L'évaluation de la cognition sociale dans la pratique clinique

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Table des matières

Introduction

Les travaux présentés dans ce document visent à exposer mon parcours de recherche et mes réflexions sur le thème de l'évaluation de la cognition sociale en pratique clinique. Ces travaux de recherche clinique partagent les points communs de viser à une meilleure caractérisation des dysfonctionnements de la cognition sociale observés dans certaines pathologies et à une meilleure compréhension des répercussions de ces troubles sur la vie quotidienne des patients.

Mon expérience de recherche a démarré dans le cadre de mon travail de thèse, sous la direction du professeur Martial Van der Linden (Delbeuck, 2006). Cette thèse avait pour ambition de démontrer l'impact de la maladie d'Alzheimer sur le fonctionnement cognitif non comme la conséquence d'atteintes focales au niveau du cerveau, mais plutôt en termes de perturbations de la connectivité cérébrale (hypothèse de dysconnexion de la maladie d'Alzheimer, Delbeuck et al., 2003, 2007). Cette question de la connectivité cérébrale dans la maladie d'Alzheimer reste d'ailleurs un axe de mes projets de recherche actuels, avec notamment des travaux sur l'étude du corps calleux dans cette affection neurodégénérative (projet mené en collaboration avec la docteure Christine Delmaire, neuroradiologue et la docteure Stéphanie Bombois, neurologue). J'ai par ailleurs poursuivi de manière plus générale mes recherches sur la caractérisation de ces patients d'un point de vue cognitif, que cela soit dans une perspective de diagnostic différentiel (voir par exemple, Delbeuck et al., 2013) ou encore pour une meilleure caractérisation de l'hétérogénéité sur le plan cognitif des patients atteints d'une maladie d'Alzheimer. Dans cette dernière perspective, nous avons récemment évalué dans une cohorte de patients atteints de maladie d'Alzheimer du sujet jeune, la possibilité d'existence de profils cognitifs distincts et nous avons évalué les conséquences de ces profils sur le plan clinique et paraclinique (Pollet et al., soumis).

Mon expérience clinique de psychologue spécialisé en neuropsychologie m'a par ailleurs confronté à des patients avec des présentations plus comportementales que « cognitives ». Dans le domaine des pathologies neurodégénératives, les patients présentant une démence fronto-temporale manifestent dans leur quotidien, de manière plus saillante, des troubles comportementaux que cognitifs. Le profil cognitif de ces patients était réputé comme pouvant être sans particularité à des stades débutants (Jenner et al., 2006). La rencontre de ces patients m'a amené à m'interroger en conséquence sur l'origine de ces modifications comportementales et la possibilité de les appréhender au-delà des descriptions réalisées par leurs proches. Ce questionnement m'a dirigé vers les travaux initiés par Gregory et al. (2002) sur l'évaluation de

la cognition sociale dans la démence fronto-temporale. Ces travaux m'ont rapidement convaincu de l'importance de pouvoir proposer dans le cadre des évaluations cognitives, un point sur les capacités de cognition sociale des patients. L'adoption dans la pratique clinique d'outils d'évaluation de cognition sociale est toutefois freinée par différents facteurs.

Le premier et le plus fondamental est de savoir quels outils sont pertinents pour une telle évaluation mais également quels aspects de la cognition sociale doivent être évalués ou encore quels outils ont les propriétés psychométriques suffisantes pour fournir des indices valides de ces compétences. Dans ce contexte, je présenterai dans ce document une recherche en cours visant à répondre à certains aspects de ce point. Dans ce travail, nous nous sommes intéressés à analyser notre expérience autour du test des faux pas. Ce test est parmi les plus utilisés pour évaluer certaines compétences de cognition sociale (Eddy, 2019). Nous avons en conséquence repris nos données issues de différents projets menés au cours des dernières années auprès de volontaires sains (sans trouble psychiatrique ou neurologique spécifique). Notre objectif est ici de caractériser au mieux les prédicteurs des performances à cette épreuve et d'en proposer une normalisation afin de permettre une utilisation de l'outil dans la pratique clinique.

Le second frein à l'utilisation des outils d'évaluation de la cognition sociale dans la pratique clinique est de pouvoir en appréhender au mieux la signification et l'interprétation. En effet, des troubles de cognition sociale peuvent être observés dans différentes pathologies avec des présentations cliniques pourtant différentes (Cotter et al., 2018). Initialement investiguées chez des personnes avec un trouble du spectre autistique, ces difficultés ont été largement documentées dans d'autres populations psychiatriques ou neurologiques. Ainsi, une personne atteinte d'un trouble du spectre autistique et une personne présentant une schizophrénie, partagent le fait d'être en difficulté dans des épreuves évaluant la cognition sociale mais pourtant leur symptomatologie respective ne s'exprime pas de la même manière dans la vie quotidienne (une hétérogénéité au sein même de ces populations cliniques peut par ailleurs être également discutée). Il semble en conséquence important de caractériser au mieux les troubles présentés dans ces populations avec une analyse tant quantitative que qualitative, mais également d'en étudier les difficultés dans la vie quotidienne qui en résultent. Cette étape est primordiale pour que l'évaluation de la cognition sociale prenne un sens dans la prise en charge clinique de ces personnes. J'aborderai les travaux que j'ai effectués dans cette perspective au sein de différentes populations avec des recherches menées auprès de patients atteints de démence fronto-temporale, de patients souffrant d'épilepsie du lobe temporal ou encore de personnes présentant une dystrophie myotonique de type 1.

Enfin, le troisième frein à l'évaluation de la cognition sociale que je soulèverai dans ce travail, est la question du caractère écologique des évaluations actuellement utilisées en pratique clinique. Ces évaluations sont en effet généralement concentrées sur une perspective à la 3ème personne (le participant doit réfléchir à une situation à laquelle il n'a pas directement pris part). Je présenterai ainsi comme dernier point l'intérêt que peut avoir l'évaluation des émotions auto-conscientes pour témoigner des caractéristiques de fonctionnement social de l'individu dans une approche à la première personne ainsi que mon projet d'évaluation transnosologique de ces émotions.

1. Évaluation de la cognition sociale dans la population générale.

La possibilité de recourir à des tests évaluant la cognition sociale dans la pratique clinique, implique d'en connaître certaines propriétés psychométriques au préalable. De nombreuses épreuves ont été développées pour évaluer la cognition sociale, et plus particulièrement les capacités de mentalisation ou théorie de l'esprit (TDE[1]). Après une revue des outils développés auprès des adultes, nous avons décidé avec la professeure Christine Moroni, de concentrer notre travail sur l'un des outils les plus utilisés dans la littérature scientifique, le test des faux pas. Ce test développé par Stone et Baron-Cohen (1998) consiste à présenter des histoires décrivant une interaction entre différents protagonistes. Au décours de certaines histoires, un des personnages fait une remarque maladroite susceptible de blesser ou surprendre un autre protagoniste. Cette remarque n'est pas intentionnelle mais liée à une méprise ou non-connaissance de certains aspects de la situation par le personnage commettant le faux pas. Pour d'autres histoires, l'échange entre les personnages se déroule sans remarque malheureuse. Le participant doit en conséquence être capable d'identifier les histoires au sein desquelles un faux pas est commis et, si un tel faux pas est détecté, répondre à des questions visant à faire expliciter ce faux pas au participant (voir figure 1). Plus particulièrement, l'objectif de ces questions est de mettre en avant la capacité de prise de perspective d'un état mental cognitif (celui de la personne commettant le faux pas, celui-ci étant commis de manière non intentionnelle) et d'un état mental affectif (celui de la personne victime de ce faux pas). Cette épreuve a été largement utilisée dans les recherches auprès d'adultes et a été adoptée,

[1] La théorie de l'esprit fait partie des habiletés de cognition sociale et peut se définir comme l'ensemble des connaissances conceptuelles à propos des états mentaux ainsi que les processus de prise de perspective qui nous permettent de raisonner explicitement à propos de nos propres états mentaux et ceux des autres, afin de comprendre et prédire nos propres comportements et ceux des autres (Premack & Woodruff, cité par Samson, 2014)22/02/2021 18:32:00

souvent dans une version abrégée, dans de nombreuses batteries d'évaluation de la cognition sociale en cours de normalisation (comme le test des situations combinées proposé au sein de la BICS, Batterie Intégrée de la Cognition Sociale, par Achim et al. (2012) ou encore au sein de la mini-SEA, Bertoux et al., 2012).

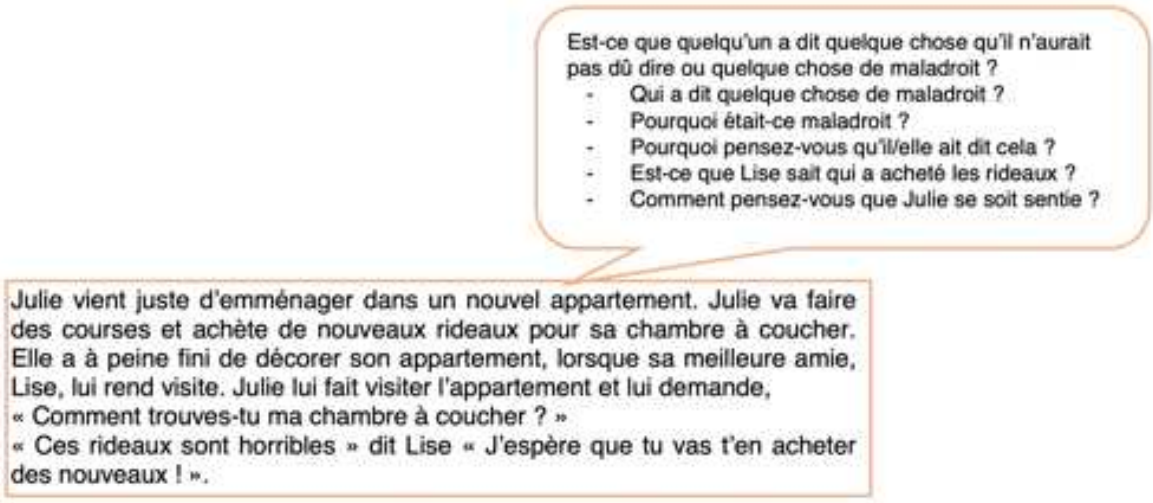


Figure 1 : Exemple de situation issue du test des faux pas et des questions posées au participant en cas de détection par ce dernier d'un faux pas dans l'histoire.

Nos travaux sur ce test ont démarré en 2005 par une adaptation en langue française du test original (modification de certains prénoms, recours plus régulier au prénom du protagoniste plutôt qu'à un pronom personnel, simplification de la structure syntaxique des phrases pour diminuer la charge en mémoire de travail, etc.)[2]. Ce test a ensuite été proposé dans différents projets au cours des années (notamment au sein de travaux réalisés par des étudiants en psychologie ou en orthophonie). Nous avons décidé de collecter l'ensemble de ces données pour proposer des données normatives aux cliniciens en contrôlant l'influence de variables démographiques, mais également pour déterminer les facteurs cognitifs et comportementaux prédisant la performance au test (Delbeuck et al., en préparation). Au total, les résultats au test de faux pas de 334 participants âgés entre 20 et 91 ans (moyenne=52,5±17) ont été analysés ; ces participants ont été sélectionnés en s'assurant de l'absence de trouble neurologique ou psychiatrique significatif (les conditions de participation des participants étaient similaires à celles utilisées lors de la normalisation de tests évaluant les fonctions exécutives par le groupe du GREFEX, Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives, Godefroy & GREFEX, 2008). A côté des performances au test des faux pas, nous avons collecté pour ces participants des données démographiques (âge, genre et niveau d'études) ainsi que leur

[2] Notre adaptation de l'épreuve en français peut être téléchargée librement à l'adresse suivante : https://psitec.univ-lille3.fr/presentation/membres/membres-titulaires/moroni-c/

performance à une mesure d'estimation du quotient intellectuel (f-NART, french-National Adult Reading Test, Mackinnon & Mulligan, 2005) et à des échelles cognitives globales (les plus jeunes participants ont été évalués sur base du MoCA, Montreal Cognitive Assessment, Nasreddine et al., 2005 ; alors que les plus âgés avaient généralement été soumis à l'échelle de démence de Mattis, Mattis, 1973). Nous avons, de plus, extrait des projets au sein desquels ces personnes avaient été impliquées, leurs réponses à des questionnaires comportementaux, plus particulièrement ceux relatifs à leur état émotionnel (BDI, Beck Depression Scale, Beck et al., 1961 ; et STAI, State Trait Inventory Anxiety, Spielberger et al., 1993) mais également l'évaluation de leurs capacités d'empathie[3] par le biais du questionnaire *Interpersonal Reactivity Index* (IRI, Davis, 1983 ; version française proposée par Berthoz et al., 2008). Cette mesure est particulièrement importante dans ce contexte pour pouvoir établir une relation entre les performances au test et l'expression d'une capacité sociale dans la vie quotidienne ; la mise en évidence d'une telle relation justifierait en effet, d'un point de vue psychométrique, de la validité du test des faux pas.

Les analyses réalisées sur ces données montrent la large étendue du score global au test des faux pas (moyenne et écart-type = 48,96±8.95 ; minimum = 21, maximum = 60), justifiant de s'interroger sur les facteurs influençant les performances des individus. Par ailleurs, cette hétérogénéité des scores dans une population de volontaires sains confirme l'importance pour le clinicien de disposer de normes pour une utilisation pertinente de cette épreuve auprès de populations cliniques. Nous avons, en conséquence, évalué les associations existantes entre les scores des individus et leurs caractéristiques démographiques. L'âge est associé négativement avec le score global et les différents sous-scores du test des faux pas ($p<.001$ pour toutes les corrélations), le niveau d'études est quant à lui positivement associé au score global et à ses différents sous-scores (excepté le score demandant d'attribuer l'état mental affectif de la personne victime du faux pas, $p=.28$) et le sexe ne semble en revanche n'avoir qu'un effet plus restreint sur la performance au test (seul le sous-score d'attribution de l'état mental affectif diffère entre hommes et femmes avec de meilleurs scores pour ces dernières, $p<.05$). Au vu de ces résultats, nous avons eu recours à la méthode Barona (Barona et al., 1984) pour permettre de contrôler simultanément l'influence des variables démographiques sur les scores au test. L'application de cette méthode résulte en une équation permettant de calculer le score attendu pour un individu en fonction de ses caractéristiques et de comparer en conséquence le score du

[3] « L'empathie fait référence au partage, à la compréhension et à la réponse aux expériences émotionnelles uniques d'une autre personne, et est considérée comme un phénomène émergent qui dépend de multiples composantes de la cognition sociale » (Green et al., 2015, p 627).

patient à celui-ci et d'en déterminer s'il s'en écarte significativement (pour une application de cette méthode au test de Stroop Victoria, voir Bayard et al., 2011). Le clinicien pourra ainsi aisément confronter tout nouveau patient qu'il évalue avec le test des faux pas à cette base de données de 334 individus (nous avons d'ailleurs eu recours à cette technique dans notre travail sur la démence fronto-temporale exposé ci-dessous, Delbeuck et al., 2020). Parallèlement, nous avons cherché à déterminer si d'autres facteurs ne devraient pas être considérés comme de possibles prédicteurs indépendants de la performance au test. Dans cette perspective, nous avons regardé l'influence du niveau intellectuel estimé du participant ainsi que du niveau de fonctionnement cognitif global (et cela indépendamment des effets des variables socio-démographiques). Nous avons constaté que le niveau intellectuel était susceptible d'impacter la performance au test, notamment pour le score global mais également concernant les scores de prise de perspective tant cognitive qu'affective. Concernant l'effet du niveau de fonctionnement cognitif global, nos résultats se sont révélés plus contrastés. Pour les participants ayant été évalués par l'échelle de MoCA, nous ne constations pas d'effet entre le score à cette échelle et les scores au test des faux pas. En revanche, au sein du groupe de participants évalués par le biais de l'échelle de Mattis, une relation du fonctionnement cognitif global était relevée avec le score global au test des faux pas et avec les performances aux questions demandant la clarification du contexte du faux pas (Pourquoi était-ce maladroit ? Pourquoi pensez-vous qu'il/elle ait dit cela ?) ; il n'y avait pas de relation entre le score à l'échelle de Mattis et les questions demandant de se positionner quant à l'état mental cognitif (non intentionnalité) et affectif (sentiment de la victime du faux pas). Ces éléments illustrent les difficultés de l'évaluation de compétences de haut niveau comme la TDE, avec des épreuves qui ne peuvent être pures (n'évaluant que la composante cognitive désirée) et demandent l'intervention d'autres processus influençant également la performance des individus au test. Il est en conséquence, important de pouvoir les identifier et de réfléchir à la conception d'épreuves capables de distinguer l'influence de ces autres facteurs. Une des critiques pouvant être adressée au test des faux pas est d'ailleurs, de ne pas permettre d'isoler l'influence des autres facteurs cognitifs.

Notre deuxième objectif était par ailleurs de considérer ce que les performances à cette épreuve des faux pas pouvaient révéler du comportement des personnes. Dans cette perspective, notre première analyse s'est penchée sur la question des relations avec les capacités d'empathie des individus. Nous avons pu constater une relation entre le score global à l'échelle IRI et la variable état mental cognitif de l'épreuve (en revanche il n'existait pas de relation avec la dimension affective de la TDE évaluée par le test). Lorsque nous nous intéressons aux processus

d'empathie évalués par le biais de l'IRI[4], nous constatons comme attendu, une corrélation positive entre le test des faux pas (pouvant être considéré comme un test de raisonnement sur les états mentaux) et l'empathie cognitive (définie comme la capacité cognitive de régulation temporaire de sa propre perspective afin d'adopter celle d'autrui, sans confusion avec soi). De plus, l'empathie cognitive est associée positivement avec les sous-scores du test des faux pas reflétant les capacités d'inférence tant de l'état mental cognitif que de l'état mental affectif. Ces relations plaident en faveur d'une validité de l'épreuve à rendre compte de certaines capacités empathiques d'un individu. Enfin, nous avons recherché quelles relations le test des faux pas pouvait entretenir avec l'intensité de la symptomatologie affective dans une population non clinique puisque de telles relations ont généralement été mises en évidence dans des populations cliniques (voir, par exemple, Maleki et al., 2020). Nous avons, d'une part, constaté des relations entre l'intensité de la symptomatologie dépressive et l'ensemble des scores du test des faux pas (les scores étaient meilleurs chez les patients présentant une faible symptomatologie dépressive). D'autre part, nous ne retrouvions pas de relation entre test des faux pas et l'anxiété trait (trait de personnalité de propension à l'anxiété) mais une relation était en revanche significative entre l'anxiété état (jugeant de l'état d'anxiété actuel de l'individu) et le score global au test des faux pas. Il n'existait en revanche pas de relation spécifique avec les indices spécifiques de prise de perspective cognitive ou affective.

En résumé, les travaux menés au cours de ces années sur le test des faux pas au sein de différents projets nous permettent de mieux comprendre dans une population non clinique, les facteurs prédictifs des performances de participants. Ce travail a permis de vérifier la validité du test (en montrant ses relations avec une mesure d'empathie cognitive) mais également de construire des données normatives sur une population adulte de 20 à 91 ans. Par ailleurs, nous avons également observé que d'autres facteurs cognitifs (notamment le niveau d'efficience intellectuelle) mais également émotionnels (tel que l'intensité d'une symptomatologie dépressive) étaient susceptibles d'influencer le score obtenu à cette épreuve. Ces différentes informations participent à une meilleure compréhension de l'outil et à son utilisation éclairée dans la pratique clinique. Ce travail est nécessaire pour les différents outils d'évaluation de la cognition sociale, cela d'autant qu'ils ont été conçus en l'absence de cadre théorique spécifique (voir Samson, 2014 pour une discussion sur le thème des composants de la cognition sociale). Notre attention s'est d'ailleurs portée, dans cette recherche d'outils d'évaluation de la cognition sociale, sur d'autres épreuves comme la tâche de compréhension de sarcasmes ou de

[4] Nous avons adopté dans ce travail, la structure factorielle de l'IRI en deux facteurs distinguant d'une part une empathie cognitive d'une empathie affective (Davis, 1983)

compréhension d'actions mentales et physiques (Channon et al., 2005, 2007). Des données normatives sont également en cours pour ces épreuves que nous avons utilisées notamment dans nos travaux auprès de patients atteints d'épilepsie du lobe temporal.

2. Évaluation de la cognition sociale au sein de populations cliniques

La cognition sociale est devenue un élément important de l'évaluation neuropsychologique auprès de patients souffrant de pathologies psychiatriques ou neurologiques. En neurologie, l'évaluation de la cognition sociale a notamment pris une place dans la phase diagnostique de la démence fronto-temporale. Mes travaux sur cette population ont d'ailleurs eu pour objectif d'évaluer la capacité des outils de cognition sociale à identifier spécifiquement ce syndrome clinique et de permettre un diagnostic différentiel par rapport à d'autres syndromes. Au-delà de son utilité dans le processus diagnostique d'une affection neurodégénérative, l'évaluation de la cognition sociale dans la sphère neurologique est plus régulièrement réalisée dans une perspective de diagnostic cognitif (quelles sont les capacités préservées et déficitaires d'un individu) mais également dans la perspective de comprendre comment leur condition neurologique affecte leur comportement et d'envisager en conséquence le soin et la planification du futur. C'est dans cette optique que se situent les travaux que je présenterai dans les populations de patients présentant une épilepsie du lobe temporal ou encore de patients présentant une dystrophie myotonique de type 1.

a. Cognition sociale et démence fronto-temporale

La démence fronto-temporale (ou variant comportemental des dégénérescences lobaires fronto-temporales ; vc-DFT) est une affection neurodégénérative se caractérisant au premier plan par des modifications progressives du comportement, de la personnalité et des interactions sociales. D'un point de vue neuropathologique, ce tableau clinique a été mis en relation avec différentes lésions histologiques (inclusions cytoplasmiques ubiquitine-positives, inclusions de protéines Tau, etc.) ayant en commun d'induire une dégénérescence lobaire frontale et temporale antérieure (Leroy et al., 2021). En l'absence de biomarqueurs de ces lésions, une caractérisation précise de ces patients sur le plan clinique constitue une part importante du processus diagnostique.

Les critères cliniques actuellement utilisés pour le diagnostic des vc-DFT (Rascovsky et al., 2011) mettent en avant différentes modifications du comportement pouvant survenir chez ces patients :

- désinhibition précoce (comportements socialement inadaptés, perte des conventions sociales, etc.)
- apathie ou inertie précoce
- perte précoce des capacités de sympathie ou d'empathie (indifférence, réactivité diminuée aux besoins/sentiments d'autrui, diminution de l'engagement social, etc.)
- manifestations précoces de comportements persévératifs, stéréotypés ou compulsifs, ritualisés
- hyperoralité ou modifications alimentaires

Au niveau cognitif, ces critères cliniques suggèrent la présence d'un profil caractérisé par des difficultés exécutives et une relative préservation des fonctions visuo-spatiales ainsi que de la mémoire (la préservation de cette mémoire pourrait toutefois être un critère non pertinent pour certains patients, Hornberger & Piguet, 2012). Ces difficultés cognitives rendent cependant peu compte des modifications comportementales manifestées par ces patients. Un intérêt croissant s'est en conséquence, porté ces dernières années sur les capacités de cognition sociale dans cette population et leur rôle vis-à-vis des modifications comportementales observées. Ces difficultés de cognition sociale ont été mises en évidence par le biais d'une perte d'empathie chez ces patients, rapportée par leur proche (Lough et al., 2006) mais également ont été objectivées sur base d'épreuves évaluant la perception d'indices sociaux (Goodkind et al., 2015), la TDE (Adenzato et al., 2010) ou encore la cognition morale (Baez et al., 2016). Ces épreuves se sont révélées sensibles à cette pathologie (Diehl-Schmid et al., 2007) et associées aux modifications comportementales de ces patients (Gregory et al., 2002) et au fardeau ressenti par l'aidant (Brioschi Guevara et al., 2015). Parmi ces épreuves de cognition sociale, il a été démontré à plusieurs reprises que le test des faux pas avait une sensibilité aux changements cognitifs des patients vc-DFT (Brioschi Guevara et al., 2015; Giovagnoli et al., 2019; Gregory et al., 2002; Torralva et al., 2007) et une version abrégée de ce test est d'ailleurs incluse dans la batterie mini-SEA développée pour le diagnostic des vc-DFT (Bertoux et al., 2013). Le test des faux pas a de plus, démontré une bonne capacité de diagnostic différentiel de ce syndrome clinique par rapport à d'autres affections neurodégénératives, telles que la maladie d'Alzheimer (Bora et al., 2015).

Dans ce contexte, notre étude a cherché à mettre ce test des faux pas à l'épreuve du contexte de la pratique clinique (Delbeuck et al., 2020). Les travaux sur l'intérêt de ce test pour

le diagnostic du vc-DFT se sont en effet, focalisés sur des groupes initialement bien caractérisés. Ainsi, un groupe de patients vc-DFT (présentant au premier plan des changements comportementaux) a généralement été comparé à un groupe de patients atteints d'une maladie d'Alzheimer (dont la symptomatologie est plus souvent caractérisée par des troubles mnésiques) ; les performances aux tests de cognition sociale ont ensuite, été comparées entre ces deux groupes aux symptomatologies distinctes. Cette situation ne correspond toutefois pas à la pratique clinique puisque le diagnostic n'y est pas connu à l'avance et seuls les symptômes (recueillis par le biais de la plainte exprimée par le patient ou son entourage) peuvent alors être déterminés. Notre démarche a en conséquence été de considérer l'intérêt du test des faux pas dans ce contexte. Les patients étaient inclus dans notre étude sur base de la présence de troubles du comportement amenant à suspecter la possibilité d'une vc-DFT. Le diagnostic final posé pour ces patients était alors récolté ; aucun diagnostic n'a toutefois été considéré si le patient n'avait pas bénéficié d'un suivi minimum de 3 ans ou obtenu un diagnostic de certitude de vc-DFT (soit par des analyses génétiques avec mise en évidence d'une mutation pathogène soit post-mortem par un examen neuropathologique). A l'issue du suivi, le diagnostic posé était utilisé pour classifier nos patients dans le groupe vc-DFT ou non vc-DFT. Ce délai de 3 ans nous semblait indispensable à considérer afin que la probabilité du diagnostic de vc-DFT soit optimale. Rappelons en effet, que de nombreux suivis de cohorte de patients vc-DFT ont montré que certains patients ne présentaient pas d'évolutivité au cours du temps. Ces patients présentant des modifications comportementales mais sans évolutivité, ont été discutés en tant que phénocopies de vc-DFT (Kipps et al., 2010). Dans le cadre de notre étude, tous les patients inclus comme présentant une vc-DFT ont montré une évolutivité de leur profil au cours du suivi, à l'exception d'un d'entre eux pour lequel nous n'avons pas pu établir une évolution sur son suivi mais son diagnostic a été confirmé post-mortem par une preuve neuropathologique de lésions histologiques de dégénérescence lobaire fronto-temporale.

Au total, 42 patients rencontrés entre 2006 et 2014 au Centre Mémoire de Ressources et de Recherche (CMRR) de Lille, répondaient aux critères d'inclusion :

- être référé au CMRR pour suspicion de vc-DFT en raison de troubles comportementaux,
- avoir bénéficié d'une évaluation neuropsychologique incluant le test des faux pas
- et avoir été suivi pour un minimum de 3 ans ou avoir reçu un diagnostic de certitude suite à un prélèvement cérébral (avec examen neuropathologique) ou à un test génétique mettant en évidence une mutation pathogène connue de vc-DFT.

Un diagnostic final de vc-DFT a été posé pour 14 d'entre eux (quatre avaient un diagnostic de certitude dont trois par le biais de la génétique et un suite à un examen

neuropathologique, 10 un diagnostic probable selon les critères de Rascovsky et al., 2011) et 25 patients (non vc-DFT) avaient un autre diagnostic (15 patients avec un diagnostic psychiatrique, neuf patients avec une problématique neurologique, et un patient présentant un syndrome d'apnées du sommeil, voir tableau 1 pour la répartition des diagnostics). Les patients de ce dernier groupe (non vc-DFT) sont restés relativement stables durant le suivi (ce suivi au CMRR était en moyenne de 9,4±5,1 années), excepté celui atteint d'une maladie d'Alzheimer (notons que son diagnostic avait été appuyé par un examen par tomographie par émission de positons, amyloïde démontrant l'accumulation de la protéine Aβ amyloïde au niveau cérébral). Enfin, le diagnostic de trois patients restait incertain à la fin du suivi (le diagnostic d'un vc-DFT possible était toujours évoqué sans élément suffisant pour un diagnostic probable) et ces derniers ont été écartés des analyses au vu de la persistance d'un doute diagnostique significatif.

Patients psychiatriques n=15	Patients neurologiques n=9	Autre n=1
Troubles bipolaires (n=10) Dépression (n=3) Psychose (n=2).	Étiologie Vasculaire (n=5) Maladie d'Alzheimer (n=1) Maladie de Parkinson (n=1) Démence liée à l'alcool (n=1) Traumatisme crânien (n=1)	Syndrome d'apnées du sommeil (n=1)

Tableau 1 : Répartition des diagnostics au sein du groupe de patients non vc-DFT (diagnostics posés après minimum 3 ans de suivi).

Nos analyses ont ensuite examiné si le pourcentage de patients considérés comme déficitaires au test des faux pas (selon des normes établies sur 165 volontaires sains, un score z était attribué à chaque patient selon la méthode Barona, cf. ci-dessus) différait selon le diagnostic final posé (vc-DFT vs. non vc-DFT). Parallèlement, le nombre de patients déficitaires aux épreuves évaluant les fonctions exécutives (BREF, Dubois et al., 2000) et le langage (dénomination orale de 36 items de Bachy-Langedock, Bachy-Langedock, 1988), était également relevé (ces domaines étaient examinés au vu de leurs relations avec les troubles observés dans le contexte des dégénérescences lobaires fronto-temporales). Au final, seul le score au test des faux pas était plus fréquemment déficitaire dans le groupe vc-DFT que non vc-DFT ; notons que ces deux groupes ne différaient ni en termes d'âge et de niveau d'études (mais la proportion d'hommes était plus importante dans le groupe non vc-DFT que vc-DFT) ni au niveau du fonctionnement cognitif global (MMSE, Folstein et al., 1975) ni sur le plan des

troubles du comportement rapportés par un proche à l'échelle de dysfonctionnement frontal (EDF, Lebert et al., 1998).

La sensibilité du test des faux pas s'est révélée équivalente à celle de travaux antérieurs (Gregory et al., 2002) contrastant un groupe de patients vc-DFT à des volontaires sains. Cette sensibilité (.83) témoigne que le test capture des modifications cognitives fréquemment présentées par les patients vc-DFT. Une analyse plus fine des changements de comportements pouvant être reliés à ces difficultés de cognition sociale, nécessiterait cependant d'être menée afin d'en comprendre plus précisément le sens clinique (les données que nous avons pu collecter à ce niveau ne le permettaient malheureusement pas). La spécificité du test s'est en revanche, révélée plus modérée avec huit patients non vc-DFT faux positifs. Ces derniers avaient reçu des diagnostics très variées : 3 patients avec un diagnostic de trouble bipolaire, 1 patient vasculaire, 1 patient avec maladie de Parkinson, 1 patient atteint de maladie d'Alzheimer, 1 patient avec une démence liée à l'alcool et 1 patient avec un traumatisme crânien. Cette diversité de diagnostic parmi les patients déficitaires au test des faux pas mais non diagnostiqué comme vc-DFT (rappelons en revanche que pour être inclus des troubles du comportement devaient être identifiés), souligne la nécessité d'une meilleure compréhension du sens de ce score sur la présentation clinique des patients. Cette analyse devrait également considérer dans son interprétation l'influence des autres capacités cognitives sur les performances au test. En effet, les résultats de notre étude ont suggéré que les performances au test des faux pas dans le groupe non vc-DFT, étaient associées positivement avec le niveau d'efficience cognitive globale et avec une épreuve évaluant les fonctions exécutives alors que de telles associations n'étaient pas observées dans le groupe vc-DFT. Si nous ne pouvons exclure un problème de puissance statistique expliquant l'absence d'association dans le groups vc-DFT (ce résultat est cependant consistant avec les données de la littérature), ces résultats soulignent l'importance d'intégrer les résultats au test des faux pas dans le cadre d'un profil cognitif et non en tant que seul élément à considérer (voir par exemple, Dodich et al., 2018).

En résumé, ce travail confirme l'intérêt pour le clinicien d'incorporer une évaluation de la cognition sociale (notamment par le biais du test des faux pas) dans le processus d'évaluation de patients pour lesquels une vc-DFT est suspectée. Cependant, l'interprétation doit en être réalisée dans une perspective globale en considérant les facteurs associés et en estimant si le dysfonctionnement constaté rend bien compte des modifications comportementales manifestées par le patient. Une analyse plus fine des processus de cognition sociale pourrait probablement également aider le clinicien dans cette meilleure caractérisation du fonctionnement cognitif de l'individu. Nous n'avons pas pu montrer dans notre travail, d'effet des sous-scores du test des

faux pas sur la discrimination des groupes. Certains de ces sous-scores peuvent pourtant être interprétés comme reflétant une atteinte des processus de prise de perspective d'un état mental cognitif alors que d'autres reflètent la prise de perspective d'un état mental affectif. Une atteinte plus marquée de ce processus affectif de TDE par rapport au processus cognitif, a été documentée dans le vc-DFT (Dodich et al., 2016; Torralva et al., 2015) mais notre épreuve du test des faux pas ne s'est pas révélée capable de le révéler lors de notre étude. L'utilisation d'épreuves directement dédiées à distinguer la nature de l'état mental à inférer, pourrait en conséquence, être à explorer dans de futurs travaux dans cette population. Un travail de notre équipe du CMRR auquel j'ai participé, suggère également l'intérêt d'une procédure de dissociation des processus à l'œuvre lors d'épreuves de TDE (Le Bouc et al., 2012). Dans cette étude, nous avons pu montrer que l'analyse des erreurs produites par les patients pourrait être plus adaptée pour caractériser le fonctionnement cognitif des patients vc-DFT. Ce travail repose sur les travaux de la professeure Dana Samson (voir par exemple Samson, 2014) et ses théories sur l'implication de différents processus pour la TDE (connaissances liées à la TDE vs. utilisation de la TDE). Nous avons ainsi adopté son approche de dissociation de processus en regardant si les erreurs des patients (deux groupes étaient comparés à des volontaires sains, un groupe de patients vc-DFT et un groupe de patients atteints de maladie d'Alzheimer) reflétaient plutôt :

- un déficit de la représentation de l'autre en raison d'un raisonnement simplifié sur la situation ne prenant pas en compte l'ensemble de la séquence des événements
- ou une incapacité à inhiber sa propre perspective (le participant adopte une perspective égocentrique)

Notre étude a révélé une prépondérance de ce dernier type d'erreur dans le groupe de patients vc-DFT, à savoir une incapacité à inhiber sa propre perspective, alors que ceux atteints de maladie d'Alzheimer étaient plus enclins au déficit de représentation de l'autre. Ce travail suggère tout l'intérêt de considérer des procédures permettant une analyse plus détaillée des difficultés du patient et d'en évaluer l'intérêt dans le contexte du diagnostic des patient vc-DFT mais également pour leur prise en charge.

Au-delà de ce rôle dans une perspective clinique, il nous semble également important de souligner ici toute l'importance de l'étude des capacités de cognition sociale dans cette population de patients vc-DFT pour la recherche et notre compréhension du fonctionnement normal de la cognition sociale. Ces patients vc-DFT ont en effet, eu un développement a priori normal de ces capacités de cognition sociale. L'apparition de lésions du spectre des dégénérescences lobaires fronto-temporales va cependant compromettre le bon fonctionnement

de leurs capacités de cognition sociale et offrir pour la recherche un modèle lésionnel pour l'étude de ces capacités. L'existence de mutations génétiques pour ces patients vc-DFT pourrait par ailleurs, permettre d'identifier des personnes à un stade préclinique et de suivre longitudinalement ces individus afin de caractériser l'évolution de leurs capacités de cognition sociale, comme le permettent les suivis de cohorte, tels que PREV-DEMALS (NCT02590276) au sein duquel je suis impliqué en tant que collaborateur.

b. Cognition sociale et épilepsie du lobe temporal

L'épilepsie de lobe temporal (ELT) est la plus fréquente des épilepsies chez l'adulte et la plus résistante aux traitements pharmacologiques. La ligue internationale contre l'épilepsie (ILAE, International League Against Epilepsy, 1989) distingue au sein des épilepsies temporales, les ELT mésiales des ELT latérales. Le diagnostic de ces épilepsies est réalisé principalement sur la base des manifestations cliniques et d'enregistrements EEG. D'autres techniques d'imagerie mais également l'évaluation neuropsychologique peuvent également participer à ce processus diagnostique. L'évaluation neuropsychologique peut ainsi participer à estimer la localisation du foyer et l'étendue du réseau épileptogène. Mais son intérêt plus général est de permettre un diagnostic cognitif des compétences de l'individu, à savoir ses capacités déficitaires et préservées, et évaluer les conséquences fonctionnelles pour l'individu de ce profil cognitif. Notons que l'évaluation neuropsychologique joue également un rôle dans le cadre de la chirurgie de l'épilepsie (Brissart et al., 2019). Dans le contexte de l'ELT, des troubles de mémoire épisodique antérogrades sont attendus au vu de la localisation du foyer épileptique. Toutefois, des troubles plus diffus ont également pu être observés et plus généralement une hétérogénéité des profils cognitifs a été décrite. Ce constat nous a amené dans nos travaux sur les troubles de cognition sociale dans l'ELT, à considérer, à côté de la recherche d'effets de groupe (patients épileptiques vs. volontaires sains), la fréquence des difficultés à un niveau plus individuel : le score du patient doit-il être considéré comme déficitaire par rapport au groupe de volontaires sains ? A cette fin, nous avons eu recours à des techniques de statistiques de cas unique (Crawford et al., 2010). Cette approche plus individuelle nous a en conséquence, permis d'établir des fréquences de troubles dans la population de patients ELT mais également d'évaluer la concomitance de difficultés au sein des patients ELT.

A côté des troubles cognitifs, des modifications comportementales ont pu être constatées dans l'ELT. L'intérêt s'est plus particulièrement porté dans cette pathologie neurologique sur la dépression. La dépression dans l'épilepsie est fréquemment observée mais avec certaines

atypies de présentation par rapport aux tableaux cliniques observés dans les pathologies psychiatriques (Kanner, 2006). Les relations entre dépression et épilepsie sont aujourd'hui considérées comme bidirectionnelles (Garcia, 2012). D'un côté, les patients épileptiques sont plus à risque de développer des troubles dépressifs et ces affects dépressifs auraient une incidence sur le contrôle des crises d'épilepsie ainsi que sur la réponse du patient au traitement qu'il soit pharmacologique ou chirurgical. D'un autre côté, le risque d'épilepsie est plus important dans une population de patients dépressifs que dans la population générale. Ces relations ont amené différentes études à se pencher sur la question des liens entre dépression et épilepsie avec notamment la formulation de l'hypothèse d'un médiateur cognitif entre ces deux conditions. Parmi ces possibles médiateurs cognitifs, les capacités de cognition sociale nous ont semblé être pertinentes à considérer, compte tenu de leur implication dans l'établissement de relations sociales satisfaisantes et adaptées.

Ces dernières années, la présence de troubles de cognition sociale a été documentée dans différents travaux (Bora & Meletti, 2016; Edwards et al., 2017). Nos travaux réalisés avec la docteure Sophie Hennion dans le cadre de sa thèse de Neurosciences se sont inscrits dans cette thématique et ce contexte des connaissances sur l'ELT. Nos objectifs étaient d'une part de réaliser une meilleure caractérisation des troubles de cognition sociale des patients ELT en considérant les capacités de ces patients à percevoir des indices sociaux, leurs capacités d'expérience émotionnelle et également leurs capacités de TDE. Dans ces travaux, nous avons cherché à identifier quelles difficultés étaient constatées mais également quelles relations ces troubles potentiels pouvaient avoir avec les caractéristiques cliniques de l'épilepsie des patients. Par ailleurs, nous avons évalué les conséquences de ces difficultés sur le fonctionnement émotionnel des individus (en caractérisant ce fonctionnement sur base de différentes dimensions comme l'empathie, l'alexithymie, l'anhédonie, l'apathie, etc.) et sur la présence de symptomatologies dépressives et/ou anxieuses (avec la BDI et STAI). Enfin, nous avons recherché si ces difficultés de cognition sociale avaient une incidence sur la qualité de vie rapportée par le patient.

Ces études ont été réalisées sur un même groupe de participants ELT recrutés au sein de l'unité d'épileptologie du CHRU de Lille (Professeur Derambure). Au total, 50 patients ELT (ne présentant pas d'autres pathologies neurologiques) ont été inclus et comparés à 50 volontaires sains appariés sur base des données démographiques. Les résultats sur les différentes échelles comportementales des patients ELT par rapport aux volontaires sains étaient significativement différents (moindre empathie, plus fréquente apathie, symptomatologie dépressive et anxieuse plus importante, etc.) justifiant de rechercher les

facteurs pouvant prédire ces modifications émotionnelles. Dans le cadre de nos travaux, nous avons en conséquence plus particulièrement recherché si des dimensions de la cognition sociale pouvaient être le médiateur de ces difficultés émotionnelles des patients ELT.

i. Perception d'indices sociaux dans l'épilepsie du lobe temporal

Notre étude (Hennion, Szurhaj, et al., 2015) dans ce domaine s'est concentrée sur la reconnaissance d'émotions par les canaux visuel et auditif. Nous avons ainsi conçu deux épreuves, l'une de reconnaissance d'émotions faciales et l'autre de reconnaissance de cris émotionnels (nous avons privilégié le cri émotionnel pour ne pas ajouter de dimension langagière à ces stimulations). Dans les deux modalités, des stimuli émotionnels (joie, peur, colère, dégoût et tristesse) mais également « non émotionnels » (stimuli neutres sans connotation émotionnelle) devaient être correctement classifiés par les participants. Le recours à deux modalités pour l'évaluation de la reconnaissance émotionnelle était motivé par la volonté de montrer des difficultés « amodales » de reconnaissance émotionnelle, c'est-à-dire observées quel que soit le mode d'entrée (visuel ou auditif). Notons que nous nous étions assurés que nos patients ELT n'avaient pas de difficulté à des tests évaluant la prosopagnosie et les gnosies auditives.

