20 min, 30 sec ramp-on ramp-off.

Each treatment was administered twice per day. After each session, patients were asked to avoid mind wandering by taking a short nap or engaging in a task (reading, etc.) for an hour. Side-effects were systematically screened at the end of each day of stimulation. The procedure was repeated five days a week for two consecutive weeks, so that patients had 20 sessions of each treatment. Evaluation scans and clinical assessment were performed within 5 days before and after each therapeutic arm. Treatments were separated by a minimal one-week wash-out period.

Group-level anomalies in TRD

This analysis aimed at looking for differences in perfusion and gray matter volume between TRD patients and a set of 40 controls matched for age and gender. All images preprocessing and analyses were performed with SPM12 (Wellcome Department of Imaging Neuroscience, University College, London, UK, www.fil.ion.ucl.ac.uk/spm/) running on Matlab®R2022b (Mathworks®, Natick, MA, USA). Standard procedures and parameters were applied for perfusion and voxel-based morphometry except for spatial smoothing which was done with a larger gaussian kernel than usual ($12 \times 12 \times 12 \text{ mm}$ full width at half maximum). This choice was intended to promote the detection of changes even in case of imperfect spatial overlap between patients. Patients and controls were compared on ASL-9.7 and ASL-21 measurements separately with age and global brain perfusion as covariates before

computing the conjunction between the two statistical parametric maps (SPM). The overall threshold for the t-test was set at $p \leq 10^{-4}$ (unilateral t-test, uncorrected, i.e. $p \leq 10^{-2}$ in each SPM) with a cluster extent $k \geq 2.5 \text{ cm}^3$ (i.e. adapted to the spatial filter). Regarding VBM, gray matter probability maps were compared using age and total intracranial volume as covariates and the threshold was set at $p \leq 10^{-3}$ (unilateral, uncorrected) and $k \geq 2.5 \text{ cm}^3$. The risk was set at $\alpha_{\text{FWER}} = 0.05$ at the cluster level (family wise error rate).

Primary outcome: change in cerebral blood flow (CBF)

All pre-/post- ASL-fMRI sequences (9.7 and 21 msec) were preprocessed in the same way as for the group-comparison including spatial smoothing ($12 \times 12 \times 12 \text{ mm}$ Gaussian kernel). Contrasts statistics were computed from the same design matrix with age, order and global brain perfusion as covariates. ASL-9.7 and ASL-21 measurements were processed separately, before combining the results in conjunction SPMs. In what follows, we will make the distinction between the main effect of a treatment, the superior effect of a treatment (as compared to another), and the specific effect of one treatment (relative to all the others) whereas the global effect will refer to the series as a whole. Unless specified, $p \leq 10^{-4}$ (unilateral test, uncorrected, i.e. $p \leq 10^{-2}$ in both SPM) with extension $k \geq 2.5 \text{ cm}^3$ (cluster level $\alpha_{\text{FWER}} = 0.05$).

Main effect

A **main effect** hereafter refers to the changes in brain perfusion following a given treatment, e.g. pre/post S-rTMS:

$$\Delta CBF_{tDCS} = CBF_{tDCS}^{post} - CBF_{tDCS}^{pre}$$

Positive ($\Delta CBF_{S-rTMS}^{\oplus}$) and negative ($\Delta CBF_{S-rTMS}^{\ominus}$) main effects are tested against the null hypothesis. Importantly, a significant main effect of treatment A and not of treatment B cannot be interpreted as a superiority of A over B.

Superior effect

Here the main effect of one treatment is tested against the main effect of another, e.g. the superior increase in CBF after tDCS vs rTMS:

$$\Delta \Delta CBF_{rTMS}^{tDCS^{\oplus}} = \Delta CBF_{tDCS}^{\oplus} - \Delta CBF_{rTMS}^{\oplus}$$

$\Delta\Delta CBF_{rTMS}^{tDCS^{\oplus}}$ corresponds to the interaction between two factors (pre/post and tDCS/rTMS). SPMs of such interaction are ambiguous since this contrast is mathematically equivalent to the one of a superior decrease in CBF after rTMS relative to tDCS.

$$\Delta\Delta CBF_{rTMS}^{tDCS^{\oplus}} = \Delta\Delta CBF_{tDCS}^{rTMS^{\ominus}} = \Delta CBF_{rTMS}^{\ominus} - \Delta CBF_{tDCS}^{\ominus}$$

Hence, to disambiguate the SPMs between superior incremental ($\Delta\Delta CBF_{rTMS}^{tDCS^{\oplus}}$) and decremental effects ($\Delta\Delta CBF_{tDCS}^{rTMS^{\ominus}}$), the results were masked (inclusively) by the main effect of the superior treatment (permissive threshold of $p \leq 0.05$, unilateral, uncorrected).

Specific effect

The effect of a treatment will be referred to as specific if it is superior to the two others and if the two others fail to show the same main effect (or show the opposite effect). This was performed: (i) by computing the conjunction of the two superior effect SPM, (ii) to use inclusive masking by the main effect of the superior treatment and (iii) to use exclusive masking by the main effect of the two others. Because of the conjunction, the significance threshold was set to $p = 3.9 \cdot 10^{-7}$ with $k \geq 2.5 \text{ cm}^3$ (unilateral t-test, uncorrected, i.e. $p \leq 0.025$ in the 4 SPM, 2 superior effect, ASL-9.7/21; cluster level $\alpha_{FWER} = 0.05$).

Overall effect

This is nothing but the main effect of the whole trial, i.e. the comparison of the last visit to baseline. The results were inclusively masked by the main effect of the different treatments ($p \leq 0.05$) to evaluate their possible contribution to final changes.

Secondary outcome measures: clinical improvements

Many patients already started with low QIDS values, which limited the range of available scores to rate an improvement; a ‘floor effect’ which artifactually reduced their weight in the effect size of each treatment. To equalize the contribution of each patient, $\Delta QIDS$ (pre/post-treatment scores) were expressed in percent of scoring range (maximum-minimum scores of each patient – details in Figure 2).

All clinical data analyses were carried out with the JASP 0.17 software [41]. Repeated measures analysis of variance assessed significant changes between pre- and post-assessments (within-subject) with treatment and order as between-subjects factors, and post-hoc Tukey’s test corrected for multiple comparisons. All tests were performed at $\alpha = 0.05$.

Results

Population characteristics

Twenty-seven patients were screened for inclusion at the TRD expert center of Strasbourg, between 2015 and 2019. Twenty-two were retained in present analysis: three did not match inclusion criteria, one withdrew consent, one patient stopped during first treatment arm (tDCS) and had to be hospitalized due to a severe mixed state.

In this paragraph, unless otherwise indicated, characteristics are summarized by their median (see Table 1 for mean \pm standard deviation). Patients had a long history of depression (19 y), with two previous episodes. About one-fifth of the sample had a diagnosis of bipolar disorder and another fifth had a diagnosis of personality disorder. As suggested by concurrent treatments and according to the Massachusetts General Hospital TRD staging score, the current episode was highly resistant (MGH-s = 6). It had most often begun in mid-life (52 y) and had lasted for 4 years at the time of inclusion, so that 68% were chronic (> 2 y).

At the group level, there was no significant difference in brain perfusion and gray matter volume between TRD patients and controls.

[Table 1](#)

Patients' specific perfusion anomalies, individualized protocols and treatment tolerance

All patients but one had significant perfusion anomalies, mostly consisting in perfusion decreases (77%) and being distributed in both hemispheres (77%; Figure 2). The L-DLPFC was hypoactive in 59% and hyperactive in 18% of the sample. Regarding I-rTMS, on average 18 regions were targeted per patient. These were mostly distributed on both hemispheres (73%), and unilateral stimulations involved left and right hemisphere in the same proportion of cases (14% each). The neuro-modulation protocol was generally homogeneous among the targets, i.e. mostly up-regulatory (10-Hz – 77%), sometimes down-regulatory (1-Hz – 18%). For one patients both protocols were used on different targets (Figure 2).

With the exception of the patient who stopped because of the rapid development of mixed state during the first treatment arm (tDCS), all side effects were mild and transient. Most were related to tDCS: 12 erythema (n = 12 – 5% of daily sessions), headache (n = 6; 3%), trouble falling asleep (n = 5;

2%), miscellaneous ($n = 3 - 1\%$). Only two were reported during S-rTMS (1 vagal reaction at the first session, 1 transient headache), none during I-rTMS.

[Figure 2](#)

Clinical assessments (secondary outcomes)

Treatments were significantly different ($F(2, 45) = 5.2, p = 0.009$) with I-rTMS being superior to both S-rTMS and tDCS ($p = 0.012$, and $p = 0.042$ respectively; Figure 2). Of the 38% of patients who achieved remission after either treatment ($QIDS-C \leq 5$), only 24% were still in remission at the last visit. See Table 2 for overall effect on other scales.

[Figure 3](#)

[Table 2](#)

Main outcome: ΔCBF

Main effects and treatment specific changes (Figure 4)

The main effect of I-rTMS was a decrease in perfusion of left-sided regions (Figure 4a in blue). This effect was specific as it remained significant when comparing I-rTMS to both S-rTMS and tDCS. Regions involved in I-rTMS specific effect encompassed (i) caudally the left precuneus and the left temporal, angular and supramarginal gyri, (ii) around the anterior sylvian sulci the left anterior insula, inferior pre-motor, and Broca area, (iii) rostrally the left fronto-polar cortex with a slight extension in the L-DLPFC, and (iv) medially the pregenual anterior cingulate cortex extending on both sides to the head of caudate nuclei (Figure 4b, Table 3a). Intriguingly, these regions were virtually never targeted during I-rTMS.

There was no main effect of S-rTMS but there was a main effect of tDCS (Figure 4a in red). The latter consisted in an increase in perfusion in regions belonging to the right dorsal fronto-parietal network. The only significant left-sided region was the anterior frontal cortex, just below the anode, which might not be a direct effect according to current densities simulation (SimNIBS, Figure 4a, lower part) [42]. There was no specific effect of tDCS.

[Figure 4](#)

[Table 3](#)

Overall (treatment unspecific) effects

After the last treatment, the right dorsal fronto-parietal regions were significantly more perfused relative to baseline (Figure 5a, Table 3b). Most of this effect corresponded to tDCS and S-rTMS main effect (Figure 5b, upper row). I-rTMS perfusion decrease were no longer significant at the end of the protocol, because they have been antagonized by the other treatments, most significantly by tDCS (Figure 5b, lower row).

[Figure 5](#)

Discussion

While at the individual level most patients had significant abnormalities in cerebral perfusion, these were too inconsistent to reach significance when comparing patients to controls as a group. The first result was to demonstrate the feasibility of I-rTMS from these idiosyncratic anomalies. The second was to show that I-rTMS had robust and specific effects on brain activity relative to S-rTMS and tDCS which came with first evidence of superior clinical efficacy. The effectiveness of rTMS-I suggests that these functional heterogeneities are meaningful and may contribute to the finding of more homogeneous TRD phenotypes. However, this is only a proof-of-concept. This study has many limitations, the most obvious of which being its small sample size, the mild severity of the symptoms, and the cross-over design. We will limit the discussion to the interpretation of the group-level imaging results, which raised new issues worth addressing in forthcoming second-level patient-based analyses.