Nos résultats ont confirmé que, comparativement aux volontaires sains, les patients ELT présentaient des difficultés tant pour l'identification visuelle qu'auditive des émotions. Au niveau d'une analyse émotion par émotion, notre étude a retrouvé une atteinte plus spécifique de la peur (seule émotion permettant de discriminer avec suffisamment de puissance notre groupe de patients ELT par rapport au groupe de volontaires sains), et cela quelle que soit la modalité d'entrée. La proportion des patients déficitaires pour la catégorisation de peur était de 36% en modalité visuelle et de 20% en modalité auditive. Le profil d'erreur (approche qualitative) était également similaire entre les modalités avec une confusion de la peur avec le dégoût. Par ailleurs, nous retrouvions également des déficits dans l'ELT pour l'identification de l'émotion de dégoût et d'absence d'émotions (confondue avec de la tristesse) mais cela uniquement pour le canal visuel ; les comparaisons de ces émotions au niveau auditif n'étaient pas significatives mais une tendance statistique pouvait cependant être relevée. Ces résultats semblent suggérer un pattern d'atteinte relativement consistant entre les modalités de reconnaissance de l'émotion chez les patients ELT. Toutefois, une analyse plus individuelle de ces difficultés relativise ce résultat. Ainsi, pour l'émotion de peur, bien que plus fréquemment altérée chez les patients ELT tant en modalité auditive que visuelle, cette atteinte ne semble pas

concerner les mêmes individus : seulement 8% des patients ELT avaient un déficit combiné dans les deux modalités (les autres individus présentant des difficultés d'identification de la peur, avaient un déficit sélectif soit dans la modalité visuelle, soit dans la modalité auditive).

Les relations de ces atteintes avec les variables cliniques liées à l'épilepsie ou encore avec les variables comportementales, se sont révélées par ailleurs relativement limitées. Concernant l'identification de la peur, le seul effet observé était la présence de meilleurs scores en modalité visuelle dans le cadre d'une épilepsie du lobe temporal gauche sans sclérose hippocampique associée mais aucune relation avec nos variables de fonctionnement émotionnel n'était constatée. Les répercussions sur le fonctionnement des patients ELT de cette difficulté d'identification de la peur restent en conséquence, à déterminer plus précisément mais également les raisons expliquant cette hétérogénéité des profils de nos patients ELT (certains étant déficitaires pour une seule modalité) pour cette émotion de peur. En modalité visuelle, elle est la seule émotion à permettre de discriminer significativement le groupe ELT des volontaires sains. A cette fin, d'autres méthodologies plus fines pourraient être considérées, comme par exemple les épreuves développées par l'équipe du docteur Marc Sollberger mettant l'accent sur une analyse plus qualitative des performances (voir par exemple, Chiu et al., 2018). Concernant les capacités d'identification du dégoût et de l'absence d'émotion en modalité visuelle, nous retrouvions un lien avec le support social estimé par l'échelle de qualité de vie pour le premier (moins bon était estimé ce support social, moins le patient ELT était capable d'identifier le dégout sur les visages) et un lien avec l'apathie pour le second. Ce dernier lien suggérait que plus les patients étaient apathiques, meilleurs ils étaient pour considérer un visage comme ne dénotant pas d'émotion particulière. Cette association, tout comme la possibilité de difficultés à identifier l'absence d'émotion sur un visage, étaient peu attendues. Cette condition « neutre » était, comme dans d'autres études, pensée initialement comme une condition contrôle. Nos résultats soulignent plutôt que cette condition de détection d'absence d'émotion pourrait être au centre de prochaines investigations compte tenu du biais émotionnel constaté chez nos patients ELT. En effet, ces derniers avaient tendance à attribuer de la tristesse à ces visages neutres. Ce type de biais a été documenté dans le cadre de la dépression (Maniglio et al., 2014) et la question des biais émotionnels est d'ailleurs considérée dans certaines prises en charge des troubles de l'humeur (Penton-Voak et al., 2017). Bien que nous n'ayons pas pu relever une telle relation dans notre étude, des investigations plus spécifiques pourraient être intéressantes à mener en considérant également la question du rôle de l'apathie dans ce contexte.

En résumé, ce travail souligne la nécessité de poursuivre les investigations pour une meilleure compréhension de ces difficultés de perception d'indices sociaux chez les patients ELT. Pour cela, il nous semble important d'adopter des approches plus « processus dépendantes » des difficultés des patients ELT pour essayer de rendre compte de l'hétérogénéité constatée dans nos travaux. Des investigations plus poussées de certaines conditions, notamment du concept d' « absence d'émotions », semblent également importantes à considérer.

ii. Expérience émotionnelle dans l'épilepsie du lobe temporal

Une autre facette de la cognition sociale que nos travaux nous ont amené à aborder, est celui de l'expérience émotionnelle des patients ELT. Ainsi, nous nous sommes interrogés à savoir si les patients ELT étaient susceptibles de manifester des modifications de leur expérience émotionnelle pouvant rendre compte de changements dans leur fonctionnement émotionnel au quotidien (Hennion, et al., 2015). Dans cette étude, nous avons repris un design relativement classique des études dans ce domaine avec la présentation de stimuli de la base de données d'images de l'IAPS (International Affective Picture System). Les participants étaient ainsi confrontés à des images considérées comme négatives, neutres ou positives. Suite à la présentation de chaque image, une évaluation de la valence (jugement du caractère plaisant ou déplaisant de l'image) suivie d'une évaluation de l'arousal (mesurant l'intensité de l'expérience émotionnelle ressentie) était demandée.

Nos résultats ont constaté la préservation de la valence émotionnelle ressentie par les patients ELT face à ces images. Ainsi, comme pour les volontaires sains, les images négatives étaient jugées les plus déplaisantes et les images positives comme les plus plaisantes, les images neutres recevant une évaluation intermédiaire. En revanche, l'arousal différait et cela plus particulièrement pour les images de valence émotionnelle neutre. En effet, le profil attendu est d'une moindre activation des images neutres par rapport aux images positives ou négatives mais dans le cas des patients ELT, le niveau d'activation pour les images neutres était plus élevé que pour les volontaires sains (voir figure 2).

Cette modification du seuil d'activation émotionnelle pour les images neutres, n'était pas associée aux caractéristiques cliniques de l'ELT. En revanche, nous avons pu constater une relation du niveau de l'arousal pour les images négatives avec le niveau d'apathie des patients ELT. Comparés aux patients ELT non apathiques, les patients ELT apathiques attribuaient un niveau d'intensité émotionnelle plus important aux images neutres.

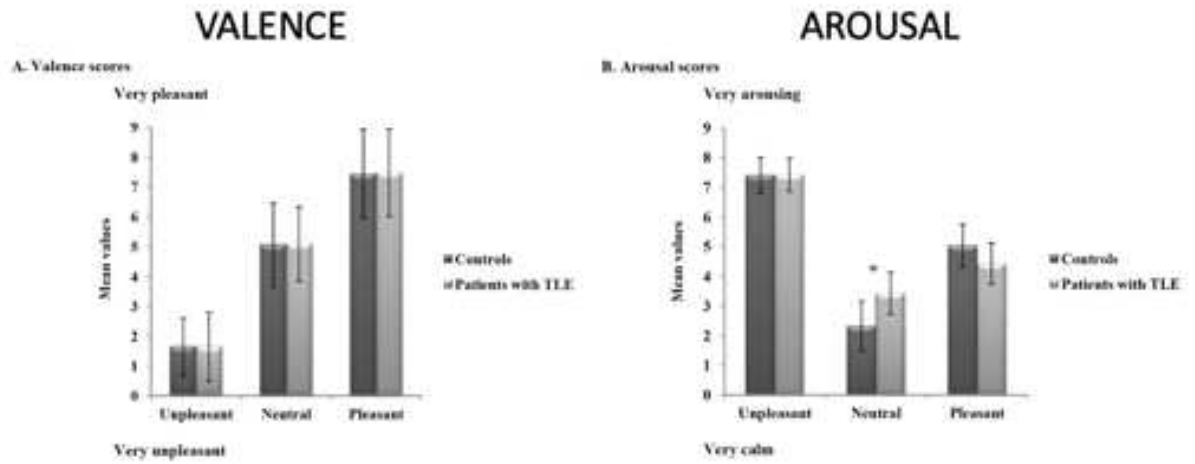


Figure 2 : évaluation de la valence (plus le score est élevé plus l'image est jugée plaisante) et de l'arousal (plus le score est élevé, plus l'expérience émotionnelle est jugée intense) des patients ELT et des volontaires sains. Les différences significatives sont signalées par un astérisque. Représentation tirée de (Hennion, Sequeira, et al., 2015).

Les résultats de ce travail montrent en conséquence une préservation de la dimension de valence de l'expérience émotionnelle mais une modification spécifique de la dimension d'activation. Cette modification porte sur les stimuli neutres et incite, comme nous l'avons abordé au vu de nos résultats sur la reconnaissance de l'émotion de visages neutres, à reconsidérer les résultats de certains travaux ayant intégré cette condition en tant que condition de contrôle. Une étude plus approfondie de cette élévation du seuil d'activation déclenchée par des stimuli neutres est conseillée afin de mieux comprendre ces liens avec des modifications comportementales comme l'apathie. Rappelons que ce trouble de la motivation était également impliqué pour les difficultés à reconnaitre l'absence d'émotions au sein de visages. Dans cette perspective, nous sommes actuellement engagés avec la docteure Sophie Hennion à mieux caractériser la question de l'apathie dans notre population de patients ELT. En effet, 58% des patients ELT obtenait un score à l'échelle LARS (Sockeel et al., 2006) significatif pour une problématique d'apathie. Des analyses sur les dimensions spécifiques de l'apathie affectées dans le cadre de l'ELT sont actuellement en cours.

Par ailleurs, au-delà de ces modifications de l'activation déclenchée par des images neutres, nous avons pu observer d'autres modifications pour des expériences émotionnelles plus complexes chez les patients ELT. Nous détaillerons ce travail (Hennion et al., 2019) sur les émotions auto-conscientes dans la troisième partie de ce rapport.

iii. Théorie de l'esprit dans l'épilepsie du lobe temporal

Le dernier volet de la cognition sociale que nous avons évalué dans nos travaux, a été de caractériser les troubles de TDE dans cette population de patients ELT et d'en documenter les conséquences dans la vie quotidienne des patients (Hennion, Delbeuck, et al., 2015). Dans ce contexte, nous avons proposé aux participants, différentes épreuves demandant l'inférence d'états mentaux, dont le test des faux pas.

Nos résultats ont montré que le test des faux était le plus discriminant entre les groupes de patients ELT et volontaires sains, avec 84% des patients ELT échouant à cette épreuve. Notons que seuls 6% des patients ELT n'avaient aucun déficit (comparativement à notre groupe de volontaires sains) sur l'ensemble des tâches de cognition sociale proposées dans notre étude. La capacité supérieure du test des faux pas à discriminer les deux populations a été interprétée en considérant que l'inférence d'états mentaux affectifs était uniquement sollicitée dans cette épreuve ; les autres épreuves incluses dans notre batterie reposaient essentiellement sur une inférence d'états mentaux cognitifs (le test des faux pas demande pour sa part de combiner une inférence d'un état mental cognitif et d'un état mental affectif).

Ce score au test des faux pas était par ailleurs en relation avec certaines variables cliniques de l'épilepsie des individus. Plus particulièrement, une association était constatée avec l'âge de début de l'épilepsie (les patients ayant démarré leurs crises d'épilepsie avant l'âge de 5 ans avaient des scores inférieurs au test des faux pas par rapport à ceux dont les crises se sont manifestées après cet âge), suggérant un possible effet de l'épilepsie sur la maturation cérébrale et la construction des capacités de TDE. Cependant, un effet de la durée de l'épilepsie sur le score au test des faux pas, était également retrouvé. Ces deux facteurs (âge de début d'épilepsie et durée d'épilepsie) sont particulièrement corrélés, notamment dans notre population, et nos analyses complémentaires ont privilégié le facteur durée d'épilepsie comme étant le plus prédicteur des performances au test des faux pas (voir également Stewart et al., 2019), témoignant que le nombre d'années à vivre avec des crises d'épilepsie (et les conséquences potentielles de ces crises sur le fonctionnement cérébral) pourrait être déterminant pour l'efficience des capacités de TDE du patient.

Des relations entre scores au test des faux pas et variables émotionnelles, étaient, de plus, constatées chez les patients ELT. Premièrement, une relation du score au test des faux pas avec les capacités d'empathie était observée, validant que les difficultés observées avaient une répercussion sur le quotidien des patients (moins le patient se décrivait comme empathique, moins bons étaient ses scores au test des faux pas). De plus, des associations positives étaient

également relevées entre le score au test des faux pas et le niveau d'affectivité positive (relevé à l'échelle PANAS) ainsi que le niveau d'anhédonie physique. Bien que nous ayons constaté ces relations avec des variables associées classiquement à des problématiques dépressives, nous n'avons pas retrouvé dans notre étude de lien entre score au test des faux pas et dépression. Une relation positive existait en revanche entre ce test des faux pas et la qualité du support social rapporté par le patient ELT à une échelle de qualité de vie.

En résumé, ce travail a montré une fréquence élevée de troubles de TDE dans le cadre de l'ELT avec un test des faux pas (nécessitant d'inférer un état mental cognitif et affectif) plus particulièrement sensible à cette pathologie. Notre interprétation en termes de processus impliqué dans cette épreuve nécessiterait cependant d'être confirmée par le recours à des épreuves distinguant spécifiquement l'intervention de ces facteurs (voir par exemple l'épreuve du MASC utilisée dans le contexte de nos travaux sur les patients atteints de dystrophie myotonique de type 1, Dziobek et al., 2006). Des conséquences de ces troubles de TDE sur le fonctionnement émotionnel des patients ont pu être mises en évidence permettant de mieux cerner la signification clinique de ces troubles observés (tels qu'une moindre capacité d'empathie ou encore une diminution de l'affectivité positive). Comme dans nos autres études, nous avons en revanche observé peu de relations des troubles de cognition sociale avec les caractéristiques cliniques de l'épilepsie, notamment par rapport à sa latéralité ou encore son type (mésiale ou latérale). Ce constat interroge sur la possibilité que ces troubles soient essentiellement liés à des effets à distance du foyer épileptique, s'intégrant dans une perturbation de réseaux fonctionnels causée par l'ELT. Dans ce contexte, nous avons mené une étude en imagerie fonctionnelle pour investiguer les bases neuronales des troubles de TDE dans l'ELT.

iv. Bases neuronales des capacités de théorie de l'esprit dans l'épilepsie du lobe temporal

Afin d'investiguer les bases neuronales de la cognition sociale dans l'ELT (pour une revue récente sur cognition sociale et imagerie dans l'ELT, voir Ives-Deliperi & Jokeit, 2019), nous avons axé notre étude sur les capacités de TDE (ce choix était lié aux difficultés significatives observées dans ce domaine lors de nos études comportementales). Cette étude a évalué des patients ELT et volontaires sains soumis à l'épreuve des « moving shapes » (Abell et al., 2000) lors d'acquisitions de séquences en IRM fonctionnelle (Hennion et al., 2016). Cette épreuve des moving shapes (aussi appelée « tâche des animations de Frith-Happé ») est une

épreuve non verbale au cours de laquelle deux triangles se déplacent sur l'écran. Le déplacement de ces triangles est dans certaines conditions, purement aléatoire (ils semblent dériver sur l'écran), dirigés vers un but (par exemple, ils peuvent bouger en symétrie comme s'ils dansaient) ou implique une manipulation des émotions ou des pensées d'un triangle par l'autre triangle (condition TDE, un des triangles semble, par exemple, vouloir séduire l'autre). Cette épreuve a l'intérêt de permettre d'appréhender non pas uniquement une composante explicite de TDE (raisonnement sur les états mentaux) mais également une composante plus implicite de la TDE (le participant traite de manière implicite des informations sur les actions et mouvements des entités biologiques). De manière plus pragmatique, cette épreuve a l'avantage d'avoir des versions spécifiquement développées pour l'utilisation dans le cadre de protocoles d'IRM fonctionnelle (Pedersen et al., 2012). Dans ces études, la condition TDE est comparée aux deux autres situations (mouvements aléatoires ou dirigés vers un but ; condition non TDE).

L'épreuve a été uniquement proposée à des patients avec une ELT mésiale (n=25) afin de pouvoir limiter l'influence de la localisation du foyer épileptique sur les résultats obtenus. Nous avons distingué dans cette population les individus avec une latéralisation du foyer épileptique à gauche (n=13) vs. à droite (n=12). Les données d'IRM fonctionnelle de ces patients ont été comparées à celles d'une population de 25 volontaires sains appariés sur les données démographiques.

Nos résultats ont montré que chez les volontaires sains, une activation d'un réseau de régions cérébrales relativement étendu était observée lorsque le contraste des acquisitions lors des situations TDE était réalisé par rapport aux situations non TDE (figure 3). En revanche pour ce même contraste, le pattern d'activation était relativement limité dans l'ELT mésiale droite (figure 4) et aucune activation n'était constatée chez les patients atteints d'une ELT mésiale gauche. Ces résultats étaient consistants avec l'observation sur le plan comportemental d'une moindre capacité chez les patients TLE (par rapport aux volontaires sains) à catégoriser correctement les situations TDE (le participant devait en effet, après le visionnage des interactions entre les triangles catégoriser celle-ci comme : pas d'interaction, interaction physique ou interaction mentale). De plus, lorsque les patterns d'activation entre patients ELT et volontaires sains étaient comparés pour ce même contraste (condition TDE vs. non TDE), une altération plus importante de l'activité de certaines régions cérébrales, était constatée chez les patients ELT mais ces régions dépendaient de la latéralité de l'épilepsie. De plus, les régions plus activées chez les patients ELT par rapport aux volontaires sains dans ce contraste (TDE vs. non TDE) dépendaient également de la latéralité de l'épilepsie.

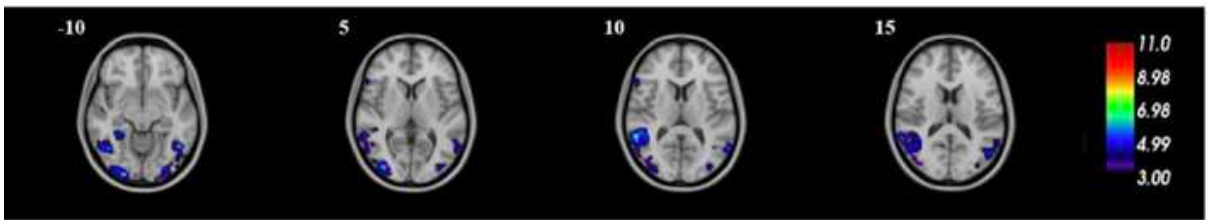


Figure 3 : pattern d'activation observé chez les volontaires sains lors du contraste entre situation TDE vs. non TDE. Ce contraste met en évidence une activation large des régions occipito-temporo-pariétales de manière bilatérale ; représentation tirée de Hennion et al., 2016.

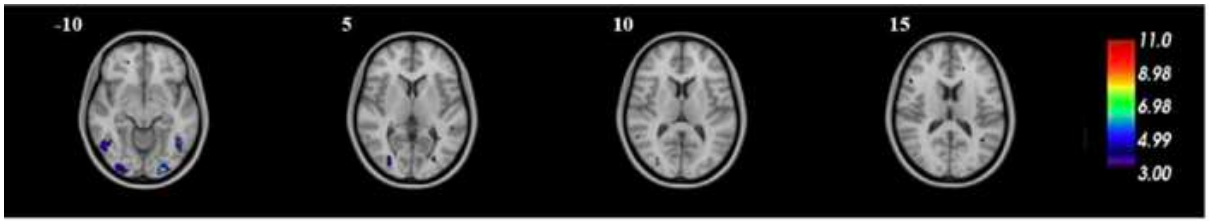


Figure 4 : pattern d'activation observé chez les patients présentant une ELT mésiale droite lors du contraste entre situation TDE vs. non TDE. Ce contraste met en évidence une activation limitée au gyrus occipital inférieur et moyen ; représentation tirée de Hennion et al., 2016.

De manière générale, les résultats de cette étude ont montré des modifications des patterns d'activation chez les patients ELT mésiaux lors de la réalisation d'une tâche de TDE. Ces modifications étaient pour une grande partie en dehors de la zone épileptogène du patient, confirmant que les difficultés de TDE dans l'ELT sont liées à des conséquences à distance de ce foyer épileptique (potentiellement en raison d'une perturbation de réseaux fonctionnels). De plus, ces modifications du pattern d'activation étaient dépendantes de la latéralisation de l'épilepsie. En conséquence, bien que nous n'ayons pas observé d'effet de la latéralité de l'épilepsie dans nos études comportementales, les dysfonctionnements neuronaux à la base des troubles de TDE suggèrent la possibilité que des processus différents puissent expliquer les perturbations de TDE dans l'ELT en fonction de la latéralité de celle-ci. Le recours à des épreuves permettant de distinguer différents processus de TDE, serait en conséquence, intéressant à adopter dans les futurs travaux sur ce thème pour investiguer si des processus spécifiques pourraient être impliqués selon la latéralisation de l'épilepsie.

v. Conclusions de ces travaux

Nos travaux avaient pour premier objectif, de mieux caractériser les difficultés de cognition sociale pouvant être constatées dans le contexte de l'ELT. Nous avons ainsi pu relever des difficultés à différents niveaux du fonctionnement de la cognition sociale, et plus particulièrement pour ce qui concerne les capacités de TDE. Cependant, ces études ont également mis en évidence une hétérogénéité de ces difficultés et la nécessité d'adopter des

procédures plus fines d'évaluation pour une meilleure identification des processus responsables des difficultés propres à chaque patient. Cette meilleure caractérisation permettrait potentiellement de mieux appréhender les liens de ces difficultés avec les caractéristiques de l'épilepsie du patient. Nos résultats comportementaux n'ont en effet, montré que peu d'ancrage de ces difficultés par rapport aux variables cliniques alors que l'influence de ces facteurs (notamment la latéralité de l'épilepsie) est fortement suggérée par notre étude en imagerie.

Les relations de ces difficultés de cognition sociale avec des modifications comportementales, ont essentiellement été observées avec des épreuves évaluant la TDE. En conséquence, il nous semble important que des mesures de TDE soient considérées dans le contexte de la prise en charge clinique de ces patients et également lors de la décision d'une intervention chirurgicale (notons que certains résultats suggèrent une absence d'effet de la chirurgie sur les capacités de TDE des patients ELT, Giovagnoli et al., 2016). Cette intégration des outils de cognition sociale dans la pratique clinique, nous semble indispensable pour une optimisation de la prise en charge.

Des limites doivent toutefois être signalées sur l'étendue des conclusions de nos travaux. La première est liée à la prise de traitements anti-épileptiques par nos patients ne nous permettant pas d'exclure la possibilité d'un rôle de ce traitement sur les difficultés que nous avons observées. La seconde est liée à notre méthodologie qui s'est centrée sur une population de patients avec une épilepsie du lobe temporal et la spécificité de nos conclusions par rapport à d'autres types d'épilepsie ne peut être garantie (voir pour des travaux sur des populations plus générales de patients souffrant d'épilepsie: Morou et al., 2018; Stewart et al., 2016).

c. Cognition sociale et dystrophie myotonique de type 1

La dystrophie myotonique de type I (DM1) ou maladie de Steinert se caractérise par une atteinte au niveau musculaire (myotonie, déficit moteur, atrophie) mais également sur le plan d'autres systèmes à des degrés divers (système nerveux central, oculaire, cardio-vasculaire, endocrinien, etc.). La DM1 est une pathologie génétique liée à une expansion de triplets CTG (plus le nombre est élevé, plus la maladie est sévère) dans le gène DMPK sur le chromosome 19. Des troubles cognitifs ont été documentés chez ces patients mais le profil de ces troubles semble relativement hétérogène (Okkersen et al., 2017). De manière relativement consistante, des troubles de cognition sociale ont par ailleurs été documentés que cela soit dans le domaine de la perception d'indices sociaux (reconnaissance d'émotions faciales) ou de la TDE (Kobayakawa et al., 2010, 2012; Labayru et al., 2018; Serra et al., 2016, 2020; Winblad et al., 2006).

A côté de ces difficultés cognitives, différents travaux se sont penchés sur les problématiques psychologiques rencontrées par ces patients. Malgré une forte hétérogénéité des observations également à ce niveau, plusieurs études ont souligné la présence de difficultés psychologiques au niveau interpersonnel, pouvant potentiellement participer aux problèmes observés chez ces patients dans les situations sociales (Minier et al., 2018). L'hypothèse a été formulée par certains auteurs que ces difficultés sociales pourraient être liées aux déficits de cognition sociale de ces patients (Kobayakawa et al., 2012) mais n'a pas été clairement établie.

Dans ce contexte, le projet élaboré en collaboration avec la docteure Céline Tard vise à investiguer cette question. A cette fin, nous avons décidé en premier lieu de caractériser au mieux ces difficultés de cognition sociale. Fort de nos précédents travaux, nous avons décidé de recourir à une épreuve permettant de distinguer différents processus au sein d'une même tâche. Le *Movie for the Assessment of Social Cognition* (MASC, Dziobek et al., 2006) est une épreuve au cours de laquelle le participant visionne un film mettant en scène quatre personnages se rencontrant au cours d'un dîner (montrant ainsi des interactions de la vie quotidienne, plus écologiques). Ce film est entrecoupé de questions sur les pensées, intentions ou encore émotions d'un des personnages. Face à ces questions, différentes alternatives de réponse sont proposées au participant : l'une adéquate par rapport à la situation et dénotant une prise de perspective d'autrui adaptée et trois autres alternatives. Ces réponses alternatives permettent une analyse qualitative de la performance du participant en identifiant des patterns d'erreurs. En effet, les propositions alternatives à la réponse correcte proposent une explication dénotant, (i) une absence de TDE (ou compréhension littérale de la situation), (ii) un recours minimal/insuffisant à la TDE ou sous-mentalisation, (iii) ou encore une surmentalisation (ou surinterprétation en termes de TDE). Dans le contexte de la schizophrénie, cette analyse du pattern d'erreurs a permis de montrer des associations entre les symptômes positifs de la schizophrénie avec les réponses de surmentalisation (Fretland et al., 2015) et a suggéré une association possible entre symptomatologie négative et absence de TDE (Montag et al., 2011). Notons qu'une sous-mentalisation a par ailleurs été observée chez des apparentés au premier degré de patients schizophrènes (Montag et al., 2012). Par ailleurs, cette épreuve présente également l'avantage de permettre de discriminer des difficultés impactant les dimensions cognitive (Que pense X ? Pourquoi X dit/fait cela ?) et affective (Qu'est-ce que X ressent ?) de la TDE (voir figure 5 pour une illustration des situations). Ainsi, cette épreuve a pu montrer que la dimension cognitive pouvait être sélectivement touchée, comme c'est le cas dans l'anxiété sociale (Buhlmann et al., 2015), alors qu'à l'inverse, la dimension affective se révèle dans certaines populations, plus

perturbée que la dimension cognitive, comme cela a été montré dans la sclérose en plaques (Pöttgen et al., 2013).

Figure 5 : illustration des situations d'inférence d'un état mental vs. un état mental affectif ainsi que les propositions de réponse proposées au participant sous forme de QCM avec une réponse correcte par rapport à la situation, une interprétation relativement littérale de la situation (absence de TDE), un recours minimal à la mentalisation (sous-mentalisation) ou une surmentalisation (Dziobek et al., 2006).

Les avantages de cette épreuve (dissociation des processus et analyse qualitative des erreurs) et son adaptation en français par une équipe canadienne du CHU Sainte-Justine (Chartier et al., 2017) nous ont décidés à sélectionner cet outil comme mesure des capacités de TDE pour notre étude auprès des patients DM1. Les objectifs de notre travail sont de :

- Caractériser les performances de TDE des patients DM1 en termes de processus touchés et capacités préservées : quelle composante de TDE est atteinte : affective ou cognitive ? quel type de raisonnement prédomine : sous-utilisation de TDE ? surmentalisation ?
- Quelles relations existent entre ces difficultés et d'autres caractéristiques de la pathologie des patients DM1 ? Existe-t-il des liens avec la sévérité de la maladie des patients ? avec l'âge de début de leurs troubles ?
- Quels effets d'autres variables cognitives sur les performances de TDE ? Une batterie cognitive incluant une estimation du QI mais également des épreuves évaluant

la mémoire de travail, la mémoire épisodique, les fonctions exécutives et attentionnelles ainsi que les fonctions instrumentales (langage, gnosies et aptitudes visuo-constructives), est également proposée aux participants DM1

- Quelles relations avec des données psychologiques et comportementales ? Des questionnaires sur différentes dimensions sont remplis avec les participants DM1 couvrant la dépression et l'anxiété, l'apathie, la fatigue, les traits autistiques, la participation sociale et la qualité de vie.
- Quelles bases neuronales à ces difficultés de TDE ? Parallèlement à l'évaluation neuropsychologique, les patients DM1 bénéficient d'une IRM, en l'absence de contre-indication (pacemaker chez les patients ayant des conséquences cardiaques de la maladie). Différentes séquences IRM sont réalisées pour permettre des analyses en volumétrie, connectivité structurale et fonctionnelle (DTI et IRM fonctionnelle de repos).

Nos résultats préliminaires (50 patients DM1 et 50 volontaires sains) confirment une atteinte de la TDE auprès des patients DM1 (score global à l'épreuve du MASC). Cette atteinte significative est retrouvée pour les items cognitifs et affectifs, mais plus particulièrement marquée sur cette dernière dimension. Les groupes (DM1 vs. volontaires sains) ne diffèrent pas en termes de recours à la surmentalisation. En revanche, nous constatons des différences sur le plan des réponses dénotant une moindre utilisation de TDE, que cela soit par le choix de réponses dénotant une absence de TDE ou une moindre TDE qu'attendue par la situation. L'analyse du pattern d'erreurs en fonction de la composante de TDE (affective vs. cognitive) montre que ce profil est essentiellement relevé pour la dimension affective de TDE (il n'y a pas de différence de pattern d'erreurs entre patients DM1 et volontaires sains pour la dimension cognitive).

Nos résultats préliminaires suggèrent par ailleurs une absence de relation de ces performances avec le niveau intellectuel des patients DM1. Sur le plan cognitif, quelques associations se révèlent significatives avec notamment une relation positive du score global au MASC avec un indice de vitesse de traitement. Nous ne notons pas d'association particulière des difficultés au MASC avec les variables comportementales recueillies lors de notre évaluation. En revanche, ces difficultés de TDE semblent être en relation avec d'une part des variables liées à la maladie (le nombre de triplets CTG, indicateur de la sévérité de la maladie, semble associé négativement au score global de l'épreuve) et d'autre part des modifications au niveau cérébral (le score global est associé positivement au volume de substance blanche : plus ce dernier diminue, plus le score au MASC est faible).

Ces premiers résultats nécessitent d'être analysés plus finement pour donner une interprétation pertinente des relations observées. Ils confirment toutefois, la présence de difficultés de TDE auprès des patients DM1 avec un profil d'erreurs plus fréquent dans cette population, à savoir un moindre recours à la TDE. Ces difficultés semblent par ailleurs plus particulièrement notables sur la dimension affective de la TDE, comme cela avait été observé dans la sclérose en plaques (Pöttgen et al., 2013). De manière intéressante, ces difficultés à une tâche de TDE semblent également, dans le cadre de la DM1, liées à des modifications de la substance blanche. Une seconde étude devrait d'ailleurs être menée autour des données d'imagerie collectées auprès des patients DM1 afin de pouvoir préciser au mieux les bases neuronales de ces difficultés de TDE. L'accent sera plus particulièrement mis sur l'étude de la connectivité cérébrale chez ces patients, notamment concernant l'intégrité du fonctionnement du réseau par défaut (Li et al., 2014) ou encore de celui de saillance (Toller et al., 2018).

Ce travail s'inscrit par ailleurs dans le cadre d'un projet plus large (coordonné par la docteure Céline Tard) visant à un suivi des patients DM1, avec l'objectif d'étudier le rôle du diabète par rapport à l'atteinte cérébrale de ces patients. Nos travaux sur la cognition sociale dans cette pathologie, se basent sur les patients rencontrés dans le cadre de cette cohorte et s'intègrent dans une démarche plus générale d'étudier le fonctionnement cognitif des patients DM1. Ce dernier objectif a été formalisé dans le cadre du projet de thèse de neurosciences du Dr Jean-Baptiste Davion que je supervise. Le projet de cette thèse s'intitule « Étude des profils cognitifs et comportementaux dans la dystrophie myotonique de type 1 et de leur association avec des paramètres d'IRM structurelle et fonctionnelle ». Il inclut ce travail axé sur la cognition sociale mais s'intéressera également au fonctionnement cognitif plus général des patients DM1. Une hétérogénéité sur le plan cognitif a été constatée et nous chercherons à établir la présence de profils cognitifs potentiellement différents au sein de ce groupe de patients et d'en étudier ensuite les facteurs prédictifs en termes cliniques et paracliniques.

d. Conclusions de cette section

Ces différents travaux montrent la présence de difficultés de cognition sociale dans différentes populations neurologiques d'étiologies variées (voir également, Cotter et al., 2018). Ces travaux ont montré l'importance d'une approche plus individuelle de ces difficultés au vu de l'hétérogénéité des atteintes pouvant être observées, notamment dans l'ELT. Nos travaux soulignent que ces difficultés nécessitent d'être mieux caractérisées pour optimiser l'intérêt que peut avoir l'évaluation de la cognition sociale dans la pratique clinique, que cela soit dans une

perspective de diagnostic (comme dans le cadre de la vc-DFT) ou au niveau plus général de la prise en charge des patients. Cette caractérisation nécessite cependant d'aborder la question de la cognition sociale avec des outils permettant de distinguer différents processus à l'œuvre au sein de l'épreuve. Cette approche nous semble indispensable pour appréhender au mieux, le sens de ces difficultés sur le fonctionnement quotidien de ces patients.

Mes travaux se poursuivent dans cette optique, notamment par le recours à des épreuves tels que le MASC auprès des patients DM1. Cette épreuve n'est toutefois pas la seule alternative à considérer et d'autres procédures sont à envisager (voir par exemple, Biervoye et al., 2018), voire à concevoir, pour améliorer notre analyse des capacités de cognition sociale d'un individu. Ces investigations ne doivent d'ailleurs pas uniquement se concentrer sur les aspects de TDE mais doivent considérer d'autres aspects de la cognition sociale, comme la cognition morale. Nous sommes actuellement en réflexion avec la professeure Christine Moroni et la docteure Sophie Hennion sur une procédure pour une évaluation implicite de la cognition morale utilisable auprès de populations cliniques.

Par ailleurs, ces évaluations des capacités de cognition sociale doivent également considérer l'importance d'impliquer le participant dans les situations d'interactions sociales. Cette intégration de l'individu aux situations, permet en effet, d'observer concrètement la manière dont il est susceptible de mettre en œuvre ses compétences de cognition sociale dans des situations données. Cette approche plus écologique est l'objet de la dernière section de ce document.

3. Évaluation de la cognition sociale à la première personne

Nos précédents travaux se sont essentiellement basés sur l'évaluation des capacités de cognition sociale à la troisième personne. Ainsi, nos participants devaient généralement se prononcer sur l'état mental d'un protagoniste (perspective à la 3ème personne) en réaction à l'action ou aux propos d'un autre personnage (perspective allocentrique : le participant n'est ainsi pas directement impliqué dans les situations mais simplement spectateur de ces interactions). Cette différence de perspective entre la capacité à inférer des états mentaux à autrui (TDE à la 3ème personne) et la capacité à prendre conscience de ses propres états mentaux (TDE à la 1ère personnes) sont toutes deux importantes dans nos interactions sociales et semblent interagir l'une avec l'autre (Dimaggio et al., 2008). Ces deux processus reposent toutefois sur des bases neuronales au moins en partie différentes (Vogeley et al., 2001). Cette

distinction est en conséquence importante à considérer également dans la caractérisation des capacités de cognition sociale d'un individu et de ses éventuels dysfonctionnements.

Dans cette perspective, Bosco et al. (2009) ont développé un entretien semi-structuré (Theory of Mind Assessment Scale, Th.o.m.a.s. ; voir également Bosco et al., 2016) visant notamment à distinguer la TDE à la première personne de la TDE à la troisième personne en interrogeant le participant sur des croyances, des pensées et des émotions (négatives ou positives), qu'il peut avoir ou qu'une autre personne peut avoir. Cet entretien a permis en conséquence, de distinguer ces deux perspectives dans la pathologie et de mettre en évidence des profils, comme une meilleure capacité dans la schizophrénie pour la perspective à la première personne que pour la troisième personne (Bosco et al., 2009).

Ma réflexion sur la cognition sociale, m'a également amené à investiguer les capacités de cognition sociale à la première personne par l'étude des émotions auto-conscientes. Les émotions auto-conscientes ont en commun, d'être déclenchées par des événements interpersonnels négatifs (honte, culpabilité, embarras) ou positifs (fierté) dont la cause est attribuée à soi. Elles jouent un rôle important dans le maintien de bonnes relations avec autrui en orientant de façon adaptée, nos comportements et en témoignant de notre conscience morale. Ces émotions auto-conscientes sont en effet catégorisées comme des émotions morales (contrairement aux émotions non morales que sont par exemple, la joie, la peur ou encore la colère ; Haidt, 2003)[5]. Ces émotions auto-conscientes sont suscitées par des processus de réflexion et d'évaluation sur soi dans des contextes sociaux (Tangney et al., 2007). Comparées aux émotions plus « basiques » (comme la joie ou la colère), ces émotions auto-conscientes semblent avoir une maturation plus tardive chez l'enfant (Garcia et al., 2015) et reposent sur des réseaux neuronaux différents (Gilead et al., 2016).

De nombreuses relations entre ces émotions auto-conscientes et les capacités de cognition sociale à la troisième personne, ont été mises en évidence. Ainsi, le sentiment de culpabilité pourrait être associé à une meilleure capacité de prise de perspective chez autrui alors que le sentiment de honte pourrait avoir un effet inverse (Yang et al., 2010). Une tendance à la culpabilité pourrait également amener à une meilleure capacité de reconnaissance des émotions faciales chez autrui (Treeby et al., 2016). De manière plus générale, les émotions auto-conscientes jouent un rôle dans le comportement social adaptatif, tel que le comportement moral (Tangney et al., 2007), la coopération (Dorfman et al., 2014), etc. Ces émotions semblent

[5] Il est important de ne pas confondre les émotions auto-conscientes et les émotions sociales. Par exemple, la colère est une émotion interpersonnelle (typiquement dirigée vers les autres) mais elle ne nécessite pas de réflexion sur soi, contrairement aux émotions auto-conscientes.

en conséquence, importantes à investiguer pour éclairer les comportements sociaux. Notre projet vise à caractériser le fonctionnement de ces émotions auto-conscientes dans une approche transnosologique afin d'en appréhender les répercussions éventuelles sur le fonctionnement social des patients neurologiques. Pour contextualiser ce projet, j'aborderai dans un premier temps quelques résultats issus de travaux sur les émotions auto-conscientes dans les populations cliniques ; suivra une présentation de nos résultats obtenus avec la docteure Sophie Hennion sur notre cohorte de patients ELT puis la présentation du projet de recherche.

a. Émotions auto-conscientes dans les populations cliniques

Les émotions auto-conscientes ont été plus particulièrement étudiées auprès des populations psychiatriques (Muris & Meesters, 2014). Ainsi, un sentiment exagéré de honte a été mis en évidence dans des problématiques anxieuses, telles que l'anxiété généralisée (Muris et al., 2015) ou encore la phobie sociale (Hedman et al., 2013). Le sentiment de culpabilité pourrait quant à lui, être plus marqué en cas de dépression (O'Connor et al., 2002). Au-delà de ces augmentations spécifiques de certaines émotions par rapport à des symptomatologies spécifiques (voir également, Kealy et al., 2020), des profils de régulation de ces émotions ont également été discutés. Ainsi, le trouble de personnalité de type borderline pourrait être caractérisé, d'une part, par une augmentation du sentiment de honte et, d'autre part, une diminution du sentiment de culpabilité (Peters & Geiger, 2016). Ces derniers résultats soulignent l'intérêt de pouvoir évaluer la gestion de différentes émotions auto-conscientes pour pouvoir au mieux témoigner du fonctionnement de l'individu. Ce profil nécessiterait d'intégrer une émotion auto-consciente positive, comme la fierté. Une augmentation de ce dernier sentiment a été relevé dans la schizophrénie (Macaulay & Cohen, 2014) ou encore par rapport au narcissisme (Tracy et al., 2009). En résumé, la manière dont un individu régule ces émotions auto-conscientes, pourrait participer aux symptomatologies émotionnelles et comportementales. Une meilleure caractérisation de ces émotions auto-conscientes dans ces populations, pourrait offrir de nouvelles perspectives sur leur prise en charge.

Les émotions auto-conscientes ont été moins investiguées dans les populations neurologiques. Des travaux intéressants sont toutefois, à relever par rapport à la vc-DFT. Ces travaux ont porté sur la réaction d'embarras chez ces patients. Cette dernière a été mobilisée par différentes méthodologies : une tâche de type « startle response » (Sturm et al., 2006) ou encore une tâche de karaoké (Sturm et al., 2008). Ces expérimentations ont mis en évidence une diminution de la réaction d'embarras des patients vc-DFT par rapport à des volontaires

sains, que cela soit au niveau de la réaction émotionnelle faciale (Sturm et al., 2006) ou encore sur des mesures plus physiologiques (Sturm et al., 2008). Cette modification de réactivité auto-consciente a pu être mise en relation avec une réduction du volume de substance grise dans une sous-région ventrale du cortex cingulaire antérieur droit (Sturm et al., 2013). Ces éléments suggèrent l'intérêt de considérer ces émotions auto-conscientes dans la vc-DFT et d'en évaluer les répercussions sur le quotidien des patients : un lien pourrait ainsi être supposé entre cette diminution du sentiment d'embarras et les comportements inappropriés socialement que peuvent manifester ces patients.

Ces résultats m'ont motivé à m'interroger sur l'expérience de ces émotions auto-conscientes dans d'autres populations neurologiques. Nous avons en collaboration avec la docteure Sophie Hennion, étudié ces émotions auprès des patients ELT évalués lors de nos précédents travaux (nous avons considéré les données des patients de nos études comportementales mais également ceux de notre étude de neuroimagerie, n=61).

b. Émotions auto-conscientes dans l'épilepsie du lobe temporal

Notre objectif visait à relever l'expérience d'émotions auto-conscientes des patients ELT et d'en rechercher les conséquences dans la vie quotidienne de ces patients (Hennion et al., 2019). Notre hypothèse était que ces émotions auto-conscientes pourraient être reliées aux symptomatologies dépressive et anxieuse observées chez ces patients, compte tenu des liens documentés dans les études sur des populations psychiatriques. A cette fin, nous avons repris les réponses des patients ELT et volontaires sains à l'échelle PANAS (Positive and Negative Affect Schedule, Watson et al., 1988) qui comprend notamment une évaluation sur une échelle en 5 points des émotions auto-conscientes que sont la fierté, la honte et la culpabilité (le participant doit juger à quel point il a ressenti cette émotion sur les dernières semaines).

Nos résultats ont mis en évidence des différences au niveau du report d'expérience émotionnelle auto-consciente entre patients ELT et volontaires sains. Un profil d'expérience émotionnelle auto-consciente dépendant de la valence, était ainsi observé : une proportion plus importante de patients ELT (que de volontaires sains) ressentaient des émotions auto-conscientes négatives fortes (que cela soit la honte ou la culpabilité) et une émotion auto-consciente positive (fierté) faible (voir figure 6). Au sein des patients ELT, les patients ressentant les niveaux de honte plus élevés, avaient une fréquence de crises d'épilepsie plus importante (sur les 3 derniers mois) que ceux avec des niveaux de honte faible (fréquence de crise par mois dans le groupe ELT avec niveau de honte élevé = 7.72 ± 5.62 vs. 2.68 ± 2.35

dans le groupe ELT avec un niveau de honte faible). Ce résultat nous interroge sur la possibilité de relations directes (liées à une altération neuronale commune) ou indirectes (les patients expérimentant de nombreuses crises susceptibles de se manifester dans des situations sociales pourraient développer un sentiment de honte plus marqué) entre ces deux facteurs. Une analyse plus spécifique pourrait être considérée dans de futurs travaux sur le sujet (voir notre projet ci-dessous).

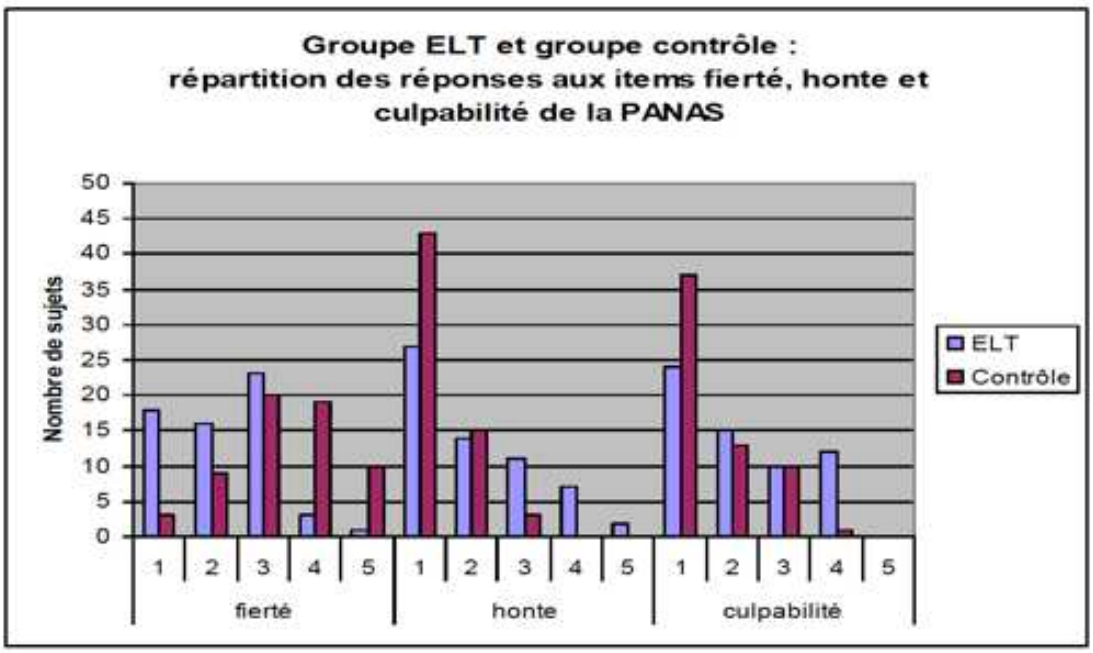


Figure 6: Nombre d'individus ELT (n=61) et volontaires sains (contrôle : n=61) selon la note donnée aux items de la PANAS évaluant la fierté, honte et culpabilité (plus la note est élevée, plus l'émotion a été ressentie fortement sur les dernières semaines (Hennion et al., 2019).

Concernant les variables psychologiques, les patients ELT avec un sentiment de honte et de culpabilité plus élevé (comparativement à ceux avec des niveaux faibles), étaient ceux qui présentaient les niveaux de symptomatologie anxieuse et dépressive les plus importants. Une diminution du sentiment de fierté était également relevée chez les patients ELT avec les symptômes anxieux les plus marqués. Ces résultats confirment l'importance de considérer ces émotions auto-conscientes par rapport aux problématiques émotionnelles des patients ELT et suggèrent un intérêt à considérer ces émotions auto-conscientes dans le cadre d'une prise en charge psychologique. Nous n'avons cependant pas observé dans ce travail de relations aussi spécifiques de la dépression et de l'anxiété avec respectivement la culpabilité et la honte (comme cela a été montré dans les populations psychiatriques) mais cette absence de spécificité pourrait être liée à la mesure des émotions auto-conscientes que nous avons adoptée. Des mesures plus fines de l'expérience de ces émotions et plus particulièrement des tendances d'un

individu à les ressentir, seraient en conséquence conseillées pour une meilleure compréhension des relations entre ces différents facteurs.

Notre dernier résultat a été de montrer que ces émotions auto-conscientes avaient par ailleurs, des conséquences sur la qualité de vie des patients. Une moindre qualité de vie était exprimée par les patients ELT avec un sentiment de honte ou de culpabilité augmenté, ainsi que par ceux avec un sentiment de fierté plus faible.

Au total, ces résultats nous ont permis de faire des liens entre émotions auto-conscientes et différentes caractéristiques des patients ELT. Certaines de ces relations nécessiteraient d'être plus approfondies (lien avec la fréquence des crises, relations entre émotions auto-conscientes et symptomatologie psychologique, etc.) et une comparaison avec d'autres populations neurologiques pourrait permettre de juger de la spécificité du profil de modifications de l'expérience des émotions auto-conscientes. Ces réflexions ont amené à la construction d'un projet d'évaluation des émotions auto-conscientes dans une perspective transnosologique.

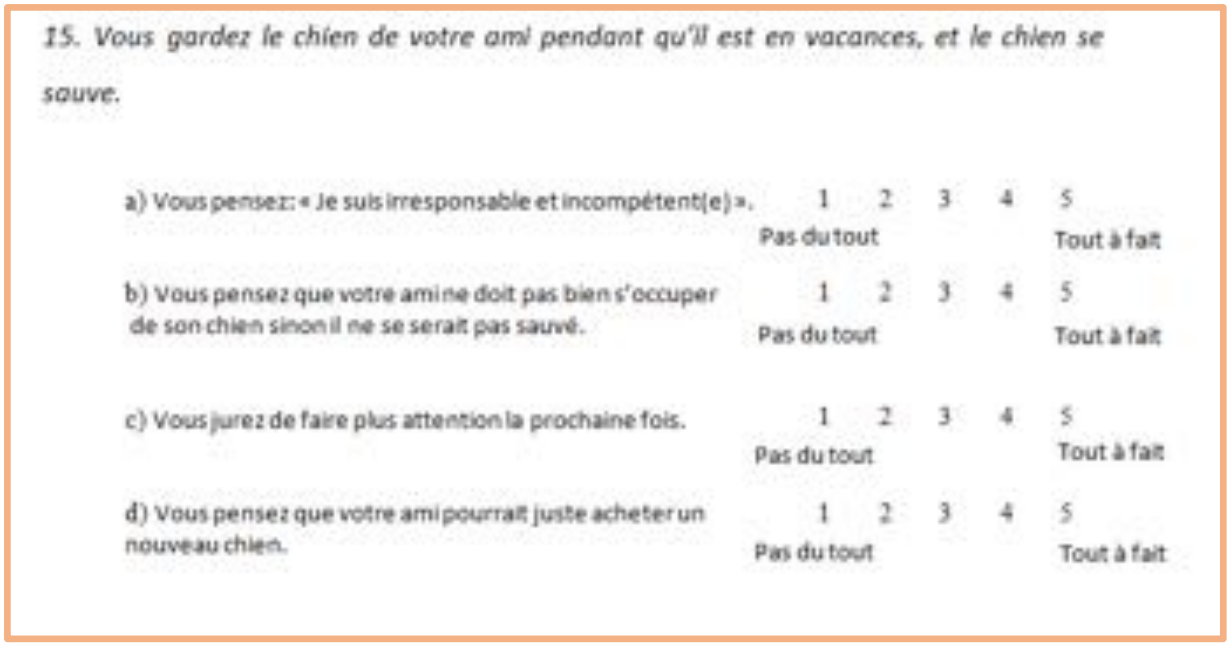
4. Approche transnosologique des émotions auto-conscientes (projet de recherche)

L'objectif de ce projet est d'investiguer l'expérience des émotions auto-conscientes dans différentes populations de patients souffrant de troubles neurologiques et d'en explorer le rôle dans la présentation clinique de ces patients. Plus particulièrement, nous centrerons notre analyse sur le rôle de ces émotions auto-conscientes par rapport aux troubles comportementaux et émotionnels que peuvent présenter ces patients. Au-delà des troubles cognitifs, des troubles affectifs et comportementaux sont, comme nous l'avons décrit ci-dessus, observés dans les maladies neurologiques et peuvent compliquer en conséquence les capacités de l'individu à maintenir des relations interpersonnelles appropriées. Une forte prévalence de problématiques dépressives et anxieuses est ainsi rencontrée chez les patients souffrant de maladie de Parkinson (Broen et al., 2016; Reijnders et al., 2008), de maladie de Huntington (Dale & van Duijn, 2015), de sclérose en plaques (Boeschoten et al., 2017) ou encore d'épilepsie du lobe temporal (García-Morales et al., 2008). Par ailleurs, comme nous l'avons décrit, d'autres troubles neurologiques comme la démence fronto-temporale (vc-DFT), sont caractérisés par des troubles du traitement émotionnel (émoussement affectif, etc.) qui sont actuellement discutés en tant que conséquence d'un trouble plus global de la cognition sociale. Les quelques données actuellement disponibles sur les émotions auto-conscientes dans les pathologies neurologiques ont suggéré que celles-ci peuvent être sous-exprimées (comme cela a été montré pour l'embarras dans la vc-DFT ou pour

la fierté dans l'ELT) ou encore surexprimées (comme nous l'avons montré pour la honte et la culpabilité dans l'ELT). En conséquence, la caractérisation de profils d'expérience de ces émotions auto-conscientes pourrait donner un nouvel éclairage sur les modifications comportementales et émotionnelles rencontrées dans ces pathologies. Le présent projet propose d'adopter une évaluation transversale de ces émotions auprès de différentes populations neurologiques (vc-DFT, maladie de Parkinson, ELT et sclérose en plaques), avec les objectifs suivants :

- Évaluer la propension aux émotions auto-conscientes positives et négatives et observer si une mauvaise régulation de ces émotions est présente chez ces patients neurologiques et en comparer le profil dans différentes pathologies afin d'en appréhender la spécificité.
- Recourir à une approche transnosologique pour améliorer notre compréhension des aires cérébrales impliquées dans la régulation des émotions auto-conscientes : par exemple, l'hypothèse pourrait être formulée d'une diminution de ces émotions auto-conscientes en cas de dysfonctionnement frontal comme dans le vc-DFT, alors qu'il pourrait ne pas en être de la sorte en cas de dysfonctionnement striatal, comme cela peut être observé dans la maladie de Parkinson
- Évaluer les relations dans ces différentes populations neurologiques entre ces émotions auto-conscientes et l'existence de troubles affectifs (dépression et anxiété) ou d'autres troubles du comportement (tels qu'émoussement affectif, désinhibition comportementale ou encore apathie)
- Évaluer les conséquences de ces modifications potentielles de l'expérience des émotions auto-conscientes sur le fonctionnement quotidien et la qualité de vie de ces patients
- Évaluer les relations entre ces changements possibles des émotions auto-conscientes avec les performances dans des épreuves de TDE à la troisième personne.

Afin de réaliser ces différents objectifs, le projet sera axé autour d'un outil d'évaluation des émotions auto-conscientes, le TOSCA-3 (Test of Self-Conscious Affect 3, Tangney et al., 2000). Cette épreuve permet d'évaluer la propension aux émotions auto-conscientes négatives (honte et culpabilité) et positives (fierté). Seize scenarios courts sont ici présentés en demandant au sujet d'évaluer la probabilité qu'il réagisse de telle ou telle façon dans cette situation (figure 7).



15. Vous gardez le chien de votre ami pendant qu'il est en vacances, et le chien se sauve.

a) Vous pensez: « Je suis irresponsable et incompétent(e) ».	1	2	3	4	5
	Pas du tout				Tout à fait
b) Vous pensez que votre ami ne doit pas bien s'occuper de son chien sinon il ne se serait pas sauvé.	1	2	3	4	5
	Pas du tout				Tout à fait
c) Vous jurez de faire plus attention la prochaine fois.	1	2	3	4	5
	Pas du tout				Tout à fait
d) Vous pensez que votre ami pourrait juste acheter un nouveau chien.	1	2	3	4	5
	Pas du tout				Tout à fait

Figure 7 : Scénario issu du TOSCA-3 (Tangney et al., 2000), validé en langue française par Nugier et al. (2012)

Cette épreuve a l'avantage de ne pas cibler une seule émotion auto-consciente et d'inclure des émotions de valence positive (fierté) et négative (honte et culpabilité). Elle a de plus été validée en langue française (Nugier et al., 2012).

Cette épreuve sera administrée aux patients afin de caractériser leurs profils de régulation des émotions auto-conscientes et d'en évaluer la spécificité en fonction de la pathologie neurologique et de leur atteinte cérébrale. Au sein de chacun des groupes de patients neurologiques (vc-DFT, maladie de Parkinson, ELT et sclérose en plaques), nous évaluerons le fonctionnement cognitif par une échelle globale mais également leurs éventuelles difficultés psychologiques et comportementales. Ces échelles seront sélectionnées en fonction des spécificités de ces pathologies afin de privilégier des échelles possédant une validité de construction par rapport à la problématique neurologique du patient. Ainsi, dans le cadre de la maladie de Parkinson, nous adopterons les échelles pour les troubles émotionnels construites pour cette pathologie, comme l'échelle d'anxiété de la maladie de Parkinson (Leentjens et al., 2014). Des échelles spécifiques pour certaines pathologies seront également considérées. Par exemple, dans l'ELT, nous évaluerons le sentiment de stigmatisation ressenti par ces patients (Jacoby, 2002), compte tenu des relations mises en évidence dans notre précédent travail entre honte et fréquence des crises.

L'impact plus général des émotions auto-conscientes sur la qualité de vie du patient (et du proche, notamment pour les patients vc-DFT), sera également appréhendé par le biais de questionnaires dans ces différentes pathologies.

Enfin, parallèlement à cette évaluation des émotions auto-conscientes, des investigations de la TDE à la troisième personne, seront également proposées au vu des relations précédemment mises en évidence entre émotions auto-conscientes et les capacités de TDE. Nous considérerons d'une part la reconnaissance des émotions avec une procédure permettant une analyse qualitative des performances (confusions entre des émotions, surestimation de certaines émotions, etc., Chiu et al., 2018). D'autre part, la TDE sera évaluée par le biais du MASC (Dziobek et al., 2006) en raison également de l'analyse qualitative permise par cette épreuve (dimension affective vs. cognitive, surmentalisation vs. sous-mentalisation, etc.). Les relations entre ces différentes épreuves seront en conséquence, examinées dans ces différentes populations neurologiques connues pour manifester des difficultés de TDE à la 3ème personne (les épreuves que nous avons sélectionnées, permettront un éclairage plus détaillé en termes de type de processus perturbés).

Ce projet démarrera par une phase pilote pour évaluer la faisabilité du projet au sein de populations neurologiques. Cette phase sera suivie de la phase de recrutement des populations de patients avec un objectif de 40 patients par groupe (excepté pour le groupe de patients présentant une démence fronto-temporale, pour lequel nous espérons inclure une 20aine de patients au vu de la fréquence moins élevée de cette pathologie).

Ce projet sera rendu possible par l'implémentation de mon équipe de recherche (LilNCog - Lille neurosciences & cognition ; UMR-S 1172) au sein du CHRU de Lille. Des équipes avec une grande expertise sur ces pathologies, comme l'Unité d'Expertise Cognitivo-Motrice, offrent le cadre idéal pour une mise en place de ce projet. Les différents neuropsychologues des services prenant en charge ces patients, ont été sensibilisés au thème des émotions auto-conscientes et ont exprimé un vif intérêt à la mise en place du projet auprès de leurs patients.

Des fonds devront toutefois soutenir ce projet et nous prévoyons de le soumettre à différents appels d'offres (Fédération pour la Recherche sur le Cerveau, fonds de recherche du CHRU de Lille, Vaincre Alzheimer, France Parkinson, etc.) afin de permettre le soutien matériel, administratif et logistique.

Les objectifs à plus long terme de ce projet, sont de considérer l'importance que peuvent avoir les émotions auto-conscientes pour la prise en charge de patients et si des interventions spécifiques peuvent conduire à une amélioration de la qualité de vie du patient et de son entourage.

Autres projets

Parallèlement à ces projets axés sur la cognition sociale, d'autres travaux sont également en cours. Ainsi, comme nous l'avons abordé précédemment, notre suivi de de patients DM1 devrait également permettre des études sur le fonctionnement cognitif de ces patients. Plus particulièrement, nous prévoyons de rechercher au sein de cette population de patients, la présence de profils cognitifs différents. Une hétérogénéité des atteintes cognitives est en effet discutée dans cette pathologie (Okkersen et al., 2017). Nous voudrions sur base d'analyses statistiques, identifier des profils cognitifs et comparer ces sous-groupes sur le plan clinique et paraclinique (travaux qui seront intégrés dans la thèse de neurosciences du docteur Jean-Baptiste Davion). Nous avons précédemment eu recours à ce même type d'analyse au sein d'une cohorte de patients atteints d'une maladie d'Alzheimer du sujet jeune (cohorte COMAJ, Cohorte Maladie Alzheimer Jeunes) et avons retrouvé 2 profils distincts de patients (Pollet et al., soumis). L'un des groupes de patients ainsi constitué, se caractérisait par une prédominance des troubles mnésiques et l'autre présentait un profil marqué par une relative préservation de la sphère mnésique. Des différences sur le plan clinique et paraclinique entre les groupes ont pu être constatées, ainsi que des différences quant à l'évolution des troubles au cours du suivi (avec une plus rapide évolutivité pour les patients du groupe présentant une relative préservation de la mémoire).

D'autres travaux sur cette cohorte de patients atteints d'une maladie d'Alzheimer du sujet jeune sont également en cours d'élaboration, notamment une collaboration avec les docteures Christine Delmaire et Stéphanie Bombois, concernant l'impact du corps calleux et des relations interhémisphériques sur le profil clinique de ces patients. Ce projet s'inscrit dans une perspective plus générale de voir la maladie d'Alzheimer en tant que syndrome de dysconnexion (Delbeuck et al., 2003). Dans cette perspective, le corps calleux représente un marqueur potentiel de ces phénomènes de dysconnexion. La première des études de ce projet sera basée sur des mesures de volumétrie et de texture du corps calleux et nous chercherons si des modifications régionales spécifiques du corps calleux peuvent rendre compte de profils cognitifs différents. Les projets suivants sur ce thème viseront à évaluer l'évolutivité de cette atrophie du corps calleux (suivi à un an) et son rôle potentiel en tant que prédicteur d'une aggravation plus rapide du tableau clinique. Parallèlement, des analyses plus globales des relations interhémisphériques sont prévues sur base d'une analyse en tractographie des différents faisceaux interhémisphériques (corps calleux, fornix et commissure antérieure) mais

également par le biais de l'étude de la connectivité interhémisphérique (analyses du connectome).

Mon implication dans les activités de recherche du CMRR de Lille m'a également permis de participer à l'élaboration de l'évaluation cognitive proposée dans la cohorte BALTAZAR (Hanon et al., 2018). Cette cohorte multicentrique a pour objectif premier, de tester l'hypothèse que le taux d'Aβ plasmatique libre est associé au risque de progression vers la maladie d'Alzheimer chez les patients ayant un trouble cognitif léger (ou Mild Cognitive Impairment, MCI) mais également d'en évaluer le rôle en tant que marqueur de l'aggravation clinique chez des patients ayant une maladie d'Alzheimer à un stade léger à modéré. Cette étude inclut des données cliniques, cognitives, biologiques et IRM avec un suivi des patients sur 3 ans (certains patients ont participé à une extension de suivi de 2 années). Des travaux axés sur le fonctionnement cognitif des patients suivis dans cette cohorte, sont en cours de réalisation. Nous nous sommes notamment intéressés à identifier, au sein des patients avec un trouble cognitif léger, l'existence de groupes de patients dont les résultats seraient divergents à des épreuves de mémoire épisodique réputées sensibles au risque de progression vers la maladie d'Alzheimer. Nous avons ainsi constaté que certains patients pouvaient avoir un risque de progression vers une maladie d'Alzheimer selon une épreuve de mémoire épisodique verbale alors que ce risque ne semblait pas transparaitre lorsque les scores du patient à une épreuve non verbale étaient considérés (groupe atteinte verbale) ; le profil inverse était également retrouvé dans la cohorte (groupe atteinte non verbale). Nous avons montré des différences entre ces groupes sur le plan clinique (atteinte des épreuves verbales plus généralisée dans le groupe avec une atteinte de la mémoire épisodique verbale / symptomatologie dépressive plus marquée dans le groupe avec une atteinte de la mémoire épisodique non verbale). Ces groupes se différenciaient également en termes de biomarqueurs évocateurs d'une maladie d'Alzheimer sur base des données de la ponction lombaire (protéines tau et phospho-tau plus élevées dans le groupe avec une atteinte verbale) mais également en imagerie (atrophie hippocampique sur base de l'échelle de Scheltens plus marquée à gauche comme à droite dans le groupe avec une atteinte verbale). Nous sommes en attente des données de progression vers une maladie d'Alzheimer de ces patients au cours du suivi pour établir le risque d'évolution dans ces groupes aux performances dissociées entre mémoire épisodique verbale et non verbale, et potentiellement confirmer le risque de maladie d'Alzheimer prodromale plus significatif en cas d'atteinte de la modalité verbale.

Enfin, d'autres cohortes en cours de développement feront également l'objet de travaux. Une cohorte devrait prochainement être constituée pour évaluer les variations des paramètres

IRM au sein d'une population de volontaires sains (projet coordonné par le docteur Renaud Lopes). Parallèlement à l'acquisition de séquences en IRM, nous avons établi en collaboration avec la professeure Kathy Dujardin et la docteure Sophie Hennion, une évaluation cognitive et comportementale qui sera proposée aux différents participants. Ces données devraient nous permettre des travaux sur les relations entre le fonctionnement cérébral et la réserve cognitive[6] des individus ; la réserve cognitive sera estimée par le biais d'un questionnaire évaluant la fréquence d'investissement du participant dans des activités stimulantes intellectuellement tout au long de la vie mais également par des mesures du fonctionnement intellectuel. Par ailleurs, le second grand axe cognitif de ce projet consistera à évaluer le fonctionnement de réseaux attentionnels au cours de la vie (des volontaires sains de 18 à 90 ans seront inclus).

[6] La réserve cognitive (Stern & Barulli, 2019) définit la capacité d'un individu à utiliser un réseau cérébral de façon accrue en réponse aux exigences d'une tâche mais également sa capacité à utiliser des stratégies cognitives alternatives ou d'autres réseaux cérébraux en réponse à une atteinte cérébrale ou un déclin. Cette réserve cognitive est conçue comme dynamique et se construisant au cours de la vie sous l'influence de facteurs comme le niveau socio-culturel, l'insertion sociale et les activités quotidiennes.

Conclusions

L'ensemble des travaux présentés dans ce document, et plus généralement mes travaux de recherche, s'inscrivent dans une perspective de recherche clinique. Ces travaux ont pour ambition, de faire la transition entre recherche et clinique. Les résultats de la recherche ne sont en effet pas toujours directement transposables dans la pratique clinique. Ainsi, des épreuves utilisées dans le cadre de la recherche ne peuvent être utilisées auprès de patients dans une perspective clinique, que si tout un travail de validation et normalisation a été réalisé. Ce travail est plus particulièrement nécessaire dans le domaine de la cognition sociale pour lequel les propriétés psychométriques des outils d'évaluation sont encore peu établies. C'est dans cette perspective que notre travail de validation et normalisation du test des faux pas s'est inscrit.

Parallèlement, il est également important pour le clinicien, de pouvoir comprendre au mieux le sens clinique de ses observations réalisées auprès de patients. Mes travaux dans les populations cliniques ont ainsi cherché à appréhender l'intérêt de l'évaluation de la cognition sociale pour le diagnostic (notamment dans le cadre d'une suspicion de démence fronto-temporale) mais également plus généralement pour la prise en charge des patients. Les travaux que nous avons réalisés dans le cadre de l'épilepsie du lobe temporal témoignent de cet objectif. Nous avons examiné les difficultés de ces patients en adoptant une perspective de groupe (ces patients ont-ils en moyenne des performances significativement différentes de volontaires sains ?) mais également plus individuelle (quelle proportion de ces patients peut être considérée comme déficitaire par rapport à des volontaires sains ?) pour connaitre la fréquence de ces troubles. Cette notion est nécessaire pour savoir à quel point cette caractéristique peut être attendue dans cette population. Il est ensuite capital de pouvoir donner un sens à ce déficit. Pour cela, nous avons examiné quels comportements pouvaient être prédits par ces difficultés de cognition sociale dans l'épilepsie du lobe temporal. Une amélioration de notre compréhension de ces liens est indispensable avant de pouvoir considérer l'intérêt de revalidation de ces compétences de cognition sociale dans cette population.

D'une manière plus générale, nos travaux ont souligné une hétérogénéité des performances de cognition sociale dans l'épilepsie du lobe temporal entre les différents patients. Ce constat est probablement à mettre en relation avec la nature complexe des capacités de cognition sociale et souligne l'importance de pouvoir décomposer ces compétences selon la nature ou les processus impliqués. Cette analyse plus détaillée pourrait permettre une meilleure individualisation de la prise en charge des patients. Cette approche est celle que nous avons adoptée dans notre projet portant sur la dystrophie myotonique de type 1. Nous avons ainsi eu

recours à une épreuve de théorie de l'esprit permettant de distinguer des processus d'inférence selon leur nature (cognitive vs. affective) mais également d'analyser plus finement le type de raisonnement sur ces états mentaux. Cette approche nous semble plus propice à discerner des profils de performances responsables de présentations cliniques différentes des patients.

Cette recherche d'une meilleure caractérisation des compétences de cognition sociale nous a également amené à nous intéresser à la théorie de l'esprit à la première personne par le biais des émotions auto-conscientes. Cette perspective a l'intérêt d'aborder plus directement le comportement que l'individu pourrait être susceptible d'aborder et témoigner de ce fait de ses aptitudes sociales. Notre projet a pour objectif d'investiguer les émotions auto-conscientes dans une perspective transnosologique afin de déterminer si des modifications spécifiques de ces émotions peuvent être constatées et permettre de déterminer quelles atteintes cérébrales peuvent en modifier l'expression.

Pour conclure, l'objectif des travaux présentés était de mieux comprendre les modifications de la cognition sociale rencontrées par un patient suite à l'apparition d'un dysfonctionnement cérébral. Progresser dans notre compréhension de ces modifications pourrait permettre de définir de nouvelles pistes de prise en charge et améliorer la qualité de vie du patient et de son entourage.

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Curriculum Vitae

XAVIER DELBEUCK

Coordonnées professionnelles

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Psychologue

Spécialisé en neuropsychologie

Parcours académique

Nov. 2006 **Obtention du titre de Docteur en Psychologie décerné par l'Université de Genève, Suisse**

Thèse : Maladie d'Alzheimer : Un syndrome de dysconnexion ? ; Directeur de thèse : Professeur M. Van der Linden

Fév. 2005 Reconnaissance par le Ministère Français de l'Education, de l'Enseignement Supérieur et de la Recherche (Direction de l'enseignement supérieur) de l'équivalence aux diplômes nationaux français exigés en vue de faire usage professionnel du titre de psychologue en France

1999 **Licence en Psychologie (BAC+5) décernée par l'Université de Liège (ULg), Belgique**

Mémoire de Licence : Effet d'un apprentissage implicite sur l'architecture du sommeil chez le sujet sain ; Promoteur : Professeur M. Van der Linden

Expérience Professionnelle

Activités cliniques :

Depuis oct. 2004 **Psychologue à 100% au sein du Centre Mémoire de Ressources et de Recherche (CMRR) de Lille**, dirigé par la Professeure Florence Pasquier
Hôpital Roger Salengro, CHRU Lille, France

- Cette unité accueille des patients dans le cadre du diagnostic des troubles cognitifs
- Activité au sein de ce service d'une part clinique et d'autre part de recherche, mais également encadrement d'étudiants et animation de l'équipe de neuropsychologie.

Fév. 2001 – Sep. 2004 **Psychologue à 50%, Unité de Réhabilitation Mémoire**
Département de Gériatrie, HUG, Suisse

- Pendant un an, travail au sein du Centre de Jour de l'Unité de Réhabilitation Mémoire accueillant des patients Alzheimer à un stade débutant pour des prises en charge cognitive individuelles ou en groupe
- Pendant deux ans, travail à l'Unité de Réhabilitation Mémoire pour le diagnostic des troubles cognitifs auprès de personnes âgées

Activités d'enseignement :

Interventions dans le cadre de formations et enseignements auprès de professionnels (aides familiales, ergothérapeutes, infirmiers, médecins, orthophonistes, psychologues, etc.) ainsi qu'auprès du grand public (5 à 7 de l'Institut Pasteur, etc.).

Depuis 2014, participation au **comité de pilotage du Diplôme Universitaire (DU) de Neuropsychologie Clinique** de l'université de Lille 2 (sous la direction de la Professeure K. Dujardin) et interventions dans le cadre de ce DU sur les thèmes suivants : généralités sur l'évaluation neuropsychologique, apprentissage et mémoire, émotion et cognition sociale, vieillissement des fonctions cognitives, neuropsychologie de la maladie d'Alzheimer, neuropsychologie de la démence fronto-temporale, tumeurs cérébrales et conséquences du traitement des cancers. Participation aux travaux dirigés de ce DU et au processus d'évaluation des étudiants.

Entre 2013 et 2016, **Chargé de cours** suppléant pour l'Unité de Recherche en neuropsychologie et neuroimagerie fonctionnelle (Professeur P. Peigneux) au sein de l'**Université Libre de Bruxelles**. Prise en charge des unités d'enseignement « Neuropsychologie Clinique » (5ECTS), « Neuropsychologie Cognitive du vieillissement normal et pathologique » (3ECTS) et « Séminaire d'Etude Approfondie de Cas en Neuropsychologie » (3 ECTS)

Interventions annuelles actuelles dans le cadre de formations/enseignements :

- Depuis 2005, intervention dans le cadre du M2 de Neuropsychologie et du DU de Neuropsychologie clinique de l'université de Caen sur le thème : Démence fronto-temporale : aspects neuropsychologiques.
- Depuis 2006, intervention dans le cadre du certificat de « Neurosciences cognitives » du M1 de l'université de Lille 2 sur le thème : Explorations psychométriques de la mémoire
- Depuis 2011, intervention dans le cadre du Master de Psychologie des processus neurocognitifs et sciences affectives, organisé par l'université de Lille 3 sur le thème : Evaluation des pathologies neurodégénératives.
- Depuis 2014, intervention dans le cadre du Master 2 Biologie de l'Université de Lille 2 sur le thème : Etude du comportement de l'Homme à l'Animal.
- A partir de 2019 : interventions dans le cadre de l'AUEC VasCog "cognition : les enjeux de la prévention vasculaire" : interventions sur les thèmes de l'évaluation du fonctionnement cognitif, du vieillissement normal et de l'intérêt de l'entrainement cognitif.

Activités de recherche :

Rattaché à l'unité de recherche **LilNCog** (Lille neurosciences & cognition, **UMR-S 1172**, directeur : Professeur Luc Buée) au sein de l'équipe « **Troubles cognitifs dégénératifs et vasculaires** », dirigée par le Professeur Régis Bordet

Oct. 2001 – Sep. 2004 **Assistant universitaire (équivalent attaché temporaire d'enseignement et de recherche) à 50 %**
au sein de l'Unité de Psychopathologie et Neuropsychologie Cognitive du Professeur Martial Van der Linden, FPSE, Université de Genève, Suisse

• Poste impliquant la supervision de travaux d'étudiants dans les domaines de la neuropsychologie et de la psychopathologie cognitive ainsi que des activités d'enseignement.

Oct. 1999 – Sept. 2001 **Chercheur Boursier de Doctorat au Centre de Recherches du Cyclotron à 100%**
Université de Liège (ULg), Belgique

• Engagé dans le cadre d'une étude européenne (NEST-DD ; Network for Efficiency and Standardization of Dementia Diagnosis) visant à améliorer et standardiser le diagnostic de la démence à un stade précoce
• Passation d'évaluations neuropsychologiques auprès de personnes présentant des troubles cognitifs et travaux autour des relations entre bilan cognitif et examens de neuroimagerie.

Divers

Né le	3 Août 1976, à Verviers (Belgique)
Nationalité	Belge
Situation Familiale	Célibataire

Anglais lu, écrit, parlé ; Allemand (connaissances scolaires)

Maîtrise de logiciel informatique (Word, Excel, Powerpoint, Eprime, etc.)

Numéro ADELI	59 93 0801 2
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h-index (Google Scholar) : 19

Articles en tant que 1er auteur

	IF	Catég.	Score SIGAPS
Delbeuck, X., Pollet, M., Pasquier, F., Bombois, S., & Moroni, C. The clinical value of the faux pas test for diagnosing behavioral-variant frontotemporal dementia. *Journal of Geriatric Psychiatry and Neurology. In press.* https://doi.org/10.1177/0891988720964253	2,125	D	12
Delbeuck, X., Debachy, B., Pasquier, F., & Moroni, C. (2013). Action and noun fluency testing to distinguish Alzheimer's disease and dementia with Lewy bodies. *Journal of Clinical and Experimental Neuropsychology*. 35(3), 259-268.	2,158	D	12
Delbeuck, X. (2009). Intérêt de l'évaluation neuropsychologique. *Soins (dossier spécial sur les gliomes)*, 54(733), 47.		NC	4
Delbeuck, X., Collette, F., & Van der Linden, M. (2007). Is Alzheimer's disease a disconnection syndrome? Evidence from a crossmodal audio-visual illusory experiment. *Neuropsychologia*, 45(14), 3315-3323.	3,63	C	16
Delbeuck, X., Van der Linden, M., & Collette, F. (2003). Alzheimer's disease as a disconnection syndrome ?. *Neuropsychology Review*, 13(2), 79-92.	1,625	D	12
Delbeuck, X., Van der Linden, M., Collette, F., Bechet, S., Lekeu, F., Adam, S., & Salmon, E. (2000). Le diagnostic précoce de la maladie d'Alzheimer : apport de la neuropsychologie. *Neurone*, 5(6), 198-203.		NC	4

Articles en tant que dernier auteur

	IF	Catég.	Score SIGAPS
Hennion, S., Szurhaj, W., Skrobala, E., Davière, J., Tyvaert, L., Derambure, P., & Delbeuck, X. (2019). Experiences of self-conscious emotions in temporal lobe epilepsy. *Epilepsy & Behavior: E&B, 90*, 1-6. https://doi.org/10.1016/j.yebeh.2018.10.028	2,508	D	12
Pollet, M., Moroni, C., Jacquemont, C., Debachy, B., Kurth S., Pasquier, F., Kubiak I., & Delbeuck, X. (2019). Le Repeat and Point test : un outil de screening discriminant des profils de troubles langagiers dans le cadre des affections neurodégénératives. *Revue de Neuropsychologie*, 11(2), 151-158.		NC	4
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- Leroy, A., Moroni, C., Colin M-M, Selingue, B., Pasquier, F., Peigneux, P. & Delbeuck, X. (2010). Consolidation mnésique lors du sommeil dans le vieillissement normal. 34èmes journées de printemps de Société de Neuropsychologie de Langue Française, Lille, 28-29 Mai 2010 [communication orale].
- Delbeuck, X., Bruandet, A., Bombois, S., Mackowiak, M.A., & Pasquier, F. (2009). Cognitive decline in Alzheimer's disease, vascular dementia and mixed dementia. Quatrième Congrès de l'International Society for Vascular Behavioural and Cognitive Disorders (VASCOG), Singapoure, 15 janvier 2009 [communication écrite].
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- Delbeuck, X., Boutantin, J., Leroy, A., Jean, A.S., & Pasquier, F. (2007). Intérêt d'un outil de screening de la mémoire prospective auprès de patients déments. Neuvième Réunion Francophone sur la maladie d'Alzheimer et les syndromes apparentés, Nice, 20-22 novembre 2007 [communication écrite].
- Delbeuck, X., Mayer, E., Collette., F., Rimbault, A., Seron, C., & Van der Linden, M. (2005). Transfert interhémisphérique d'informations motrices et somesthésiques dans la maladie d'Alzheimer. Journées d'hiver de la Société de Neuropsychologie de Langue Française (SNLF), Paris, 9 décembre 2005 [communication écrite].
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- Pasquier, F., Lepoittevin, S., Bombois, S., Debette, S., Laurier-Grymonprez, L., Mackowiak, M.A., Mémin, A., Lebert, F. & Delbeuck, X. (2005). Verbal episodic memory in Vascular dementia : Comparison with Alzheimer's disease and other dementia. Vas-Cog, Florence, 9 juin 2005 [communication écrite].
- Delbeuck, X., Baeriswyl-Cottin, R., Juillerat Van der Linden, A.-C., Van der Linden, M. (2004). Apports d'une situation de jeu à la prise en charge en groupe de patients Alzheimer à un stade débutant. Journées de printemps de la Société de Neuropsychologie de Langue Française (SNLF), Angers, 4-5 juin 2004 [communication écrite].

- Roig, I., Delbeuck, X., Juillerat Van der Linden, A.-C., Van der Linden, M. (2004). Comment apprendre aux personnes proches à mieux communiquer avec les patients Alzheimer ? Journées de printemps de la Société de Neuropsychologie de Langue Française (SNLF), Angers, 4-5 juin 2004 [communication écrite].
- Delbeuck, X., Collette, F., Comhaire, G., Colin, C., Salmon, E., & Van der Linden, M. (2002). Intégration multisensorielle dans la maladie d'Alzheimer à un stade débutant. Journées d'hiver de la Société de Neuropsychologie de Langue Française (SNLF), Paris, 6 décembre 2002 [communication orale].
- Delbeuck, X., Van der Linden, M., Seron, C., Collette, F., Mayer, E., & Salmon, E. (2002). Effet du vieillissement sur le transfert interhémisphérique. Colloque du Programme Plurifacultaire de Neurosciences Cognitives, Genève, 28 février-1er mars 2002 [communication écrite].
- Delbeuck, X., Van der Linden, M., Seron, C., Collette, F., Mayer, E., & Salmon, E. (2001). Evaluation du transfert interhémisphérique dans le vieillissement normal. Journées d'hiver de la Société de Neuropsychologie de Langue Française (SNLF), Paris, 7 décembre 2001 [communication écrite].
- Delbeuck, X., Peigneux, P., Merbah, K., Degueldre, C., & Van der Linden, M. (2000) Priming for possible, but not impossible, gestures. Annual Meeting of the Belgian Psychological Association, Liège, 12 mai 2000 [communication écrite].