Most of the changes in cerebral perfusion were not anticipated, and those that were expected are missing. The best illustration was the absence of perfusion increase in the L-DLPFC though the same region was targeted in S-rTMS, tDCS and about a third of I-rTMS sessions. Conversely, none of the regions that showed a change in perfusion have been directly stimulated. On the one hand, it reminds us of the simplistic nature of the 'corrective effect' theory that underlay the design of I-rTMS protocols. On the other hand, it invites not to establish a too direct link between the interventions and the brain changes. Studies reporting perfusion changes in the targeted regions measured it shortly after the stimulation [43] while the latter fails to show up in most studies which measured it days after the last session as in our case [44]. It is tempting to interpret S-rTMS and tDCS contralateral increases as distant systemic effects, e.g. release phenomena due to change in the dynamic or connectivity [45]. But this is unlikely to account for I-rTMS related decreases in perfusion that was common enough to show up in group analysis when none of the patients had the same protocol. It is more likely that these changes are only a very remote and indirect consequence of I-rTMS. Indeed, the reduced perfusion of the subgenual cingulate, the left anterior insula or the left frontal pole might more likely reflect the

disengagement of the negative emotional systems [20][21] then the mechanisms by which I-rTMS alleviated depressive symptoms. The latter, on the other hand, might be specific to a given phenotype or biotype. This question can only be addressed by subject-level analyses using subject-specific abnormalities in a reverse phenotyping perspective [25].

Declaration of competing interest

The authors report no conflicts of interest or significant financial support associated with this publication.

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CRedit authorship contribution statement

LD-J: investigation, data curation, formal analysis, writing- original draft preparation, writing- reviewing and editing, visualization. CP: data curation, formal analysis. OM: supervision, investigation. CB, AO, BS, CM, GB, SW: investigation. PLS, JL: methodology, validation, resources. AM, LL: methodology, validation. JRF: conceptualization, funding acquisition, project administration, methodology, software, validation, supervision, investigation, writing- original draft preparation, writing- reviewing and editing.

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Tables

Table 1

General		Current episode		
Nbr	22	Severity (QIDS-C)	13.4 (\pm 4)	
Gender (F/M)	14/8 (64%)	Age at episode onset (y)	49.1 (\pm 14.3)	
Age (y)	53.3 (\pm 12.8)	Duration current episode (y)	4.1 (\pm 3.5)	
Education (year)	15.5 (\pm 1.5)	Resistance (MGH-s)	6.6 (\pm 2.8)	
Disorder – lifetime		Concurrent treatments		
Age at 1 st episode (y)	36.2 (\pm 19.1)	Antidep.	SSRI / SNRI	4 (14%)
Lifetime since 1 st episode (y)	25.5 (\pm 24.6)		TCA	3 (14%)
			Dose (FXT eq., mg / d)	48.3 \pm 28 mg / d
Nbr of episodes	3.8 (\pm 7.9)		non-selective MAOI (TRP)	4 (18%)
Unipolar/Bipolar	18/4 (82%)		Dose TRP (mg / d)	62.5 \pm 13 mg / d
Affected 1 st degree rel.	11 (50%)	Mood stabilizers	14 (64%)	
Comorbid.	Abuse (NIC, OH, THC)	8 (36%)	Direct dopamine agonist	3 (14%)
	Anxiety disorder	7 (32%)		
	Personality disorder	4 (18%)		
	Brain anomalies*	6 (18%)		

Table 1: Population characteristics. *Pre-stimulation MRI allowed the incidental discovery of brain abnormalities in 6 patients. Although their contribution to depression or its resistance to treatment was not considered in any of the patients, their contribution to perfusion abnormalities cannot be formally excluded in 3 cases (details in [28] Supplementary material). Comorbid: comorbidities. NIC: nicotine (n = 8). OH: alcohol (n = 1). THC: cannabis (n = 2). QIDS-C: quick inventory of depressive symptoms, clinician rated version. MGH-s: Massachusetts General Hospital Staging Model – score. Antidep: antidepressant drugs. SNRI: serotonin and norepinephrine reuptake inhibitors. SSRI: selective serotonin reuptake inhibitors. MAOI: monoamine oxidase inhibitors. FXT eq: fluoxetine equivalent doses [46].

Table 2

	Baseline	Last visit		Δ	p-value
QIDS-C	13.4 (\pm 4)	9 (\pm 4.1)	19	- 4.1 (\pm 4)	$5 \cdot 10^{-4}$
IDS-SR	41.8 (\pm 11.1)	30.2 (\pm 14)	16	- 12.5 (\pm 14.5)	$3.5 \cdot 10^{-3}$
GAF	47 (\pm 8.8)	56.2 (\pm 13.1)	15	+ 6.6 (\pm 13.1)	ns
RRS	37 (\pm 9.4)	31.8 (\pm 12.2)	16	- 7.4 (\pm 10.7)	0.014
RRQ	85.8 (\pm 14.5)	80.9 (\pm 16.5)	19	- 4.7 (\pm 9.3)	0.057

Table 2: Overall effect of the trial on clinical assessments. Δ : difference between last-visit and baseline (small digits on the left are the number of patients for whom the Δ and t-test could be calculated – some data were lost due to a computer server failure). The overall effect of the interventions was a significant decrease of depressive symptoms intensity, both on clinical rated assessment (QIDS-C: quick inventory of depressive symptoms, clinician rated version) and on self-rated reports (IDS-SR: inventory of depressive symptoms, patient rated version), as well as ruminations (RRS: rumination response scale). GAF: global assessment of functioning; RRQ: rumination-reflection questionnaire.

Table 3

a. I-rTMS specific effect								
Cluster Level			Peak Level					
n°	k (cm ³)	p _{FWE}	t	p _{FWE}	x	y	z	Peak location (BA)
1	21.46	<.000	16.19	1.6 · 10 ⁻⁷	-48	-66	-6	L inf. temporal gyrus (20)
			15.77	2.7 · 10 ⁻⁷	-50	-64	4	L mid. temporal gyrus (21)
2	16.54	<.000	15.07	6 · 10 ⁻⁷	-14	58	8	L sup. medial frontal gyrus (10)
			13.81	2.7 · 10 ⁻⁶	-30	50	14	L mid. frontal gyrus (10)
			10.53	1.2 · 10 ⁻⁴	-44	28	30	L mid. frontal gyrus (10)
3	2.87	<.000	14.18	1.7 · 10 ⁻⁶	-50	-40	34	L supramarginal gyrus (40)
4	8.55	<.000	11.95	2.1 · 10 ⁻⁵	-50	-4	44	L precentral gyrus (6)
			10.18	1.8 · 10 ⁻⁴	-52	4	34	L precentral gyrus (6)
			10.1	2.1 · 10 ⁻⁴	-34	14	10	L frontal operculum (44)
5	5.14	<.000	10.6	1.1 · 10 ⁻⁴	14	14	2	R caudate
			9.61	3.9 · 10 ⁻⁴	-12	16	-4	L caudate
			9.39	5.3 · 10 ⁻⁴	6	14	-4	R caudate
b. Overall effect								
Cluster Level			Peak Level					
n°	k (cm ³)	p _{FWE}	t	p _{FWE}	x	y	z	Peak location (BA)
1	227.2	<.000	10.36	1.2 · 10 ⁻⁴	50	-57	23	R sup. temporal gyrus (22)
			9.69	4 · 10 ⁻⁴	18	23	51	R frontal eye field (8)
2	8.22	<.000	8.23	0.003	-2	15	0	L caudate
			7.07	0.016	-11	20	9	L caudate
3	9.65	<.000	7.22	0.013	6	-47	41	R precuneus (7)
			6.4	0.046	-12	-56	45	L precuneus (7)
			6.11	0.072	-5	-39	44	L post cingulate cortex (31)
4	8.1	<.000	6.57	0.035	63	-35	11	R sup. temporal gyrus (22)
			6.38	0.047	50	-39	23	L supramarginal gyrus (40)

Table 3: Imaging results. a) I-rTMS specific effect (rCBF decrease). Talairach coordinates x, y, z in mm. b) Results of the SPM analysis on the I-rTMS specific effect (rCBF decrease). ACC: anterior cingulate cortex, SPM: statistical parameter mapping, I-rTMS: individualized repetitive transcranial magnetic stimulation, rCBF: regional cerebral blood flow.

Figures

Figure 1

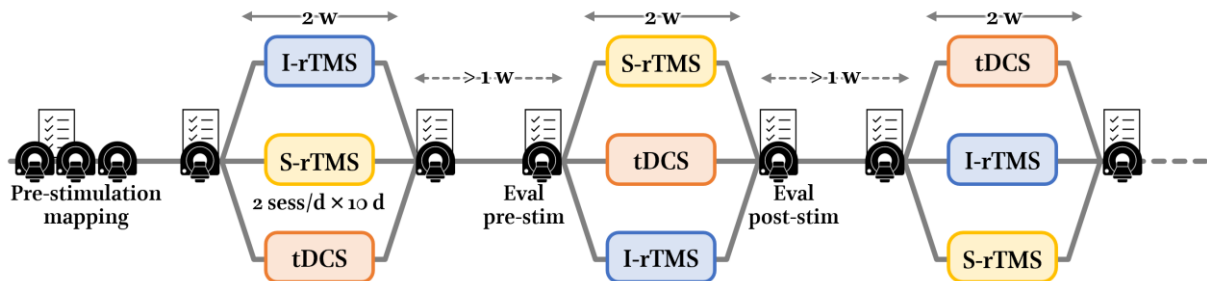


Figure 1: Study design. The iADAPT study – individualized Anti-Depressive Adapted to Perfusion TMS (NCT02863380) is a superiority augmentation trial comparing individualized rTMS (I-rTMS) to two classical neuromodulation procedures: standard rTMS (S-rTMS) and anodal transcranial direct current stimulation (tDCS). The cross-over design was preferred to accommodate the heterogeneity of TRD patient: each patient was his own control. In order to keep patients' participation as short as possible, each treatment was delivered twice daily over 2 weeks (20 sessions) and patients could switched rapidly from one treatment arm to the other (from 1 to 4 weeks). The study was aimed at TRD outpatients as an add-on to the best therapeutic regimen (see Supplementary Material – Table S1 for inclusion and exclusion criteria). Medications and doses were kept the same during the entire participation in the study. The ordering of treatment arms was equilibrated and randomized. To mitigate the carry-over effect that was expected from to the rapid succession of the interventions, treatments were delivered at suboptimal 'doses'. Moreover the primary outcome was the correction of brain perfusion anomalies, chosen as surrogate endpoint biomarker for clinical efficacy. Improvement in depressive symptoms was considered as secondary outcome measure.

Figure 2

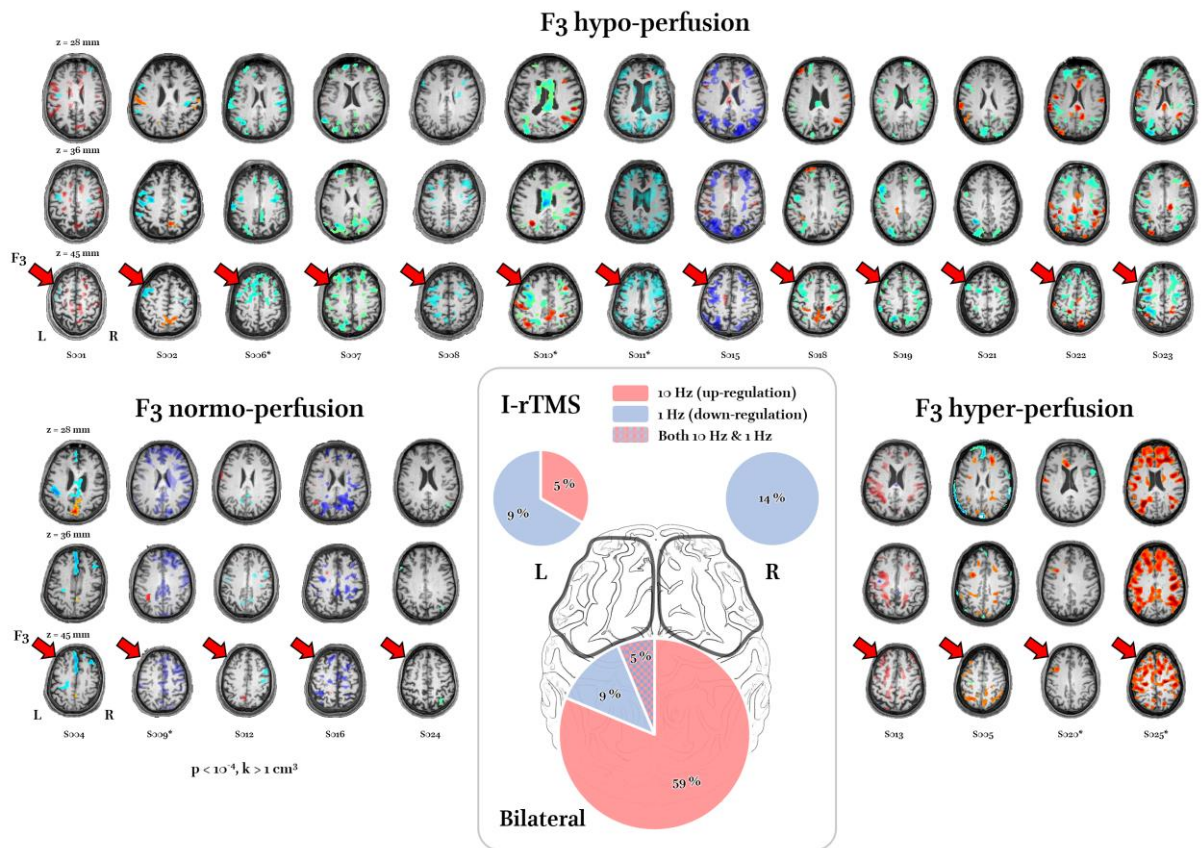


Figure 2: Patient's specific change and I-rTMS protocols.