Conférences invitées

- Intervention dans le cadre de la journée "Vieillir avec une lésion cérébrale acquise : état des lieux et questionnement" organisée par le réseau TC-AVC 59/62, sur le thème : "Le vieillissement pathologique", à Lille (4 avril 2019).
- Intervention dans le cadre des Journées de Neurologie de Langue Française sur le thème : "L'hypothèse calleuse dans la maladie d'Alzheimer", à Bordeaux (10 mars 2018).
- Intervention dans le cadre de la réunion Cognition de la SFSEP sur le thème : "La cognition sociale", à Lille (15 juin 2017).
- Intervention dans le cadre du 52ième congrès de la Société Française de Psychologie sur le thème : "Intérêt de l'évaluation de la cognition sociale dans la pratique clinique", à Lille (8 septembre 2010).
- Intervention dans le cadre du 11ème International multisensory Research Forum sur le thème : "Multisensory integration in Alzheimer's disease", à Liverpool (17 juin 2010).
- Intervention dans le cadre des 34èmes journées de printemps de la Société de Neuropsychologie de Langue Française, sur le thème : "Trouble de la cognition sociale et démences fronto-temporales", à Lille (29 mai 2010).
- Intervention dans le cadre de la 23ème réunion internationale du groupe de recherche sur la maladie d'Alzheimer et de l'association de familles Provence Alzheimer, sur le thème : "Troubles émotionnels dans la démence fronto-temporale", à Marseille (29 janvier 2010).
- Interventions dans le cadre des 4èmes Journées d'Étude organisées pour le service de neurologie d'Orléans, sur le thème : "Actualités sur les démences : diagnostic et prise en charge, particularités des patients jeunes", à Orléans (22 et 23 janvier 2010).
- Intervention en collaboration avec le Dr Stéphanie Bombois dans le cadre d'un atelier clinique organisé lors du Congrès Euro-Régional de Médecine (CERM), sur le thème : "Démences: quelles thérapeutiques (médicamenteuse ou non médicamenteuse) ? ", à Lille (17 septembre 2009).
- Intervention dans le cadre du symposium du CMRR d'Amiens, sur le thème : "Epreuve de rappel libre/rappel indicé 16 items :: Expérience lilloise", à Amiens (14 avril 2009).
- Intervention dans le cadre de la journée organisée par le laboratoire Janssen Cilag, sur le thème des troubles de la cognition en oncologie et hématologie : "La rééducation cognitive", à Lille (29 septembre 2007).
- Intervention dans le cadre de la session « Troubles cognitifs de la personne âgée : démence ou dépression » lors des réunions du Congrès Euro-Régional de Médecine (CERM), sur le thème : "Bilan neuropsychologique et démence", à Lille (21 septembre 2006).
- Intervention dans le cadre du forum de la SNLF (Société de Neuropsychologie de Langue Française) intitulé « Actualités sur les démences : aspects cliniques et neuropsychologiques », sur le thème : "Variante frontale de la démence fronto-temporale : aspects neuropsychologique", à Paris (6 décembre 2005).
- Intervention en collaboration avec Mme Anne-Claude Juillerat Van der Linden dans le cadre d'une formation organisée par l'Association Suisse des Ergothérapeutes, sur le thème : "Prise en charge cognitive des patients avec troubles démentiels débutants", à Genève (28-29 avril 2005).
- Intervention au sein de l'Unité de Réhabilitation Mémoire des Hôpitaux Universitaires de Genève, sur le thème : "Le test de rappel libre/rappel indicé 16 items dans la démence", à Genève (27 avril 2005)
- Intervention dans le cadre du workshop clinique organisé dans la cadre des journées de printemps par la Société de Neuropsychologie de Langue Française (SNLF), sur le thème : "Prise en charge chez un patient atteint de démence de type Alzheimer débutante", à Angers (3 juin 2004).
- Intervention en collaboration avec Mme Anne-Claude Juillerat Van der Linden dans le cadre d'une formation organisée par l'Association Suisse des Ergothérapeutes, sur le thème : "Prise en charge cognitive des patients avec troubles démentiels débutants", à Genève (5-6 février 2004).
- Intervention en collaboration avec Mme Anne-Claude Juillerat Van der Linden dans le cadre d'une formation organisée par l'Association Suisse des Ergothérapeutes, sur le thème : "Prise en charge cognitive des patients avec troubles démentiels débutants", à Genève (6-7 février 2003).

- Intervention en collaboration avec Mme Françoise Jermann dans le cadre du colloque de l'Unité de Neurogérontopsychologie des Hôpitaux universitaires de Genève, sur le thème : "Les spécificités du traitement cognitif chez la personne âgée dépressive", à Genève (21 mai 2002).
- Intervention en collaboration avec Mme Anne-Claude Juillerat Van der Linden dans le cadre d'une formation organisée par l'Association Suisse des Ergothérapeutes, sur le thème : "Prise en charge cognitive des patients avec troubles démentiels débutants", à Genève (2-3 mai 2002).
- Intervention dans le cadre du colloque du Service de Neuropsychologie des Hôpitaux Universitaires de Genève, sur le thème : "Syndrome de dysconnexion calleuse dans la maladie d'Alzheimer", à Genève (23 avril 2002).
- Intervention au sein de l'Unité de Réhabilitation Mémoire des Hôpitaux Universitaires de Genève, sur le thème :"Pathologies cérébrales et problèmes de dysconnexion", à Genève (6 mars 2002).
- Intervention en collaboration avec Mme Anne-Claude Juillerat Van der Linden au sein de l'Unité de Réhabilitation Mémoire des Hôpitaux Universitaires de Genève, sur le thème :"Prise en charge des patients Alzheimer débutants dans le cadre d'un centre de jour", à Genève (13 décembre 2001).
- Intervention au sein de l'Unité de Réhabilitation Mémoire des Hôpitaux Universitaires de Genève, sur le thème :"L'hypothèse de déconnexion dans la maladie d'Alzheimer", à Genève (16 mai 2001).

Participation à des projets ayant bénéficié de financements

- Essai multicentrique évaluant le BF.2.649 dans la maladie à corps de Lewy (laboratoire Schwartz-Bioprojet). Participation à l'élaboration de l'évaluation neuropsychologique du protocole.
- MNEMOSYNE: Étude prospective randomisée ouverte et multicentrique évaluant les effets sur les fonctions cognitives de l'hormonothérapie adjuvante dans le cancer du sein chez la femme ménopausée (Pr J. Bonneterre, Centre Oscar Lambret, Lille). Participation à l'élaboration de l'évaluation neuropsychologique du protocole.
- BALTAZAR: Intérêt du dosage plasmatique des peptides amyloïdes pour le diagnostic et le pronostic de la maladie d'Alzheimer (Pr O. Hanon, APHP, Hôpitaux de Paris). Participation à l'élaboration de l'évaluation neuropsychologique du protocole auprès de patients atteints de maladie d'Alzheimer ou d'un déclin cognitif léger (MCI).
- T-GLIALES: Étude prospective évaluant l'impact de la tumeur et des traitements sur les fonctions neurocognitives (dont langagières) et la qualité de vie, chez des patients ayant un gliome de grade II (Dr MP. Sunyach, Centre Léon Bérard, Lyon). Participation à l'élaboration de l'évaluation neuropsychologique du protocole.
- Cohorte COMAJ (Cohorte Maladie Alzheimer Jeunes): participation au développement de cette cohorte et à la caractérisation des patients atteints d'une maladie d'Alzheimer avant l'âge de 60 ans pour le centre de Lille. Ce projet est porté par le CMRR de Lille (Pr F. Pasquier), Paris (Pr B. Dubois) et de Rouen (Pr D. Hannequin).
- PACTE-I (méthylPhenidAte and Cognitive Training in Elderly): Projet déposé visant à évaluer la potentialisation des capacités cognitives chez le sujet âgé par l'association du méthylphenidate et de l'entrainement cognitif : Essai thérapeutique de preuve de concept en double aveugle versus placebo (Pr D. Devos, UMR-S 1172). Participation à l'élaboration du programme de rééducation cognitive et au plan d'évaluation de l'efficacité sur le plan cognitivo-comportemental.
- Variations IRM chez le sujet sain: Projet déposé visant à évaluer les variations des indicateurs d'imagerie dans la population tout-venant (Dr R. Lopes, UMR-S 1172). Participation à l'élaboration de la batterie neuropsychologique et comportementale.
- Rôle de l'insulinorésistance dans les troubles cognitifs chez des patients atteints de dystrophie myotonique de type I. Projet déposé par le Dr C. Tard (UMR-S 1172). Mise en place de la batterie d'évaluation cognitive, comportementale et sociale et participation au développement de cette cohorte de suivi de patients.

Divers

Participation à l'expertise de dossiers pour les Fonds AXA pour la Recherche en 2010

Supervision de travaux de recherche

Thèse de Sciences

- Davion, J.B. (2020-…). Étude des profils cognitifs et comportementaux dans la dystrophie myotonique de type 1 et de leur association avec des paramètres d'IRM structurelle et fonctionnelle. Thèse de Sciences – Faculté de Médecine, Université de Lille.

Master 2 ou diplôme de fin d'études de psychologie

- Lefebvre, M. (2019). La cognition sociale chez des patients atteints d'une dystrophie myotonique de type 1. Mémoire de master 2 réalisé à l'université de Lille (UFR de Psychologie).
- Kubiak, I. (2017). Validation d'un outil de screening discriminant les troubles du langage observés dans la démence sémantique et l'aphasie primaire progressive non fluente. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie).
- Leleu, M. & Mikolajczyk, S. (2016). Vieillir est-il synonyme d'amélioration, de maintien ou de déclin de la cognition sociale ? Mémoire réalisé dans le cadre du Master de Logopédie de l'université libre de Bruxelles.
- Grosz, L. (2016). Le recours aux stratégies de compensation mnésique dans le trouble cognitif léger (MCI) Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie).
- Lamare, M. (2015). Dissociation entre mémoire épisodique verbale et visuelle dans les pathologies neurodégénératives. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie).
- Brion, M. (2014). Troubles de théorie de l'esprit chez les patients épileptiques du lobe temporal médian : Facteurs prédictifs, influence du temps sur les performances, lien avec les perturbations psycho-affectives et l'affaiblissement de la qualité de vie. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université Lille Nord de France).
- Bouchet, P. (2014). Reconnaissance émotionnelle dans le cadre des affections démentielles. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université Lille Nord de France).
- Poulain, A. (2013). Reconnaissance émotionnelle dans le cadre des affections neurodégénératives. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université Lille Nord de France).
- Travers, R. (2013). Recours aux stratégies de compensation mnésique au sein d'une population de patients présentant un déclin cognitif léger. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université Lille Nord de France).
- Lang, B. (2012). Evaluation de la Théorie de l'Esprit dans la maladie d'Alzheimer : Intérêt d'un outil d'évaluation bref auprès de patients Alzheimer. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université Lille Nord de France).
- Monboisse, P. (2010). L'effet de la maladie d'Alzheimer sur le buffer épisodique. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Van Miegem, M. (2011). Intérêt d'une épreuve de mémoire épisodique visuelle dans la pratique clinique en consultation mémoire. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université Lille Nord de France).
- Remmery, D. (2011). L'optimisation de l'évaluation des fonctions attentionnelles au sein des consultations mémoire : Intérêt de l'introduction d'épreuves informatisées Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université de Savoie).
- Navarro, J. (2011). Troubles neuropsychologiques et dosage des biomarqueurs du liquide céphalorachidien dans la maladie d'Alzheimer à début précoce. Mémoire de Master 2 de Psychologie spécialisé en Neuropsychologie (Université de Savoie).
- Pelletier, Y. (2010). Intérêt de l'évaluation d'un outil clinique évaluant la paresse mentale en consultation mémoire. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Cardon, C. (2010). Création et sélection d'un nouvel outil pour tester la mémoire épisodique non verbale. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Lagourgue L. (2009). Mémoire procédurale dans la démence à corps de Lewy: Utilisation d'une tâche de lecture en miroir. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Bulzacka, E. (2008). Contribution sensorielle et cognitive de la couleur sur les performances en mémoire épisodique dans la maladie d'Alzheimer. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Lamouroux, M. (2008). Transfert interhémisphérique d'informations visuelles dans la maladie d'Alzheimer. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Saadi, F. (2008). La théorie de l'esprit dans la démence fronto-tepmporale. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Poissonnet H. (2007). Transfert et coopération interhémisphérique dans la maladie d'Alzheimer. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Lys, H. (2007). Etude de la théorie de l'esprit dans la démence fronto-temporale. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Lepoittevin, S. (2006). Validation d'une tâche de fluence d'action : Etude des performances de patients atteints de la maladie d'Alzheimer et de démence fronto-temporale. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Ewert, V. (2006). La contribution de la couleur sur les performances en mémoire épisodique dans la maladie d'Alzheimer. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.

- Leroy, A. (2006). Reality monitoring, perception visuo-spatiale et hallucinations visuelles dans la démence à corps de Lewy. Mémoire de master 2 réalisé à l'université de Lille 3 (UFR de Psychologie) en co-direction avec C. Moroni.
- Rochat, L. (2005). Maladie d'Alzheimer et hypothèse de déconnexion: illusion intermodale de la main en plâtre. Mémoire de DESS réalisé à l'université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Ragueneau, M. (2005). Le Stroop sémantique: nouvelle méthode d'évaluation de la mémoire sémantique ? Mémoire de master 2 recherche : neuropsychologie (université de Toulouse III) en co-direction avec F. Pasquier.
- Meresse, E. (2005). La réactualisation des connaissances de Soi chez les malades Alzheimer. Mémoire de master 2 recherche : neuropsychologie (université de Toulouse III) en co-direction avec F. Pasquier.
- Pizzo, R. (2005). Contribution sensorielle et cognitive de la couleur pour la reconnaissance de scènes naturelles dans la maladie d'Alzheimer. Mémoire de DESS réalisé à l'université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Rimbault, A. (2004). Le transfert interhémisphérique dans la maladie d'Alzheimer. Mémoire de DESS réalisé à l'université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Simioni, S. (2004). Elaboration d'une batterie neuropsychologique pour l'évaluation cognitive de personnes atteintes de démence modérée à sévère. Mémoire de DESS réalisé à l'université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Roig, I. (2004). Comment améliorer la communication entre patients Alzheimer et leur proche? Mémoire de DESS réalisé à l'Université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Baud, V. (2004). Apprentissage sans erreur et mémoire sémantique. Mémoire de DESS réalisé à l'Université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Baeriswyl-Cottin, R. (2004). Elaboration d'une situation de jeu adaptée à la prise en charge cognitive de patients présentant une maladie d'Alzheimer débutante. Mémoire de DESS réalisé à l'Université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Maillard-Wermelinger, A. (2003). Du sel dans le thé? Evaluation des distractions chez des patients souffrant d'une démence de type Alzheimer. Mémoire de DESS réalisé à l'Université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Emmenegger, J. (2003). Effet d'un fond musical sur la performance attentionnelle de patients Alzheimer. Mémoire de DESS réalisé à l'Université de Genève (Faculté de Psychologie et des Sciences de l'Education) sous la direction du Professeur Martial Van der Linden.
- Comhaire, G. (2002). Hypothèse de déconnexion dans la démence de type Alzheimer : Evaluation de l'intégration multimodale. Mémoire de licence réalisé à l'Université de Liège (Faculté de Psychologie et des Sciences de l'Education) sous la direction de Madame Fabienne Collette.
- Seron, C. (2001). Hypothèse de déconnexion et maladie d'Alzheimer : Evaluation du transfert interhémisphérique de l'information. Mémoire de licence réalisé à l'Université de Liège (Faculté de Psychologie et des Sciences de l'Education) sous la direction de Madame Fabienne Collette.

<u>Master 1 en psychologie</u>

- Labonne, C. (2014). Influence des variables sociodémographiques sur les performances à une tâche de reconnaissance des émotions faciales chez le sujet âgé sain. Mémoire de Master 1 de Psychologie (Université Lille Nord de France).
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Title: The clinical value of the faux pas test for diagnosing behavioral-variant frontotemporal dementia

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Abstract:

Objective: We studied the clinical value of the faux pas test for diagnosing behavioral-variant frontotemporal dementia.

Method: The faux pas test was administered to patients referred to a memory clinic in a context of behavioral disturbances. These patients had a follow-up of, at least, three years allowing for a diagnosis of behavioral-variant frontotemporal dementia (n=14) or not (n=25).

Results: The faux pas test displayed a high sensitivity for behavioral-variant frontotemporal dementia (.83) however its specificity was only moderate (.64).

Conclusions: The faux pas test is frequently impaired in case of behavioral-variant frontotemporal dementia. However, some patients with psychiatric disease or other neurological diseases may also show impaired scores.

Keywords:

Frontotemporal dementia – behavioral symptoms – social cognition - theory of mind – differential diagnosis – bipolar disorder

Impairments in social cognition in general and theory of mind in particular have often been considered as cognitive markers of behavioral-variant frontotemporal dementia (bvFTD) (Dodich et al., 2018). In this perspective, the results of the original study by Gregory et al. (2002) emphasized the value of the faux pas test (FPT) for evidencing a theory of mind impairment in patients with bvFTD. This value has been confirmed in subsequent studies - notably for the differential diagnosis of bvFTD vs. other neurological conditions, such as Alzheimer's disease (Bora, Walterfang, & Velakoulis, 2015). The primary objective of the present retrospective study was to evaluate the clinical value of the FPT for patients referred to a memory clinic for the aetiological diagnosis of behavioral disturbances and suspected bvFTD. Most previous studies of the FPT compared well-defined groups of patients with an established diagnosis. In contrast, we wanted to determine the test's clinical value at a time when the patient's aetiological diagnosis had not been established. To this end, we assessed patients with at least three years of follow-up data on disease progression and a final aetiological diagnosis.

Method

Participants

Consecutive patients referred to Lille University Hospital's memory clinic for suspected bvFTD were recruited between October 2006 and February 2014. The inclusion criteria included administration of the FPT and at least three years of follow-up after the test. Data acquisition complied with local institutional research standards for human research and was completed in accordance with the Helsinki Declaration.

Procedure

A French-language adaptation of the FPT (Stone, Baron-Cohen, & Knight, 1998) was considered in this study (https://psitec.univ-lille3.fr/presentation/membres/membres-titulaires/moroni-c/). The

FPT consists of 20 short descriptions of interactions between people. Ten stories (the “faux pas” stories) describe a situation in which a protagonist says something awkward (i.e. something that should not have been said), and the ten other stories (control stories) do not contain any faux pas. For each story, participants have to state whether or not a faux pas is committed. If a participant detects a faux pas in the story, he/she is then asked to state (i) who committed the faux pas, (ii) why the person should not have said that, (iii) why the person said that, (iv) whether the faux pas was intentional, and (v) how the victim might have felt. For each faux pas story, six points are awarded: one point is awarded when the faux pas is correctly detected in a story (if the faux pas is not detected, the patient had a score of 0 for the story) and if so, each of the five subsequent clarification questions about the context of the faux pas in the story (who committed it, why, and so on…) is awarded one point for a correct answer (maximum score for the 10 faux pas stories is 60). For each control story, two points are awarded when a story is correctly classified as not containing a faux pas and no point when a faux pas is detected (maximum score for the 10 control stories is 20). An overall score was calculated by summing the scores from the faux pas stories and the control stories (maximum score is 80).

Additional information was collected from the patient’s medical records. On the cognitive level, the Mini Mental State Examination (MMSE) score (Folstein, Folstein, & McHugh, 1975) was taken into account, along with measures of executive function (the Frontal Assessment Battery (FAB), Dubois, Slachevsky, Litvan, & Pillon, 2000)) and language (the Bachy naming test, Bachy-Langedock, 1988). On the behavioral level, the Frontotemporal Behavioral Scale (FBS) score (Lebert, Pasquier, Souliez, & Petit, 1998) was considered. Lastly, we recorded the final diagnosis at the end of the follow-up period.

Statistical analyses

Patients were classified retrospectively into a bvFTD group or a non-bvFTD group, depending on the final diagnosis. The two groups were compared with regard to demographic, cognitive and

behavioral characteristics, using a non-parametric Mann-Whitney U test or (for dichotomous variables such the sex) Fischer's exact test.

The FPT scores were compared with a database of 165 individuals with no cognitive impairment (mean performance of controls was 64.28 ± 8.9), in order to calculate a z-score; this standard score took into account the influence of sex, education level and age on the FPT performance. Using the z-score, we then determine whether the patient performance was impaired or not. Based on contingency tables (bvFTD/non-bvFTD vs. impaired/non-impaired FPT score), the sensitivity, specificity and likelihood ratio values were reported when a difference was statistically significant in Fischer's exact test. We conducted similar analysis for cognitive variables (the FAB and Bachy naming test scores) and behavioral variable (the FBS score). Moreover, we analyzed associations between cognitive variables, behavioral variable and the FPT scores with the Kendall Tau test.

Results

Forty-two patients were included in the study. The final diagnosis at the end of follow-up was as follows: 4 cases of definite bvFTD (1 patient had post-mortem neuropathological evidence of argyrophilic grain disease, and 3 had a pathogenic mutation: two C9ORF72 mutations and one MAPT mutation); 10 cases of probable bvFTD, according to the current criteria (Rascovsky et al., 2011); 25 cases of disease other than bvFTD: 15 patients had a psychiatric disorder (10 with bipolar disorders, 3 with depressive disorder, and 2 with psychosis), 9 had a neurological disease (5 with vascular dementia, one with Alzheimer's disease, one with Parkinson's disease, one with alcohol-related dementia, and one with the sequelae of a traumatic brain injury) and one had sleep apnoea syndrome. Three patients were diagnosed with possible bvFTD at the end of follow-up, and were thus excluded from the analysis because their diagnosis was still uncertain.

The two groups of patients (14 in the bvFTD group and 25 in the non-bvFTD group) did not differ in terms of age and educational level. There were proportionally more men in the non-bvFTD group

than in the bvFTD group. The groups did not differ significantly with regard to the MMSE score. The groups' demographic, cognitive and behavioral characteristics are summarized in Table 1.

Administration of the FPT was not possible in two patients in the bvFTD group (due to attentional problems for one patient, and verbal comprehension difficulties for a patient with the C9ORF72 mutation) and three patients in the non-bvFTD group (due to misunderstanding of the situations displayed in the test by a patient with psychosis, a patient with depression and a patient with cerebrovascular disease). The discontinuation rate was similar in the two groups.

[INSERT TABLE 1 HERE]

The overall FPT score was more frequently impaired in the bvFTD group than in the non-bvFTD group ($p<.05$). The overall FPT score's sensitivity for the diagnosis of bvFTD was high (.83) but the specificity was only moderate (.64). The likelihood ratio for the overall FPT score was 2.29. The two "false negative" bvFTD patients both had a negative z-score: the patient with post-mortem evidence of argyrophilic grain disease, and a patient with probable bvFTD had respectively a z-score of -1.57 and -1.25. At the end of follow-up, the "false positive" patients in the non-bvFTD group were diagnosed with a psychiatric disorder (n=3; all bipolar disorder) or a neurological disease (n=5: one cases of vascular dementia, one of Alzheimer's disease, one of Parkinson's disease, one of alcohol-related dementia, and one with sequelae of a traumatic brain injury). Note that we did not find any specific profile of impairment for the five clarification questions related to the faux pas neither in the bvFTD nor in the non-bvFTD groups. There were no significant intergroup differences in other cognitive variables (the FAB and naming test scores) or behavioral variables (the FBS score).

[INSERT TABLE 2 HERE]

Considering the relationships between the overall FPT performance with other cognitive scores (MMSE, FAB and Bachy naming test) or behavioral variables (FBS), we didn't find any association in the bvFTD group ($p>.05$) but MMSE and FAB scores were positively associated with the overall FPT score in the non-bvFTD group (respectively, *Kendall Tau*= .47, $p<.01$; and *Kendall Tau*= .58, $p<.01$).

Discussion

In the present study, the FPT was the only instrument that significantly discriminated between patients with bvFTD and patients presenting with behavioral disorders attributed to other pathologies. Tests probing general cognitive, executive and language abilities and questionnaires on behavioral disturbances did not discriminate between the bvFTD and non-bvFTD groups. The absence of group differences for the behavioral scale was expected because just patients presenting with behavioral problems were included in this study. However, differences for cognitive scales such as the FAB might have been postulated as executive functions are also impaired in FTD patients, but our results suggest that executive functioning might be less discriminatory for bvFTD than social cognition test (Schroeter et al., 2018). In fact, we found in agreement with previous studies (Gregory et al., 2002) that the FPT displayed good sensitivity for the diagnosis of bvFTD. This result might be considered to contradict the recent report by Gossink et al. (2018), which did not evidence a difference in the FPT score between patients with bvFTD and patients with other neurodegenerative or psychiatric diseases. In the latter study, another social cognition test (the Ekman 60 faces test) was the only tool that significantly discriminated between bvFTD and other conditions. The discrepancy between Gossink et al.'s results and our present study might be due to the scoring systems used to determine performance in the FPT. We used a broad score (ranging from 0 to 80) that captured not only the participant's ability to detect a faux pas but also the adequacy of the participant's explanations for the faux pas' cognitive component (i.e. the faux pas was not intentional) and the affective component (i.e. the victim of the faux pas might have felt hurt or surprised). In contrast, Gossink et al.'s FPT score ranged from 0 to 10 only; this might have made it less sensitive to intergroup differences. In fact, when we analyzed proportion of bvFTD and non-bvFTD patients scoring in the deficit range for the faux pas detection score (which varied from 0 to 10, one point being awarded each time a patient correctly identified a faux pas in the faux pas stories), we did not observe any differences between the groups (p=.69). Furthermore, in the FTD group, performance to FPT test was not associated with cognitive scores, such as the FAB (which

evaluated executive functioning). This is in accordance with previous studies which have not shown evidence of an association between social cognition tests and other cognitive tests (Shany-Ur et al., 2012) but the small size of patient in the bvFTD group might have limit the possibility to observe such an association in our study. This small size might also potentially explain why we did not find any specific profile of impairment to the different component of the FPT in bvFTD patients as it has been observed in Torralva et al. (2007) study with bvFTD having more difficulty to explain the affective part than the cognitive component of the FPT.

Even though the FPT's sensitivity was high, its specificity was moderate: impaired scores were also observed for patients in the non-bvFTD group. Note that, in this latter group, FPT performance was associated with global cognitive as well as executive functioning which suggest a link between a FPT deficit and impairment in other cognitive domains for non-bvFTD patients. All the false-positive patients ultimately diagnosed with a psychiatric disease were those with bipolar disorder (n=3), although seven other patients diagnosed with bipolar disorder were included in the non-bvFTD group and had an FPT z-score in the normal range (mean z-score: -1.33±1.66). This suggests that the impairment in FPT performance in patients with bipolar disorder is relatively heterogeneous – perhaps because different symptom profiles have differing impacts on performance in the FPT (see Mitchell & Young, 2015, for a discussion on theory of mind in bipolar disorders). In this regard, future works should consider to add more information about the current but also past (e.g., whether the patient had a history of manic or hypomanic episode) emotional status of the patient. Moreover, neurological patients that were classified as "false positives" according to the FPT result had various neurological diseases. Considering this lower specificity of the FPT, it might be interesting in future works to include a better characterization of these patients at the cognitive, behavioral and emotional levels. This information might help to adopt a transnosological approach of social cognition deficits and to determine the symptomatology profile involves in the performance into the FPT test.

Taken as a whole, the data results confirm that the FPT capture's specific cognitive impairments in patients with bvFTD. However, performance in the FPT might also be impaired in patients with

behavioral disorders related to other pathologies and who might share some characteristics with bvFTD patients. Further studies are thus needed to better understand the specific relationship between impaired performance in the FPT and impaired behavior in everyday life.

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Table 1. Characteristics of patients in the bvFTD and non-bvFTD groups, and the statistical significance of intergroup comparisons (p-values)

	bvFTD n=14	**non-bvFTD** n=25	**p-values**
Demographic characteristics			
Age (years)	62.51 ± 6.27	59.66 ± 7.65	p=.71
Sex (male, %)	28.00	80.00	p<.01
Educational level (years of full-time education)	10.79 ± 3.42	10.32 ± 3.04	p=.28
Cognitive characteristics			
MMSE score (from 0 to 30)	24.5 ± 3.63	26.36 ± 3.55	p=.08
Overall FPT score (from 0 to 80)	24.33 ± 10.99	35.82 ± 14	p<.05
FAB score (from 0 to 18)	10.67 ± 5.21	13.21 ± 4.34	p=.16
Bachy naming test score (from 0 to 36)	31.92 ± 3.43	33.44 ± 3.43	p=.19
Behavioural characteristics			
FBS score (from 0 to 4)	3.33 ± 1.07	3.21 ± 0.85	p=.45

Abbreviations: bvFTD = behavioural variant frontotemporal dementia; MMSE = Mini Mental State Examination; FPT = Faux Pas Test; FAB = Frontal Assessment Battery; FBS = Frontotemporal Behavioral Scale; SD = standard deviation. Data are quoted as the mean ± SD or the percentage.

Table 2. Proportion of patients with impaired performance (relative to normative data) among the bvFTD and non-bvFTD groups, and the statistical significance of intergroup comparisons (p-values)

	bvFTD	non-bvFTD	p-values
Faux pas test			
Overall score	10 out of 12	8 out of 22	p<.05
Other cognitive variables			
FAB	9 out of 12	11 out of 19	p=.45
Bachy naming test	4 out of 12	2 out of 18	p=.18
Behavioural variables			
FBS	9 out of 12	16 out of 19	p=.65

Abbreviations: bvFTD = behavioural variant frontotemporal dementia; FAB = Frontal Assessment Battery; FBS = Frontotemporal Behavioral Scale

Article 2: Le Bouc, R., Lenfant, P., Delbeuck, X., Ravasi, L., Lebert, F., Semah, F., & Pasquier, F. (2012). My belief or yours? Differential theory of mind deficits in frontotemporal dementia and Alzheimer's disease. *Brain: A Journal of Neurology*, *135*(Pt 10), 3026-3038.

My belief or yours? Differential theory of mind deficits in frontotemporal dementia and Alzheimer's disease

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Keywords: behavioural variant frontotemporal dementia, Alzheimer's disease, theory of mind, FDG-PET.

Essential abbreviations: bvFTD: behavioural variant frontotemporal dementia; AD: Alzheimer's disease; HCs: healthy controls; ToM: theory of mind; TB: true belief; FB: false belief; EFs: executive functions.

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ABSTRACT

Theory of mind reasoning - the ability to understand someone else's mental states such as beliefs, intentions, and desires - is crucial in social interaction. It has been suggested that a theory of mind deficit may account for some of the abnormalities in interpersonal behaviour that characterize patients affected by the behavioural variant of frontotemporal dementia (bvFTD). However, there are conflicting reports as to whether understanding someone else's mind is a key difference between bvFTD and other neurodegenerative conditions, such as Alzheimer's disease (AD). Literature data on the relationship between theory of mind abilities and executive functions are also contradictory. These disparities may be due to underestimation of the fractionation within theory of mind components. A recent theoretical framework suggests that taking someone else's mental perspective requires two distinct processes: inferring someone else's belief and inhibiting one's own belief, with involvement of the temporoparietal and right frontal cortices, respectively.

Hence, we performed a neuropsychological and neuroimaging study to investigate the hypothesis whereby distinct cognitive deficits could impair theory of mind reasoning in AD patients and bvFTD patients. We used a three-option false belief task to assess theory of mind components in 11 bvFTD patients, 12 AD patients and 20 healthy elderly controls. The bvFTD and AD patients were matched for age, gender, education and global cognitive impairment. [^{18}F]FDG-PET imaging was used to investigate neural correlates of theory of mind reasoning deficits.

Performance in the three-option false belief task revealed differential impairments in the components of theory of mind reasoning; AD patients had a predominant deficit in inferring someone else's belief, whereas bvFTD patients were selectively impaired in inhibiting their

own mental perspective. Moreover, inhibiting one's own perspective was strongly correlated with inhibition in a Stroop task but not with other sub-processes of executive functions. This finding suggests that self-perspective inhibition may depend on cognitive processes that are not specific to the social domain. Lastly, the severity of the deficit in inferring someone else's beliefs correlated significantly over all subjects with hypometabolism in the left temporoparietal junction, whereas the severity of the deficit in self-perspective inhibition correlated significantly with hypometabolism in the right lateral prefrontal cortex.
In conclusion, our findings provided clinical and imaging evidence to support differential deficits in two components of theory of mind reasoning (subserved by distinct brain regions) in AD and bvFTD patients.

INTRODUCTION

There is growing interest in the neural basis of the abnormal social and behavioural symptoms observed in neuropsychiatric disorders such as frontotemporal dementia (FTD), autism and schizophrenia. It has been suggested that these symptoms may be explained (at least in part) by impairments in the social cognition domain (Baron-Cohen, 1985; Frith, 1992; Gregory et al., 2002; Kipps & Hodges, 2006). A decade ago, social cognition was defined as a sum of different processes, including (i) mechanisms for perceiving, recognizing and evaluating socially relevant stimuli and (ii) the ability to construct representations of the social environment and to use them flexibly to guide social behaviour (Adolphs, 1999, 2001).

A distinction is often made between two components of social cognition that rely on partially distinct neural circuitries: the ability to understand other people's feelings or thoughts. Firstly, empathy refers to the ability to recognize and share someone else's emotions and sensations (De Vignemont & Singer, 2006). Impaired empathy has been reported in bvFTD

patients (Lavenu et al., 1999; Lough et al., 2006) but will not be addressed here. Secondly, "theory of mind" (ToM) reasoning (also known as "mentalizing") refers to the ability to explain and predict other people's behaviour by attributing them mental states such as beliefs, desires and intentions (Premack & Woodruff, 1978; Leslie, 1987; Baron-Cohen, 1995; Frith & Frith, 2003, 1999).

Although many tests have been used to explore ToM abilities, the original first-order false belief (FB) test - suggested by the philosopher Daniel Dennett (1978) and later developed (Wimmer & Perner, 1983; Baron-Cohen, 1985) - is still extensively used. In this test, participants are asked to predict someone else's actions based on that person's mistaken belief about the state of the world. A more complex version, the second-order FB test, requires more than inferring a person's beliefs about reality; it requires inference of a person's beliefs about another's beliefs.

Recent studies have used these FB tests to investigate ToM deficits in different neurodegenerative conditions, such as Alzheimer's disease (AD) and frontotemporal dementia. In the latter condition, the behavioural variant (bvFTD) has received most attention. Early-stage bvFTD is characterized by a progressive deterioration of behaviour, with a profound alteration in personality and social skills (the Lund and Manchester Groups, 1987; Neary et al., 1998; McKhan et al., 2001; Rascovsky et al., 2011). The most common social impairments exhibited by bvFTD patients are disinhibition, inappropriate behaviour that violates social norms, loss of manners, tactless remarks, impulsive and careless actions and loss of empathy and sympathy (Raskovsky et al, 2011). It has been suggested that some of these asocial symptoms reflect a specific dysfunction in ToM abilities (Gregory et al., 2002; Kipps & Hodges, 2006).

A number of studies have investigated the hypothesis of a specific ToM deficit in bvFTD but have given rise to controversial results and conclusions. The first case studies in this field

studied the performances of two bvFTD patients with severe behavioural symptoms. The patients showed limited cognitive impairments in a general neuropsychological assessment but severely impaired performances in ToM tests (particularly the first- and second-order FB tests) (Lough et al., 2001, 2002). In the first group study to compare bvFTD patients with healthy controls (HCs) and AD patients (Gregory et al, 2002), the authors found similar results. The bvFTD group's impairment in the first- and second-order FB test suggested a specific ToM deficit. In contrast, AD patients were only impaired in the second-order FB test, which is thought to place higher demands on working memory and other general cognitive abilities. This profile has thus been interpreted as reflecting a general cognitive impairment in AD patients, rather than a specific ToM deficit (Gregory et al., 2002; Zaitchik et al, 2006). More recently, several studies using other ToM tasks have reported greater impairments in bvFTD patients than in HCs or AD patients (Lough et al., 2006; Torralva et al., 2009, 2007; Shany-Ur et al., 2011; Funkiewiez et al., 2011), Huntington's disease patients (Snowden et al., 2003), patients with the language variant of FTD (Eslinger et al., 2007) and patients with progressive supranuclear palsy or vascular dementia (Shany-Ur et al., 2011) (for a review, see Adenzato et al., 2010). Crucially, however, a recent study found no difference in ToM abilities between a group of bvFTD patients and a cognitively matched group of AD patients - despite a striking difference in their behavioural symptoms (Fernandez-Duque et al., 2009). The two groups performed poorly in the second-order FB task (compared with HCs) but reached ceiling performance levels in the first-order FB test. This result cast doubt on the presence of a specific deficit in understanding other people’s minds in bvFTD patients. Furthermore, the relationship between ToM abilities and executive functions (EFs) remains controversial. In several of the above-mentioned studies, ToM deficits in bvFTD patients were found to be independent of the level of EF impairment (Lough et al., 2001; Lough & Hodges, 2002; Gregory et al., 2002; Lough et al., 2006). In contrast, other studies reported a

correlation between these processes (Snowden et al., 2003; Torralva et al., 2007; Eslinger et al., 2007) and suggested that they might rely (at least in part) on common neural substrates.

A recently proposed theoretical framework may, however, reconcile these apparently conflicting findings (Leslie et al., 2004, 2005; Samson et al., 2007). According to the framework, FB reasoning can be subdivided in distinct components: (i) representation of reality, (ii) belief inference and (iii) self-perspective inhibition. Firstly, subjects would have to represent the true state of reality (corresponding to their own belief), which would constitute their prepotent response (Leslie et al., 2004, 2005). This type of a process is likely to involve general cognitive functions (*i.e.* attention, perception, semantic and episodic memory). Secondly, subjects would need to infer someone else's belief. An increasing number of studies suggest a role for the temporoparietal junction in attributing mental states to others (Saxe & Kanwisher, 2003; Samson et al., 2004, 2007; Saxe et al., 2005, 2006a, 2006b). Lastly, adopting someone else's mental perspective would require first detection of the discrepancy between one's own belief and the other person's belief and then inhibition of the prepotent tendency to respond according to one's own perspective (Samson et al., 2007). Several recent neuropsychological and neuroimaging studies have highlighted the role of the right prefrontal cortex in this inhibition process (Apperly et al., 2004; Samson et al., 2005, 2007; Rothmayr et al., 2011; Vandermeer et al., 2011).

This framework suggests that AD and bvFTD patients might be equally impaired in FB tasks but for very different cognitive reasons. Although classical FB tests can highlight a deficit in ToM abilities, they do not show which cognitive processes are spared or impaired. In the present study, we administered a newly developed non-verbal FB task (enabling the analysis of the different ToM components (Samson et al., 2007)) to bvFTD patients, AD patients and HCs. As the neurodegenerative process is predominant in the temporal and parietal lobes in AD patients and in the frontal and temporal lobes in bvFTD patients, we tested the hypothesis

whereby the former would be selectively impaired in the belief-inferring component and the latter would be selectively impaired in inhibiting their own perspective. We also tested whether the inhibition component of ToM-reasoning could be correlated with EFs in general and the inhibition subcomponent of EFs in particular. Lastly, we investigated the neural basis of ToM deficits by correlating them with the severity of cerebral hypometabolism in an [^{18}F]FDG-PET study.

METHODS

Subjects

Twenty-three right-handed patients (12 AD patients, 11 bvFTD patients) and 20 right-handed HCs were enrolled in the study. The HCs were aged between 45 and 75, had no history of neurological or psychiatric diseases, and had a Montreal Cognitive Assessment score (Nasreddine et al., 2005) of 26 or over. This cutoff was used to limit possible inclusions of controls with mild cognitive impairment. The patients had been referred to the Memory Clinic at Lille University Hospital (Lille, France) and had all undergone extensive medical, neurological, neuropsychological and neuroradiological examinations. Patients who met the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria for probable Alzheimer's disease (McKhann et al., 2011) were included in the AD group. Patients who met the revised International bvFTD Consortium criteria for probable bvFTD (Rascovsky et al., 2011) were included in the bvFTD group. The exclusion criteria were as follows: (i) Mini Mental State Examination (MMSE) score below 18 (Folstein et al., 1975), (ii) presence of multiple or extensive infarcts, hemorrhages, multiple microbleeds (≥5), or severe white matter hyperintensity burden (Fazecas score ≥2) on MRI (iii) history of stroke (iv) history of psychiatric illness, major depression or generalized anxiety disorder as described in DSM-IV

within the past 12 months.

Patients and HCs participated voluntarily and gave their written, informed consent prior to recruitment into the study. The study was approved by the regional independent ethics committee (CPP Nord-Ouest IV, reference 2009-A00620-57) and by the French Agency for Health Product Safety (AFSSAPS, reference B90739-28).

Neuropsychological assessments

The belief-reasoning task

Patients performed a non-verbal, three-option FB test (Samson et al, 2007). Each trial consisted of three animated scenes (Figure S1, see Table S2 for examples) showing a protagonist acting on the basis of a correct representation (a true belief, TB) or incorrect (FB) representation of reality. A first scene showed a neighbour stopping at a window of a house and observing the occupier placing an object in a box. In half of the TB and FB trials (denoted as TB1 and FB1), the object initially placed in the box was related to the box (*e.g.* a pizza in a pizza box). In the other half of the trials (denoted as TB2 and FB2), an unrelated object (*e.g.* a passport) was initially placed in the box. A second scene showed that the neighbour had either walked away from the window (FB condition) or had remained in front of it (TB condition) while the occupier replaced the first object by another object (*e.g.* a pizza was replaced by a passport). In the third scene, the neighbour was shown wondering which object was inside the box at that point in time. The subject had to point to one of three objects – the "box-related" object (*e.g.* the pizza) and two unrelated objects (*e.g.* a passport and a pair of scissors). Eight different boxes were used under four conditions (TB1, TB2, FB1 and FB2), yielding a total of 32 different trials in two blocks of 16 trials. Before the participants performed the task, a pre-test ensured that they knew which contents were related to each of the eight boxes.

The three-option FB task was used to distinguish between three neuropsychological profiles. Participants with spared belief reasoning would give a correct response for each trial. Patients with difficulty in inferring someone else's belief are unable to reason about mental states. They should, however, be able to rely on a simplified mentalizing strategy consisting in using what the neighbour sees at the time when the belief question is asked to infer what he is thinking. As shown previously (Samson et al., 2007), these subjects choose the most likely contents of the box under all conditions, leading to "appearance-based errors" in the TB1, TB2, FB2 conditions and the correct response in the FB1 condition. Patients with a self-perspective inhibition deficit can rely only on their own perspective. Thus, they choose the object they last saw in the box in all conditions, leading to "reality-based errors" in FB conditions and the correct response in TB conditions (Samson et al., 2007). Finally, non-specific errors are possible, a distractor error (choosing a non-presented object) or a strategy-based error (choosing the replaced object in TB2).

We used two indexes to characterize patients' profile: a deficit criterion previously published (Samson et al., 2007), and a deficit score developed for the current study. For each deficit, the deficit criterion was defined when (*i*) performance was below chance in conditions corresponding to the deficit (TB1, TB2, and FB2 for the belief inference deficit; FB1 and FB2 for the self-perspective inhibition deficit), (*ii*) and above chance in the non-corresponding condition, (*iii*) and when the majority of the errors were from the expected type (appearance-based error or reality-based errors respectively). For each deficit, the deficit score was defined as the lowest number of the expected errors among the corresponding conditions (See supplementary material for detailed explanations). The deficit criterion is a categorical index, suitable to identify significant and isolated deficits, but inappropriate to detect multiple or moderate deficits. Conversely, the deficit score is sensitive to multiple or moderate deficits and it may be used in correlation studies because it is numerical.