Figure 3

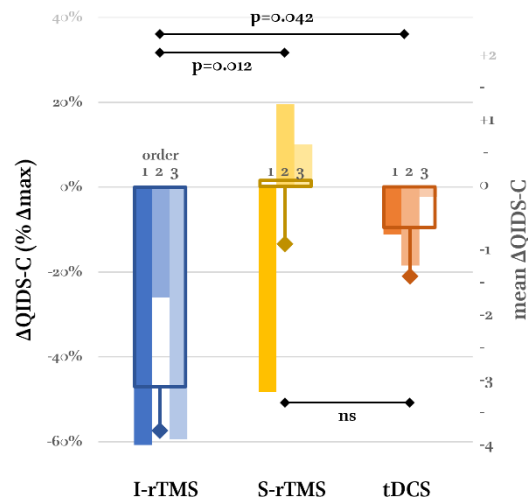


Figure 3: Clinical changes after each treatment according to its ordering. To equate the contribution of each patient to the group variance, Δ QIDS-C, that is the differences between pre-/post-treatment scores are expressed in percentage of the scoring range of each patient (Δ max = maximal-minimal QIDS-scores). As some patients were getting worse on certain treatments Δ max is not the same as global change (Δ Global, baseline vs last visit): Δ max = 6.5 ± 2 (100%) whereas Δ Global = 3.9 ± 2 (60% of Δ max). Right scale: percentages are converted in absolute Δ QIDS-C values to give a better flavor of clinical changes. The narrow color bars on the background represent mean clinical changes of each treatment according to the moment it was performed in the series, i.e. first, second or last (order). The large transparent bars (\pm standard-error) represent the main effect of each treatment. Significant treatment effect: $F(2,45) = 5.3$, $p = 0.009$. Δ QIDS-C between I- and S-rTMS = 46 ± 15 %, between I-rTMS and tDCS = 38 ± 15 % (p-values are adjusted for comparing a family of 3).

Figure 4

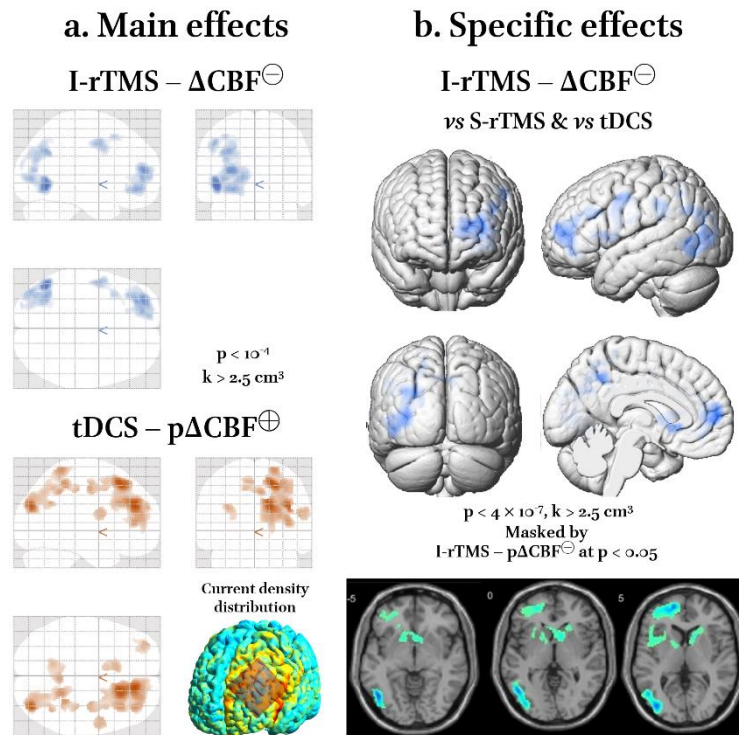


Figure 4: Main and specific effects of the different treatment. a) Main effect of I-rTMS and tDCS. Illustration for current density distribution in one patient computed with SimNIBS 4 [42]. There was no significant effect of S-rTMS. b) I-rTMS was the only treatment being superior to both S-rTMS and tDCS.

Figure 5

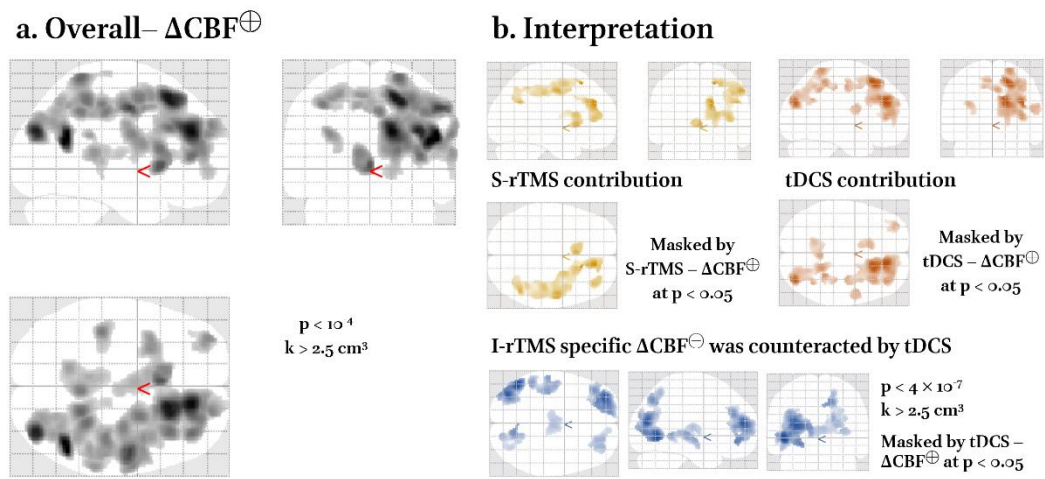


Figure 5: Overall effect and interpretation.

3 Discussion

3.1 Les limites de l'intégration des résultats dans les paradigmes actuels en psychiatrie

Les résultats de nos deux premières études, qui ont été menées dans le cadre conceptuel du modèle "trouble", illustrent les limites que ce cadre impose à la recherche en psychiatrie. Au-delà de l'impossibilité de valider les diagnostics de troubles mentaux - impossibilité intrinsèque au modèle - nous pouvons nous demander si ces biomarqueurs constituent des validateurs externes des troubles mentaux étudiés.

Dans notre première étude, seule la réponse cortisolique au test à l'apomorphine, plus fréquemment observée chez les patients schizophrènes, a semblé permettre d'isoler le trouble schizophrénique et pourrait constituer un tel validateur. Au contraire, l'observation de profils endocrinologiques semblables dans les catégories diagnostiques "trouble bipolaire" et "trouble schizo-affectif" a affaibli la séparation établie entre les deux troubles en supposant que certaines caractéristiques physiopathologiques pourraient être communes (voir **Article 1, Figure 5**).

Notre deuxième étude, quant à elle, a montré que le test à l'hormone thyroïdienne (TRH), que nous considérons comme le plus performant dans ce contexte, n'était positif que pour une partie de la population cliniquement dépressive. Ce résultat laisse entendre qu'une rupture biologique existe au sein d'une population que le modèle "trouble" considère homogène.

Cette observation est cohérente avec les données antérieures dont nous disposons et qui montraient une forte stabilité de ce biomarqueur dans la population dépressive : entre 64% et 76% de patients étaient positifs au test TRH, avec une estimation de sensibilité = 76% et de spécificité = 98% (à noter que ces paramètres ont été évalués à partir d'une étude antérieure, sans tenir compte d'un potentiel chevauchement entre patients souffrant d'une atteinte dépressive unipolaire, bipolaire ou d'un trouble schizo-affectif)⁷⁹⁻⁸¹. Si nous devons utiliser le test à la TRH comme biomarqueur diagnostique de la dépression, en se fondant sur les résultats de nos deux études, il est probable que, d'une part, entre un tiers et un quart des patients cliniquement "trouble dépressif" soient considérés sains ; et, d'autre part, que plus de 90% des patients cliniquement "trouble bipolaire" ou "trouble schizo-affectif" soient considérés dépressifs. Cet état de fait constitue une illustration concrète de la dissociation entre observation d'un processus physiopathologique et un modèle "trouble" détaché du modèle biomédical classique.

Une hypothèse alternative serait que les anomalies endocrines observées soient le reflet de l'atteinte d'une dimension commune à ces différents troubles. L'existence d'un continuum entre troubles affectifs et troubles psychotiques a déjà été proposée via la notion de "*spectre schizophrénie-schizo-affectif-bipolarité*" (pour revue, voir ⁸²). L'hypothèse de ce continuum repose sur l'observation de biomarqueurs communs (p. ex. variants génétiques, observations chimiques et en neuroimagerie, etc.)⁸²⁻⁸⁴. Cependant, ces travaux ont fait appel aux biomarqueurs comme validateurs externes, les reléguant au rôle de facteurs favorisants, ou de regroupement, ce qui ne permet pas la validation de ce modèle dimensionnel. La mise en évidence de biomarqueurs discordants avec le modèle est, quant à elle, un argument en défaveur de la validité de ce dernier. Or, les résultats de nos deux premières études plaident en faveur d'une rupture biologique au sein du "*spectre schizophrénie-schizo-affectif-bipolarité*" d'une part, et d'une continuité du spectre "*spectre schizo-affectif-bipolarité-dépression*" d'autre part. Notons que, pas plus que les biomarqueurs génétique ou chimique ne validaient

complètement le premier spectre, nos résultats ne valident le second, se bornant encore à identifier des facteurs favorisants communs ou de regroupement.

Nos résultats pourraient se heurter aux modèles dimensionnels d'une seconde façon, en particulier à celui proposé par les RDoCs. Les résultats de notre deuxième étude plaident en faveur d'une interaction entre plusieurs systèmes neurologiques (en l'occurrence entre le système dopaminergique et l'axe thyroïdien). L'existence d'interactions physiologiques ou physiopathologiques est également soutenue par la distribution des données que nous avons obtenues (distribution log-normale). Or, le modèle normatif des RDoCs suppose que les effets observés, théoriquement distribués selon une loi normale, soient le résultat de l'addition sans interaction de multiples causes mineures.