Other neuropsychological tests

The patients' inhibition performance was evaluated with two different Stroop tasks, depending on the subject's ability: the Stroop-GREFEX (Godefroy and GREFEX, 2008), when possible or the French translation (Moroni et al., 2009) of the Stroop-Victoria (Spreen and Strauss, 1991) if not. The number of uncorrected errors and the interference ratio (Inference time/color time) were used as inhibition indexes. A 5-minute time limit was set for each test. Patients who failed to complete the task within this time limit were attributed with the highest index observed within the study population. The patients' shifting abilities were evaluated with the GREFEX version (Godefroy and GREFEX, 2008) of the Trail Making Test (TMT). Part-B completion time and the difference between Part-B and Part-A completion times were used as shifting indexes. The clinical assessment also included global cognitive scales (the Mattis Dementia Rating Scale (DRS), Mattis, 1976; and the MMSE, Folstein et al., 1975), a behavioral scale (Frontotemporal behavioral scale (FBS), Lebert et al., 1998), and tests to assess EFs (the frontal assessment battery, Dubois et al., 2000), short term memory (digit spans, Wechsler, 2000), category and letter fluency (word generation tasks, Godefroy & GREFEX, 2008), spatial and temporal orientation, episodic memory, praxis, and attention.

Positron emission tomography

Data acquisition

[^{18}F]FDG-PET exams were performed within six months of the neuropsychological assessment. Data were acquired on a GE Advance SL PET/CT device (GE Medical Systems) with a 4-5mm full-width at half-maximum (FWHM) and a 30cm transaxial field-of-view. Patients were scanned under resting conditions, after fasting. The blood glucose level was checked before intravenous injection of [^{18}F]FDG (185 MBq). Thirty minutes later, a low-

dose CT scan of the brain was acquired for attenuation correction of the PET data and emission images were subsequently acquired in 3D mode. Images were reconstructed iteratively using an ordered-subset expectation-maximization algorithm (with 2 iterations and 21 subsets) in a 256x256 matrix.

Data pre-processing and analysis

Voxel-based analyses were performed using statistical parametric mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 7.9 (The Mathworks). All reconstructed PET images were spatially normalized (using default transformation parameters) against the SPM8 standard PET brain template in Montreal Neurological Institute standard space (McGill University, Montreal, Canada) and smoothed by convolution, using an isotropic Gaussian kernel with a 8mm FWHM. Voxel-wise multiple regression analyses were performed to identify brain regions within which glucose metabolism was correlated with performance in the FB task. We could have looked directly for group effects; however, to lend our region-specific correlates a psychological specificity, we chose to look for correlations between regional activity and deficit scores over all subjects - exploiting the between group variance in deficit scores as a parametric explanatory variable. Deficit scores in belief inference and self-perspective inhibition were entered as covariates of interest in the same regression model. Effects were tested for, having adjusted for any effect of gender, pathology and age (entered as covariates of no interest). A global normalisation was applied by including each subject's mean global activity as another covariate of no interest. T-maps were obtained at a threshold of $p<0.005$ (uncorrected), with an extent threshold of 200 voxels. Our reporting criteria do not account for the multiple comparisons problem - although it is fairly conservative. We use these criteria for a complete descriptive

report of our results, and applied a correction for multiple comparisons by testing for anatomically constrained effects – using the uncorrected P value based upon spatial extent associated with the cluster closest to the a priori locations of interest (Friston, 1997). Individual regional activities were normalized to the grand mean as 30 µmol/min/100g, corresponding to the mean glucose metabolism (Phelps et al., 1979), and were extracted from the eligible clusters with MarsBaR software (Brett et al., 2002).

Statistical analyses

Not all the psychological and behavioural variables were normally distributed and so we used non-parametric tests: a Mann-Whitney test to investigate continuous variables in independent groups (*i.e.* demographic and neuropsychological measures), a Wilcoxon test to compare paired samples of continuous variables (*i.e.* the number of correct responses in TB and FB conditions) and a chi-squared test to compare categorical variables in independent groups (*i.e.* gender, deficit criterion). Performance levels in the three-option FB task were analysed by using a mixed-design ANOVA. All computations were performed with the statistics toolbox in MATLAB 7.9.

RESULTS

Clinical data

The three groups' demographic and clinical characteristics are presented in Table 1 and S1. Healthy controls, AD and bvFTD patients did not differ significantly in terms of age, gender or educational level (all $p>0.05$). Importantly, the two groups of patients were homogeneous in terms of the global cognitive decline (either assessed by the Mattis DRS ($p=0.418$) or the

MMSE (p=0.078)). However, they significantly differed in their behavioural symptoms (assessed by the FBS, p=0.017).

Behavioural results

Differential impairments in mentalizing in AD and bvFTD patients

To analyse the performance in the three-option FB task (Figure 1A), we performed a mixed-design ANOVA, including group as a between factor and task condition as a within factor. We found a main effect of group ($F=29.7$, $p<0.001$), task condition ($F=4.9$, $p=0.003$), and a significant interaction between group and condition ($F=9.4$, $p<0.001$). Post-hoc comparisons showed that AD and bvFTD patients performed worse than HCs (both $p<0.001$), with a similar level of impairment ($p=0.48$). When comparing TB and FB conditions, HCs made no error in TB and very few in FB conditions (TB – FB=6.9%, $p=0.020$). The AD patients had a similar magnitude of impairment under both conditions (FB – TB=12.0%, $p>0.05$), whereas bvFTD patients had a more severe deficit for the FB conditions than for the TB conditions (TB – FB=36.4%, $p=0.014$).

When considering the deficit criterion, AD and bvFTD patients exhibited opposite patterns. Four bvFTD patients (36%) fulfilled the deficit criterion for self-perspective inhibition (Figure 1B, Table 1), versus none of the AD patients ($p=0.021$) and only one HC (5.0%, $p=0.023$). Conversely, two AD patients (17%) fulfilled the deficit criterion for belief inference, versus none of the bvFTD patients ($p=0.156$) or the HCs ($p=0.059$).

When considering deficit scores (Figure 1C), 16 HCs made no error, and 4 had a slight or moderate inhibition deficit score. AD patients had high inference deficit scores and low inhibition deficit scores, whereas bvFTD patients had low inference deficit scores and high inhibition deficit scores. The inference deficit scores were significantly greater in AD patients than in HCs ($p<0.001$), whereas the inhibition deficit scores were significantly greater in

bvFTD patients than in HCs ($p<0.001$), supporting differential impairments in ToM components compared to controls (Figure 1D, Table 1).

Correlations between ToM sub-processes and executive functions

The above-mentioned framework suggests that ToM abilities require an inhibition mechanism. To investigate whether this inhibition process is specific to the social domain or relies on more general functions, we studied the correlation between self-perspective inhibition deficits and performance in EFs tasks. We found a significant correlation (Figure 2) between the severity of the self-perspective inhibition deficit and the number of uncorrected errors in the Stroop task ($p<0.001$, surviving a Bonferroni correction for multiple comparisons), but not with the interference ratio ($p=0.70$). None of the other measures of EFs showed a significant correlation. Similarly, we found no correlation between EFs and the severity of the deficit in inferring someone else's belief (Figure S2).

Functional imaging results

In order to investigate the neural basis of ToM-reasoning subcomponents, we performed an [^{18}F]FDG-PET study in bvFTD and AD patients. Imaging data for one bvFTD patient was not available due to behavioural problems and one AD patient was excluded from the analysis because the time interval between [^{18}F]FDG-PET acquisition and neuropsychological assessment was more than 6 months. Consequently, [^{18}F]FDG-PET analyses were performed for 21 patients (AD, n=11; bvFTD, n=10). The severity of the belief inference deficit correlated significantly with the decrease in [^{18}F]FDG uptake in a single cluster (Figure 3A, Table 2), in the left temporoparietal junction (TPJ). The severity of the deficit in self-perspective inhibition correlated significantly with the decrease in [^{18}F]FDG

uptake in the right middle frontal gyrus (Figure 3B). When testing for anatomically constrained effects (Friston, 1997), in the temporal and frontal regions, we found that these clusters survived a corrected P value of $p<0.05$. Lastly, we extracted the regional cerebral metabolic rate of glucose (CMRglc) from the eligible clusters in the left TPJ and the right prefrontal cortex (Figure 4). In the left TPJ, CMRglc was significantly lower in AD patients than in bvFTD patients ($p=0.0018$), whereas the CMRglc in the right prefrontal cortex was significantly lower in bvFTD patients than in AD patients ($p=0.005$).

DISCUSSION

Differential impairments in ToM-reasoning in AD and bvFTD patients.

Previous reports of a ToM deficit in bvFTD patients (Lough et al., 2001; Lough & Hodges, 2002; Gregory et al., 2002; Snowden et al., 2003; Lough et al., 2006; Torralva et al., 2007; Eslinger et al., 2007) prompted the ToM deficit hypothesis, whereby a specific impairment in understanding other people's minds underlie the abnormal social behaviour in bvFTD and can distinguish the latter from other neurodegenerative disorders. To date, only two studies have investigated performance differences between bvFTD and AD patients in FB tasks (Gregory et al., 2002; Fernandez-Duque et al., 2009). Fernandez-Duque et al. challenged the ToM deficit hypothesis. They compared the performances of bvFTD patients and cognitively matched AD patients in a first-order FB test (with a low cognitive load) and a more cognitively demanding second-order FB test. Since the two groups reached ceiling performances in the first-order FB test but were similarly impaired in the second-order FB test, Fernandez-Duque et al. reasoned that bvFTD patients did not suffer from a genuine mentalizing deficit because it would have been apparent in the less cognitively demanding

test. They concluded that bvFTD and AD patient's performance levels in FB tasks depend primarily on the task's cognitive demands.

However, the classic FB task used in these studies only provides a binary choice between a wrong and a right answer and does not identify the cognitive deficit responsible for any error. Thus, Fernandez-Duque et al. were not able to rule out the possibility whereby the equivalent impairments seen in AD and bvFTD patients in the second-order FB task were due to distinct cognitive deficits.

Indeed, our behavioural results show that inference of someone else's beliefs is selectively impaired in AD patients, whereas inhibiting one's own belief is selectively impaired in bvFTD patients. Since belief inference is necessary in both TB and FB trials, AD patients showed similar impairments in the two situations. Previous studies featured FB but not TB trials. However, in Fernandez-Duque et al.'s study, patients were included only if they answered control questions correctly. One of the control questions was equivalent to a TB question and required belief inference. Interestingly, 4 of the 17 AD patients (24%) failed to correctly answer these control questions and were excluded from the analysis, compared with only 1 of the 11 bvFTD patients (9%). This might suggest that the AD patients in Fernandez-Duque et al.'s study had a belief inference deficit.

In contrast, self-perspective inhibition is only required when the subject's belief differs from the character's belief (*i.e.* in FB trials). In our study, bvFTD patients made a significantly greater number of errors in FB trials than in TB trials. In Fernandez-Duque et al.'s study, the absence of impairment in bvFTD patients in the first-order FB test may have been due to two factors. Firstly, their bvFTD patients were less cognitively impaired than our bvFTD patients (with mean MMSE scores of 26.4 ± 1.6 and 24.8 ± 0.9, respectively) and thus probably had a

milder inhibition deficit. In addition, there were fewer inhibitory demands in the first-order FB test used by Fernandez-Duque and colleagues.

While our results show that distinct ToM deficits can indeed distinguish bvFTD patients from AD patients (in contrast to Fernandez-Duque et al.'s report), we nevertheless agree with their conclusion that the impairment observed in bvFTD patients does not reflect a deficit in attributing mental states. In fact, we consider that it reflects a deficit in self-perspective inhibition.

In our study, performance could have been lowered by a difficulty in representing the reality, (by a memory impairment, for instance). It is very likely that such impairment influenced the AD patients' overall performance, as they made a number of non-specific errors. Such impairment, however, would unlikely be specific of any condition or error type, and could not account alone for the specific patterns of errors observed. Furthermore, AD patients made more appearance-based errors in the first block than in the second (30.6% versus 14.6%, p=0.001). Such an improvement would be unlikely if errors were caused by a memory deficit alone. Samson and colleagues (2007) reported a similar improvement in a patient with a lesion in the left TPJ. They proposed that a lesion in the TPJ might cause an initial difficulty with accessing the elements required to infer others' beliefs (accessing a "social semantic knowledge" of how the mind works), rather than impairing the inference *per se*.

With regards to clinical symptoms, bvFTD patients, on the one hand, exhibited a self-perspective inhibition deficit, that could account for their self-centered behaviour. Their belief inference deficit scores, however, approached significance compared to controls, and might have been significant in a larger sample. In addition to a self-perspective inhibition deficit, other reasons might contribute to disturb social functioning in bvFTD patients. For instance, we did not investigate affective aspects of ToM-reasoning, although they might strongly contribute to the social disturbances observed in FTD patients. The ventromedial

prefrontal cortex has been linked to the ability to understand irony and Faux-pas, highlighting its importance to represent the affective components of mental states, and to understand beliefs about other's emotional states (Gregory et al., 2002; Shamay-Tsoory et al., 2005). AD patients, on the other hand, exhibited significant deficit scores for belief inference. The impact of this deficit is debatable, as behavioural symptoms are not distinctive of AD patients. A deficit in inferring other's mental states might impair their comprehension of new or unusual social situations, but might have no consequence in routine situations. In addition, it has been suggested that a deficit in inferring other's mental states may contribute to AD patient's anosognosia (Ruby et al., 2009). In the context of impaired episodic memory, it might be impossible to detect a mismatch between one's own abilities and one's own expectations other than by relying on the online representation of the opinion of others.

Relationships between theory of mind and executive functions

Executive functions (EFs) are defined as the set of cognitive skills that allow complex, goal-directed behaviours (Lezak et al, 2004). Several classifications have been suggested and draw distinctions between various sub-processes: inhibition, shifting, updating, dual-task coordination (Miyake et al., 2000), access (Fisk & Sharp, 2004) or alternatively inhibition, maintenance and shifting, divided attention, initiation, planning, generation, deduction and retrieval (Godefroy et al., 2003, 2010).

On one hand, a growing body of empirical evidence suggests that ToM abilities and EFs are tightly linked. Theory of mind abilities develop progressively in children, since they successfully complete first-order FB tests at about four years of age (Wimmer & Perner, 1983; Wellman et al., 2001) and second-order FB tests between the ages of 6 and 7 (Perner & Wimmer, 1985). A child's developmental acquisition of ToM abilities is concomitant with progress in EFs (Perner & Lang 1999; Pellicano, 2007). Moreover, correlations between ToM

abilities and EFs have been observed in autistic children (Pellicano et al., 2007) and significant improvements in ToM task performance were observed after EFs training (Kloo & Perner, 2003; Fisher & Happé, 2005). It has been suggested that inhibition is the EF sub-process that is most strongly associated with ToM performance (Carlson et al., 2001).

On the other hand, several studies have demonstrated a lack of association between ToM abilities and EFs in neurological patients with focal lesions (Fine et al., 2001; Rowe et al, 2001; Bird et al., 2004; Havet-Thomassin et al., 2006; Muller et al., 2010) and bvFTD patients (Lough et al., 2001; Lough & Hodges, 2002; Gregory et al., 2002; Lough et al., 2006). The extent to which EFs and ToM abilities constitute overlapping or separate functions remains controversial. Studying relationship between sub-processes of ToM abilities and EF sub-processes could be the key to solving this problem, since previous studies may have underestimated fractionation within these systems (German & Hehman, 2006).

Leslie and colleagues have suggested a fractionated model of ToM-reasoning with two components, namely: a mechanism for belief inference and a "selection processor" that arbitrates between competing responses via an inhibition process. Leslie proposed that these two components were specific for the domain of mental states. Although the presence of components is supported by several studies (Apperly et al., 2004; Samson et al., 2004, 2005, 2007; Saxe et al., 2006b; Qureshi et al., 2010), recent results have caused Leslie's initial proposal to be refined: belief inference is thought to be domain-specific and independent of EFs, whereas selection is thought to be EF-dependent and thus domain-general (Saxe et al., 2006b; Qureshi et al., 2010). Our results are consistent with the latter framework, since we found that self-perspective inhibition (as opposed to the belief inference) was correlated with EFs, more specifically with the number of Stroop inhibition errors. Interestingly, the right lateral prefrontal cortex was shown to be the region most related to Stroop errors (Vendrell et

al., 1995). This result fits our neuroimaging results, suggesting that making an inhibition error in a Stroop task or in a ToM task might rely on similar or close regions in the right prefrontal cortex.

We interpret our results in the framework of "Simulation Theories" (STs) of ToM, whereby, based on the target's initial belief, one predicts the target's behaviour by using one's own mind to simulate the target's mental processes. Here, the inhibition process is interpreted as the mechanism decoupling one's own beliefs from the simulation processes. The egocentric bias could thus correspond to a deficit in this decoupling mechanism, *i.e.* an inability to inhibit one's own knowledge. Alternatively, "Theory-Theories" (TTs) of ToM state that the prediction step depends on our ability to apply principles and rules (a theory of how the mind of others works) that predict the resulting behaviour. In TTs, the egocentric bias could be viewed as a bias in the context-sensitive rule selection (Apperly, 2009), *i.e.* a deficit in inhibiting rules that are not appropriate in the context to predict others' behaviour.

The effect of normal aging on perspective selection

In our study, four of the 20 HCs did not achieve ceiling performances in the ToM test. Interestingly, all four made reality-based errors consistent with a self-perspective inhibition deficit but none exhibited a deficit in mental state inference. One of the eldest controls (aged 65) even had a significant deficit, with a score of 4/8. However, these observations were not unexpected. Despite initial contradictory results (Happé et al., 1998), there is now increasing evidence of an age-related decline in adults in ToM performance in general (Maylor et al., 2002; Uekermann et al., 2006; McKinnon et al., 2007; Slessor et al., 2007; Charlton et al., 2009, Duval et al., 2011), and in FB tasks in particular (German & Hehman, 2006; Bailey et al., 2008; Phillips et al., 2011). This decline is partially due to a decline in EF, whether

mediated by a deficit in inhibitory control (German & Hehman, 2006; Bailey et al., 2008; Charlton et al., 2009) or by difficulties in updating information in working memory (McKinnon et al, 2007; Philipps et al., 2011). Likewise, higher demands on EFs induce egocentric biases in perspective-taking tasks - even in young adults (Epley et al., 2004).

Correlations between cerebral glucose metabolism and theory of mind deficits

Our neuroimaging findings are consistent with our behavioural results and suggest that two mentalizing processes can be differentiated at the neuropsychological and neural levels. We found a specific correlation between the belief inference deficit and low brain metabolism within the left TPJ. This region has been found to be activated in numerous ToM studies (Vogeley et al., 2001; Saxe et al., 2003, 2006a) and damage to the TPJ has been shown to cause selective deficits in representing someone else's beliefs (Samson et al., 2004). However, definite evidence of the lateralisation of functional specialisation in the TPJ remains elusive. Some studies reporting bilateral involvement of the TPJ (Saxe & Kanwisher 2003), whereas others report selective involvement of the left (Samson et al., 2004) or the right (Saxe et al., 2005; Perner et al., 2006; Aichhorn et al., 2009).

The TPJ has been consistently identified as one element of the metabolic and structural brain alterations in AD, in terms of either glucose metabolism (Friedland, 1983; Foster et al., 1984; Ibanez, 1998; Herholz et al., 2002; Matsuda, 2002; Nestor et al., 2003; Mosconi et al, 2005; Kawachi, 2006), brain perfusion (Varma et al., 2002) or cortical volume (Fox et al., 2001; Baron et al., 2001; Withwell et al., 2008), but is less affected in bvFTD (Charpentier et al., 2000; Hu et al., 2010; Womack et al., 2011). Only half of our AD patients made errors compatible with a belief inference deficit - possibly because TPJ shrinkage only occurs in late-stage AD (Frisoni et al., 2009).

Neural correlates of self-perspective inhibition were found in the right medial frontal gyrus (rMFG), a region that is more affected in bvFTD than in AD patients (Hu et al., 2010). These results are in agreement with two reports of a self-perspective inhibition deficit after a right, lateral, prefrontal stroke that particularly affected the inferior frontal gyrus (IFG) and the rMFG (Samson et al., 2005, 2007). Our results are also in line with previous imaging studies indicating the involvement of a largely right-side, prefrontal network in response inhibition tasks, such as the Go/No-Go task (Garavan et al., 2006; Aron et al., 2007; Chambers et al., 2007) and, more recently, in self-perspective inhibition *per se* (Rothmayr et al., 2011; van der Meer et al., 2011). Self-perspective inhibition in a ToM task was also shown to elicit late neural activity in the right IFG, whereas perspective representations led to early activity in the TPJ (McCleery et al., 2011). This temporal relationship is consistent with the involvement of multiple, sequential processes in perspective-taking.

CONCLUSION

Our study provides clinical evidence to support differential changes in two components of ToM-reasoning in AD and bvFTD. Belief inference, which is mediated by the left TPJ, was selectively impaired among AD patients, whereas self-perspective inhibition involves right prefrontal regions and was preferentially impaired in bvFTD patients. The strong correlation between self-perspective inhibition and inhibition in a Stroop task suggests that selecting a correct response or selecting a correct mental state could rely on identical or spatially close brain regions. Surprisingly, and despite the striking difference between AD and bvFTD patients in terms of social behaviour, the deficit in AD appears to be more specific to the social domain than that in bvFTD, which might rely on more general processes (e.g. EFs). Although impaired self-perspective inhibition may account for the self-centred bias observed

in bvFTD patients, it is very likely that the latter's social impairments arise from a combination of multiple cognitive deficits in ToM-reasoning, EFs, empathy and decision-making, rather than ToM-reasoning alone.

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Figure legends

Figure 1. Performance in the three-option false belief task.

(A) Distribution of responses in the 3-option false-belief task, for the true belief-predictable object (TB1), true belief-non-predictable object (TB2), false belief-predictable object (FB1), false belief-non-predictable object (FB2). For any condition, 75% correct responses or more is significantly above chance level. (B) Histograms of theory of mind deficit criterion showing differential changes in components, in healthy controls (HC, green), Alzheimer's disease patients (AD, red), and patients with the behavioural variant of frontotemporal dementia (bvFTD, blue). (C) Distribution of deficit scores in belief inference (on the y-axis) and self-perspective inhibition (on the x-axis) for HCs, AD patients and bvFTD patients. Filled symbols represent individual subjects and open symbols show the group average. Random jitter was added to prevent superposition. (D) Histograms of theory of mind deficit scores showing differential changes in components: bvFTD patients have a significant deficit in inhibiting their own perspective (compared with HCs) and AD patients have a significant deficit in inferring someone else's perspective (compared with HCs). (*) $p<0.05$, (**) $p<0.01$, (***) $p<0.001$.

Figure 2. Correlations between the self-perspective inhibition deficit and various measures of executive function: (A) global function (measured with the Frontal Assessment Battery), (B, C) inhibition in the Stroop Test (proportion of errors, interference ratio), (D, E) shifting assessed with the Trail Making Test (TMTB, TMTB-TMTA), (F) initiation and shifting (assessed with the Mattis Dementia Rating Scale initiation subtest), (G, H) maintenance in working memory (assessed with digit spans) and (I, J) generation (assessed by letter and categorical fluencies).

Figure 3. Correlation between cerebral glucose hypometabolism and deficits in belief inference (A, in blue) and self-perspective inhibition (B, in red) ($p<0.005$, minimal cluster size = 200 voxels).

Figure 4. Regional cerebral metabolic rate of glucose (CMRglc). Individual CMRglc values were extracted from significant clusters associated with deficits in belief inference (left temporoparietal junction, TPJ) and self-perspective inhibition (right prefrontal cortex, PFC). It is worth mentioning that CMRglc values are clearly dependent on the voxel-based analyses (because the deficit scores showed group effects). They are therefore reported purely as a supplement to the SPM results to quantify the effect size - from the perspective of group membership.

AD: Alzheimer's disease. bvFTD: behavioural variant of frontotemporal dementia.

Table 1. Demographic characteristics and ToM reasoning profile in the three-option false belief task

	HC (n=20) (Mean±SE)	**AD (n=12)** (Mean±SE)	**FTD (n=11)** (Mean±SE)	**AD vs. FTD** p value	**AD vs. HC** p value	**FTD vs. HC** p value
Demographics						
Gender (% male)	0.3	0.5	0.27	0.733	0.662	0.973
Age (years)	59.8 (1.5)	61.9 (1.8)	58.7 (1.5)	0.139	0.339	0.576
Formal education (years)	11.6 (0.7)	11.6 (1.1)	11.5 (1.0)	0.731	0.797	0.933
Theory of mind						
Deficit criterion (% patients)						
Self-perspective inhibition	5.0 (5.0)	0 (0)	36.4 (15.2)	**0.021***	0.431	**0.023***
Belief inference	0 (0)	16.7 (11.2)	0 (0)	0.156	0.059	-
Deficit score						
Self-perspective inhibition	0.4 (0.2)	0.6 (0.2)	3.6 (0.8)	**0.006***	0.139	**< 0.001***
Belief inference	0.0 (0.0)	0.9 (0.3)	0.3 (0.2)	0.110	**< 0.001†**	0.058

HC: healthy controls; AD: Alzheimer's disease; bvFTD: behavioural variant of frontotemporal dementia; SE: standard error.

*bvFTD worse than AD or HC

†AD worse than bvFTD or HC

Table 2. SPM results for the correlation between [^{18}F]FDG hypometabolism and ToM deficits

Anatomical regions	Cluster-level		Peak-level					
	KE	$P_{uncorrected}$	T-value	Z-score	$P_{uncorrected}$	X	Y	Z
Self-perspective inhibition deficit								
Right middle frontal gyrus (BA 8)	959	0.006	4.36	3.41	0.000	38	24	48
Right middle frontal gyrus (BA 9)			4.20	3.32	0.000	26	32	38
Left medial frontal gyrus (BA 9)			4.02	3.22	0.001	-2	40	36
Right middle frontal gyrus (BA 46)	458	0.045	3.83	3.12	0.001	40	42	10
Right middle frontal gyrus (BA 10)			3.44	2.88	0.002	26	54	2
Right medial orbital frontal gyrus (BA 32)			3.40	2.86	0.002	12	48	-6
Belief inference deficit								
Left middle temporal gyrus (BA 39)	489	0.039	4.66	3.56	0.000	-46	-64	24

Figure 1.

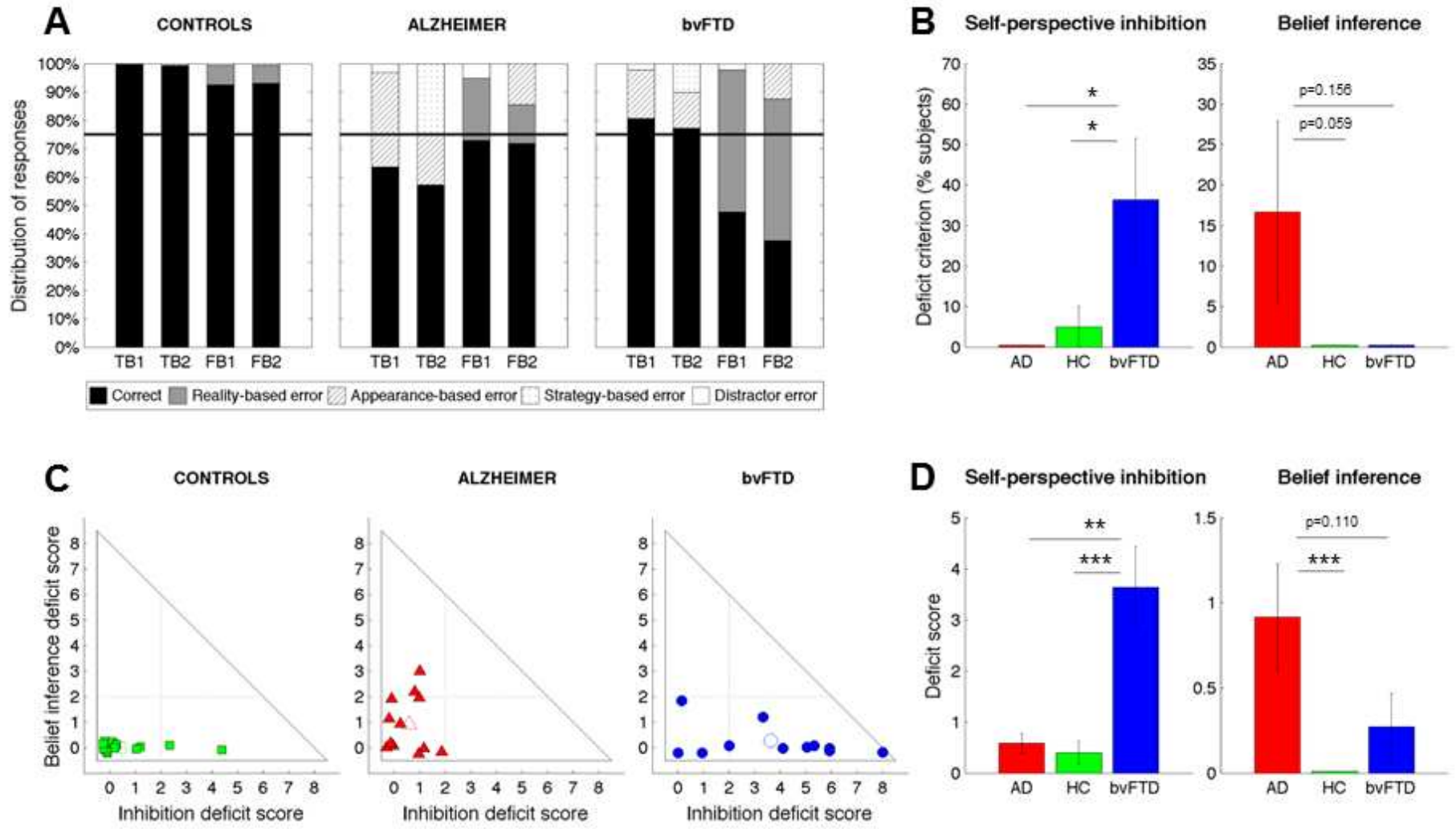

A
CONTROLS
ALZHEIMER
bvFTD
Distribution of responses
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
TB1 TB2 FB1 FB2
Correct
Reality-based error
Appearance-based error
Strategy-based error
Distractor error
B
Self-perspective inhibition
Belief inference
Deficit criterion (% subjects)
*
*
p=0.156
p=0.059
AD HC bvFTD
C
CONTROLS
ALZHEIMER
bvFTD
Belief inference deficit score
Inhibition deficit score
D
Self-perspective inhibition
Belief inference
Deficit score
**
***
p=0.110
***
AD HC bvFTD

Figure 2.

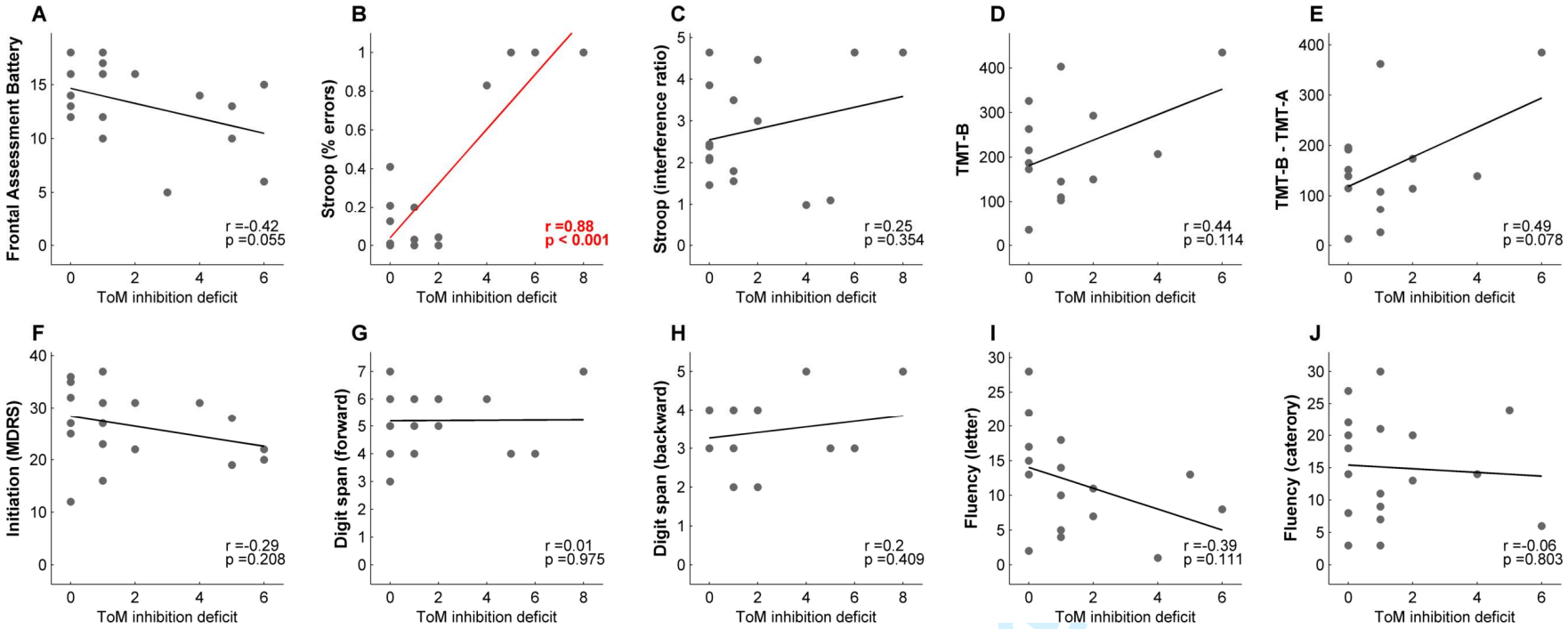

A
Frontal Assessment Battery
r =-0.42
p =0.055
ToM inhibition deficit
B
Stroop (% errors)
r =0.88
p < 0.001
ToM inhibition deficit
C
Stroop (interference ratio)
r =0.25
p =0.354
ToM inhibition deficit
D
TMT-B
r =0.44
p =0.114
ToM inhibition deficit
E
TMT-B - TMT-A
r =0.49
p =0.078
ToM inhibition deficit
F
Initiation (MDRS)
r =-0.29
p =0.208
ToM inhibition deficit
G
Digit span (forward)
r =0.01
p =0.975
ToM inhibition deficit
H
Digit span (backward)
r =0.2
p =0.409
ToM inhibition deficit
I
Fluency (letter)
r =-0.39
p =0.111
ToM inhibition deficit
J
Fluency (caterory)
r =-0.06
p =0.803
ToM inhibition deficit

Figure 3.

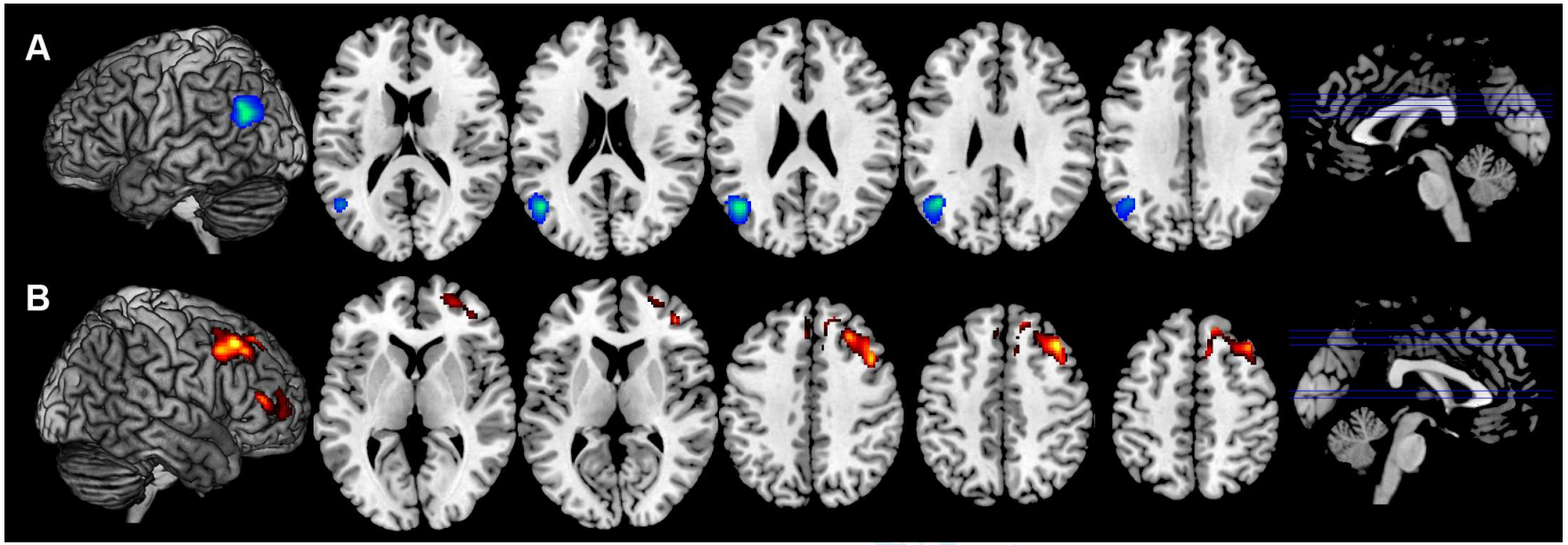
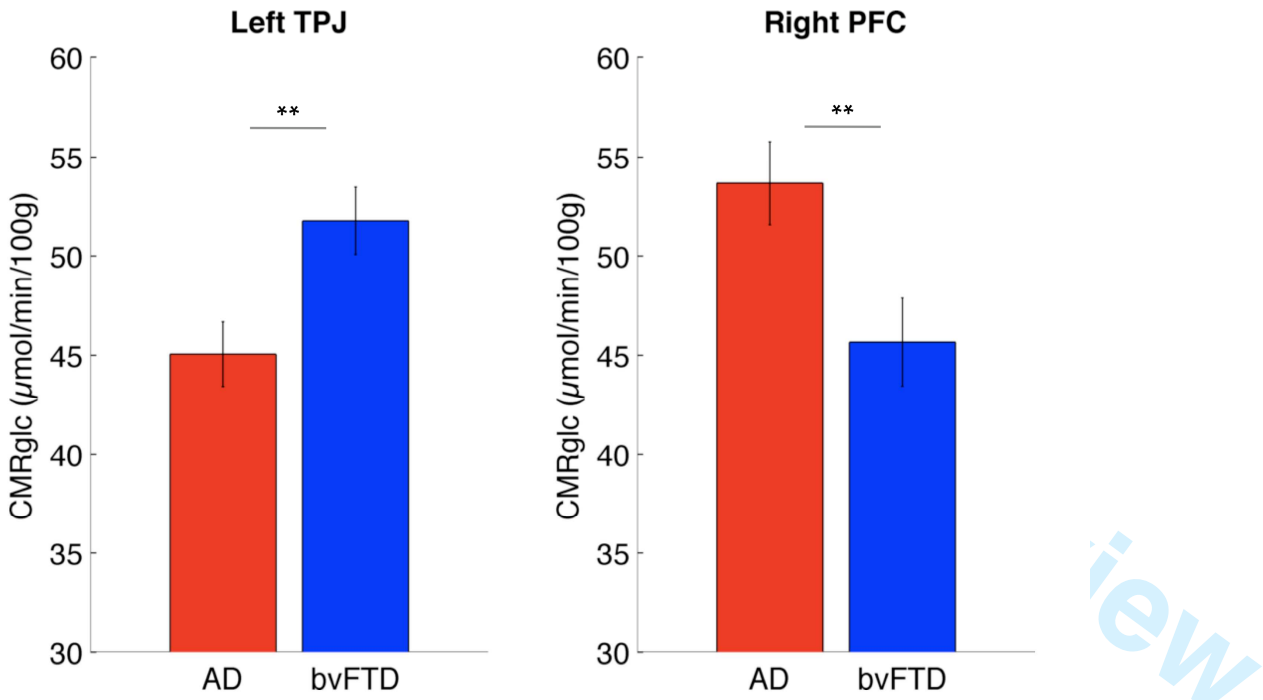


Figure 4.


Left TPJ
Right PFC
CMRglc (μmol/min/100g)
60
55
50
45
40
35
30
**
AD
bvFTD

Supplementary data: Tables (2); Figures (2).

Supplemental methods

Deficit criterion

According to Samson et al. methodology (2007), and given the 3-choice option, the probability of giving a correct response by chance is 0.33 for each trial. For any condition, 75% of correct responses (6 out of 8) or more is significantly above chance (p=0.0187, one tailed binomial test). Thus, a ToM reasoning deficit is defined when the following statements are met:

- subject is below chance (<6/8) in the conditions corresponding to the deficit (TB1, TB2, FB2 for the belief inference deficit; FB1, FB2 for the self-perspective deficit).
- subject is above chance (≥6/8) in the non-corresponding conditions.
- the majority of errors consist in the expected type for the deficit (appearance-based errors for the belief inference deficit, reality-based errors for the self-perspective deficit).

This index is suitable when deficits are expected to be isolated (either an inhibition deficit or an inference deficit) and severe (as it occurs in case of focal lesions *e.g.* strokes). However, it has several limitations in the context of neurodegenerative disorders, given the diffuse nature of the lesions. It is not appropriate to identify multiple deficits (combining a belief inference deficit and a self-perspective inhibition deficit). A subject impaired in both processes would fail to score above chance level in any condition, and would not be characterized by this index, despite suffering from both deficits. Moreover, this index is very conservative, and not appropriate to characterize mild or moderate deficits. A patient, for instance, could have a mild deficit in inhibiting his own mental perspective, and could make 2 reality-based errors in both false-belief conditions. This patient would be considered above chance level, and would thus be classified as unimpaired, despite failing four times to hold a correct reasoning. That is unlikely to be expected from a truly unimpaired subject. Finally, this categorical index gives no indication on the level of impairment, and does not allow correlation studies with other neuropsychological or brain metabolic measures.
For the above-mentioned reasons, for the current study, we developed the deficit score, a numerical index, which is sensitive to multiple and/or moderate deficits, that allows correlation analyses.