3.2 Une alternative existante et fondée sur le modèle biomédical : la classification WKL

3.2.1 Un modèle sur la voie de la validation

La classification de Wernicke-Kleist-Leonhard (WKL) est une classification nosographique qui ne concerne que les psychoses endogènes (le terme "psychoses" revêt ici une définition large, incluant les dépressions et la maladie maniaco-dépressive comme des psychoses endogènes affectives) ⁷⁴. Elle repose sur trois principes : **1)** que les maladies mentales sont des entités discrètes causées par une atteinte spécifique du fonctionnement cérébral. Cette atteinte provoque alors des symptômes directement liés à la fonction cérébrale touchée : les symptômes primaires. Les symptômes primaires peuvent provoquer des symptômes secondaires, selon une organisation nommée "complexe symptomatique" ; **2)** que si un patient présente différents tableaux cliniques au cours de son évolution, il s'agit de différentes

manifestations de la même pathologie (principe longitudinal) ; et enfin **3**) que si différents membres d'une famille sont touchés par des manifestations symptomatiques, il s'agit probablement de la même atteinte⁸⁵.

La classification WKL se situe résolument proche du paradigme biomédical dans la mesure où elle est catégorielle et suppose systématiquement une atteinte étiologique biologique (et une physiopathologie associée). Non limités par le consensus, les modèles de maladies qui la composent demeurent des paradigmes modifiables, ce qui offre une possibilité d'évolution par l'approche hypothético-déductive. Une présentation détaillée de cette classification, ainsi que des travaux de validation, a été publiée par notre équipe (voir **Annexe 1**)⁸⁶.

Le développement du biomarqueur en imagerie ASL pour la catatonie périodique (KP), que nous avons réalisé dans notre troisième étude, partait d'un postulat fondamentalement compatible avec le paradigme biomédical classique. En effet, l'hypothèse causale physiopathologique de la catatonie périodique est l'atteinte du système psychomoteur, expliquant que tous les symptômes primaires de la KP aient un lien avec la psychomotricité (incluant une apathie qui peut mimer une présentation dépressive)^{74,87}. Évolution par rapport aux deux précédentes études qui demeuraient exploratoires : l'hypothèse physiopathologique pouvait alors être formulée *a priori* et l'étude recérait une volonté confirmative. Les résultats que nous avons obtenus, qui montrent le haut niveau de plausibilité de ce biomarqueur, sont en faveur d'une confirmation de cette hypothèse une fois celle-ci confrontée avec la réalité.

Peut-on pour autant parler de validation du modèle de la KP grâce à ces résultats ? Si le modèle était athéorique, ce biomarqueur pourrait n'être vu que comme un validateur externe, dans la mesure où il marque la différence entre la KP et les autres pathologies avec lesquelles le diagnostic différentiel clinique est incertain (c.a.d. le trouble dépressif dont la KP peut mimer la présentation, surtout lors des premiers épisodes, et la cataphasie dont la KP partage le mode évolutif). Dans le modèle WKL proche du paradigme biomédical, il devient une observation de la réalité qui conforte l'hypothèse physiopathologique formulée *a priori*. Il

permet en fait de réaliser **l'étape corrélative** de la validation d'un modèle de la pathologie par un biomarqueur. Cependant, il ne permet ni une validation complète, qui nécessiterait de confirmer par l'expérimentation qu'une atteinte du système psychomoteur provoque le tableau symptomatique de KP, ni de déterminer les étiologies de la KP.

3.2.2 La problématique des troubles de l'humeur dans la classification WKL

La classification de WKL a montré qu'elle pouvait offrir une alternative proche du modèle biomédical, susceptible d'être validé et des modèles de maladie fiables ^{88,89}. Ses meilleures performances sont, pour l'instant, obtenues dans le champ des schizophrénies avec des progrès à la fois sur la validation des diagnostics et sur l'identification de validateurs externes ^{86,90,91}. Le secret de ces performances ? D'une part, la formulation précoce d'hypothèses physiopathologiques fondées sur la connaissances de systèmes neurologiques suffisamment différenciés qui ont pu être identifiés au cours des observations des auteurs de la classification (p. ex. psychomoteur, langagier) ⁸⁵ ; et, d'autre part, l'établissement de tableaux symptomatiques fondés non seulement sur l'observation empirique des patients, mais aussi sur la symptomatologie théoriquement présente lors d'une atteinte du système suspecté – une théorisation fondée sur la connaissance du fonctionnement physiologique normal des systèmes en question. En conséquence, les tableaux symptomatiques se sont enrichis d'une symptomatologie liée à l'hypothèse physiopathologique, ce qui n'aurait peut-être pas été remarquée en l'absence de théorisation préalable ^{87,92-96}.

De l'aveu même de Karl Leonhard (1904 – 1988), il en est autrement pour les troubles de l'humeur⁹⁷. La difficulté à caractériser ces entités reposerait sur plusieurs facteurs : **1)** l'absence d'identification d'un système neurologique spécifique avec les moyens dont les auteurs disposaient, probablement parce que les systèmes affectifs concernent des systèmes de régulation qui sont largement intégrés et distribués dans le cerveau⁹⁸ ; **2)** la forte prévalence des formes exogènes (c.a.d. liées à une pathologie organique ou à un facteur

externe), ou de celles qui sont liées à des facteurs psychologiques ou environnementaux (c.a.d. troubles psychosociaux et de la personnalité, traumatismes complexes, etc., Leonhard utilisait le terme "névroses" pour ces formes) ; et, **3**) le chevauchement symptomatique entre les formes de dépression (qu'elles soient endogènes ou exogènes)⁹⁷. La classification WKL présente donc une limite de taille : elle n'est pas exhaustive et les psychoses affectives qu'elle décrit ne reposent pas sur des hypothèses physiopathologiques, mais sur l'observation empirique^{74,85}. Il n'était donc pas possible de se reposer sur une approche similaire à celle de notre troisième étude pour développer un biomarqueur utilisable dans les troubles de l'humeur.

3.3 L'approche par *phenotyping* inverse pour contourner les limites des modèles diagnostiques existant dans la dépression

Au cours de nos travaux précédents, nous avons vu que les modèles consensuels présentaient des limites intrinsèques qui empêchaient leur validation par des biomarqueurs. De plus, le modèle alternatif dont nous disposons, bien qu'adapté par sa conception à la validation par un biomarqueur, n'offre que des performances réduites dans les troubles de l'humeur (c.a.d. les psychoses affectives dans la terminologie WKL) à défaut de pouvoir ségréger les entités diagnostics et d'hypothétiser une atteinte physiopathologique ou étiologique sous-jacente.

Comment contourner ces limitations ? La solution que nous avons proposée débute par l'identification un biomarqueur, les anomalies de rCBF préfrontales, dont nous savions déjà l'hétérogénéité (ainsi que son incapacité à servir de biomarqueur capable de valider un modèle de dépression en tant que tel), et de le supposer lié à l'existence d'un tableau

dépressif. Notre cinquième étude avait pour objectif de confirmer l'existence de ce lien. Les résultats que nous avons obtenus à l'échelle du groupe nous amènent à plusieurs conclusions : d'une part, nous avons observé que l'hétérogénéité des anomalies de rCBF était encore plus importante qu'attendue, dans une population réelle (population qui incluait des patients unipolaires, bipolaires et souffrant de dépressions comorbides d'affections neurologiques), avec une proportion significative de patients qui présentaient des anomalies différentes des modèles usuels (c.a.d. hyperactivité du DLPFC-G et hypoactivité au niveau du DLPFC-D) ; d'autre part, l'effet commun en imagerie et l'amélioration clinique obtenus en "rééquilibrant" ces anomalies de rCBF nous ont amené à penser que ces anomalies étaient effectivement liées aux processus physiopathologiques dépressifs (et qu'elles ne relevaient pas d'un bruit statistique ou d'une simple variabilité interindividuelle).

Cette étape isolée ne peut aboutir à la proposition d'hypothèses quant aux processus physiopathologiques des dépressions. Pour cela, nous projetons de conduire une analyse supplémentaire de chaque individu afin d'identifier quels systèmes neurologiques sont potentiellement impliqués dans la physiopathologie de chaque patient. Par recoupement et regroupement, il devient possible d'identifier des catégories qui reposent sur l'hypothèse que tel système neurologique ou tel autre est atteint – permettant enfin de se rapprocher du modèle biomédical classique et d'en utiliser les outils. Cette démarche de phénotypage inverse est illustrée en **Figure 3**.

D'un point de vue thérapeutique, il s'agissait d'un traitement qui ne reposait ni sur un biomarqueur associé à la maladie (traitement de précision), ni sur une amélioration de l'abord d'un processus physiopathologique en tenant compte de variables individuelles (traitement personnalisé). Au contraire, il s'appuyait sur des caractéristiques individuelles dont la relation avec la physiopathologie était incertaine, bien que fortement suspectée. En cela il s'agissait donc d'une approche individualisée (reposant uniquement

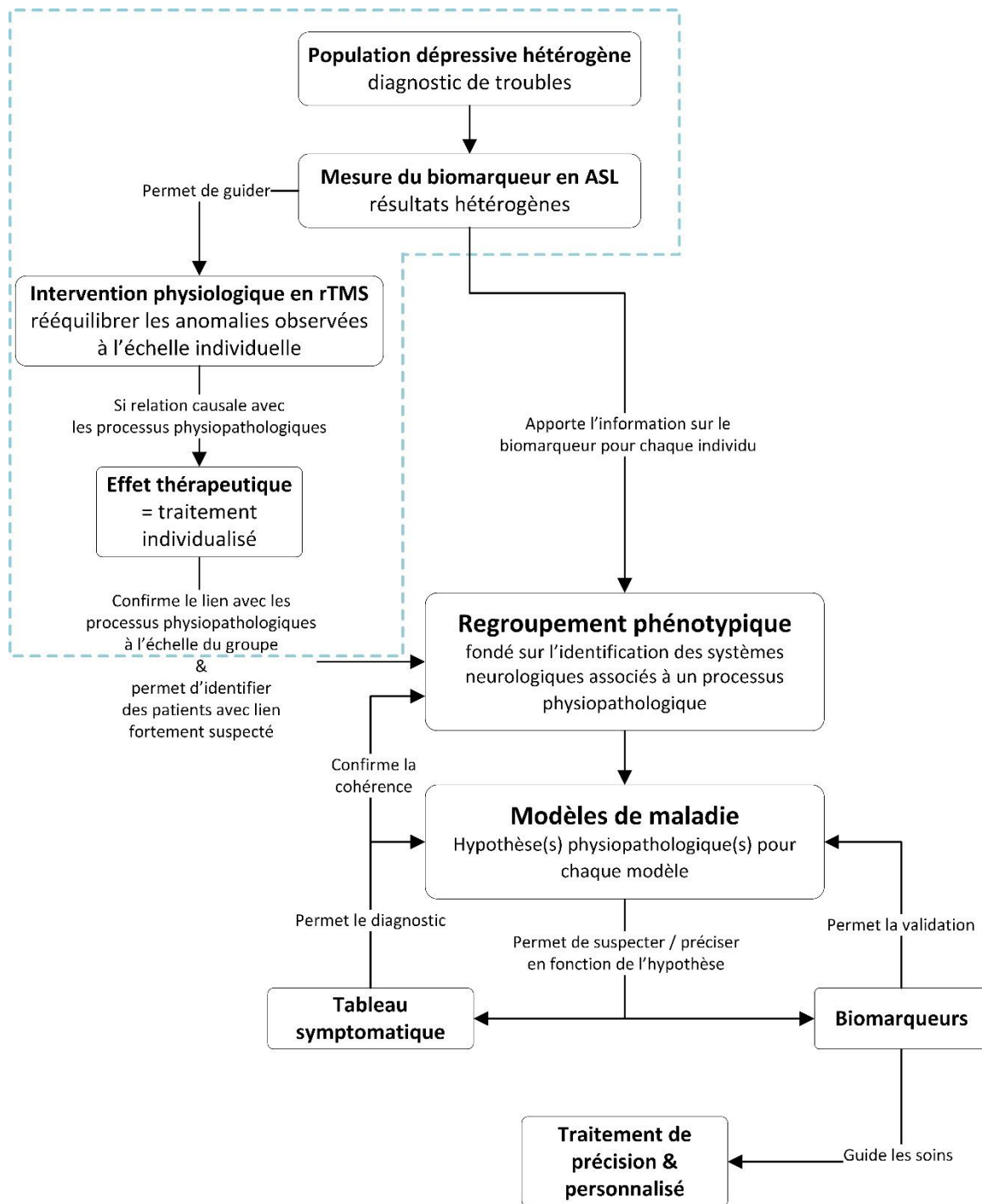


Figure 3 : représentation schématique de la démarche de phénotypage inverse proposée par notre équipe dans le domaine des troubles de l'humeur

La partie du schéma entourée d'un cadre en pointillés correspond aux travaux déjà réalisés.
 ASL : arterial spin labelling, rTMS : repetitive transcranial magnetic stimulation

sur des caractéristiques de l'individu, sans modèle physiopathologique sous-jacent). Le phénotypage inverse pourrait, à l'avenir, nous permettre d'identifier des biomarqueurs thérapeutiques et de savoir quelles sont les caractéristiques individuelles dont nous devons tenir compte pour proposer un traitement à la fois de précision et personnalisé.