Deficit Score

For each deficit, the deficit score was defined as the lowest number of the expected errors among the corresponding conditions. Since a deficit in self-perspective inhibition should lead to reality-based errors in FB trials, we compared the number of these errors in FB1 and FB2, and took the lower of the two as a deficit score. For example, a patient making two reality-based errors in FB1 and three in FB2 would receive a score of 2 out of 8. However, making five errors in FB1 and zero in FB2 (which is not consistent with a deficit in self-perspective inhibition) would yield a score of 0 out of 8. Similarly, the score for a belief inference deficit

was defined as the lowest number of appearance-based errors in any of the TB1, TB2 and FB2 conditions. Another patient making three appearance-based errors in TB1, three in TB2 and two in FB2 would receive a score of 2 out of 8 for the belief inference deficit. However, making eight of these errors in TB1 and none in TB2 and FB2 (which is not consistent with a deficit in belief inference) would yield a score of 0 out of 8. Each condition included 8 repetitions and so each deficit score ranged from 0 to 8.

Figure legends:

Figure S1. The three-option false belief task.

Figure S2. Correlations between the belief inference deficit and various measures of executive functions: (A) global function (measured with the Frontal Assessment Battery), (B, C) inhibition in the Stroop Test (proportion of errors, interference ratio), (D, E) shifting assessed with the Trail Making Test (TMTB, TMTB-TMTA), (F) initiation and shifting (assessed with the Mattis Dementia Rating Scale initiation subtest), (G, H) maintenance in working memory (assessed with digit spans) and (I, J) generation (assessed by letter and categorical fluencies).

Table S1. The patients' neuropsychological characteristics

	AD (n=12) (Mean±SE)	FTD (n=11) (Mean±SE)	AD vs. FTD p value
Global scales			
MMSE	22.6 (0.8)	24.8 (0.9)	0.078
Mattis DRS	117.1 (3.3)	122.5 (3.5)	0.418
Attention	33.8 (0.6)	34.3 (0.9)	0.558
Initiation	26.9 (2.3)	26.1 (2.1)	0.642
Construction	5.4 (0.4)	5.9 (0.1)	0.507
Concept	36.1 (0.6)	35.1 (2.1)	0.754
Memory	14.9 (0.8)	21.1 (1.2)	**0.002**†
Behavioural scale			
Frontotemporal Behavioral scale	2.42 (0.5)	3.88 (0.1)	**0.017***
Executive functions			
Frontal Assessment Battery	14.8 (0.7)	11.6 (1.3)	**0.048***
Digit span (forward)	5.3 (0.4)	5.1 (0.4)	0.811
Digit span (backward)	3.3 (0.3)	3.6 (0.3)	0.567
Stroop (% error)	9.2 (4.6)	57.6 (18.3)	0.134
Stroop (interference ratio)	2.9 (0.4)	2.6 (0.6)	0.679
Trail Making Test B (s)	214.2 (38.8)	223.4 (56.3)	0.898
Trail Making Test B-A (s)	152.3 (32.8)	163.2 (59.6)	0.864
Letter fluency	13.7 (2.2)	8.5 (2.0)	0.143
Categorical fluency	14.4 (2.6)	16.2 (2.9)	0.599
Orientation			
Spatial orientation	3.7 (0.3)	4.2 (0.5)	0.359
Temporal orientation	3.6 (0.3)	4.6 (0.2)	0.109
Memory (FCSRT)			
Sum immediate free recall (/48)	11.0 (2.8)	18.2 (3.9)	0.174
Sum immediate cued recall (/48)	23.5 (3.6)	41.0 (3.3)	**0.007**†
Delayed free recall (/16)	3.6 (1.3)	6.3 (1.3)	0.136
Delayed cued recall (/16)	7.9 (1.4)	14.1 (1.3)	**0.014**†
Praxis (Limb apraxia battery)			
Meaningful gestures (D)	14.3 (1.2)	15.8 (1.1)	0.418
Meaningful gestures (ND)	15.3 (1.1)	15.4 (1.2)	0.852
Meaningless gestures on verbal command (D)	15.6 (0.5)	16.0 (0.7)	0.763
Attention			
WAIS score	4.9 (0.9)	4.1 (1.3)	0.514

HC: healthy controls; AD: Alzheimer's disease; bvFTD: behavioural variant of frontotemporal dementia; SE: standard error; D: dominant hand; ND: non-dominant hand; SE: standard error. FCSRT: free and cued selective recall test; WAIS: Wechsler Adult Intelligence Scale.

*bvFTD worse than AD

†AD worse than bvFTD

Figure S1.

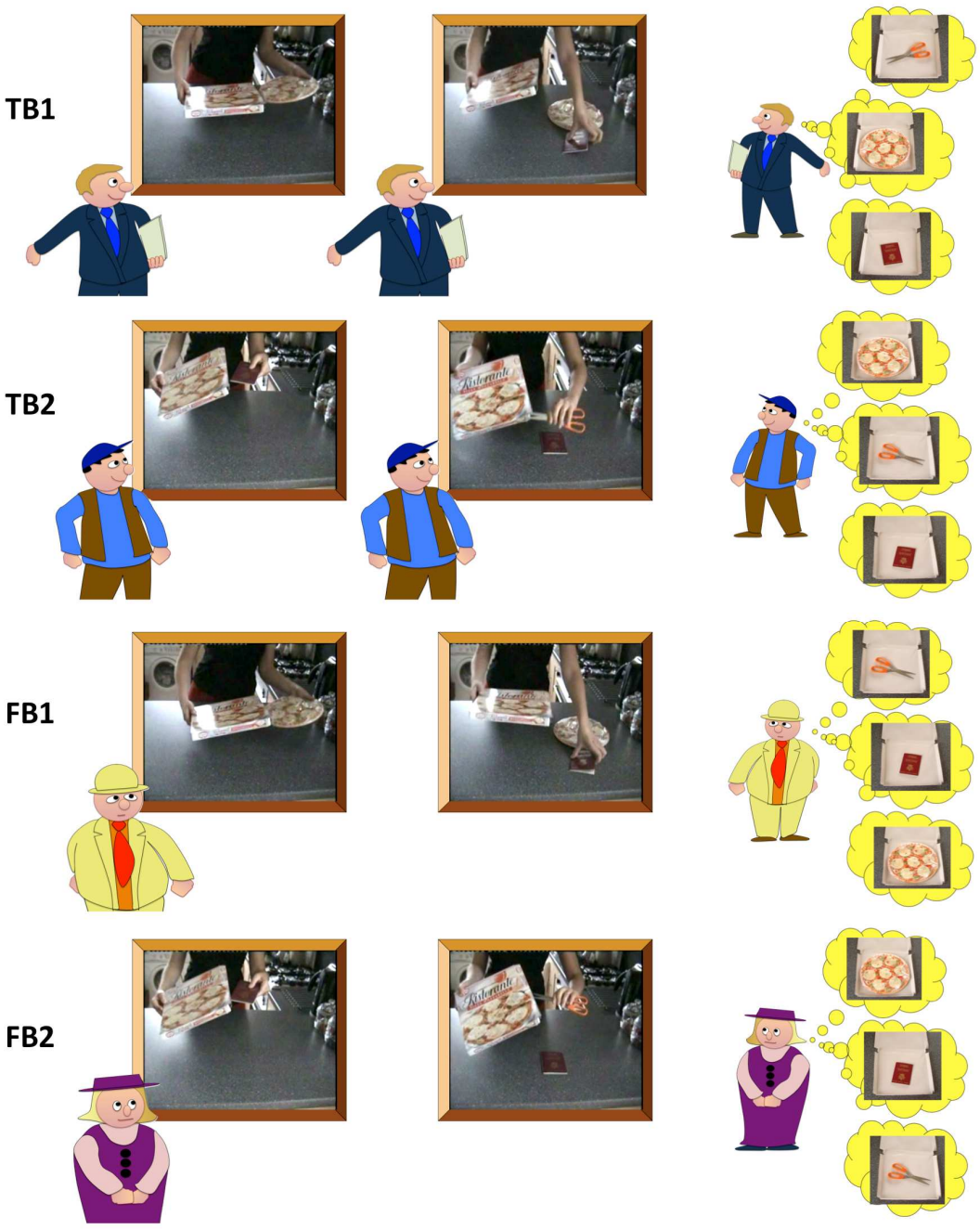
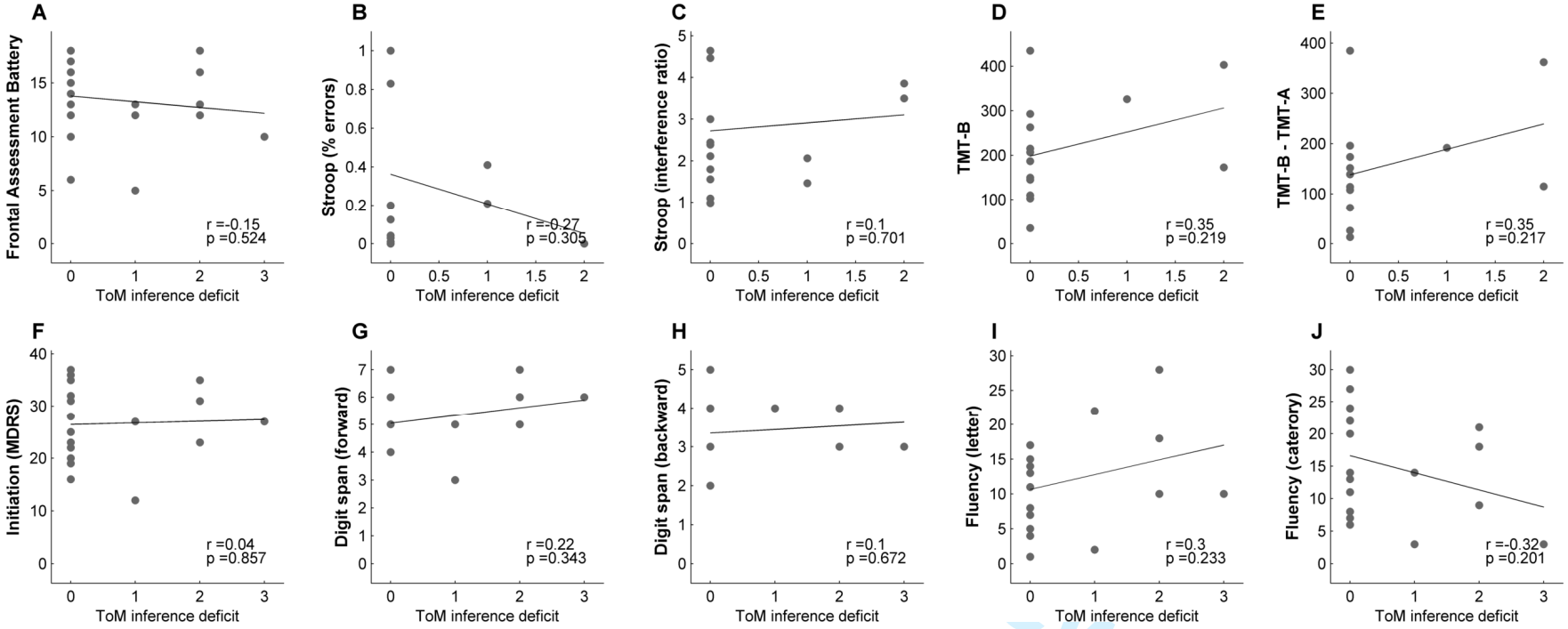


Table S2. Reasoning strategies and type of errors in the 3-option false belief task (Adapted from Samson et al., 2007)

	True belief (the neighbour sees the change)		False belief (the neighbour does NOT see the change)	
	Predictable object (TB1)	Non-predictable object (TB2)	Predictable object (FB1)	Non-predictable object (FB2)
Scene 1: A neighbour stops at the window and watches as the occupier puts an object A inside the box	Box: **Pizza-box** Object A: **Pizza**	Box: **Pizza-box** Object A: **Passport**	Box: **Pizza-box** Object A: **Pizza**	Box: **Pizza-box** Object A: **Passport**
Scene 2: The neighbour stays at the window (TB), or goes away (FB), and the occupier replaces object A by object B.	The neighbour **stays** at the window Object B: **Passport**	The neighbour **stays** at the window Object B: **Scissors**	The neighbour **goes away** Object B: **Passport**	The neighbour **goes away** Object B: **Scissors**
Scene 3:	On half of the trials, the neighbour stays at the window. On the other half of the trials, the neighbour goes away. Then, the belief question is asked.		On half of the trials, the neighbour comes back in front of the window. On the other half of the trials, the neighbour stays away. Then, the belief question is asked.	
Possible choices	Pizza (appearance based error) Passport (correct) Scissors (unrelated distractor)	Pizza (appearance based error) Passport (strategy-based error) Scissors (correct)	Pizza (correct) Passport (reality-based error) Scissors (unrelated distractor)	Pizza (appearance based error) Passport (correct) Scissors (reality-based error)
Reasoning strategy				
Genuine belief reasoning	Correct (e.g., Passport)	Correct (e.g., Scissors)	Correct (e.g., Pizza)	Correct (e.g., Passport)
Reality-based strategy	Correct (e.g., Passport)	Correct (e.g., Scissors)	Incorrect (e.g., Passport)	Incorrect (e.g., Scissors)
Appearance based strategy	Incorrect (e.g., Pizza)	Incorrect (e.g., Pizza)	Correct (e.g., Pizza)	Incorrect (e.g., Pizza)

Eight different boxes were used (a sweets box, an egg box, a cornflakes packet, a pizza box, a tea box, a crisp bag, a waste bin and a beer pack) under four conditions (TB1, TB2, FB1 and FB2), yielding a total of 32 different trials in two blocks of 16 trials.

Figure S2.


A
Frontal Assessment Battery
r =-0.15
p =0.524
ToM inference deficit
B
Stroop (% errors)
r =-0.27
p =0.305
ToM inference deficit
C
Stroop (interference ratio)
r =0.1
p =0.701
ToM inference deficit
D
TMT-B
r =0.35
p =0.219
ToM inference deficit
E
TMT-B - TMT-A
r =0.35
p =0.217
ToM inference deficit
F
Initiation (MDRS)
r =0.04
p =0.857
ToM inference deficit
G
Digit span (forward)
r =0.22
p =0.343
ToM inference deficit
H
Digit span (backward)
r =0.1
p =0.672
ToM inference deficit
I
Fluency (letter)
r =0.3
p =0.233
ToM inference deficit
J
Fluency (caterory)
r =-0.32
p =0.201
ToM inference deficit

Article 3 : Hennion, S., Szurhaj, W., Duhamel, A., Lopes, R., Tyvaert, L., Derambure, P., & Delbeuck, X. (2015). Characterization and prediction of the recognition of emotional faces and emotional bursts in temporal lobe epilepsy. *Journal of Clinical and Experimental Neuropsychology*, *37*(9), 931-945.

Characterization and prediction of the recognition of emotional faces and emotional bursts in temporal lobe epilepsy

Authors

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Abstract

Introduction: The present study sought to characterize and predict the recognition of emotional stimuli (presented in a visual or auditory modality) by patients with temporal lobe epilepsy (TLE).

Method: Fifty TLE patients and 50 matched controls performed two emotion recognition tasks (emotional faces and emotional bursts). Neutral stimuli were also presented, and emotional biases were monitored by analyzing errors. Demographic, cognitive, psychobehavioral and (in TLE patients only) clinical and quality of life data were also recorded.

Results: Compared with controls, TLE patients were impaired in the recognition of fear expressions in both visual and auditory modality tasks. However, impairments in the two channels were not always concomitant on the individual level. In the visual modality, recognition of disgust and neutral expressions was significantly worse in TLE patients. In the auditory modality, non-significant trends toward poor recognition of disgust and neutral expressions were observed. Negative biases were noted in TLE patients; expressions of fear (faces and bursts) were more frequently misinterpreted as disgust, and neutral facial expressions were more frequently misinterpreted as sadness. Impairments in the recognition of facial fear were less pronounced in left TLE patients who (according to structural MRI) did not have any brain lesions. In TLE patients, low levels of social support (a quality of life parameter) were associated with worse recognition of facial disgust, and higher levels of apathy were associated with better recognition of neutral faces.

Conclusions: TLE patients are impaired in some aspects of emotion recognition with both visual and auditory stimuli, although the differential impact of TLE on these modalities requires further research. These emotional impairments are related to quality of life and psychobehavioral parameters.

Key words: temporal lobe epilepsy, emotion recognition, emotional face, emotional burst, negative bias, quality of life, apathy

Introduction

As a key factor in nonverbal communication, emotional processing subtends appropriate, satisfactory social functioning. Consequently, emotional processing disorders may affect interpersonal relationships (Adolphs, 2009). Over the last decade, a growing number of studies have described emotional processing disorders (such as difficulty in decoding other people's emotions) in patients with temporal lobe epilepsy (TLE) (Bonora et al., 2011; Broicher et al., 2012; Meletti et al., 2003, 2009).

Most studies of emotional processing in this context have focused on the ability of mesial TLE patients with mesial temporal damage (such as hippocampal sclerosis (HS)) to recognize basic facial emotions displayed by other people. In most cases, mesial TLE patients were found to have difficulty categorizing negative emotions (Bonora et al., 2011; Broicher et al., 2012; Meletti et al., 2003, 2009; Reynders, Broks, Dickson, Lee, & Turpin, 2005). Moreover, it has been hypothesized that TLE patients can suffer from negative biases (i.e. by misinterpreting neutral or vague emotional expressions as negative emotions) (Shaw et al., 2007; Yamada et al., 2005). The mesial temporal structures (and particularly the amygdala) are essential components of the brain's system for emotional processing (Adolphs, 2002, 2010). Hence, the presence of impaired emotional processing in mesial TLE patients with mesial temporal damage is thus not surprising. Nevertheless, the categorization of emotional facial expressions may be impaired to the same extent in mesial TLE patients without brain damage and in those with damage (Tanaka et al., 2013). Furthermore, it is clear that the brain network involved in the recognition of emotional facial expressions is not limited to the mesial temporal structures; several surrounding regions may also have a major role. Indeed, the occipitotemporal, temporal, orbitofrontal and frontoparietal cortices contribute to the recognition of emotional facial expressions (Adolphs, 2002). Consequently, patients with other forms of TLE might also suffer from impaired ability to recognize emotional facial expressions. This hypothesis has not been extensively explored but is supported by the results of Meletti et al.'s study (2009); that lateral TLE patients showed impaired categorization of emotional facial expressions, albeit to a lesser extent than mesial TLE patients (Meletti et al., 2009). Nevertheless, the laterality of TLE was not considered in the

studies by Tanaka et al. (2013) and Meletti et al. (2009), both of which featured a mixture of participants with right, left or bilateral TLE. In fact, laterality appears to be an important factor; since several studies have reported that left mesial TLE patients displayed fewer impairments in the recognition of emotional facial expressions than right mesial TLE patients (Meletti et al., 2003, 2009). However, hemispheric dominance in emotional processing is subject to debate, since left and right mesial TLE patients do not always differ significantly in their performance levels (Bonora et al., 2011; Broicher et al., 2012).

Patients with TLE and mesial temporal damage also appear to be impaired in categorizing negative emotional prosody in sentences, although this topic has been less extensively investigated (Bonora et al., 2011; Broicher et al., 2012). Hence, emotional processing disorders may not be limited to a single sensory channel. Nevertheless, emotional prosody in sentences cannot be considered as a true counterpart of emotional facial expressions (Belin, Fillion-Bilodeau, & Gosselin, 2008). Indeed, interactions between emotional prosody processing in sentences and linguistic processing cannot be completely ruled out. Interestingly, Fowler et al. (2006) did not find a significant impairment in the auditory emotion recognition of emotional nonverbal sounds by mesial TLE patients (relative to controls) (Fowler et al., 2006). However, the latter study included a mixture of pre- and postsurgery TLE patients, and it is possible that temporal lobe surgery had an impact on emotion recognition. The recognition of emotional vocal expressions also involves a broad brain network: the primary and secondary auditory cortices, mesial temporal structures, and the inferior frontal and superior temporal cortices (Frühholz, Trost, & Grandjean, 2014; Schirmer & Kotz, 2006). Although right hemisphere dominance in the emotional processing of vocal expressions has been suggested, bilateral involvement of the above-mentioned brain network appears to be more likely (Frühholz & Grandjean, 2013a, 2013b). Consequently, TLE patients might also be at risk of developing emotional recognition disorders in the auditory modality - regardless of the etiology and laterality of their epilepsy.

Lastly, young age at onset of epilepsy and a long duration of epilepsy might be associated with greater emotional impairments - although these risk factors have yet to be fully characterized (Bonora et al., 2011; Broicher et al., 2012; Meletti et al., 2003, 2009; Reynders et al., 2005; Tanaka et al., 2013).

An important issue concerns the impact of emotional disorders on a TLE patient's everyday life. In fact, TLE patients frequently exhibit social and psychobehavioral difficulties, such as depression (often with concomitant anxiety) and poor quality of life (Hermann, Seidenberg, & Jones, 2008; Kanner, 2009; Lin, Mula, & Hermann, 2012; Quintas et al., 2012). However, social and psychobehavioral disturbances in epilepsy are often atypical and thus difficult to assess with conventional nosological tools (Krishnamoorthy, Trimble, & Blumer, 2007). This might explain the failure of two recent major studies to find associations between self-reported depression and poor quality of life on one hand and performances in emotion recognition tasks on the other (Bonora et al., 2011; Broicher et al., 2012). We have suggested that a more specific, comprehensive assessment of the symptoms of affective disorders and poor quality of life might be able to detect this type of association (Hennion et al., 2014).

Hence, the present study sought to evaluate emotion recognition by TLE patients and controls in both visual and auditory modalities. Visual emotion recognition was tested with facial emotional expressions, whereas auditory emotion recognition was studied using a validated set of non-verbal "emotional bursts" (the Montreal Affective Voices (Belin et al., 2008)). Emotional bursts are short, emotional, non-speech expressions that (along with the corresponding emotional facial expressions) usually accompany an intense emotional experience. Participants were instructed to categorize the emotion. Neutral stimuli were also presented, and emotional biases were monitored by analyzing errors. Putative clinical risk factors for impaired emotional processing in TLE patients were also investigated. Lastly, we probed relationships between emotional processing disorders on one hand and psychobehavioral and quality of life factors on the other.

In view of (i) the results of previous studies in TLE patients and (ii) the brain networks involved in processing emotional stimuli, several hypotheses can be formulated. Firstly, TLE patients are likely to suffer from emotional recognition disorders (compared with controls) in both visual and auditory modalities. Secondly, these emotional recognition disorders are likely to be associated with emotional biases. Thirdly, given the contribution of both mesial temporal and cortical temporal regions to emotional processing, emotional recognition disorders could potentially be encountered in all patients with TLE, regardless of the latter’s etiology (i.e. impairments might also be observed in

TLE patients lacking mesial temporal damage such as hippocampal sclerosis) – although the laterality of TLE must be considered in this context. Fourthly and lastly, emotional impairments in TLE patients are likely to be related to psychobehavioral and quality of life parameters.

Methods

Participants

The data presented here were collected as part of a larger study of social cognition disorders in TLE patients (Hennion et al., 2014). The study protocol had been approved by the local investigational review board (CPP Nord Ouest IV, Lille, France; reference: 2012-A00339-34).

Fifty TLE patients consulting at Lille University Medical Center's Epilepsy Unit (Lille, France) were consecutively recruited on the basis of clinical evaluation, electroencephalographic monitoring, neuropsychological data and neuroimaging results. The inclusion criteria were (i) unilateral TLE and (ii) right-handedness (according to the Edinburgh Handedness Inventory) (Oldfield, 1971). The exclusion criteria were (i) impaired intellectual capacity (an intellectual quotient below 75, according to a French adaptation of the National Adult Reading Test: fNART) (Mackinnon & Mulligan, 2005) or non-verbal reasoning (according to Raven's Coloured Progressive Matrices: PM-47) (Raven, 1965); (ii) significant amnesia or a marked impairment in instrumental capacities (agnosia, aphasia, apraxia, alexia or agraphia); (iii) a history of neurological disease other than epilepsy; (iv) a history of psychiatric disease (other than depression or anxiety disorders); and (v) a seizure in the 24 hours preceding the experimental session. For TLE patients, the following clinical characteristics were recorded: the presence of febrile seizures, age at first seizure, age at onset of epilepsy, duration of epilepsy, seizure frequency, laterality of epilepsy (right vs. left), type of epilepsy (mesial vs. lateral) and the presence of hippocampal sclerosis (HS, classified as "with HS", "with no brain lesions" or "with lesions other than HS"). The lesions other than HS included focal gliosis, focal atrophy and focal dysplasia. The presence of HS, the presence of brain lesions other than HS or the absence of brain lesions were established on the basis of structural neuroimaging data (3 Tesla MRI).

The diagnostic criteria for HS included a volume decrease on T1-weighted images and high signal intensity in fluid-attenuated inversion recovery images (Blümcke et al., 2013). Except for one new-onset TLE patient, all patients included in the study were taking antiepileptic medication to control seizures (8 were taking a single antiepileptic drug and 41 were taking more than one antiepileptic drug; mean ± standard deviation (SD) number of antiepileptic drugs: 2.14 ± .81). The antiepileptic regimen had not been modified in the six weeks immediately prior to the study, and none of the included TLE patients were taking phenobarbital (which reportedly impairs the ability to recognize emotions (Meletti et al., 2009)).

The control group included 50 right-handed participants (according to the Edinburgh Handedness Inventory), each of whom was matched for demographic characteristics (age, gender and educational level) with a TLE patient. The exclusion criteria for controls were: (i) impaired intellectual capacity (an intellectual quotient below 75, according to the fNART) or non-verbal reasoning (according to the PM-47), and (ii) a history of neurological or psychiatric disease.

It should be noted that all study participants (TLE patients and controls) had normal visual and auditory perceptual capacities (according to the Benton Facial Recognition Test (Benton & Van Allen, 1968) and the Protocol of Auditory Gnosis Assessment (Agniel, Joanette, Doyon, & Duchein, 1992)).

All the participants underwent the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), which assesses attention, executive functions, memory, language, visuoconstruction skills, conceptual thinking, calculation, and orientation. The study participants' demographic and cognitive characteristics and the TLE patients' clinical characteristics are summarized in Table 1.

Table 1. Characterization of TLE patients and the statistical significance of intergroup comparisons (p-values)

	Controls n = 50	**TLE patients** n = 50	**p-values**
Demographic characteristics			
Age in years (mean±SD)	42.81±12.46	42.40±11.82	p=.8660
Gender (male %)	46.00	46.00	p=1.00
Educational level (≥ 12 years %)	42.00	42.00	p=1.00
Cognitive characteristics			
MoCA score (from 0 to 30, mean±SD)	28.22±1.31	25.12±2.43	p<.0001
Clinical factors			
Presence of febrile seizures (with febrile seizures %)		26.00	
Age at onset in years (mean±SD)		21.06±15.27	
Onset ≤ 5 years of age (%)		20.00	
Duration of epilepsy in years (mean±SD)		21.34±14.59	
Seizure frequency per day over 3 months (mean±SD)		0.44±2.12	
Laterality (right/left, %)		46.00/54.00	
Type (mesial/lateral, %)		62.00/38.00	
Presence of HS (with HS/with no brain lesions/with lesions other than HS, %)		46.00/34.00/20.00	

Abbreviations: TLE = temporal lobe epilepsy; SD = standard deviation; MoCA = Montreal Cognitive Assessment; HS = hippocampal sclerosis

Assessment of emotional processing

The facial emotion recognition task

Stimuli: 60 faces were selected from the NimStim Set of Facial Expressions (Tottenham et al., 2009). Each face (with the mouth closed) represented one of five basic emotional expressions (happiness, sadness, fear, disgust, anger) or a neutral emotional expression. Five male faces and five female faces were presented for each emotional category.

The test procedure: using a computer interface, faces were presented one by one and in pseudorandom order. Each face was presented once for just 500 ms because it has been found that long or repeated presentations can promote the use of compensatory strategies and thus prevent the detection of subtle impairments (Graham, Devinsky, & Labar, 2007). After each face had been presented, the participant was asked to categorize the emotional facial expression as quickly as possible. In each trial, six verbal labels were explicitly suggested as words on a computer screen. They corresponded to the five categories of emotional facial expression (i.e. happiness, sadness, fear, disgust or anger) or a neutral facial expression. The participant's answer (corresponding to the selection of a verbal label) was recorded. One point was given for each correct emotional categorization. An overall 0-to-60 recognition score for visual stimuli was computed. Six 0-to-10 subscores (one for each emotional category) were also calculated. For each emotional category, the number of errors (i.e. when the selected emotional category did not correspond to the presented emotional expression) was recorded. Hence, five 0-to-10 subscores were obtained for the five possible types of error. The participant did not receive any feedback on his/her performance. It should be noted that before the emotional task was administered, the experimenter checked whether the participant understood each of the emotional verbal labels (by asking him/her to each to describe a situation that might elicit the emotion in question). Furthermore, a training session (with six trials) was provided before the start of the experimental task, in order to familiarize the patient with the test procedure.

The emotional burst recognition task

Stimuli: 60 bursts were selected from the Montreal Affective Voices (Belin et al., 2008). Each burst represented one of five basic, non-verbal emotional expressions (happiness, sadness, fear, disgust or anger) or a neutral expression. Again, five male bursts and five female bursts were presented for each emotional category.

The test procedure: apart from the nature of the stimuli, the test procedure (including the score calculation and the presence of a training session) was the same as in the facial emotion recognition task. The mean ± SD presentation time for an auditory stimulus was 1063±620 ms.

Assessments of psychobehavioral parameters and quality of life

On the basis of self-reports, we estimated: (i) depression (according to the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)) and anxiety (according to the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983)); (ii) disturbances of affective regulation commonly associated with mood disorders, such as apathy (according to the Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006)), alexithymia (according to the Toronto Alexithymia Scale (TAS-20) (Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994)), and anhedonia (according to the Physical Anhedonia Scale (PAS) and the Social Anhedonia Scale (SAS) (Chapman, Chapman, & Raulin, 1976)); for all the above-mentioned instruments, the higher the score, the more intense the psychobehavioral factor; (iii) the frequency with which the participant experienced positively or negatively valenced affective states (according to the Positive and Negative Affectivity Scales (PANAS) (Watson, Clark, & Tellegen, 1988)); and (iv) empathy abilities (according to the Interpersonal Reactivity Index (IRI) (Davis, 1983)); the higher the score, the more intense the positive or negative affectivity or level of empathy. In TLE patients, quality of life was also estimated (according to the Quality of Life Inventory in Epilepsy (QOLIE-89)) (Devinsky et al., 1995). We calculated the overall score and the subscores for role limitations-emotional, emotional

well-being, social support, social isolation, and work/driving/social function; the higher the score, the better the quality of life.

Data analysis

All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA). The threshold for statistical significance was set to $p<.05$. Parametric tests were used for normally distributed datasets; otherwise, non-parametric tests were applied. Scores are quoted as the mean ± SD.

Controls and TLE patients were compared in terms of their demographic characteristics (age, gender, and education level) and cognitive characteristics (the MoCA score). Patients with TLE were classified according to the laterality of epilepsy (right or left) and then compared in terms of their demographic, cognitive and clinical parameters (the presence of febrile seizures, age at onset, duration of epilepsy, seizure frequency, type of epilepsy, and the presence of HS). The same approach was applied to the comparison of TLE patients as a function of both the laterality of epilepsy and the presence of HS (right TLE with HS, right TLE with no brain lesions, left TLE with HS, and left TLE with no brain lesions) and, lastly, as a function of both the laterality and the type of epilepsy (right-lateral, right-mesial, left-lateral and left-mesial). All variables that differed significantly when comparing groups were considered as adjustment variables for the subsequent analyses of emotional scores. Bonferroni corrections for multiple comparisons were applied.

The TLE patients' and controls' respective categorization scores in each emotional task were compared using a mixed model, with *subject* as a random effect. In TLE patients, emotional performances that were considered to be impaired (relative to controls) were analyzed against clinical characteristics (age at onset, duration of epilepsy, and seizure frequency) in correlation analyses. We compared emotional categorization scores in early-onset TLE patients (onset at ≤5 years of age) vs. late-onset TLE patients (onset at >5 years of age), and in TLE patients with or without febrile seizures. Effects of the laterality of epilepsy, both the laterality of epilepsy and the presence of HS or the type of epilepsy on categorization scores were also tested, using mixed models with *subject* as a random

effect. For each impaired emotional categorization score, the effect size (Cohen's *d*) was calculated and error analyses were performed using mixed models with *subject* as a random effect.

The model's accuracy was measured as the area under the receiver operating characteristic curve (AUC). The percentages of TLE patients with a score that differed significantly from the control group were calculated with Crawford's test (Crawford, Garthwaite, & Porter, 2010).

Hence, TLE patients and controls were compared in terms of a set of psychobehavioral symptoms. Emotional performances that were impaired in TLE patients were analyzed against psychobehavioral and quality of life factors. Variables with a p-value below .20 in a univariate analysis were selected for multivariate stepwise linear regression analysis.

Results

Characterization of TLE patients

The mean MoCA score was lower in the TLE patient group than in the control group (Table 1). The laterality and the type of epilepsy did not have group effects on demographic, cognitive or clinical parameters (Supplementary data - Tables 5 and 6). There was a group effect of laterality and the presence of HS on the educational level, the MoCA score, the presence of febrile seizures and the duration of epilepsy (Supplementary data - Table 7). The variables that differed significantly when comparing groups were considered as adjustment variables for subsequent analyses of emotional scores.

The TLE patients' performance in emotional recognition tasks

Facial emotion recognition

- *Emotional categorization* (Table 2 and Figure 1)

There was a *group* effect (TLE patients vs. controls) on the categorization scores (F(1, 587)=14.49, p=.0002). The mean ± SD overall categorization score was lower in TLE patients than in controls (44.24±6.31 and 50.36±3.71, respectively; d=1.18).

Furthermore, there was an interaction between *group* (TLE patients vs. controls) and *condition* (emotional categories of faces: happiness, sadness, fear, disgust, anger and neutral); F(5, 587)=6.74, p<.0001. A *post hoc* analysis indicated that relative to controls, TLE patients were impaired in the categorization of fear, disgust and neutral expressions (d=.96, .40 and .68, respectively). In TLE patients, the categorization scores for fear, disgust and neutral expressions were not significantly correlated with age at onset, the duration of epilepsy or the seizure frequency. Moreover, there were no significant differences in these scores as a function of age at onset (early vs. late) or the presence or absence of febrile seizures.

In TLE patients, the *group* effects of the laterality of epilepsy, both the laterality of epilepsy and the presence of HS and both the laterality and the type of epilepsy on the categorization scores were tested using mixed models; there were no significant interactions in any of the three analyses (F(5, 288)=1.00, p=.4150; F(15, 212)=.70, p=.7878 and F(15, 276)=.91, p=.5484, respectively). However, there were significant effects of *condition* (emotional categories of faces: happiness, sadness, fear, disgust, anger and neutral; F(5, 288)=23.16, p<.0001; F(5, 212)=19.16, p<.0001; F(5, 276)=21.48, p<.0001 in the three analyses, respectively). The laterality of epilepsy did not have a significant *group* effect (F(1, 288)=1.08, p=.2997). Nevertheless, there was a *group* effect of both the laterality of epilepsy and the presence of HS (F(3, 212)=4.08, p=.0076). A *post hoc* analysis indicated that left TLE patients with HS were impaired in the recognition of fear expressions, relative to left TLE patients with no brain lesions (4.91±2.74 and 7.88±1.46, respectively; t_{212}=3.05, p=.0156; d=1.37; Figure 2). There were no other significant intergroup differences in categorization scores for

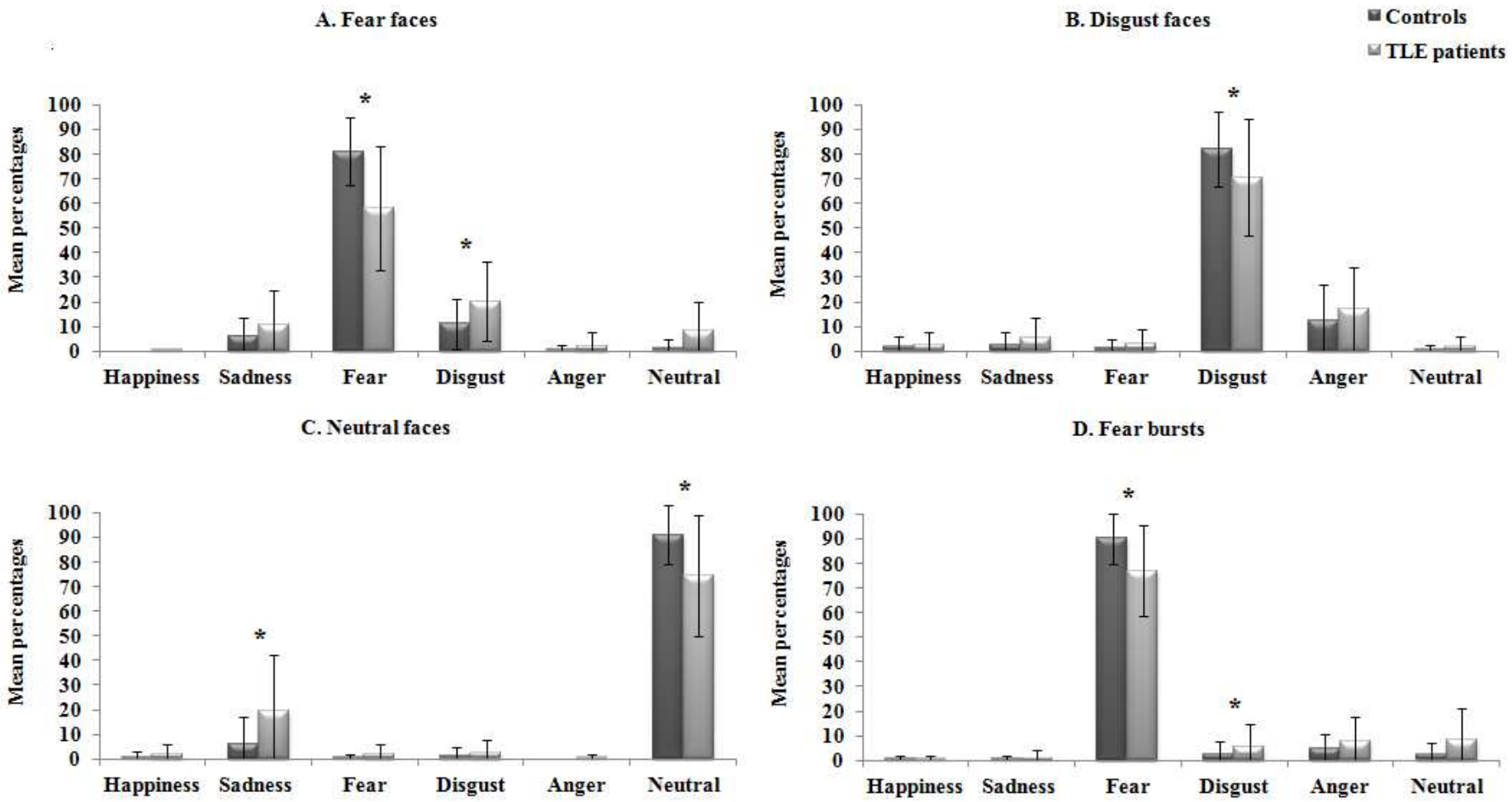
fear expressions (6.00±2.00 in right TLE patients with HS and 5.89±2.80 in right TLE patients with no brain lesions). Furthermore, there was a *group* effect of both the laterality and type of epilepsy ($F(3, 276)=3.79$, $p=.0108$). However, a *post hoc* analysis did not detect a significant intergroup difference.

Table 2. Scores for categorization of emotional tasks for controls and TLE patients, significance of contrasts (p-values) and discriminative power (AUC) in intergroup comparisons

Categorization scores (from 0 to 10)	**Controls** mean (SD)	**TLE patients** mean (SD)	***t* and p-values and *d***
Emotional categories - faces			
happiness	9.78 (0.55)	9.82 (0.44)	t_{587}=-1.06, p=.2918
sadness	7.14 (1.57)	6.30 (2.05)	t_{587}=1.39, p=.1644
fear	8.10 (1.37)	5.82 (2.52)	t_{587}=5.40, p<.0001, AUC=.80
disgust	8.18 (1.51)	7.04 (2.37)	t_{587}=2.23, p=.0264, AUC=.64
anger	8.06 (1.32)	7.82 (1.73)	t_{587}=-.28, p=.7823
neutral	9.10 (1.18)	7.44 (2.47)	t_{587}=3.67, p=.0003, AUC=.73
Emotional categories - bursts			
happiness	9.96 (0.20)	9.98 (0.14)	t_{587}=-1.36, p=.1746
sadness	9.90 (0.30)	9.82 (0.39)	t_{587}=-.97p=.3307
fear	9.00 (1.03)	7.70 (1.82)	t_{587}=3.73, p=.0002, AUC=.73
disgust	9.46 (0.91)	8.64 (1.41)	t_{587}=1.88, p=.0605
anger	6.10 (1.58)	5.42 (2.20)	t_{587}=1.34, p=.1804
neutral	9.96 (0.20)	9.16 (1.96)	t_{587}=1.80, p=.0718

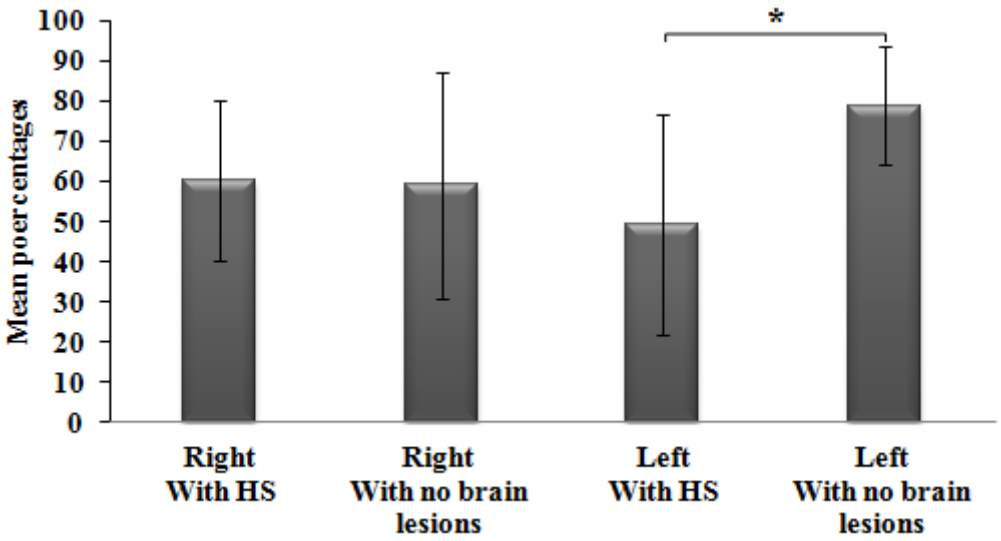
Abbreviations: TLE = temporal lobe epilepsy; AUC = area under the receiver operating characteristic curve; SD = standard deviation

Figure 1. Mean percentages and standard deviations (bars) of the distribution of emotional categorization answers (correct answers and errors) for controls and TLE patients according to the emotional category and type of stimuli presented.