3.4 Intégration de l'approche "neurosciences des systèmes" et des systèmes complexes

L'ensemble des "structures" physiologiques cérébrales que nous avons manipulées au cours de ce travail peut s'organiser autour d'unités fonctionnelles : les systèmes neurologiques. Une définition répandue des systèmes neurologiques les associe volontiers à des réseaux neuronaux ou à des voies de neurotransmission – l'idée mise en avant étant que ces réseaux analysent et transmettent de l'information, et qu'ils servent d'interface entre les différents niveaux d'intégration dans les différentes structures cérébrales ainsi que dans le reste du corps (pour revue, voir ⁹⁹). Ses principaux outils d'étude évaluent la communication entre les neurones in vivo : les connectivités (structurelle et fonctionnelle), la description des voies neurologiques neuronales, chimiques ou endocrines, et la façon dont des signaux sont transmis et intégrés dans le cerveau. Bien que les outils utilisés aient été différents, les travaux présentés dans ce corpus s'attachent à explorer les pathologies via l'étude de systèmes neurologiques (à savoir différentes voies neuroendocrines, la neurotransmission dopaminergique, le système psychomoteur, etc.). Nos résultats tendent à montrer que le dysfonctionnement de certains systèmes contribue à la dépression.

Cette observation nous a amené à améliorer nos outils d'exploration des systèmes neurologiques. La mise au point de la rTMS de précision, que nous avons réalisée au cours de

notre quatrième étude, a non seulement permis de développer la rTMS individualisée au cours de l'étude iADAPT, mais il met également à notre disposition un outil d'exploration neurophysiologique de choix. Grâce au ciblage de précision et à la simulation des champs induits, il devient possible de faire des études physiologiques avec un haut niveau de précision spatiale et d'être au plus proche des images obtenues en IRM. Nous prévoyons d'exploiter cette précision pour une étude physiologique explorant les phénomènes d'inhibition intercorticale dans la catatonie périodique. Ce faisant, nous espérons renforcer les résultats obtenus dans la troisième étude de ce corpus et pouvoir élucider les mécanismes de l'atteinte physiopathologique associée à la KP.

Nous avons donc fondé nos hypothèses sur notre connaissance de systèmes neurologiques. Et si ce modèle lui-même devait être remis en question ? L'étude des systèmes neurologiques suppose régulièrement des phénomènes d'interactions, que ce soit entre les systèmes entre eux (p.ex. entre le système dopaminergique et le système thyroïdien dans notre deuxième étude) ou entre les composantes d'un système lui-même (p. ex. entre quantité et rythmicité de la sécrétion TRH et la chronesthésie des cellules porteuses de récepteurs à la TRH)¹⁰⁰. L'existence de tels phénomènes d'interaction à différents niveaux d'organisation (au moins au niveau "systèmes neurologiques" et aux niveaux inférieurs) et avec un grand nombre de sous-systèmes en jeu (chaque système neurologique étant composé de nombreux neurones en interaction, eux-mêmes composés d'organites en interaction, etc.) les placent dans le champ des systèmes dits complexes. Le fait que les systèmes neurologiques puissent être complexes fait poindre deux corollaires inhérents à cette complexité : la possibilité d'une émergence, soit l'apparition de propriétés nouvelles d'un système qui ne sont pas la somme des propriétés des sous-systèmes qui le composent ; et la possibilité de changements d'état et de comportement d'un système, et cela de façon non-linéaire¹⁰¹.

Plusieurs études ont montré que le cerveau et les systèmes qui interagissent en son sein pouvaient être abordés comme des systèmes complexes¹⁰². Parallèlement, la variation d'états

des systèmes pourrait avoir un impact sur l'effet des thérapeutiques : certains traitements pouvant être plus ou moins efficaces en fonction des états dans lesquels se trouvent les différents systèmes neurologiques¹⁰³. Or, il est aujourd'hui habituel d'aborder ces systèmes de façon classique, supposant des états stables ou prévisibles, des liens de causalité constants et des outils d'analyses linéaires. C'est de cette façon que nous avons mené les études qui constituent ce corpus.

À l'avenir, suivant une attitude inspirée de l'approche hypothético-déductive, nous souhaitons faire évoluer ces modèles et les hypothèses qui y sont liées. Nous faisons notamment l'hypothèse que la physiopathologie de la dépression pourrait être liées à la façon dont les systèmes neurologiques se comportent en tant que systèmes complexes plutôt qu'à des anomalies structurelles ou biochimiques permanentes dans un système isolé. Pour répondre à cette question, nous proposons d'aborder la question de la connectivité cérébrale non plus comme une propriété figée dans l'espace et le temps, mais en étudiant la dynamique des changements d'état au sein de ce système ou des sous-systèmes qui le composent, soit étudier le dynome en plus du connectome¹⁰⁴. Cette approche nous est permise grâce à des collaborations récentes avec le laboratoire des neurosciences cognitives et adaptatives de Strasbourg (équipe de Demian Battaglia) et l'équipe "systèmes complexes et bioinformatique translationnelle" au sein de notre propre laboratoire (équipe de Pierre Collet). Ces échanges sont bilatéraux : ils nous permettent de profiter d'une expertise dans ces nouveaux outils d'analyse et nous offrons d'utiliser les systèmes neurologiques pathologiques humains comme cadre de développement pour ces outils et comme objet d'expérimentation.

4 Conclusion

Ce corpus de thèse illustre le cheminement de notre réflexion sur l'utilisation des biomarqueurs pour le diagnostic de dépression. Nos premiers résultats ont montré les limites des modèles "troubles" et dimensionnels et l'impossibilité d'utiliser les biomarqueurs autrement que comme validateurs externes – et seulement à condition que les résultats soient cohérents avec le découpage athéorique ou l'hypothèse normative, ce qui était rarement le cas dans nos études.

Nous avons donc pris le parti de faire évoluer notre modèle et de nous appuyer sur un modèle plus proche du modèle biomédical classique. Notre héritage Léonhardien a influencé notre vision des fonctions cérébrales par le biais des neurosciences des systèmes, notamment dans le domaine des schizophrénies⁸⁵. Dans cette perspective, chaque psychose endogène est associée à l'hypothèse physiopathologique d'un dysfonctionnement d'un ou de plusieurs systèmes identifiés. Au fur et à mesure de la conduite des différents travaux que nous avons présentés, nous nous sommes aperçus à quel point la dépression affectait, directement ou non, de nombreux systèmes neurologiques différents et intégrés : différents axes neuroendocriniens, systèmes de neurotransmission, systèmes fonctionnels, etc. Contrairement aux schizophrénies leonhardiennes, il semble aujourd'hui difficile d'identifier une (ou plusieurs) atteintes systémiques liées à la dépression.

Pour pouvoir progresser dans la compréhension de la dépression, il nous faudra sûrement encore optimiser nos modèles et nos hypothèses. Le développement de biomarqueurs d'imagerie fiables à l'échelle du sujet unique, ainsi que la mise au point de la rTMS de précision, nous ont permis de proposer une prise en charge individualisée en rTMS. Les résultats obtenus à l'échelle du groupe sont en faveur d'un lien entre les anomalies de rCBF

préfrontal repérées en imagerie et dépression. Des analyses à l'échelle du sujet unique restent à faire, elles pourraient aboutir à une démarche de phénotypage inverse et à l'identification de phénotypes dépressifs reposant sur des hypothèses physiopathologiques.

Autre possibilité d'évolution de nos modèles : prendre en compte le fait que les systèmes neurologiques puissent être des systèmes complexes. L'hypothèse selon laquelle la dépression serait liée à des anomalies de la dynamique ou à des interactions entre les systèmes pourrait expliquer la difficulté à isoler un mécanisme physiopathologique avec les moyens d'analyse traditionnels. Cette évolution va nécessiter de faire évoluer nos outils et la façon dont nous confrontons nos hypothèses à la réalité, entretenant le cycle vertueux hypohético-déductif.

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Annexe 1 : Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity

Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity

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While the *ICD-DSM* paradigm has been a major advance in clinical psychiatry, its usefulness for biological psychiatry is debated. By defining consensus-based disorders rather than empirically driven phenotypes, consensus classifications were not an implementation of the biomedical paradigm. In the field of endogenous psychoses, the Wernicke-Kleist-Leonhard (WKL) pathway has optimized the descriptions of 35 major phenotypes using common medical heuristics on lifelong diachronic observations. Regarding their construct validity, WKL phenotypes have good reliability and predictive and face validity. WKL phenotypes come with remarkable evidence for differential validity on age of onset, familiarity, pregnancy complications, precipitating factors, and treatment response. Most impressive is the replicated separation of high- and low-familiarity phenotypes. Created in the purest tradition of the biomedical paradigm, the WKL phenotypes deserve to be contrasted as credible alternatives with other approaches currently under discussion.

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Keywords: schizophrenia; deep phenotyping; catatonia; supersensitivity psychosis; *ICD*, *DSM*, endogenous psychosis; phenotype; periodic catatonia; cataphasia; affect laden paraphrenia; cycloid psychoses; hebephrenia; system schizophrenia; epistemology; bipolar; unipolar; Wernicke; Kleist; Leonhard; classification

Introduction

The field of endogenous psychoses is the one for which the hypothesis of “brain diseases” is the most likely in psychiatry. The past 40 years’ exclusive use of *International Classification of Diseases (ICD) – Diagnostic and Statistical Manual of Mental Disorders (DSM)* diagnoses,¹ although successful in the field of clinical psychiatry as an applied science, did not allow significant progress in biological psychiatry as a basic science. Two postulates of consensus

classifications might have made them unsuitable for this task. First, consensus criteria could not be changed, ruling out any attempt to optimize the descriptions. Second, the atheoretical stance negated any etiological or pathophysiological hypothesis,² eg, making no distinction between endogenous and neurotic depressions such as bereavement.³

The traditional *biomedical paradigm* starts from *phenotypes* rather than consensus-based *disorders*. Embracing the *naturalistic framework*,⁴ it posits that a disease is a

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natural entity defined by an *etio-pathophysiological model* which accounts for the phenotype.⁵ The model is given at the biological level, assuming a single and rare cause of major effect due to selection pressure. The typical correlation-experimental 2-step process is the theory-of-proof of the biomedical paradigm that validates the model, turning it into a *disease*. The major strength of this approach stems from this *model validity* or validity per se which translational research converts into the magic triplet of applied medicine: diagnosis, diagnostic test, and treatment.⁴

The limited construct validity of *ICD-DSM* disorders, even for schizophrenia,⁶ and the recurrent failures to validate any biological model that could account for them, raised doubt about the suitability of the biomedical paradigm in basic psychiatry.⁷ The leading proposals now turn towards dimensional approaches, which come with a major paradigmatic framework shift with the adoption of *normativistic* assumptions.^{8,9} Here a disease is defined as a *pathological deviance*, ie, a mere deviation from the norm, which makes the implicit hypothesis of multiple and frequent causes of very small effects.⁴ These are typically referred to as risk factors or modifiers in medicine rather than diseases, and translate into much less efficient interventions.⁴

Yet, consensus classifications never claimed to be fair implementations of the biomedical paradigm. They were mainly designed for clinical use and not for basic research. Hence, their lack of success in field does not rule out the relevance of the naturalistic framework in psychoses. Indeed, at least one research program, referred to as the Wernicke-Kleist-

Leonhard (WKL) pathway,¹⁰ was able to define clear-cut phenotypes. This paper gives an overview of the principles that guided their optimization,¹¹ and reviews the evidence supporting their construct validity. Validity per se will be only considered for periodic catatonia which currently has the most supported biological model. The terminology has been slightly changed relative to previous publications to adapt to current clinical psychiatry and neuroscience (*Appendix 1*).

Epistemological framework and methods

Major heuristics that guided the empirical elaboration of the phenotypes

The naturalistic assumptions state that, due to selection pressure, disabling phenotypes are accounted for by a single and rare cause of major effect. Hence, they are *categorical* in nature and liable to the *principle of parsimony*.⁴ A phenotype is a “typical” set of observable characteristics shared by a group of patients¹² which includes the *clinical presentation*, ie, the set of reported symptoms and clinical signs collected from the patient’s examination, but also the *course of the symptoms*, ie, how they appear, which ones persist, which ones disappear, or whether they completely change from one clinical picture to its opposite (bipolarity). Finally, typical *contextual elements* might also enrich the description. The WKL School *empirically* optimized their phenotype descriptions by sorting patients according to their long-term catamnestic observations following heuristics stemming from the principle of parsimony: symptom-complex, longitudinal and family-aggregation principles (*Box 1; Appendix 2*).

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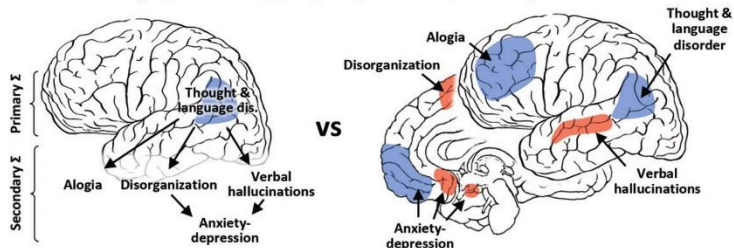
Principle of parsimony applied to brain, time, and family

Principle of parsimony: Among competing hypotheses, the one which needs the fewest assumptions should be favored. Hypothesizing endogenous psychoses being subtended by a **single cause of major effect** (due to selection pressure), allowed Wernicke, Kleist, and Leonhard to add the following **heuristics** to the **principle of Sydenham**, in order to define **phenotypes** and to test for their construct validity (see *Appendix 2* for details).

Elementary (primary) symptoms principle



Carl Wernicke (1848-1905)



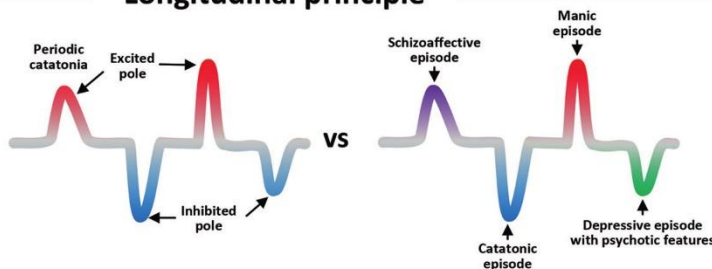
Mental illness affects only a limited part of brain functioning causing specific elementary symptoms in one neuropsychological domain (emotion, thought, or psychomotricity) which in turn induce secondary symptoms.

ICD-DSM: One part of the brain is affected independently for each symptom of a mental illness

Longitudinal principle



Karl Kleist (1879-1960)



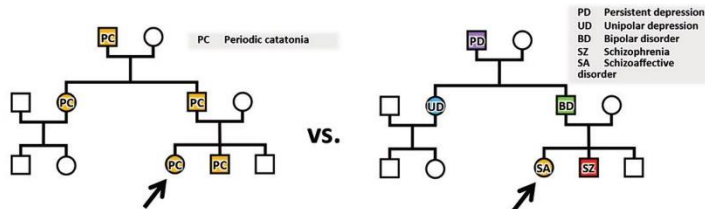
If an individual presents several clinical pictures over time, he or she is affected by the same pathology, presenting with different manifestations.

ICD-DSM: If an individual presents several clinical pictures over time, Sydenham's principle overrules the single liability thesis.

Family aggregation principle



Karl Leonhard (1904-1988)



If several members of the same family present with an endogenous psychosis, they are likely to share the same liability.

ICD-DSM: If several members of the same family present with different psychotic manifestations, Sydenham's principle overrules the single liability thesis.

Box 1.

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Validity assessment of WKL phenotypes

The *construct validity* of a phenotype encompasses many different properties. Firstly, to comply with the logical positivist's call for objectivity, a phenotype must be reliable,¹³ and this *reliability* is assessed by inter-rater reproducibility. Secondly, the fulfillment of the naturalistic assumptions behind the concept of a phenotype could be supported by its predictive, face, differential, and taxonomic validities. Test-retest reproducibility will not only be considered here as a measure of *predictive validity*¹⁴ but also of *face validity*, ie, how closely patients match the "typical" definition and to what extent it accounts for all of the patients' manifestations.¹⁵ Indeed, it shows that phenotype descriptions

are either comprehensive enough to include all possible clinical pictures or focus on an unchanging symptom-complex for the diagnosis to remain lifelong stable. Hence it avoids resorting to comorbidities other than behavioral complications, eg, drug abuse. *Differential validity* looks for the selective associations of a phenotype with *external validators* through head-to-head comparisons. These can be any clinical, contextual, or biological features that are not part of the original description,¹⁶ eg, age of onset, familiarity, gender difference, treatment response, any biological parameter etc. Finally, *taxonomic validity* appraises the fulfillment of the categorical structure of the phenotypes through taxometric analyses.¹⁷

Validity per se demands a *biological causal model* accounting for a phenotype. The model validity is assessed through a two-step process acknowledged as the "*theory of proof*"¹⁸ in medicine: the demonstration of a strong *correlation*¹⁸ with the biological cause and the outbreak or the alleviation of the phenotype with the *experimental* manipulation of the cause. It has mainly been investigated in periodic catatonia.

Overview of WKL classification

The field of endogenous psychoses

The WKL classification is limited to the field of endogenous psychoses. *Psychosis* does not have the same meaning here as in the *DSM* or the *ICD*. It is not restricted to hallucinations or delusions, but stands for a wide range of specific emotional, cognitive, and behavioral disturbances, supposed

to be mainly accounted for by some *qualitative disturbances* of one cerebral process, ie, naturalistic assumption. It is opposed to the old concept of "neuroses" which putatively results from nature-and-nurture-interactions, eg, the maladaptive response of a given personality coping with a specific life event. These are *complex diseases* mixing trait risk factors (addition of multiple causes of very small effect, ie, normativistic) interacting with other factors, ie, synergistic assumptions.⁴

The WKL phenotypes deserve to be contrasted as credible alternatives with other approaches currently under discussion

The *endogenous* feature refers to Kraepelin's, Jaspers', or Birnbaum's tripartite system in which psychiatric symptoms could be organic (exogenous, ie, secondary to a medical condition including substance-related), reactive (neurotic) or endogenous.¹⁹ Endogeneity assumes a single cause, which yet remains to be discovered.

While the *ICD* and the *DSM* distinguish exogenous disorders, the endogenous - neurotic distinction, which could be rephrased as simple vs complex diseases, has completely disappeared due to the endorsement of the atheoretic principle.¹³ Consequently, on the psychotic side, psychotic post-traumatic stress disorder, psychotic body dysmorphic disorder, or stress-related brief psychotic reactions, as observed in borderline personality disorder, are not endogenous psychoses. Yet the largest differences lie on the affective side. Reactive, eg, bereavement, and neurotic depressions, which probably account for most major depressive disorders,²⁰ are not part of the endogenous psychoses in the WKL perspective. It is worth reminding the endogenous-neurotic distinction has been repetitively supported by taxometric analyses of depressive disorders.²¹

While most WKL phenotypes are within the scope of affective and psychotic *ICD* or *DSM* disorders, there are some exceptions, eg, some system schizophrenias might be diagnosed in the autistic spectrum or in cluster A personality disorders.

Basic features and relationship with consensus classifications

The WKL school defines 35 phenotypes, accounting for about 90% of endogenous psychoses²² (*Table I*). To achieve this, descriptions do not focus on what phenotypes have in

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COURSE	FAMILY	NEUROPSYCHOLOGICAL DOMAINS				POLARITY		
		AFFECT		THOUGHT	PSYCHOMOTRICITY			
Relapsing-remitting	Phasic affective psychoses	Pure depressions (D)	Pure euphorias (E)			Mono-polar		
		Agitated D	Unproductive E					
		Hypochondriacal D	Hypochondriacal E					
		Self-torturing D	Exalted E					
		Suspicious D	Confabulatory E					
		Non-participatory D	Non-participatory E					
		Pure mania						
		Pure melancholia						
	Manic-depressive illness					Bipolar		
	Cycloid psychoses	Anxiety-happiness psychosis		Excited-inhibited confusion psychosis	Hyperkinetic-akinetic motility psychosis			
Progressive relapsing	Non-system schizophrenias	Affect-laden paraphrenias		Cataphasia	Periodic catatonia			
Progressive	System schizophrenias	(System) hebephrenias (H)		System paraphrenias (P)	System catatonias (C)	Mono-morphic		
		Foolish H		Hypochondriacal P	Parakinetic C			
		Eccentric H		Voice-hearing P	Pseudo-compulsive C			
		Shallow H		Incoherent P	Proskinetik C			
		Autistic H		Fantastic P	Negativistic C			
		Combined H n=6		Confabulatory P	Short-circuit-speech C			
				Expansive P	Absentminded C			
				Combined P n=15	Combined C n=15			

Table I. Overview of the WKL phenotypes (inspired by ref 97). Only the 35 major forms are displayed; the 36 minor forms are two by two combinations of system schizophrenias. See *Appendix 2* for the consensus on the English translation.

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common, but rather in what aspects they differ from one another. For instance, positive symptoms might occur in many phenotypes and hence are not helpful per se. Moreover, in contrast to *ICD/DSM*, symptoms have no meaning by themselves but only as part of a specific symptom-complex organized according to the primary-secondary principle (*Box 1, Appendix 2*).

Phenotypes are grouped into five families^{22,23} according to their course, mono- or bipolarity, and their primary affected neuropsychological domains: affect, thought, and psychomotricity (*Table 1*). There are one monopolar, three bipolar, and one monomorphic families, gathering not 1 but 12 monopolar affective phenotypes and not 1 but 7 bipolar phenotypes. According to the WKL perspective, the term “*schizophrenia*” only applies to phenotypes with residual symptoms which encompasses one bipolar and the monomorphic families.