Abbreviations: TLE = temporal lobe epilepsy; * = significance of the intergroup comparison ($p<.05$). Only emotional categories for which emotional performances were impaired in TLE patients relative to controls are illustrated (i.e. A. Fear faces, B. Disgust faces, C. Neutral faces and D. Fear Bursts)

Figure 2. Mean percentages and standard deviations (bars) of the scores for categorization of fear faces in TLE patients according to both the laterality of epilepsy and the presence of HS.



Abbreviations: TLE = temporal lobe epilepsy; HS = hippocampal sclerosis; * = significance of the intergroup comparison ($p<.05$).

- *Error analysis* (Table 3 and Figure 1)

We performed error analyses for the categorization scores that were impaired in TLE patients, relative to controls (i.e. fear, disgust and neutral expressions). For facial expressions of fear, we observed a *group* (TLE patients vs. controls) x *condition* (type of error) interaction that affected the error distribution ($F(4, 391)=4.30$, p=.0020). A *post hoc* analysis indicated that relative to controls, TLE patients were more likely to categorize fear as disgust (t_{97}=-2.24, p=.0271; d=.58). For facial expressions of disgust, there was no significant *group* (TLE patients vs. controls) x *condition* (type of error) interaction ($F(4, 391)=.99$, p=.4140). However, there was a significant effect of *condition* ($F(4, 391)=45.62$, p<.0001) but not of *group* ($F(1, 391)=1.87$, p=.1723). For neutral facial expressions, there was a *group* (TLE patients vs. controls) x *condition* (type of error) interaction ($F(4, 391)=11.05$, p<.0001). A *post hoc* analysis showed that relative to controls, TLE patients were more likely to categorize neutral expressions as sadness (t_{97}=-2.26, p=.0258; d=.58).

Table 3. Distribution of emotional categorization errors for controls and TLE patients

Type of error (mean (SD))	**Type of categorization (emotional expression-stimuli)**							
	Fear faces		**Disgust faces**		**Neutral faces**		**Fear bursts**	
	Controls	**TLE patients**	**Controls**	**TLE patients**	**Controls**	**TLE patients**	**Controls**	**TLE patients**
happiness	0 (0)	0.04 (0)	0.16 (0.42)	0.26 (0.49)	0.06 (0.24)	0.18 (0.39)	0.02 (0.14)	0.02 (0.14)
sadness	0.62 (0.75)	1.08 (1.37)	0.26 (0.49)	0.52 (0.84)	0.62 (1.07)	1.96 (2.25)	0.02 (0.14)	0.10 (0.30)
fear			0.14 (0.35)	0.28 (0.61)	0.02 (0.14)	0.18 (0.39)		
disgust	1.10 (1.04)	2.02 (1.62)			0.12 (0.39)	0.22 (0.55)	0.24 (0.52)	0.56 (0.93)
anger	0.04 (0.20)	0.20 (0.57)	1.22 (1.46)	1.72 (1.71)	0 (0)	0.02 (0.14)	0.48 (0.58)	0.76 (1.00)
neutral	0.12 (0.39)	0.84 (1.17)	0.04 (0.20)	0.16 (0.42)			0.22 (0.51)	0.86 (1.25)

Abbreviations: TLE = temporal lobe epilepsy; SD = standard deviation

Burst emotion recognition

- *Emotional categorization* (Table 2 and Figure 1)

There was a *group* effect (TLE patients vs. controls) on the categorization scores ($F(1, 587)=4.64$, p=.0317). The mean overall categorization score was lower in TLE patients than in controls (50.72±4.51 and 54.38±2.17, respectively; d=1.03).

There was also a *group* (TLE patients vs. controls) x *condition* (emotional categories of bursts: happiness, sadness, fear, disgust, anger and neutral) interaction ($F(5,587)=4.08$, p=.0012). A *post-hoc* analysis indicated that relative to controls, TLE patients were only impaired in the categorization of fear expressions (d=.65). Furthermore, there was a non-significant trend towards a lower score for the recognition of disgust and neutral expressions in TLE patients (relative to controls). In TLE patients, there were no significant correlations between the categorization scores for fear expressions on one hand and age at onset, the duration of epilepsy or the seizure frequency on the other. Moreover, there were no significant differences in the fear categorization scores as a function of age at TLE onset (early vs. late) or the presence or absence of febrile seizures.

Hence, the *group* effects of the laterality of epilepsy, both the laterality of epilepsy and the presence of HS, and both the laterality and the type of epilepsy on all the categorization scores were tested using mixed models. There were no significant *group* (TLE patients vs. controls) x *condition* (emotional categories of bursts: happiness, sadness, fear, disgust, anger and neutral) interactions ($F(5, 288)=1.23$, p=.2962; $F(15, 212)=.56$, p=.9059 and $F(15, 276)=.71$, p=.7780 for the three models, respectively). There were effects of *condition* ($F(5, 288)=62.03$, p<.0001; $F(5, 212)=64.80$, p<.0001 $F(5, 276)=57.75$, p<.0001 for the three models, respectively) but not of *group* ($F(1, 288)=1.36$, p=.2439; $F(3, 212)=.11$, p=.9546 and $F(3, 276)=.49$, p=.6910 for the three models, respectively).

- *Error analysis* (Table 3 and Figure 1)

We performed error analyses for the categorization scores that were impaired in TLE patients, relative to controls (i.e. fear expressions). A *group* (TLE patients vs. controls) x *condition* (type of error) interaction affected the error distribution ($F(4, 391)=3.50$, p=.0079). A *post hoc* analysis

indicated that relative to controls, the TLE patients were more likely to categorize fear expressions as disgust (t_{97}=-2.00, p=.0487; *d*=.51).

Ability of emotional performance levels to discriminate between TLE patients and controls

The emotional categorization scores for fear expressions best discriminated between TLE patients and controls in each of the two modalities (visual and auditory) (Table 2). Thirty-six percent of the TLE patients (n=18 out of 50) were impaired in categorizing faces expressing fear (cut-off value according to Crawford's method: 5; p=.0296). Twenty percent of the TLE patients (n=10 out of 50) were impaired in categorizing bursts expressing fear (cut-off: 6, p=.0058). However, the categorization score for faces expressing fear was the only score with significant power for discriminating between TLE patients and controls (AUC=.80). Eight percent of TLE patients (n=4 out of 50) were impaired in both categorizing faces and bursts expressing fear and 52% did not display any impairments. Twenty-eight percent of the TLE patients were impaired in categorizing faces expressing fear but not in categorizing bursts expressing fear. Conversely, 12% of the TLE patients were impaired in categorizing bursts expressing fear but not in categorizing faces expressing fear. The laterality of epilepsy and the presence of HS were considered, as they had been identified as clinical factors that jointly influenced the categorization of faces expressing fear (see section 2.1.). It was found that 16.67% of right TLE patients with HS, 44.44% of right TLE patients with no brain lesions, 63.63% of left TLE patients with HS, and none of the left TLE patients with no brain lesions were impaired in categorizing faces expressing fear.

Sixteen percent of the TLE patients (n=8 out of 50) were impaired in categorizing faces expressing disgust (cut-off: 5; p=.0423). Twenty-six percent of TLE patients (n=13 out of 50) were impaired in recognizing neutral faces (cut-off: 6; p=.0123).

Emotional disorders, psychobehavioral disorders and quality of life disturbances in TLE patients

Relative to controls, the TLE patients had higher scores for depression (according to the BDI), anxiety (according to the STAI), apathy (according to the LARS), alexithymia (according to the TAS-20), anhedonia (according to the PAS and SAS) and negative affectivity (according to the PANAS), and had lower scores for positive affectivity (according to the PANAS) and cognitive empathic capacities (according to the IRI) (Table 4).

In TLE patients, neither the overall categorization scores for faces and bursts nor the scores for fear categorization for faces and bursts were correlated with any of the psychobehavioral or quality of life factors.

However, the categorization score for facial expressions of disgust was negatively correlated with depression (according to the BDI; r=-.41, p=.0034) and positively correlated with the positive affectivity (according to the PANAS; r=.28, p=.0488). The categorization score for facial expressions of disgust was also positively correlated with the overall score of quality of life (according to the QOLIE-89; r=.35, p=.0123) and the latter's role limitations-emotional (r=.37, p=.0082), social support (r=.28, p=.0479) and social isolation (r=.30, p=.0316) subscores in particular. Regression analysis identified the overall quality of life score as a predictor of the ability to categorize facial expressions of disgust (r^2=.12, p=.0123). Considering the quality of life factors individually, social support was the only significant predictor identified (r^2=.08, p=.0479).

The categorization score for neutral facial expressions was positively correlated with apathy score (on the LARS; r=.34, p=.0159). Apathy was also identified as a predictor of the ability to categorize neutral faces (r^2=.12, p=.0159). In our TLE patient group, 58% were classified as apathetic (based on a cut-off LARS score of 21). Compared with non-apathetic TLE patients, the apathetic TLE patients performed better when categorizing neutral faces (6.38±2.75, and 8.21±1.95, respectively; p=.0092). It is noteworthy that non-apathetic and apathetic TLE patients did not differ in terms of demographic, cognitive or clinical characteristics.

Table 4. Psychobehavioral scores (mean (SD)) for controls and TLE patients, quality of life scores (mean (SD)) for TLE patients and the statistical significance (p-values) of intergroup comparisons

	Controls n = 50	**TLE patients** n = 50	**p-values**
Psychobehavioral scores			
BDI score (from 0 to 63)	4.88 (6.31)	15.06 (10.18)	p<.0001
STAI score (from 20 to 80)			
state	29.62 (10.08)	40.00 (11.72)	p=.0036
trait	34.32 (8.13)	47.32 (10.24)	p<.0001
LARS score (from -36 to +36)	-29.70 (4.56)	-20.12 (7.84)	p<.0001
TAS-20 score (from 20 to 100)	43.06 (11.93)	54.86 (11.79)	p<.0001
PAS score (from 0 to 61)	14.44 (7.69)	21.54 (8.20)	p=.0131
SAS score (from 0 to 41)	9.38 (5.49)	14.26 (6.38)	p=.0002
PANAS score (from 10 to 50)			
positive affectivity	36.76 (5.27)	29.70 (6.65)	p<.0001
negative affectivity	20.36 (6.68)	25.32 (6.97)	p=.0122
IRI (from 0 to 120)	69.16 (12.59)	63.54 (11.02)	p=.1140
cognitive subscore (out of 60)	33.76 (8.14)	28.38 (6.48)	p=.0088
affective subscore (out of 60)	35.40 (7.15)	35.16 (7.02)	p=.9108
Quality of life scores (QOLIE-89)			
Overall score (from 0 to 100)		60.54 (13.41)	
Social subscores (from 0 to 100)			
role limitations-emotional		66.40 (34.86)	
emotional well-being		57.20 (19.01)	
social support		57.40 (14.99)	
social isolation		70.00 (20.20)	
work/driving/social function		55.95 (19.96)	

Abbreviations: TLE = temporal lobe epilepsy; SD = standard deviation; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; LARS = Lille Apathy Rating Scale; TAS-20 = Toronto Alexithymia Scale; PAS = Physical Anhedonia Scale; SAS = Social Anhedonia Scales; PANAS = Positive and Negative Affect Schedule; IRI = Interpersonal Reactivity Index; QOLIE-89 = Quality of Life Inventory in Epilepsy-89

Discussion

Our present results suggest that emotional processing disorders in TLE patients are independent of the sensory channel (i.e. visual or auditory). Consistently, the patients' recognition of fear expressions was specifically affected in each of the two sensory channels tested. Furthermore, the patients' recognition of disgust and neutral expressions was significantly impaired for the visual channel and showed a non-significant trend towards impairment for the auditory channel.

This finding agrees with the conclusions of previous studies and extends them to a larger population of TLE patients and other types of emotional stimulus. As mentioned above, the TLE patients studied by Fowler el al. (2006) were not found to be impaired in recognizing auditory stimuli (even though the stimuli were quite similar to those used in the present study); however, the latter researchers studied a mixture of pre- and post-surgery TLE patients, which might have had an impact on emotional processing (Fowler et al., 2006). Recent investigations suggest that TLE patients' recognition disorders (for emotional faces) are similar before and after surgery - although a post-surgery decline was observed in a few patients (Amlerova et al., 2014). It would be thus useful to study changes over time in the recognition of emotion in faces and bursts in pre- and post-surgery TLE patients.

A major strength of the present study relates to its investigation of error patterns for the recognition of emotions. The error patterns for the recognition of fear in visual and auditory modalities were similar - again suggesting that the two channels have analogous mechanisms. Indeed, we found that relative to controls, TLE patients were more likely to categorize fear expressions as disgust. Furthermore, TLE patients interpreted neutral facial expressions as sadness more frequently than controls did. Thus, our findings support the hypothesis in which TLE patients are subject to negative biases (Shaw et al., 2007; Yamada et al., 2005).

However, we cannot completely rule out the possibility that emotional impairments in TLE patients are related in part to the epileptic condition in general and its associated factors (such as the adverse effects of antiepileptic drugs), rather than to TLE specifically. This question has already been addressed by other researchers, who found that extratemporal focal and idiopathic generalized

epileptic patients were less severely affected by emotional recognition disorders than TLE patients (Broicher et al., 2012; Meletti et al., 2003; Reynders et al., 2005). Furthermore, Meletti et al.'s (2009) study of the effects of several antiepileptic drugs on ability to recognize emotions found that phenobarbital was the only medication associated with a possible negative effect on performance levels (Meletti et al., 2009). None of the TLE patients included in the present study were taking phenobarbital but all were taking one or more other antiepileptic medications to control seizures (except for a recently diagnosed new-onset TLE patient). Interestingly, the latter patient was impaired in the recognition of facial expressions of fear (with a score of 5 out of 10 for correct categorizations). Hence, one can reasonably assume that TLE is a major, specific factor in emotional disorders.

Moreover, one could conceivably attribute emotional disorders in TLE to other cognitive impairments that interfere with the patients' ability to perform emotional recognition tasks. Given that all the study participants had normal visual and auditory perceptual capacities, the emotional disorders observed here in TLE patients cannot be explained by perceptual impairments. The overall cognitive impairment of TLE patients (relative to controls) were taken into account by selecting the MoCA score as a covariate in our intergroup comparisons of emotional scores. Furthermore, the procedure for administration of the emotional tasks was designed to limit the involvement of other non-emotional processes (such as memory and language processes); as mentioned in the Methods section, the experimenter checked whether the participant understood each of the emotional verbal labels prior to the administration of each emotional task. After the presentation of each stimulus, the six possible verbal labels were displayed and the participant had to select one. Additionally, each participant completed a training session. It has recently been suggested that a lack of cognitive control (i.e. inability to mobilize cognitive resources for processing relevant information and inhibiting irrelevant information) leads to interference between relevant and irrelevant emotional stimuli and thus the generation of emotional biases (Dondaine et al., 2014). The observation of correlations between emotion recognition performances and executive functioning in patients with mesial TLE and idiopathic generalized epilepsy supports this hypothesis (Gomez-Ibañez, Urrestarazu, & Viteri, 2014). However, the present study did not extensively investigate executive function. Consequently, further

studies are needed to explore the hypothetical association between the lack of cognitive control and emotional processing disorders in TLE patients.

Although intergroup differences were observed for the recognition of fear expressions with both visual and auditory modalities, only the recognition score for facial expressions of fear had enough power to discriminate between TLE patients and controls. At first sight, this could be interpreted as the result of differing task difficulties. However, we found that some patients were impaired for fear recognition with either visual material alone or auditory material alone. Indeed, the individual-level analyses showed that impairments in the recognition of fear expressions in the visual and auditory modalities (in 36% and 20% of the TLE patients, respectively) were not always combined, since only 8% of the TLE patients displayed impairments in both modalities. These results suggest that even though the visual and auditory pathways do involve similar mechanisms, they have different neural substrates and can be independently affected (Yovel & Belin, 2013).

Several clinical factors were found to modulate ability to recognize fear expressions in the visual modality. Indeed, none of the left TLE patients with no brain lesions presented impaired facial fear recognition. Previous studies have suggested that the laterality of epilepsy and the presence of mesial temporal brain damage are selectively involved in emotional processing disorders in the visual modality (Meletti et al., 2003, 2009; Tanaka et al., 2013). Our present results suggest that both factors must be taken into account. The laterality of epilepsy and the presence of mesial temporal brain damage were not identified as clinical factors that modulate emotional recognition disorders for fear expressions in the auditory modality. Nevertheless, when considering the emotional processing of vocal expressions of fear, hemispheric dominance and the involvement of mesial temporal structures (especially in lesion studies) are subject to debate (Frühholz & Grandjean, 2013a, 2013b). Differences in the brain networks involved in the processing of emotional facial expressions and vocal emotional expressions might explain the observation dissociation in performance as a function of the sensory channel. These network differences might also involve extratemporal regions (e.g. an alteration of the modular effect of the amygdala on the visual sensory pathways can influence the representation of an emotional event - especially visual stimuli related to threats (Vuilleumier, 2005)). It is now well established that TLE can also be associated with structural and functional alterations in extratemporal

regions (such as subcortical structures, frontal and occipitotemporal neocortices) that might be also related to emotional disorders (Bernhardt, Hong, Bernasconi, & Bernasconi, 2013; Cohn, St-Laurent, Barnett, & McAndrews, 2014; Labudda, Mertens, Steinkroeger, Bien, & Woermann, 2014; van Diessen, Diederen, Braun, Jansen, & Stam, 2013). Thus, imaging data would be needed for a more detailed investigation of the brain substrate(s) underlying specific emotional disorders in each sensory modality. Furthermore, given that impairments other than those related to the recognition of facial expressions of fear were not highly prevalent in TLE patients, our study might not have been sufficient powered to detect additional clinical risk factors.

At first sight, there appear to be similarities between the emotional processing impairments in TLE patients and those in non-epileptic patients with mood disorders. Indeed, patients with mood disorders, major depressive disorders or bipolar disorders also display emotion recognition deficits associated with negative biases (Bourke, Douglas, & Porter, 2010; Kohler, Hoffman, Eastman, Healey, & Moberg, 2011). In these patients, the severity of the depressive symptoms (according to the BDI score) is predictive of emotional processing impairments (Brotman, Guyer, et al., 2008; Brotman, Skup, et al., 2008; Maniglio et al., 2013). In the present study, TLE patients had higher BDI scores than controls. However, as in previous studies, we did not find any correlation between the overall emotion recognition scores in the visual and auditory modalities on one hand and the BDI score or other psychobehavioral and quality of life parameters on the other (Bonora et al., 2011; Broicher et al., 2012).

When considering the more subtle impairments in the recognition of facial disgust, we found a correlation between a lower categorization score on one hand and a higher BDI score and a lower positive affectivity score on the other. However, these psychobehavioral parameters did not predict performances for the recognition of facial disgust. In contrast, we found that the overall QOLIE-89 score predicted the facial disgust categorization score – suggesting that disgust recognition disorders may have consequences on TLE patients' quality of life. When considering social quality of life parameters in particular, we found that social support was the best predictor of the TLE patients' failure to recognize disgust. Interestingly, social support has already been identified as a predictor of mood disorders in epileptic patients (Gandy, Sharpe, & Perry, 2012; Lee, Lee, & No, 2010). Hence,

the mood disorders in TLE patients may be indirectly related to emotional processing disorders for disgust, via an alteration in social support. It is noteworthy that in previous research, we found that a lack of social support can also be correlated with other social cognition disorders (e.g. impaired attribution of mental states, i.e. theory of mind disorders) in TLE patients (Hennion et al., 2014).

Furthermore, the emotion recognition disorders for neutral faces appeared to be related to the TLE patient's apathy score. In the present study, apathetic disorders were observed in 58% of the TLE patients tested. Apathy is a complex motivational disorder that encompasses reductions in goal-directed behavior, goal-directed cognitive activity and emotions (P. Robert et al., 2009). This condition is often (but not always) strongly related to depressive symptoms. Impairments in recognition of emotional neutrality have been observed in patients with mood disorders (Bourke et al., 2010; Kohler et al., 2011). Furthermore, a high level of apathy was found to be predictive of poor recognition of emotional facial expressions by patients with Parkinson's disease, and this relationship might be mediated by an overlap in the relevant brain networks (G. Robert et al., 2014). However, in the present study, we found that a high level of apathy in TLE patients was predictive of better recognition of neutral faces. Indeed, apathetic TLE patients were better than non-apathetic TLE patients at categorizing neutral faces. Nevertheless, it should be noted that although the relationship between performances in categorization of neutral faces and apathy levels was statistically significance, it was relatively weak (accounting for 12% of the variance). Hence, it may be necessary to characterize apathy in TLE patients in more detail.

To the best of our knowledge, only one study has specifically explored the recognition of emotionally neutral stimuli in TLE patients. Banks et al. (2014) found that the recognition of neutral facial expressions was impaired in a small group that comprised participants with right, left and bilateral TLE (Banks, Bellerose, Douglas, & Jones-Gotman, 2014). Importantly, studies of emotional and cognitive processes in TLE patients often use neutral stimuli as a baseline condition for comparison with emotional conditions (for example Bonelli et al., 2009; Müller et al., 2009). Future studies should independently investigate how emotional and neutral stimuli are processed. For example, Szaflarski et al. (2014) used an event-related neuroimaging paradigm to explore the emotion processing of facial expressions by left TLE patients (Szaflarski et al., 2014).

In conclusion, our present results show that TLE patients display impairments in recognizing emotions expressed both by faces and bursts. However, the impact of TLE on the emotional processing may vary according to the sensory channel. These emotional processing disorders can result in specific error patterns that reflect negative biases. Some of the impairments in emotion recognition differ according to the laterality of epilepsy and the presence of mesial temporal brain damage. Lastly, impairments in emotion recognition by TLE patients are related to quality of life and apathy levels.

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Supplementary data

Table 5. Demographic, cognitive, clinical parameters according to the laterality of epilepsy (right vs. left) for TLE patients, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy		
	Right	**Left**	**p-values**
	n=23	n=27	
Demographic characteristics			
Age in years (mean (SD))	42.67 (13.72)	42.17 (10.20)	p=0.8841
Gender (male, %)	47.83	44.44	p=1.00
Educational level (% lacking a high school leaving qualification)	69.57	48.15	p=0.1578
Cognitive characteristics MoCA score (from 0 to 30, mean (SD))	25.74 (2.34)	24.59 (2.42)	p=0.1257
Clinical factors			
Age at onset in years (mean (SD))	24.00 (16.52)	18.56 (13.94)	p=0.2232
Duration of epilepsy in years (mean (SD))	18.67 (13.72)	23.61 (15.18)	p=0.2977
Seizure frequency per day over 3 months (mean (SD))	0.14 (0.14)	0.70 (2.86)	p=0.5429
Type of epilepsy (mesial %)	65.22	59.26	p=0.7733
Presence of HS (with HS/no brain lesions %)	52.17/39.13	40.74/29.63	p=1.00

Abbreviations: TLE = temporal lobe epilepsy; SD = standard deviation; MoCA = the Montreal Cognitive Assessment; HS = hippocampal sclerosis

Table 6. Demographic, cognitive, clinical parameters according to the laterality of epilepsy (right vs. left) and type of epilepsy (mesial vs. lateral) for TLE patients, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy*Type of Epilepsy				
	Right		**Left**		
	Mesial	**Lateral**	**Mesial**	**Lateral**	**p-values**
	n=15	n=8	n=16	n=11	
Demographic characteristics					
Age in years (mean (SD))	43.80 (15.33)	40.54 (10.64)	45.30 (11.17)	37.61 (6.70)	p=0.3740
Gender (male, %)	46.67	50.00	37.50	54.55	p=0.8392
Educational level (% lacking a high school leaving qualification)	73.33	62.50	56.25	36.36	p=0.3020
Cognitive characteristics MoCA score (from 0 to 30, mean (SD))	25.93 (2.19)	25.38 (2.72)	24.50 (2.34)	24.72 (2.65)	p=0.4588
Clinical factors (mean (SD))					
Age at onset in years	21.47 (17.38)	28.75 (14.63)	20.19 (15.93)	16.18 (10.69)	p=0.3079
Duration of epilepsy in years	22.33 (14.56)	11.79 (9.18)	25.12 (16.81)	21.43 (12.92)	p=0.2355
Seizure frequency per day over 3 months	0.12 (.14)	0.17 (.14)	0.14 (.15)	1.52 (4.47)	p=0.4188

Abbreviations: TLE = temporal lobe epilepsy; SD = standard deviation; MoCA = the Montreal Cognitive Assessment; HS = hippocampal sclerosis

Table 7. Demographic, cognitive, clinical parameters according to the laterality of epilepsy (right vs. left) and presence of HS (with HS vs. no brain lesions) of TLE patients, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy * presence/absence of HS				
	Right		**Left**		
	With HS	**No brain lesions**	**With HS**	**No brain lesions**	**p-values**
	n=12	n=9	n=11	n=8	
Demographic characteristics					
Age in years (mean (SD))	45.40 (13.56)	42.76 (13.33)	49.10 (8.41)	38.15 (5.95)	p=0.2028
Gender (male, %)	50.00	44.44	45.45	37.50	p=0.9591
Educational level (% lacking a high school leaving qualification)	75.00	77.78	63.64	14.29	p=0.0195
Cognitive characteristics MoCA score (from 0 to 30, mean (SD))	26.25 (2.09)	24.67 (2.55)	23.55 (1.86)	25.50 (2.51)	p=0.0523
Clinical factors (mean (SD))					
Age at onset in years	19.50 (14.50)	33.33 (16.45)	19.36 (17.93)	19.88 (11.69)	p=0.1984
Duration of epilepsy in years	25.90 (13.76)	9.42 (9.04)	29.74 (17.86)	18.27 (13.23)	p=0.0176
Seizure frequency per day over 3 months	0.10 (0.11)	0.20 (0.18)	0.15 (0.16)	0.12 (0.13)	p=0.4910

Abbreviations: TLE=temporal lobe epilepsy; HS=hippocampal sclerosis; SD=standard deviation; MoCA=the Montreal Cognitive Assessment

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Arousal in response to neutral pictures is modified in temporal lobe epilepsy

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Highlights

- Emotional experience was compared in patients with TLE and controls.
- Patients with TLE found neutral pictures to be more arousing.
- Arousal in response to neutral pictures was predicted by the level of apathy.
- Apathy was diagnosed in 58% of patients with TLE.
- Methodological aspects of future studies in patients with TLE are considered.

Abstract

The objectives of the present study were to (i) better characterize visual emotional experience in patients with temporal lobe epilepsy (TLE) patients, (ii) identify clinical risk factors that might be predictive of a change in emotional experience, and (iii) study the relationships between emotional experience and psychobehavioral/quality-of-life factors. Fifty patients with TLE and fifty matched controls evaluated the emotional content of unpleasant, pleasant and neutral pictures with respect to their valence (unpleasant-to-pleasant) and arousal (low-to-high) levels. Demographic, cognitive and psychobehavioral data were recorded for all participants and clinical data and factors related to quality of life were also collected for patients with TLE. There were no significant differences between the group with TLE and the control group in terms of valence evaluations. However, arousal scores for neutral pictures were significantly higher in patients with TLE than in controls. There was also a non-significant trend towards lower arousal scores for pleasant pictures in patients with TLE than in controls. Although none of the recorded clinical factors were found to be related to emotional experience, the level of apathy was predictive of greater arousal experience for neutral pictures in patients with TLE. In conclusion, emotional experience appears to be modified in TLE epilepsy and might be related to apathy. Changes in emotional experience should be taken into account in studies in which neutral stimuli are used to establish a baseline level when assessing emotional and cognitive processing.

Keywords: temporal lobe epilepsy, emotional experience, arousal, apathy, social cognition

1. Introduction

A growing number of studies have highlighted emotional processing disorders in patients with temporal lobe epilepsy (TLE) patients, with a current focus on the patients' ability to recognize emotional stimuli (such as emotional faces and prosodic sentences) [1,2]. However, the emotional experience of patients with TLE has been investigated much less extensively [3,4]. Nevertheless, it is important to consider this aspect because it is likely to be related to the psychological well-being and quality of life of patients with TLE. In fact, patients with TLE frequently exhibit social and psychobehavioral difficulties (such as depression often with concomitant anxiety) and poor quality of life [5–8]. Several researchers have hypothesized that social cognition disorders in patients with TLE (emotional processing and the attribution of mental states, i.e., theory of mind) are related to psychological well-being and quality of life [1,9,10]. However, social and psychobehavioral disturbances in epilepsy are often atypical and, thus, difficult to assess with conventional nosological tools [11]. This might explain the failure of two recent, large studies to find associations between self-reported depression and quality of life on the one hand, and performances in emotion recognition tasks on the other [1,9]. We have suggested that a more specific, comprehensive assessment of psychobehavioral disturbances and quality of life might be able to detect this type of association [12].

One of the most widely used methods for assessing emotional experience in healthy controls and patients with neuropsychiatric disorders involves the evaluation of emotional content (notably emotional pictures taken from the International Affective Picture System (IAPS)) [13]. Indeed, many neurophysiological and neuroimaging studies have shown that exposure to IAPS pictures induces emotions. The IAPS is based on a model in which emotions are defined according to two main dimensions: (i) valence, which is the level of pleasantness associated with an emotional experience (ranging from unpleasant to pleasant) and (ii) arousal, which indexes the intensity of an emotional experience (ranging from low to high). To the best of our knowledge, only one study (Batut et al. (2006)) has investigated emotional experience in a sample of patients with mesial TLE using the IAPS [3]. The results did not support a change in emotional experience in patients with mesial TLE (relative to controls). However, Batut et al. (2006) only evaluated picture valence. Furthermore, the pictures'

arousal levels were not controlled for in the experiment and were not evaluated by the participants. In a task requiring evaluation of fearful faces only, Labudda et al. (2014) did not find any change in arousal experience in patients with mesial TLE [4].

The primary objective of the present study was to better characterize emotional experience in patients with TLE (compared with controls), as judged by the valence and arousal in response to pictures from the IAPS. The study also investigated clinical risk factors capable of modifying emotional experience, and assessed the relationships between emotional experience and psychobehavioral/quality-of-life factors.

2. Material and methods

2.1. Participants

The data presented here were collected as part of a larger study of social cognition disorders in patients with TLE [12]. The study protocol had been approved by the local investigational review board (CPP Nord Ouest IV, Lille, France; reference: 2012-A00339-34).

Fifty patients with TLE seen in consultation at Lille University Medical Center's Epilepsy Unit (Lille, France) were consecutively recruited on the basis of clinical evaluation, electroencephalographic monitoring (an interictal EEG record and an ictal video/EEG record), neuropsychological data and neuroimaging results. The inclusion criteria were as follows: (i) unilateral TLE, and (ii) right-handedness (according to the Edinburgh Handedness Inventory) [14]. The exclusion criteria were as follows: (i) impaired intellectual capacity (an intellectual quotient below 75, according to a French adaptation of the National Adult Reading Test: fNART) [15] or non-verbal reasoning (according to Raven's Coloured Progressive Matrices: PM-47) [16]; (ii) significant amnesia or a marked impairment of instrumental capacities (agnosia, aphasia, apraxia, alexia, or agraphia); (iii) a history of neurological disease other than epilepsy; (iv) a history of psychiatric disease (other than depression or anxiety disorders); and (v) a seizure in the 24 h preceding the experimental session.

The control group included 50 right-handed participants (according to the Edinburgh Handedness Inventory), each of whom was matched for demographic characteristics (age, gender and

educational level) with a patient with TLE. The exclusion criteria for controls were as follows: (i) impaired intellectual capacity (an intellectual quotient below 75, according to the fNART) or non-verbal reasoning (according to the PM-47), and (ii) a history of neurological or psychiatric disease.

The patients with TLE and controls underwent the Montreal Cognitive Assessment (MoCA) [17], which assesses a number of cognitive domains (attention, executive function, memory, language, visuoconstruction skills, conceptual thinking, calculation, and orientation).

The clinical characteristics of patients with TLE were recorded, as follows: the presence of febrile seizures, age of the first seizure, age at onset of epilepsy, duration of epilepsy, seizure frequency, laterality of epilepsy (right, left), type of epilepsy (mesial, lateral) and the presence of hippocampal sclerosis (HS; classified as "with HS", "with no brain lesions" or "with other lesions"). The presence of HS was established from structural neuroimaging results (3 Tesla MRI datasets). The diagnostic criteria for HS included a volume decrease on T1-weighted images and high signal intensity in fluid-attenuated inversion recovery images.

In patients with TLE and controls, self-reporting was used to estimate psychobehavioral disturbances such as: (i) depression (according to the Beck Depression Inventory (BDI)) [18] and anxiety (according to the State-Trait Anxiety Inventory (STAI)) [19]; (ii) disturbances of affective regulation commonly associated with mood disorders, such as apathy (according to the Lille Apathy Rating Scale (LARS)) [20], alexithymia (according to the Toronto Alexithymia Scale (TAS)) [21,22], and anhedonia (according to the Physical Anhedonia Scale (PAS) and Social Anhedonia Scale (SAS)) [23]; for all the above-mentioned instruments, the higher the score, the more intense the psychobehavioral factor; (iii) positive and negative affective states experienced (according to the Positive and Negative Affect Schedule (PANAS)) [24]; and (iv) impaired empathy (according to the Interpersonal Reactivity Index (IRI)) [25]; the higher the score, the more intense the positive or negative affectivity and empathy. In patients with TLE, quality of life was also estimated (according to the Quality of Life Inventory in Epilepsy (QOLIE-89)) [26]. We calculated the overall score and the social sub-scores for role limitations-emotional, emotional well-being, social support, social isolation, and work/driving/social function; the higher the score, the better the quality of life.

Demographic, cognitive and psychobehavioral characteristics of patients with TLE and controls, and clinical characteristics of patients with TLE are presented in Table 1.

Table 1. Characterization of patients with TLE and the statistical significance of intergroup comparisons (p-values)

	Controls n = 50	**Patients with TLE** n = 50	**p-values**
Demographic characteristics			
Age in years (median; mean±SD)	41.37; 42.81±12.46	42.10; 42.40±11.82	p=.8660
Gender (% male)	46.00	46.00	p=1.00
Educational level (≥ 12 years %)	42.00	42.00	p=1.00
Cognitive characteristics			
MoCA score (from 0 to 30, median; mean±SD)	28.00; 28.22±1.31	25.00; 25.12±2.43	p<.0001
Clinical factors			
Presence of febrile seizures (with febrile seizures %)		26.00	
Age at the first seizure in years (median; mean±SD)		12.00; 16.17±15.54	
Age of onset in years (median; mean±SD)		18.00; 21.06±15.27	
Duration of epilepsy in years (median; mean±SD)		18.06; 21.34±14.59	
Seizure frequency per day over 3 months (median; mean±SD)		0.10; 0.44±2.12	
Laterality (right/left %)		46.00/54.00	
Type (mesial/lateral %)		62.00/38.00	
Presence of HS (with HS/with no brain lesions/with other lesions %)		46.00/34.00/20.00	
Psychobehavioral scores			
BDI score (from 0 to 63)	2.50; 4.88±6.31	13.50; 15.06±10.18	p<.0001
STAI score (from 20 to 80)			
state	25.50; 29.62±10.08	40.00; 40.00±11.72	p=.0036
trait	34.00; 34.32±8.13	47.00; 47.32±10.24	p<.0001
LARS score (from -36 to +36)	-31.00; -29.70±4.56	-20.00; -20.12±7.84	p<.0001
TAS-20 score (from 20 to 100)	40.00; 43.06±11.93	55.00; 54.86±11.79	p<.0001
PAS score (from 0 to 61)	13.50; 14.44±7.69	22.00; 21.54±8.20	p=.0131
SAS score (from 0 to 41)	9.00; 9.38±5.49	15.00; 14.26±6.38	p=.0002
PANAS score (from 10 to 50)			
positive affectivity	37.00; 36.76±5.27	30.00; 29.70±6.65	p<.0001
negative affectivity	20.00; 20.36±6.68	24.50; 25.32±6.97	p=.0122
IRI (from 0 to 120)	71.00; 69.16±12.59	63.00; 63.54±11.02	p=.1140
cognitive sub-score (out of 60)	34.50; 33.76±8.14	28.50; 28.38±6.48	p=.0088
affective sub-score (out of 60)	37.00; 35.40±7.15	35.00; 35.16±7.02	p=.9108
Quality-of-life scores (QOLIE-89)			
Overall score (from 0 to 100)		61.59; 60.54±13.41	
Social sub-scores (from 0 to 100)			
role limitations-emotional		88.00; 66.40±34.86	
emotional well-being		60.00; 57.20±19.01	
social support		60.00; 57.40±14.99	
social isolation		80.00; 70.00±20.20	
work/driving/social function		62.27; 55.95±19.96	

Abbreviations: TLE = temporal lobe epilepsy; SD = standard deviation; MoCA = Montreal Cognitive Assessment; HS = hippocampal sclerosis; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; LARS = Lille Apathy Rating Scale; TAS-20 = Toronto Alexithymia Scale; PAS = Physical Anhedonia Scale; SAS = Social Anhedonia Scales; PANAS = Positive and Negative Affect Schedule; IRI = Interpersonal Reactivity Index; QOLIE-89 = Quality of Life Inventory in Epilepsy-89

2.2. Assessment of emotional experience

Stimuli: 60 pictures of animals, landscapes and objects (including representations of people in context, body parts and whole bodies) were selected from the IAPS [13] (20 unpleasant pictures, 20 pleasant pictures and 20 neutral pictures) (Supplementary data - Supplementary material). For ethical reasons and in order to avoid possible ceiling effects in evaluations of emotional content, pictures featuring physical violence or sexual scenes were not selected. As in previous studies of controls [27] and patients with epilepsy [28], we controlled for the emotional parameters of the selected pictures. Indeed, standardized IAPS ratings for valence and arousal were compared in a contrast analysis (Supplementary data - Table 2). Unpleasant and pleasant pictures differed in terms of valence, and had higher arousal ratings than neutral pictures (all $p<.0001$). Again in terms of valence, neutral pictures were considered to be more pleasant than unpleasant pictures and more unpleasant that pleasant pictures (all $p<.0001$). The pictures were presented centrally (with a horizontal visual angle of 12° and a vertical visual angle of 8°) on a black background. Pictures were homogenized (using Image J Software, http://imagej.nih.gov/ij/) in terms of their major physical characteristics (luminance, spatial frequencies and color saturation levels).

The test procedure: using a computerized interface, each picture was presented (one at a time) for 500 ms in pseudorandom order (i.e. no more than two pictures of a particular valence were presented successively). After the presentation of each picture, the participants were instructed to evaluate the emotional content on a valence scale (ranging from 0, very unpleasant, to 9, very pleasant) and on an arousal scale (ranging from 0, very calm, to 9, very arousing). The participants were told to respond as quickly as possible and were not given any feedback on their performance levels.

2.3. Data analysis

All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA). The threshold for statistical significance was set to $p<.05$. Parametric tests were used for normally distributed datasets; otherwise, non-parametric tests were applied. Scores are reported as the median and mean ± standard deviation.

Controls and patients with TLE were compared in terms of their demographic characteristics (age, gender, and educational level) and cognitive characteristics (the MoCA score). Patients with TLE were then classified according to the laterality of epilepsy (right, left) and compared in terms of their demographic, cognitive and clinical parameters: the presence of febrile seizures, age of the first seizure, age of onset, duration of epilepsy, seizure frequency, type of epilepsy and the presence of hippocampal sclerosis (HS). The same approach was applied to compare patients with TLE as a function of the type of epilepsy (mesial, lateral), both the laterality and the presence of HS (right-with HS, right-with no brain lesions, left-with HS, left-with no brain lesions), and both the laterality and the type of epilepsy (right-lateral, right-mesial, left-lateral, left-mesial). Variables that differed significantly between groups were considered as adjustment variables in subsequent analyses and Bonferroni corrections for multiple comparisons were applied.

The respective emotional experiences of controls and patients with TLE were compared using a mixed model with *subject* as a random effect. Effect sizes were estimated. The modified emotional experience scores in patients with TLE (relative to controls) were analyzed against the patients' clinical characteristics (age of the first seizure, age of onset, duration of epilepsy, seizure frequency) in correlation analyses. Patients with TLE with or without febrile seizures were compared in terms of the modified emotional experiences scores. Effects of the laterality of epilepsy, the type of epilepsy, both the laterality of epilepsy and the presence of HS, or the type of epilepsy on emotional experience scores were also tested, using mixed models with *subject* as a random effect. The modified emotional experience scores in patients with TLE were then analyzed against the psychobehavioral and quality-of-life factors in bivariate correlation analyses. Variables with a p-value below .20 were selected for a linear regression analysis.