The WKL classification is strikingly different from consensus ones. While *ICD-10* and *DSM-IV* have a concordance of $\lambda=0.86$ with one another, WKL clearly gathers patients differently since its concordance is only of $\lambda=0.4$ with *ICD-10* and of 0.56 with *DSM-IV*.²⁴

Reliability of WKL phenotypes

On average, WKL phenotypes are highly reliable with 97% of inter-rater diagnostic consistency when performed by expert raters, giving an average kappa value of 0.82 to 0.93.^{25,26} In comparison, consensus disorders have kappa values of 0.84 for schizophrenia, 0.71 to 0.83 for bipolar disorder, and 0.22 for schizoaffective disorder.²⁷

Test-retest reproducibility, prognostic and face validity

In prospective studies, the test-retest reproducibility at 15 years, follow-up was 93% and ranged from 76% to 93% at 33 years follow-up.^{28,29} This stands well even in comparison to the much broader *ICD* diagnosis of schizophrenia which remains consistent in 90% of the patients in retrospective chart review after a follow-up of 25 years.³⁰

Differential validity of the main phenotypes

Monopolar affective phenotypes with purely relapsing-remitting course

Pure melancholia and pure mania

Pure melancholia and pure mania are monopolar affective

phenotypes.³¹ The term “*monopolar*” is used here rather than “*unipolar*” to emphasize the differences between the original WKL concept and consensus classifications. Monopolarity implies symptomatic stability both within and between the episodes, ie, *monomorphy*, as well as the absence of mixed or incomplete states (see manic-depressive illness). Hence, monopolarity applies also to the manic pole. The independence of the pure mania phenotype has been replicated in the Zurich cohort.³² While grounded in the affect, pure mania and pure melancholia characteristically also affect the other domains, eg, drive, speed of thought, and psychomotricity.

The prevalence of pure melancholia is many times higher, accounting for up to 10% of endogenous psychoses, whereas pure mania is below 1%. The course is purely relapsing-remitting with an average of 12 months for an episode of melancholia.³³ Symptoms typically respond to usual antidepressant or antimanic therapeutics. Both phenotypes have little inheritance with 3% of affected first-degree relatives which significantly differs from manic-depressive illness (22% to 36%).^{34,35}

Pure depressions and pure euphorias

These are also relapsing-remitting monopolar phenotypes, ie, monomorphic without mixed or incomplete states (see manic-depressive illness, MDI).³¹ The five pure depressions and the five rare pure euphorias are characterized by specific disturbances of distinct emotional systems within the affective domain sparing thought, drive, and psychomotricity. They often go along with characteristic delusions or hallucinations: delusional guilt in self-torturing depression, persecutory ideas in suspicious depression and unpleasant bodily sensations in hypochondriacal depression. These may be *ICD*-diagnosed as depression with psychotic features or schizoaffective disorders. These phenotypes only account for 4% of inpatients with endogenous psychoses.³³ In contrast to pure melancholia, their episodes typically last years with progressive beginnings and endings³⁶ and they are less responsive to therapeutics.^{36,37} They also have a low familiarity when compared with MDI (3% vs 22% to 36%).^{34,35}

Bipolar phenotypes with purely relapsing-remitting course

In the WKL sense, bipolarity is not limited to affective disorders but extends to schizophrenia-like psychoses as

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well. Only manic-depressive illness belongs to the affective disorders in the narrower sense.

Manic-depressive illness

MDI³¹ is the most frequent bipolar phenotype, accounting for 19% of patients with endogenous psychoses.³⁵ Even though the *ICD/DSM's* concept of bipolar disorder stems from the WKL-MDI one, there are major differences. Episodes have distinctive clinical features allowing MDI to be diagnosed even in patients having depressive recurrences only, in most cases from the first episode.³⁸ Affective episodes are characterized by their polymorphic manifestations and the mixed or incomplete features, both being currently rediscovered under the emerging concept of bipolar depression.³⁹ Clinical manifestations are qualified as polymorphic because they change within and between episodes. The span of MDI's clinical presentations is so large that it can mimic any monopolar or cycloid picture, yet generally not in a stable way. The trigger for these phenotypical changes can be endogenous, but these patients are also highly reactive to external events. For instance, patients can be talkative and lively during the interview, showing no outer manifestation of depression, while apathy and suffering can come back as soon as they walk out of the office. Such mood reactivity can also be observed in neurotic forms, but then of lesser magnitude. Mixed states are defined as the co-occurrence of both the manic and depressive pole among the different domains: affect, thought, and psychomotricity. This can be seen for instance in the combination of inhibited affect (sadness), excited thinking process (racing thoughts), and excited psychomotricity (agitation).³⁸ Incomplete states are an extension of the former concept, meaning that aside from being excited and inhibited, a single domain can also be completely unaffected. For instance, affect and psychomotricity might be inhibited while the speed of thought might be normal.

On average, MDI episodes are of shorter duration than monopolar ones, ie, 6 months on average for depressive episodes.³³ Acute onset, sudden cessation; or rapid switches are common. This phenotype shows more frequent relapses than monopolar phenotypes and this tendency tend to increase with aging.³³

The hereditary burden of MDI is significantly higher than for monopolar affective phenotypes and cycloid psychoses, with 22% to 36% of affected first-degree relatives.^{34,35,40}

There are two reasons for the familiarity of MDI to exceed the one of *ICD/DSM* bipolar affective disorder (9%).⁴¹ Firstly, as the MDI diagnosis can be made early, even if the clinical presentation is purely depressive, most intra-familial incongruencies vanish as nearly all of the (pseudo-) unipolar patients are diagnosed as MDI.⁴² Secondly, *ICD/DSM* bipolar disorder subsumes some cycloid psychoses which have low familiarity.

Cycloid psychoses

Cycloid psychoses are bipolar phenotypes of purely relapsing-remitting course. They have more intense psychotic manifestations, and are hence routinely diagnosed by *ICD/DSM* as schizoaffective or schizophrenic disorders. There are three different cycloid psychoses corresponding to the predominantly affected domain within which they quantitatively oscillate between opposite extremes. These are referred to as "poles," organized into three axes:

- Hyperkinetic-akinetic motility psychosis in the psychomotor domain
- Anxiety-happiness psychosis in the emotional domain
- Excited-inhibited confusion psychosis in the thought domain.

Cycloid psychoses represent 20% of all endogenous psychoses.³⁵ Their clinical manifestations are highly *polymorphic*, due to rapid changes in the intensity and even in the polarity of the manifestations within the same episode. Importantly however, the opposite poles always manifest successively and never at the same time.

The *ICD-10* diagnosis of "acute and transient psychotic disorders" or ATPD (F23), was designed to embody these phenotypes together with the "*bouffées délirantes aiguës des dégénérés*"⁴³ or BDA (acute delusional outburst of the degenerates).⁴⁴ Yet, studies have found that ATPD only overlaps with the BDA and cycloid diagnoses in half of the cases.^{44,45} Furthermore, cycloid psychoses are defined as lifelong phenotypes, while BDA and ATPD are only defined as episodes. Hence the latter diagnoses are instable on follow-up: a third of initial BDA switches to schizophrenia or schizoaffective disorder after 10 years,⁴⁶ while it happens in half of initial ATPD after 5 years.⁴⁷

Cycloid episodes usually last between 1 to 3 months, and have acute onset and ending in up to two thirds of the cases.³³

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Yet, these two features are neither sensitive nor specific enough to be used as diagnostic criteria.⁴⁸ The relapsing-remitting course means that, in the interepisode interval, patients develop full insight about their illness and do not present significant residual symptoms whatever the number of recurrences.^{48,49} Cycloid psychoses might be related to minimal brain damage. Unspecific MRI abnormalities are more frequent relative to non-system schizophrenias, eg, enlarged ventricles, white matter hyperintensity, or small cortical defects.⁵⁰⁻⁵² These might be acquired early: mothers of cycloid patients report significantly more infections of the upper airway during the first trimester of pregnancy, childbirth complications are more frequent and seasonality of birth is larger in cycloid phenotypes relative to controls and non-system schizophrenias.⁵²⁻⁵⁴ Conversely, the heritability of these phenotypes is low, with only 5% of affected first-degree relatives, indistinguishable from controls and significantly lower than in MDI, cataphasia, and periodic catatonia.^{34,35,40,55}

Patients affected by cycloid psychoses are more vulnerable to precipitating factors: stress, sleep disorders, cannabis, etc. Women are especially sensitive to estrogen drop: 88% of episodes start in the luteal phase, which is significantly higher than for any other phenotype.⁵⁶ Accordingly, cycloid phenotypes account for 60% of postpartum psychoses, with motility psychosis accounting for 36% on its own.⁵⁷

Antipsychotics shorten the episodes but should be used with caution in motility psychosis, which is especially at risk for neuroleptic malignant syndrome.⁵⁸ They are also effective in relapse prevention, bearing in mind that these patients are especially sensitive to their side effects. The maintenance of too-high doses of first-generation antipsychotics after remission favors post-psychotic depression and abulia, so that otherwise fully remitted cycloid patients might appear to suffer from residual schizophrenia.⁵⁹ Yet, once maintained for more than a month, the rapid discontinuation of antipsychotics increases the risk of relapse to a point that was unknown in the pre-neuroleptic era,^{59,60} raising the hypothesis that most these relapses might be induced dopamine supersensitivity psychosis.^{59,60} Mood stabilizers not only help as an add-on treatment in the acute phase, but might also be considered as viable alternatives to antipsychotics in the maintenance phase considering their decent relapse prevention.⁴⁸

Phenotypes with build-up of residual symptoms: the schizophrenias

In the WKL perspective, the term “*schizophrenia*” carries a prognostic value as these phenotypes progress toward a persistent residual state of which abulia is a frequent, though not characteristic, feature. WKL schizophrenias have phenotype-specific residual symptoms.

“System” and “nonsystem” schizophrenias have nothing to do with the concept of “delusion systematization,” ie, the logical organization of delusional ideas. Here, “*system*” must be understood analogously to the involvement of a specific biological function as in organic medicine, ie, system diseases. Regarding brain diseases, these systems are functional networks, eg, the pyramidal system is the one that degenerates in amyotrophic lateral sclerosis. Multiple systems can be affected, as in multiple-system atrophy, which combines the degeneration of extrapyramidal, cerebellar, and vegetative systems. Due to their clear-cut and life-long *monomorphic* residual symptoms, *system schizophrenias* are qualified as such because they are supposed to be accounted for by the impairment of such specific functional networks, whereas *non-system schizophrenias* are *polymorphic*, *bipolar*, and putatively involve many “systems.”

Non-system schizophrenias

There are three non-system schizophrenias characterized by a predominantly affected domain within which they can express both poles. In contrast to cycloid psychoses, changes are not purely quantitative, but also *qualitative*, with symptoms from both poles occurring together. Because of their bipolarity, they show a broad, yet specific, clinical spectrum. They mostly run a progressive-relapsing course and develop a characteristic set of residual symptoms of increasing severity. All have a specific heredity burden, *without crossed liability*. Interestingly, domain-specific attenuated symptoms have been reported in nonpsychotic relatives, especially in obligate carriers.⁶¹ As a whole, nonsystem schizophrenias respond much better to antipsychotics^{62,63} and to the addition of mood stabilizers³⁷ compared with system schizophrenias. However, treatments mostly improve acute manifestations but have virtually no effect on residual symptoms.

Affect-laden paraphrenia is a schizophrenic bipolar phenotype of the affective domain. It only accounts for 5% of

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endogenous psychoses but for 10% of ICD/DSM psychotic disorders.^{33,35} Its various clinical presentations have been independently described by many authors under various names around the world.^{46,64-66,46,67-69} The WKL school subsumed them under the same phenotype because individuals could change from one clinical picture to the other and because relatives could display one of the other clinical pictures (Box 1).⁷⁰ The core of affect-laden paraphrenia is a *paranoid mood* which encompasses the strong mistrust, irritability and hostility of one pole blended with the feeling of self-importance of the other pole. This specific affective state leads to more or less systematized delusions of persecution and grandiosity often accompanied by multimodal hallucinations.⁷¹ The residual picture is the *irritated reference syndrome*, which is a delusional construction about intentions of specific others regarding oneself. Besides the pathological affect underpinning the delusions, emotional responses dampen over time. A feature that repeatedly impressed many authors was the contrast between the *judgment errors*, up to the acceptance of fantastic ideas, with a generally *well-organized thought process* which is constant out of the episode.^{46,64,69} The course is mostly progressive-relapsing. Over 10 to 30 years, patients develop increasingly pervasive reference ideas of more and more fantastic coloring. Yet they remain able to adapt to the interviewer in superficially denying their delusions.

Antipsychotics help in blunting the affective pressure that ensues, but also fuels the delusions, yet never allowing the patients to fully distance themselves from their ideas (84% of responders).^{62,63} The median age of onset is 36 years, but is highly variable explaining late-onset cases. The phenotype has an autosomal recessive inheritance pattern with 12% of affected siblings vs only 2% of affected parents.^{34,35} There is also a significantly larger number of patients born from consanguineous weddings relative to other schizophrenias and cycloid psychoses (3.3% vs 1%).^{56,61}

Cataphasia (schizophasia) is a bipolar phenotype mainly affecting thoughts and language. It accounts for about 8% of endogenous psychoses and its estimated prevalence is about 0.1 to 0.2% in Germany.⁷² Its excited pole was first described by Kraepelin under the label "*schizophasia*." The observation of multiplex families allowed to relate this clinical picture to its counter-pole dominated by thought inhibition.⁷³ The core of the phenotype is a specific thought and language disorganization with incoherence and logical

derailment coming with syntactic and semantic errors, eg, paragrammatism, paraphasias, and neologisms. These core symptoms need to be specifically investigated, especially in the residual phase. As everyday concrete thinking is less affected, they frequently remain discreet in ordinary conversations and behavior. The *thought and language test*, a standardized WKL examination procedure that challenges abstract thinking, greatly sensitizes the detection of cataphasic features.^{72,74,75} Language errors must be appraised in the context of patients' skills, so are hence harder to ascertain in non-native speakers; in such cases they may be secured by long-term follow-up re-examination. As the disease progresses, nonspecific fluctuating persecutory ideas might remain but are secondary to the core residuum which impairs patients' understanding, leading to misinterpretations in close similarity with residual Wernicke's aphasias.⁷⁶ During episodes, patients exhibit a variety of affective and psychotic symptoms, that are frequently in the foreground.

Although the episodes respond to antipsychotics (up to 78% using first-generation drugs),^{62,63} the specific symptoms are treatment-resistant. The association of thought disorganization with emotional turmoil make cataphasic patients particularly at risk for suicidal behavior (52% of patients) and deaths by suicide (18% of patients).⁷² The phenotype shows familial aggregation, with 15% to 25% of affected first-degree relatives, on top of which 12% of non-psychotic first-degree relatives also show milder forms of the typical thought and language disorganization.^{34,35,72} A genetic locus has recently been found for cataphasia on Chr11p, the strongest association being found with a gene coding for cathepsin-D, a lysosomal protease which mutations can cause neurodegenerative storage disorder (Roth et al, unpublished material).

In accordance with their residual thought and language impairments, cataphasic patients have a specific dysfunction of their temporoparietal junctions bilaterally; these are hypoactive and functionally disconnected.⁷⁷ This fits with multimodal imaging results showing that the same cortices, together with their underlying white matter, were hypo-myelinated and had an increased iron content (Foucher et al, unpublished material). Considering that the latter could likely result from microglial activation, these findings are in line with those reported in cathepsin-D deficits,⁷⁸ suggesting a neurodegenerative model for cataphasia.

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Periodic catatonia is roughly as common as cataphasia, accounting for about 7% of patients suffering from endogenous psychoses. Despite its name, WKL's periodic catatonia should not be viewed as the mere recurrence of *IDC/DSM* catatonic episodes.⁷⁹ Beyond mere global bipolar quantitative motility changes, the core of this phenotype is a specific disorganization of psychomotor functions, ie, mostly affecting expressive and reactive movements. The qualitative changes manifests as the *mixing* of both akinesia and hyperkinesia but to different body parts, eg, rigid hypokinesia of the upper limb together with facial restlessness. Other qualitative anomalies are *parakinesias* that alter simple movements, making them appear stiff and/or jerky, or distort expressive movements, especially the mimics, going as far as grimacing.⁷¹ These are currently rediscovered under the name of spontaneous dyskinesias.⁸⁰ However, parakinesias have a wider spectrum and distinctive features that allow them to be differentiated from tardive dyskinesias.⁸¹ The residual state includes the persistence of these characteristic psychomotor anomalies together with abulia, while residual psychotic symptoms are rare. The social or occupational impairment is highly variable (GAF = 57±19 after an average of 13 years of progression).^{77,82}

This phenotype is responsive to antipsychotics (60% of responders with first-generation drugs),^{62,63} but also sensitive to their extrapyramidal side effects, hence its large response increment after switching to clozapine.^{37,83} It further benefits from benzodiazepines⁸⁴ and electroconvulsive therapy which are inefficient in system catatonias.⁸⁵ Yet all therapeutic efforts can only help coping with exacerbations but fail to improve the specific residual symptoms.

At the *etiological level*, several studies have confirmed the high heritability of periodic catatonia, with 21% to 26% of affected first-degree relatives,^{34,35,83} which is significantly larger than for system catatonias (4%).²⁵ Considering the extended phenotype, ie, including nonpsychotic relatives with only psychomotor signs, the percentage raises to 32% to 41% of affected first-degree relatives.^{86,87} Transmission is autosomal dominant with incomplete penetrance and anticipation. Two genome-wide linkage studies found a major susceptibility locus on Chr15q accounting for about two thirds of the pedigrees (OMIM 605419).^{88,89} This has recently been supported by an association peaking in an intergenic region between *CGNL1* and *GCOM1* (Gawlik et al, unpublished material), the latter being implicated in an NMDA-dependent

neuroprotection pathway that might be especially important for GABAergic interneurons.⁹⁰ Yet periodic catatonia is likely to be genetically heterogeneous: other pedigrees matched on other loci, eg, Chr21q13-ter.⁸⁹ The unity of the phenotype might be better explained at the *pathophysiological level*. Based on previous literature, especially on the independent replication of its specific left premotor hyperactivity^{91,77} when compared with other psychoses, periodic catatonia is currently modeled as an acquired deficit of intra-cortical inhibition possibly ensuing the degeneration of GABA interneurons. As a first validation step, the strength of the correlation between left premotor hyperactivity and the phenotype was prospectively tested in individual patients by comparing a new group of periodic catatonias to other psychoses, including system catatonias. The association was found to be both sensitive (98%) and specific (88%), making the case for this functional imaging measure to be a viable biomarker.⁹² As interventional validation step, personalized rTMS was used to correct left premotor inhibition deficit. Not only did the improvement of residual symptoms resulted in substantial functional gains, but was also specific for premotor targets (vs prefrontal and parietal ones) and for periodic catatonia (vs system catatonias).⁹³

System schizophrenias

System schizophrenias account for 21% of inpatients with endogenous psychoses.³³ They have an insidiously progressive course resembling that of slow encephalitis. They begin with a *process phase* of 1 to 5 years, in which unspecific dysthymic and psychotic manifestations can accompany the growth of a distinct symptom-complex, presumably due to the deterioration of a specific system. After processual symptoms vanish, the residual clinical picture will remain unchanged up to the end of the patient's life, ie, monomorphic.⁹⁴ Phenotypes are ordered according to the domain to which belongs the affected system:

- The four phenotypes of hebephrenias share a specific disturbance of judgement emotions which leads to affective flattening and loss of initiative. Judgement emotions are the one needed to evaluate non-concrete and non-present issues such as the course of life
- There are six major phenotypes of system paraphrenias having specific combinations of hallucinatory and delusional features
- System catatonias consist of six varieties of definite qualitative psychomotor impairment.

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The three subfamilies have different age of onset: 24 for system catatonias and 23 for hebephrenias, but 36 for system paraphrenias.³³ No significant hereditary burden has been reported. The percentage of 2% to 4% of affected first-degree relatives is not significantly different from what is seen in controls but significantly different from periodic catatonia.^{25,34,35,83} In system catatonias, 34% of the mothers report an infection of the upper airways during the second trimester of pregnancy which significantly differs from periodic catatonia (8%).⁹⁵ Neuroimaging reveals significantly more cortical atrophy in system schizophrenias than in non-system phenotypes.^{96,97} Finally, contrary to other phenotypes, interventions have little or no effectiveness: antipsychotics (1% to 40% of responders to first-generation antipsychotics),^{62,63} no advantage for clozapine,^{37,83} ECT, mood stabilizers, or antidepressants.³⁷

Conclusion

In accordance with the biomedical paradigm, the WKL School has empirically optimized the descriptions of putatively natural phenotypes inspired by neuroscience and based on common medical heuristics. They are reliable, they have good predictive validity and differential validity regarding

gender ratio, age of onset, familiarity (without crossed-heritability), pregnancy complications, and response to treatment. Only their taxonomic validity deserves to be further evaluated. While the biological model for cataphasia remain to be tested, the one for periodic catatonia has already been supported by correlational and interventional evidence.

Despite their elaboration in the purest tradition of the biomedical paradigm, yet diverging from dominant paradigms, these phenotypes received poor attention from basic researchers (see also *Appendix 2*). On the other hand, clinicians value them for their long-term stability and their prognostic and therapeutic relevance. We hope that this review will contribute to revive the interest of the psychosis research community for this research program which deserves to be confronted with others in an adversarial collaborative way.⁴ ■

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Le développement de biomarqueurs et de la neuromodulation de précision dans la dépression

préciser les diagnostics, personnaliser les soins

Résumé

Ce corpus de thèse illustre le cheminement de notre réflexion sur l'utilisation des biomarqueurs dans la dépression, une pathologie dont les contours diagnostiques demeurent flous.

Les premiers résultats d'études de neuroendocrinologie nous ont montré les limites des modèles "troubles" athéoriques et dimensionnels. Puisque la dépression affecte de nombreux systèmes neurologiques, il est difficile d'utiliser nos outils habituels pour identifier les atteintes qui pourraient servir d'hypothèses biologiques dans un modèle biomédical classique, comme nous l'avons fait pour la catatonie périodique.

Le développement de biomarqueurs d'imagerie fiables à l'échelle du sujet unique, ainsi que de la rTMS de précision, nous ont permis de proposer une prise en charge individualisée en rTMS. Les résultats à l'échelle du groupe sont en faveur d'un lien entre les anomalies de perfusion cérébrale et dépression. Des analyses individuelles restent à faire. Elles pourront aboutir à une démarche de phénotypage inverse et à un rapprochement avec le modèle biomédical classique.

Mots clefs : dépression, biomarqueurs, modèles diagnostics, rTMS, imagerie IRM, neuroendocrinologie.

Résumé en anglais

This thesis illustrates the progress of our reflection on the use of biomarkers in depression, a pathology whose diagnostic contours remain unclear.

Early results from neuroendocrinology studies have shown us the limitations of atheoretical and dimensional "disorder" models. Since depression affects many neurological systems, it is difficult to use our usual tools to identify impairments that could serve as biological hypotheses in a classical biomedical model, as we did for periodic catatonia.

Hopefully, the development of reliable imaging biomarkers at the single-subject level, as well as precision rTMS, has allowed us to propose individualized rTMS management. The results at the group level are in favor of a link between cerebral perfusion abnormalities and depression. Individual analyses remain to be done. They could lead to an inverse phenotyping approach and a comparison with the classical biomedical model.

Keywords : depression, biomarkers, diagnostic models, rTMS, MRI imaging, neuroendocrinology