3. Results

3.1. Characteristics of the patients with TLE

The mean MoCA score in the patient group was lower than that in the control group (Table 1). There was a group effect of laterality and the presence of HS on educational level, the MoCA score, the presence of febrile seizures, the age at the first seizure, and the duration of epilepsy (Supplementary data - Table 3). The laterality and the type of epilepsy (considered independently or in combination) did not have a group effect on demographic, cognitive or clinical parameters.

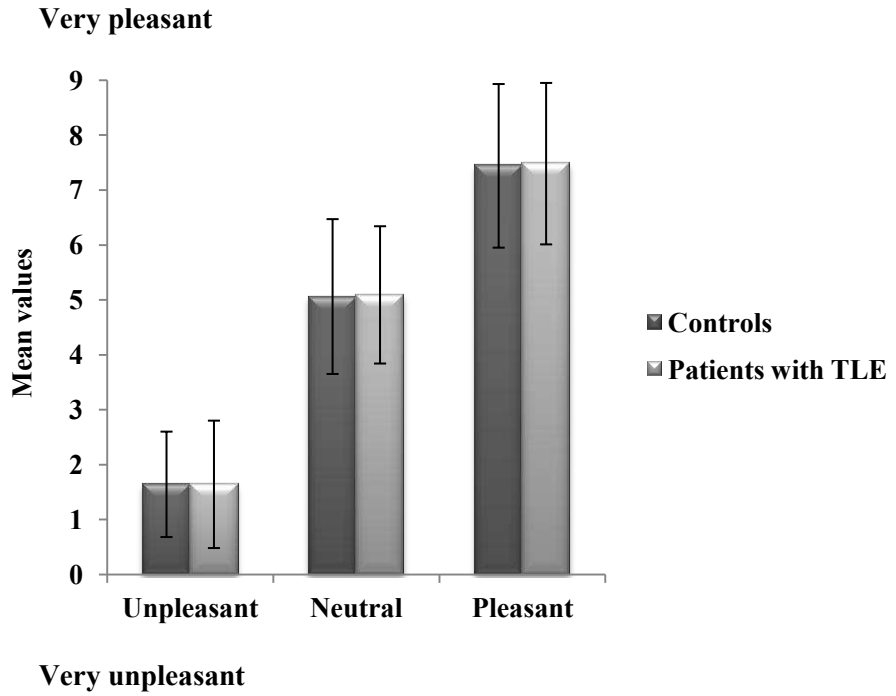
3.2. Emotional experience and clinical correlates in patients with TLE (Figure 1)

For valence scores, there was a main effect of *condition* ($F(2, 293)=1769.22$, $p<.0001$). In both the patient group and the control group, the valence score was higher for pleasant pictures than for neutral pictures ($t(293)=-24.24$, $p<.0001$), and higher for neutral pictures than for unpleasant pictures ($t(293)=-34.92$, $p<.0001$). However, no significant *group* x *condition* interaction emerged ($F(2, 293)=.02$, $p=.9783$) and there was no significant main effect of *group* ($F(1, 293)=.11$, $p=.7446$).

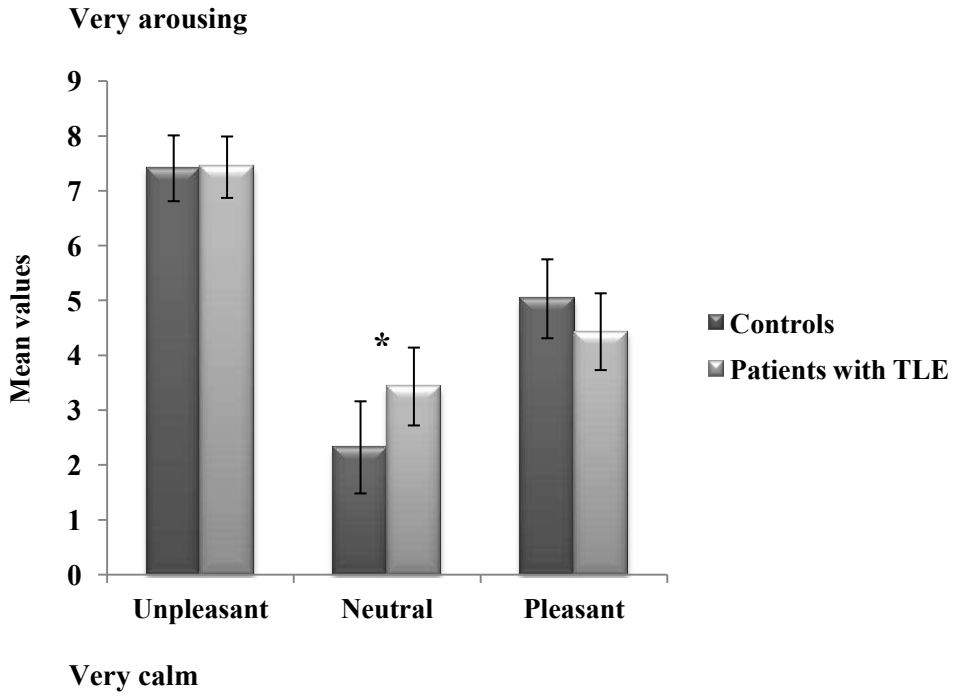
Thus, the valence scores in patients with TLE and controls did not differ significantly for unpleasant pictures (1.53; 1.64±.56, and 1.50; 1.64±.60, respectively), neutral pictures (5.03; 5.09±.71, and 5.00; 5.06±.84, respectively) or pleasant pictures (7.73; 7.48±.70, and 7.40; 7.44±.72, respectively).

Figure 1. Mean values and standard deviations (bars) in controls and patients with TLE for (A) valence scores and (B) arousal scores as a function of the type of picture presented (unpleasant, neutral, or pleasant)

A. Valence scores



B. Arousal scores



Abbreviations: TLE = temporal lobe epilepsy; * = significance of the intergroup comparison ($p<.0001$).

For arousal scores, there was a main effect of *condition* ($F(2, 293)=305.49$, $p<.0001$). In both the patient group and the control group, the arousal score was higher for pleasant pictures than for neutral pictures ($t(293)=-10.04$, $p<.0001$), and higher for unpleasant pictures than for neutral pictures ($t(293)=24.58$, $p<.0001$). A significant *group* x *condition* interaction also emerged ($F(2, 293)=10.93$, $p<.0001$). *Post-hoc* analysis indicated that the arousal scores in patients with TLE and controls did not differ significantly for unpleasant pictures (7.70; 7.43±1.16 and 7.63; 7.41±.96, respectively; $t(293)=-.40$, $p=.6885$). However, the arousal score was higher in patients with TLE than in controls for neutral pictures (3.28; 3.43±1.25 and 1.90; 2.32±1.41, respectively; $t(293)=-4.16$, $p<.0001$, $\eta 2=.1486$). Furthermore, the arousal score tended to be lower in patients with TLE than in controls for pleasant pictures (4.43; 4.43±1.47 and 4.98; 5.03±1.49, respectively; $t(293)=1.77$, $p=.0777$, $\eta 2=.0406$). The arousal scores did not appear to correlate with clinical characteristics.

3.3. Emotional experience and psychobehavioral or quality-of-life disturbances in patients with TLE

Relative to controls, patients with TLE had higher scores for depression (according to the BDI), anxiety (STAI), apathy (LARS), alexithymia (TAS-20), physical anhedonia (PAS), social anhedonia (SAS), and negative affectivity (PANAS), and lower scores for positive affectivity (PANAS), and cognitive empathy abilities (the IRI cognitive sub-score) (Table 1). In patients with TLE, only apathy was positively correlated with (and predictive of) the arousal score for neutral pictures ($r^2=.0824$, $p=.0433$). In patients with TLE, 58% were identified as apathetic (with a cut-off score of the LARS to 21). When compared with non-apathetic patients with TLE, apathetic patients with TLE had greater arousal scores for neutral pictures (2.85; 3.02±1.20 and 4.10; 3.73±1.22, respectively; $p=.0345$). Apathetic and non-apathetic patients with TLE did not differ in terms of demographic, cognitive, or clinical characteristics. None of the quality-of-life factors were correlated with the arousal score for neutral pictures. Multivariable regression analyses were not performed, since only apathy was associated with the arousal score for neutral pictures ($p>.20$ for all others psychobehavioral and quality-of-life factors). Furthermore, the valence score in patients with TLE was not found to be predictive of the arousal score for neutral pictures ($r^2=.0008$, $p=.8429$).

4. Discussion

The objectives of the present study were to (i) better characterize visual emotional experience in patients with TLE (with respect to valence and arousal levels), (ii) identify clinical risk factors that might be predictive of a change in emotional experience, and (iii) study the relationships between emotional experience and psychobehavioral/quality-of-life factors.

We found that controls and patients with TLE did not differ significantly in terms of the valence of emotional experience. Batut et al. (2006) reported very similar results in a study of a smaller sample of patients with mesial TLE and using the same type of material [3]. Thus, the present study confirms the findings of Batut et al. (2006) and extends them to a larger population of patients with TLE. However, Batut et al. (2006) did not explore emotional arousal in patients with mesial TLE [3]. By using fearful faces as stimuli, Labudda et al. (2014) suggested that emotional experience of arousal was likely to be unchanged in patients with mesial TLE (relative to controls) [4]. The present study partly confirms the latter finding with another type of material and in a larger population of patients with TLE. Indeed, patients with TLE and controls did not differ significantly in terms of arousal when exposed to unpleasant pictures. Nevertheless, arousal experience might be modified in patients with TLE (compared with controls) for other categories of emotional stimuli. Indeed, our findings suggest that the neutral pictures are significantly more arousing in patients with TLE than in controls. We also observed a non-significant trend towards lower arousal scores for pleasant pictures in patients with TLE than in controls.

It is noteworthy that none of the recorded clinical factors were significantly predictive of changes in arousal experience in patients with TLE. Thus, all patients with TLE appear to be at risk of changes in emotional experiences. Nevertheless, a lack of statistical power in the present study cannot be completely ruled out. Furthermore, other clinical parameters (such as the frequency and location of interictal abnormalities, and the length and severity of seizures) may be involved in the disruption of the emotional processing network and, thus, merit further investigations (for a review, see [29]). However, changes in arousal experience (such as a greater baseline level of arousal in response to neutral pictures) appeared to be related to apathy levels in patients with TLE. Apathy is characterized

by decreased motivation, which may translate into reduced goal-directed behavior, cognition or emotion [30]. The present study is the first to find that apathy is present in a large proportion of patients with TLE (since 58% met the diagnostic criteria for this condition) and that apathy might be related to changes in emotional processing. This relationship suggests that patients with TLE (especially those with high levels of apathy) have emotional biases, which result in changes in arousal experience. Indeed, this emotional processing disorder might be more obvious when the stimuli are more difficult to evaluate in terms of emotional content (as might be the case for neutral pictures). Nevertheless, it should be noted that the relationship between arousal experience and apathy levels was relatively weak (accounting for 8% of the variance), despite its statistically significance. Hence, further investigations of this relationship (such as determination of its neurophysiological markers) are required. Lastly, it may be necessary to characterize apathy in patients with TLE in more detail.

Changes in emotional experience (relative to controls) have been evidenced in patients with TLE having undergone medial temporal lobe resection [31,32]. Indeed, these recent studies observed that patients with TLE had a lower valence experience for neutral and negative emotional faces on the one hand, and negative emotional bursts on the other. The patients with TLE also had a less intense arousal experience for neutral and negative emotional faces. One can therefore hypothesize that emotional experience (valence and arousal levels) varies after medial temporal lobe resection in patients with TLE. Nevertheless, an effect of the type of test material on emotional experience cannot be ruled out. A longitudinal study of emotional experience of several types of material (such as IAPS pictures, faces and bursts) in pre- and postsurgery patients with TLE might be able to shed light on this issue.

Another important implication of the present study concerns methodological aspects of future studies of emotional and cognitive processing in patients with TLE. Indeed, neutral stimuli are frequently used as a control for emotional conditions (e.g. to establish baseline levels). For example, brain activation and behavioral performances in response to emotional stimuli (relative to neutral stimuli) are explored in fearful face and emotional memory paradigms [33,34]. In particular, activation of the amygdala is related to arousal experience and is frequently considered to be involved in emotional effects [35]. Thus, the arousal level of neutral stimuli (in addition to the valence) should be

controlled for in future research; this will ensure that the neutral stimuli are truly experienced as neutral by patients with TLE. Another interesting perspective would be to study the changes in autonomic activity associated with emotional experience (particularly the skin conductance response, which is reportedly a reliable neurophysiological marker of the arousal experience) [27,35].

5. Conclusions

The emotional experience of arousal by neutral pictures appears to be modified in patients with TLE and might be associated with apathy. In future research on emotional and cognitive processing, this change in arousal experience should be taken into account when neutral stimuli are used to establish a baseline level.

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Disclosure of Conflicts of Interest

None.

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Supplementary data

Supplementary material: IAPS identification numbers for selected pictures

Unpleasant pictures: 1052, 1220, 1275, 1525, 2692, 6241, 7359, 9120, 9180, 9280, 9330, 9342, 9417, 9470, 9471, 9495, 9621, 9622, 9630, 9912

Neutral pictures: 5534, 6150, 7000, 7002, 7004, 7006, 7009, 7020, 7034, 7035, 7036, 7041, 7050, 7090, 7100, 7170, 7233, 7038, 7040, 7235

Pleasant pictures: 1540, 1810, 1720, 1722, 1731, 5450, 5626, 5628, 5629, 5849, 5890, 7220, 7260, 7350, 7470, 7570, 8162, 8500, 8503, 8531

Table 2. Theoretical valence and arousal ratings (median; mean±SD) for selected pictures

Type of picture	Valence	Arousal
Unpleasant	3.16; 3.16±.22	5.20; 5.26±.72
Neutral	4.94; 4.98±.15	2.80; 2.79±.37
Pleasant	6.99; 6.92±.21	5.22; 5.22±.55

Abbreviations: SD=standard deviation

Table 3. Differences in demographic, cognitive and clinical parameters according to the laterality of epilepsy and the presence of HS in patients with TLE, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy * presence of HS				**p-values**
	Right		**Left**		
	With HS n=12	**With no brain lesions** n=9	**With HS** n=11	**With no brain lesions** n=8	
Educational level (% lacking a high school leaving qualification)	75.00	77.78	63.64	14.29	p=.0195
MoCA score (from 0 to 30, median; mean±SD)	26.50; 26.25±2.09	24; 24.67±2.55	23; 23.55±1.86	25.50; 25.50±2.51	p=.0523
Presence of febrile seizures (with febrile seizures %)	50.00	11.11	45.45	0	p=.0368
Age of the first seizure in years (median; mean±SD)	3.13; 8.55±10.69	33.00; 29.74±19.73	20.50; 19.88±11.69	3.00;12.64±16.65	p=.0271
Duration of epilepsy in years (median; mean±SD)	24.31; 25.90±13.76	4.65; 9.42±9.04	32.44; 29.74±17.86	17.12; 18.27±13.23	p=.0176

Abbreviations: TLE=temporal lobe epilepsy; HS=hippocampal sclerosis; SD=standard deviation; MoCA=the Montreal Cognitive Assessment

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Characterization and prediction of theory of mind disorders in temporal lobe epilepsy

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Abstract

Objective: Patients with temporal lobe epilepsy (TLE) have impaired theory of mind (ToM). However, ToM involves a variety of processes, such as understanding a person's intentions and beliefs ("cognitive" ToM) and emotional states ("affective" ToM). The objectives of the present study were to characterize ToM disorders in TLE patients, identify patients at risk of ToM disorders, and study the relationships between psychobehavioral and quality of life factors and ToM disorders.

Method: Fifty TLE patients and 50 controls performed ToM tasks assessing their understanding of verbal clumsiness (faux pas), sarcastic remarks and mentalistic actions. Demographic, cognitive, psychobehavioral data and (for TLE patients) clinical and quality of life factors were recorded.

Results: Compared with controls, TLE patients showed impairments in all ToM tasks: 84% misunderstood faux pas, around 50% misunderstood sarcasm. A long duration of epilepsy and young age at onset were risk factors for ToM impairments. In TLE patients, ToM impairments were associated with impaired empathy and anhedonia. Their affective states were less positively and more negatively valenced than in controls. Low positive affectivity was predictive of greater cognitive and affective ToM impairments for the faux pas task, high negative affectivity was predictive of greater cognitive ToM abilities for the sarcasm task. The lack of social support was correlated with impaired ToM but was not a predictive factor.

Conclusions: Both cognitive and affective ToM processes are impaired in TLE patients. Impaired ToM has an impact on empathy abilities and is related to affective disturbances in TLE patients.

Keywords: temporal lobe epilepsy, theory of mind, empathy, anhedonia, affective states

Introduction

Theory of mind (ToM) refers to the ability to attribute mental states and thus explain and predict another person's behavior (Adolphs, 2001). As part of the social cognition process, ToM is a prerequisite for employing appropriate social skills. Theory of mind abilities involve several multidimensional processes, including the ability to understand another person's intentions and beliefs ("cognitive" ToM) and emotional states ("affective" ToM) (Abu-Akel & Shamay-Tsoory, 2011). Whereas the recognition and understanding of verbal clumsiness ("faux pas") involve both cognitive and affective ToM processes, the ability to understand sarcasm or mentalistic actions depends mainly on cognitive ToM processes (Stone, Baron-Cohen, & Knight, 1998; Channon, Pellijeff, & Rule, 2005; Channon et al., 2007). It is known that ToM impairments are involved in the psychobehavioral symptoms of several neuropsychiatric disorders (Kennedy & Adolphs, 2012).

Psychobehavioral and social difficulties are prevalent in patients with temporal lobe epilepsy (TLE) (Lin, Mula, & Hermann, 2012; Quintas et al., 2012). Furthermore, psychobehavioral disturbances in epileptic patients - particularly in terms of mood, depression and anxiety - contribute significantly to poor quality of life and a poor response to pharmacological or surgical treatments (Kanner, 2009; Kanner et al., 2012). A growing number of studies have highlighted the presence of ToM impairments in TLE (Broicher et al., 2012; Giovagnoli et al., 2011; Giovagnoli, Parente, Villani, Franceschetti, & Spreafico, 2013; Li et al., 2013; Schacher et al., 2006). Several demographic, clinical, and cognitive characteristics may be associated with these ToM impairments: educational level, laterality, gender, age at onset, disease duration, cognitive function and the presence of hippocampal sclerosis (HS). However, the importance of these potential risk factors for ToM impairment is subject to debate and requires further investigation. In a study of patients with frontal lobe epilepsy or TLE, Giovagnoli et al. (2013) found a link between poor subjective perception of cognitive abilities, strategies for coping with stressful events, quality of life perception and ToM impairments (as evaluated with a task based on the recognition and understanding of faux pas situations) (Giovagnoli et al., 2013). However, the researchers did not find any relationships between ToM impairments and depression or anxiety, which was also the case in Broicher et al.'s study of TLE patients (Broicher et al., 2012). According to Giovagnoli et al. (2013) and Broicher et al. (2012), high-order cognitive

abilities may be distinct from mood. However, these findings could also reflect the complexity of mood disturbances in epilepsy, which are often atypical and difficult to assess with classical nosological tools (Krishnamoorthy, Trimble, & Blumer, 2007). More specific assessment of the symptoms of affective dysregulation (e.g. anhedonia, apathy, and alexithymia) and more comprehensive assessment of the frequency of positive and negative affective states might make it possible to detect associations more reliably.

Thus, the objectives of the present study were to (a) better define ToM impairments in TLE patients (relative to controls), (b) identify patients at risk of ToM impairments and (c) study the relationships between ToM impairments on one hand and psychobehavioral disturbances (with a focus on affective disturbances) and quality of life factors on the other.

Methods

Participants

Fifty TLE patients consulting at Lille University Medical Center's Epilepsy Unit (Lille, France) were consecutively recruited on the basis of clinical evaluation, electroencephalographic monitoring, neuropsychological data and neuroimaging results. The inclusion criteria were unilateral TLE and right-handedness (according to the Edinburgh Handedness Inventory) (Oldfield, 1971). The exclusion criteria were: (a) impaired intellectual capacity (an intellectual quotient below 75, according to a French adaptation of the National Adult Reading Test: fNART) (Mackinnon & Mulligan, 2005) or non-verbal reasoning (according to Raven's Coloured Progressive Matrices: PM-47) (Raven, 1965); (b) significant amnesia or a marked impairment of instrumental capacities (agnosia, aphasia, apraxia, alexia, or agraphia); (c) a history of neurological disease other than epilepsy; (d) a history of psychiatric disease (other than depression or anxiety disorders, considering that these are frequently comorbidities in TLE); (e) a seizure in the 24 hours preceding the experimental session.

The control group included 50 right-handed participants (according to the Edinburgh Handedness Inventory), each of whom was matched for age, gender and educational level with a TLE patient. The exclusion criteria for controls were (a) impaired intellectual capacity (an intellectual

quotient below 75 in the fNART) or non-verbal reasoning (according to the PM-47) and (b) a history of neurological or psychiatric disease.

The study was performed in accordance with the tenets of the Declaration of Helsinki (World Medical Association, 2013), and the study protocol had been approved by the local investigational review board (*CPP Nord Ouest IV*, Lille, France; reference: 2012-A00339-34). All participants gave their written, informed consent to participation in the study.

Theory of mind assessment

We investigated the participants' ToM abilities by administering three tasks that had previously been validated in French populations.

The faux pas task (Stone et al., 1998) involves detecting and understanding 10 social faux pas within a series of 20 stories (i.e. 10 stories with a faux pas and 10 without). After each story, the participant has to state whether a faux pas (verbal clumsiness) was present in the story, in response to the question "Did anyone say something they shouldn't have said or something awkward?". For the stories without a faux pas, two points are awarded if the story was correctly classified (the "non-faux pas rejection" score, from 0 to 20). For the stories with a faux pas, one point is awarded for each story in which verbal clumsiness was correctly attributed (the "faux pas recognition" score, from 0 to 10). If a faux pas is correctly recognized, understanding of this situation is then assessed via five questions, which test the participant's capacity to infer the mental state of the person making the faux pas and that of the victim of the faux pas. One point is attributed for each correct answer and a score (from 0 to 10) is calculated for each question: (a) "Who said something they shouldn't have said or something awkward?" ("identification"), (b) "Why shouldn't X have said it or why was it awkward?" ("explanation-1"), (c) "Why do you think X said it?" ("explanation-2"), (d) "Did X know that Y...?" ("non-intentionality"), and (e) "How do you think Y felt?" ("appropriate feeling"). Consequently, an overall faux pas score (from 0 to 60) was calculated for the stories with faux pas. Furthermore, the identification, explanation-1, explanation-2, non-intentionality, and appropriate feeling scores are expressed as percentages of the faux pas recognition score. Regardless of whether a story contains a

faux pas or not, two control questions are asked at the end of the questionnaire (to check comprehension).

The comprehension of sarcasm task (Channon et al., 2007, 2005) consists in brief scenarios describing a social context, each of which ends with a sarcastic remark or a sincere remark by one of the characters. The sarcastic remarks can be direct (i.e. they can be understood by reversal of the direct meaning) or indirect (i.e. they are indirectly related to the reversed meaning but cannot be understood by direct reversal). To interpret sarcastic remarks, it is necessary to take into account the protagonist's intentions and beliefs. The sincere remarks serve as controls and appear when the scenario's social context is congruent with the direct meaning. Eighteen scenarios (six with each type of remark) are presented. The participant is asked to explain verbally what the character meant by their remark ("open question" scores ranging from 0 to 12 for each type of remark, with 2 points per scenario). Lastly, the participant is presented with four interpretations and asked to state which is correct ("multiple choice" scores ranging from 0 to 6 for each type of remark, with 1 point per scenario).

The comprehension of action task (Channon et al., 2007, 2005) has the same presentation and scoring as the comprehension of sarcasm task. It consists of brief scenarios describing a social context that end with a mentalistic or physical action. To interpret mentalistic actions (but not physical actions), it is necessary to take account of the protagonist's mental state. The physical actions correspond to control situations.

Cognitive assessment

All the participants underwent the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), which assesses a number of cognitive domains (attention, executive functions, memory, language, visuoconstruction skills, conceptual thinking, calculation, and orientation).

Psychobehavioral assessment

On the basis of self-reports, we estimated: (a) depression (according to the Beck Depression Inventory: BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and anxiety (according to the State-Trait Anxiety Inventory: STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); (b) disturbances of affective regulation commonly associated with mood disorders, such as apathy (according to the Lille Apathy Rating Scale: LARS) (Sockeel et al., 2006), alexithymia (according to the Toronto Alexithymia Scale: TAS-20) (Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994), anhedonia (according to the Physical Anhedonia Scale: PAS, and Social Anhedonia Scale: SAS) (Chapman, Chapman, & Raulin, 1976); (c) the frequency with which the participant experienced positively or negatively valenced affective states (according to the Positive and Negative Affect Schedule: PANAS) (Watson, Clark, & Tellegen, 1988); and (d) empathy abilities, which are related to ToM abilities (Interpersonal Reactivity Index: IRI) (Davis, 1983); the higher score, the more intense the positive or negative affectivity and empathy. For (a) and (b) instruments, higher scores correspond to more intense psychobehavioral factors. For (c) and (d) instruments, the higher the score, the more intense the positive or negative affectivity and empathy.

Quality of life assessment

The Quality of Life Inventory in Epilepsy-89 (QOLIE-89) (Devinsky et al., 1995) was also administered. We calculated the overall score and the sub-scores for role limitations-emotional, emotional well-being, social support, social isolation, and work/driving/social function were calculated; the higher the score, the better the quality of life.

Data analysis

All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC). The threshold for statistical significance was set to $p<0.05$. Parametric tests were used for normally distributed datasets. If the latter condition was not met, non-parametric tests were applied.

Patients with TLE and controls were compared in terms of their demographic characteristics (age, gender, and number of years of full-time education) and cognitive characteristics (the MoCA score). Next, the data for TLE patients were analyzed as a function of the laterality of epilepsy (right or left). The two laterality subgroups were compared in terms of demographic, cognitive and clinical parameters (age at onset, duration of epilepsy, type of epilepsy, seizure frequency, and the presence of HS).

Patients with TLE were then classified into four subgroups according to the laterality and type of epilepsy (right-lateral, right-mesial, left-lateral, and left-mesial) and compared as a function of their demographic, cognitive and clinical parameters. The same approach was applied to the analysis of TLE patients as a function of the laterality of epilepsy and the presence of HS (right with HS, right with no brain lesions, left with HS, and left with no brain lesions).

Variables that differed significantly between groups were considered as adjustment variables in the analyses on ToM and psychobehavioral scores.

The TLE patients' and controls' respective performances in ToM tasks were compared using logistic regression and adjusted in a univariate analysis. The model's accuracy was measured as the area under the receiver operating characteristic curve (AUC).

For each discriminant ToM score, the percentages of patients with an impairment were calculated with Crawford's test. The most discriminant ToM scores were analyzed against the TLE patients' clinical characteristics, psychobehavioral scores and quality of life factors. Controls and TLE patients were compared in terms of their psychobehavioral symptoms. Variables with a p-value below 0.20 in the univariate analysis were selected for multivariate stepwise linear regression analysis.

Results

Demographic, cognitive and clinical characteristics of the TLE patients

The TLE patients did not differ significantly from controls in terms of their demographic characteristics. The mean MoCA score was lower in the patient group than in the control group. The TLE was mesial in 31 patients (15 right side and 16 left side) and lateral in 19 patients (8 right side and 11 left side) (Table 1). Magnetic resonance imaging (MRI) revealed unilateral lesions in 33 patients (14 right side and 19 left side). Hippocampal sclerosis was identified in 23 of these patients (12 right side and 11 left side). Right and left TLE patients did not differ significantly in terms of demographic, cognitive and clinical parameters (Supplementary data - Table 4). The laterality and the type of epilepsy did not have a group effect on demographic, cognitive or clinical parameters (Supplementary data - Table 5). However, there was group effect of laterality and presence of HS on educational level, the MoCA score, and the duration of epilepsy (Supplementary data - Table 6).

Table 1. Demographic and cognitive characteristics of controls and TLE patients, clinical factors for TLE patients and the statistical significance (p-values) of intergroup comparisons

	Controls n=50	**TLE patients** n=50	**p-values**
Demographic characteristics			
Age in years (median; mean (SD))	41.37; 42.81 (12.46)	42.10; 42.40 (11.82)	p=0.8660
Gender (male, %)	46.00	46.00	p=1.00
Educational level in years of full-time education (%)			
< 9	10.00	10.00	p=1.00
9 - 10	34.00	34.00	p=1.00
10 - 12	14.00	14.00	p=1.00
≥ 12	42.00	42.00	p=1.00
Cognitive characteristics			
MoCA score (from 0 to 30, median; mean (SD))	28.00; 28.22 (1.31)	25.00; 25.12 (2.43)	p<0.0001
Clinical factors			
Age at onset in years (median; mean (SD))		18.00; 21.06 (15.27)	
Duration of epilepsy in years (median; mean (SD))		18.06; 21.34 (14.59)	
Seizure frequency per day over 3 months (median; mean (SD))		0.10; 0.44 (2.12)	
TLE laterality (right %)		46.00	
Type (mesial %)		62.00	
MRI scan (%)			
With HS		46.00	
No brain lesions		34.00	
Other lesions		20.00	

Abbreviations: TLE=temporal lobe epilepsy; SD=standard deviation; MRI=magnetic resonance imaging; HS=hippocampal sclerosis

ToM performances in TLE patients

Of the various ToM scores, only the faux pas identification score was normal in TLE patients (relative to controls) (Table 2). The overall faux pas score (AUC: 0.93) and the open question scores for direct and indirect sarcastic remarks (AUC: 0.81 and 0.85, respectively) discriminated between TLE patients and controls: 84% of TLE patients were impaired for the overall faux pas score (cut-off value according to Crawford's method=54; p=0.0322), 52% were impaired for the open question score for direct sarcastic remarks (cut-off value: 10; p=0.0075), and 46% were impaired for the open question score for indirect sarcastic remarks (cut-off value: 9; p=0.0046). Twenty-six percent of TLE patients were impaired in three tasks and only 6% were not impaired in any of them. For TLE patients with impairment for the overall faux pas score, 45.24% were not impaired for the open question score for direct sarcastic remarks, 52.38% were not impaired for the open question score for indirect sarcastic remarks, and 28.57% were not impaired for the open question on direct and indirect sarcastic remarks. For TLE patients with no impairment for the overall faux pas score, 37.50% were not impaired for the open question score for direct sarcastic remarks and 62.50% were not impaired for the open question score for indirect sarcastic remarks.

Table 2. Scores in ToM tasks for controls and TLE patients (median; mean (SD)), and the statistical significance (p-values) of intergroup comparisons

	Controls median; mean (SD)	**TLE patients** median; mean (SD)	**p-values**
Scores in the faux-pas task			
Overall faux pas (out of 60)	58.00; 58.12 (1.85)	50.00; 48.62 (6.50)	p<0.0001
Identification (%)	100.00; 99.80 (1.41)	100.00; 99.78 (1.57)	p=0.9663
Explanation-1 (%)	100.00; 99.80 (1.41)	100.00; 93.30 (10.06)	p<0.0001
Explanation-2 (%)	90.00; 88.13 (9.76)	50.00; 52.59 (22.15)	p<0.0001
Non-intentionality (%)	100.00; 95.78 (5.77)	90.00; 86.02 (14.60)	p=0.0003
Appropriate feeling (%)	100.00; 98.80 (3.28)	90.00; 86.71 (15.06)	p< 0.001
Non-faux pas rejection (out of 20)	20.00; 19.96 (0.28)	20.00; 19.16 (1.28)	p<0.0001
Scores in the sarcasm comprehension task			
Open questions (out of 12)			
Direct sarcastic remarks	12.00; 11.72 (0.61)	10.00; 10.00 (1.96)	p<0.0001 *
Indirect sarcastic remarks	11.00; 11.28 (0.76)	10.00; 9.24 (2.05)	p<0.0001 *
Multiple choice questions (out of 6)			
Direct sarcastic remarks	6.00; 5.86 (0.35)	5.00; 5.16 (1.04)	p<0.0001 *
Indirect sarcastic remarks	5.00; 4.74 (0.78)	4.00; 4.14 (1.07)	p=0.0014 *
Scores in the action comprehension task			
Open questions on mental actions (out of 12)	12.00; 11.30 (0.93)	10.00; 9.80 (1.64)	p<0.0001 *
Multiple choice questions on mental actions (out of 6)	6.00; 5.98 (0.14)	6.00; 5.60 (0.73)	p=0.0023

* As the control situation scores (Sincere-Remarks or Physical actions) differed between TLE patients and controls, p-value was calculated with the control situation scores as covariates

Abbreviations: ToM=theory of mind; TLE=temporal lobe epilepsy; SD=standard deviation

Associations between ToM performances and clinical, psychobehavioral and quality of life factors in TLE patients.

ToM performances and clinical factors

The overall faux pas score was significantly and positively correlated with age at onset (r=0.4511, p=0.0011) and significantly and negatively correlated with the duration of epilepsy (r=-0.4757, p=0.0004). TLE patients with an early age at onset (≤ 5 years of age) had a lower overall faux pas score than TLE patients with a late age at onset (>5 years of age) (44.10±6.38 and 49.75±6.09, respectively; p=0.0152). However, early-onset TLE patients also had a longer duration of epilepsy than late-onset TLE patients (36.39±14.87 and 17.58±12.00 years, respectively; p=0.0006). For the overall faux pas score, we did not find any interactions between the onset of epilepsy (early vs. late) on one hand and the type of epilepsy (mesial vs. lateral) or gender (male vs. female) on the other. There was no difference between the early- and late-onset groups in terms of the open question scores for direct and indirect sarcastic remarks. No other relationships between ToM performances (including the open question scores for sarcastic remarks) and clinical factors were identified. The overall faux pas score and the open question scores for direct or indirect sarcastic remarks were not influenced by the laterality of epilepsy, the type of epilepsy or the presence of HS (Supplementary data - Tables 4, 5 and 6).

ToM performances and psychobehavioral factors

Relative to controls, TLE patients had higher scores for depression (BDI), anxiety (STAI), apathy (LARS), alexithymia (TAS-20), physical anhedonia (PAS), social anhedonia (SAS), and negative affectivity (PANAS), and lower scores for positive affectivity (PANAS), and cognitive empathy abilities (IRI cognitive sub-score) (Table 3). In TLE patients, the overall faux pas score was positively correlated with positive affectivity (PANAS; r=0.3298, p=0.0194) and empathy abilities (IRI; r=0.4077, p=0.0033; cognitive sub-score: r=0.3005, p=0.0340; affective sub-score: r=0.3625, p=0.0097) and negatively correlated with physical anhedonia (PAS; r=-0.2921, p=0.0396). The open question score for indirect sarcastic remarks was positively correlated with depression (BDI; r=0.2947,

p=0.0378) and negative affectivity (PANAS; r=0.3852, p=0.0057) and negatively correlated with physical anhedonia (PAS; r=-0.3136, p=0.0266). None of the psychobehavioral factors was correlated with the open question score for direct sarcastic remarks.

Table 3. Psychobehavioral scores for controls and TLE patients (median; mean (SD)), quality of life scores for TLE patients and the statistical significance (p-values) of intergroup comparisons

	Controls median; mean (SD)	**TLE patients** median; mean (SD)	**p-values**
Psychobehavioural scores			
BDI (from 0 to 63)	2.50; 4.88 (6.31)	13.50; 15.06 (10.18)	p<0.0001
STAI (from 20 to 80)			
State	25.50; 29.62 (10.08)	40.00; 40.00 (11.72)	p=0.0036
Trait	34.00; 34.32 (8.13)	47.00; 47.32 (10.24)	p<0.0001
LARS (from -36 to +36)	-31.00; -29.70 (4.56)	-20.00; -20.12 (7.84)	p<0.0001
TAS-20 (from 20 to 100)	40.00; 43.06 (11.93)	55.00; 54.86 (11.79)	p<0.0001
PAS (from 0 to 61)	13.50; 14.44 (7.69)	22.00; 21.54 (8.20)	p=0.0131
SAS (from 0 to 41)	9.00; 9.38 (5.49)	15.00; 14.26 (6.38)	p=0.0002
PANAS (from 10 to 50)			
Positive affectivity	37.00; 36.76 (5.27)	30.00; 29.70 (6.65)	p<0.0001
Negative affectivity	20.00; 20.36 (6.68)	24.50; 25.32 (6.97)	p=0.0122
IRI (from 0 to 120)	71.00; 69.16 (12.59)	63.00; 63.54 (11.02)	p=0.1140
Cognitive sub-score (out of 60)	34.50; 33.76 (8.14)	28.50; 28.38 (6.48)	p=0.0088
Affective sub-score (out of 60)	37.00; 35.40 (7.15)	35.00; 35.16 (7.02)	p=0.9108
Quality of life scores (QOLIE-89)			
Overall score (from 0 to 100)		61.59; 60.54 (13.41)	
Social sub-scores (from 0 to 100)			
Role limitations-emotional		88.00; 66.40 (34.86)	
Emotional well-being		60.00; 57.20 (19.01)	
Social support		60.00; 57.40 (14.99)	
Social isolation		80.00; 70.00 (20.20)	
Work/driving/social function		62.27; 55.95 (19.96)	

Abbreviations: ToM=theory of mind; TLE=temporal lobe epilepsy; SD=standard deviation; BDI=the Beck Depression Inventory; STAI=the State-Trait Anxiety Inventory; LARS=the Lille Apathy Rating Scale; TAS-20=the Toronto Alexithymia Scale; PAS=the Physical Anhedonia Scale; SAS=the Social Anhedonia Scale; PANAS= the Positive and Negative Affect Schedule; IRI=the Interpersonal Reactivity Index; QOLIE-89=the Quality of Life Inventory in Epilepsy

ToM performances and quality of life

We observed a positive correlation between the social support sub-score on one hand and the overall faux pas score (r=0.3258, p=0.0209) and open question score for indirect sarcastic remarks (r=0.3468, p=0.0136) on the other. None of the quality of life factors were correlated with the open question score for direct sarcastic remarks.

Predictors of ToM performances in TLE patients

The duration of epilepsy (sr^2=0.1516, p=0.0018), positive affectivity (PANAS; sr^2=0.0467, p=0.0580) and empathy abilities (IRI; sr^2=0.0526, p=0.0577) were identified as predictors of the overall faux pas score (r^2=0.3618, p=0.0001). Physical anhedonia (PAS; sr^2=0.1437, p=0.0034) and negative affectivity (PANAS; sr^2=0.1937, p=0.0008) were identified as predictors of the open question score for indirect sarcastic remarks (r^2=0.2921, p<0.0001).

Discussion

Patients with TLE exhibit impairments in the understanding of faux pas, as established in previous studies (Broicher et al., 2012; Giovagnoli et al., 2011, 2013; Li et al., 2013; Schacher et al., 2006). Our present results also showed that TLE patients present difficulties in understanding sarcasm and mentalistic actions. This process mainly requires the ability to understand another person's intentions and beliefs –again suggesting that cognitive ToM processes are impaired in TLE. However, the differences in the various faux pas task sub-scores in TLE patients also suggest that the latter have difficulty identifying another person's emotional state (subtended by affective ToM processes).

The social skills subtended by ToM abilities were not all affected to the same extent in TLE patients. Only misunderstandings of faux pas and sarcasm were specific to TLE, as suggested by our discriminant power analysis. Hence, the faux pas task and the comprehension of sarcasm task appear to be appropriate for screening for ToM impairments in clinical practice. Furthermore, a higher proportion of TLE patients were impaired in the faux pas task (84%) than in the comprehension of sarcasm task (around 50%). This finding suggests that situations that only depend on cognitive ToM processes are less affected in TLE than situations that also depend on affective ToM processes. The

fact that these impairments were not necessarily combined (i.e. an impairment for faux pas but not for sarcasm, or vice versa) suggests that cognitive and affective ToM processes are dissociable. It must be noted that the ToM task scores differed in terms of their range (with the widest range in the faux pas task), meaning that the presence of statistical bias cannot be completely ruled out. Moreover, we cannot rule out the possibility that ToM impairments in TLE patients are related in part to the epileptic condition in general and its associated factors (rather than to TLE specifically). This question has already been addressed by other researchers; Broicher et al. (Broicher et al., 2012) found that extratemporal epileptic patients (i.e. with neither temporal lobe epilepsy nor frontal lobe epilepsy) are less severely affected by social cognition disorders than TLE patients (relative to controls). Hence, it seems reasonable to assume that over and above the epileptic condition in general, TLE does specifically alter the network underlying ToM processes.

Our conclusions on ToM impairments might be limited by the fact that ToM tasks also depend on non-ToM processes. We found that in all the ToM tasks, TLE patients and controls differed in terms of non-inferential aspects of performance (MoCA, non-faux pas rejection, sincere remarks, and physical actions), which suggests that TLE patients have difficulties in general reasoning. Could the observed ToM impairments be related to a more general cognitive weakness? A number of factors argue against this hypothesis. Firstly, the MoCA scores were taken into account in our intergroup comparisons of ToM scores. Secondly, the ToM tasks included control questions to check the participant's comprehension of the social context. Thirdly, the ToM tasks' administration procedures limited the involvement of other non-inferential aspects (the participants read the story on their own sheet of paper, which could be reread if required for better understanding). Lastly, scores for control situations in the sarcasm and action comprehension tasks (sincere remarks and physical actions) were included as covariates in intergroup comparisons. These observations suggest that ToM abilities can be distinguished from other cognitive functions, as recently indicated by a factorial analysis in patients with temporal and frontal lobe epilepsy (Giovagnoli et al., 2011, 2013).

In the present study, several clinical factors were found to have an impact on ToM performances. The duration of epilepsy and age at onset were correlated with the comprehension of faux pas but not with the comprehension of sarcasm. Only the duration of epilepsy was identified as a

predictor of the comprehension of faux pas. Other studies have identified young age at onset (rather than a long duration of epilepsy) as a predictor of ToM impairments in the faux pas task (Giovagnoli et al., 2011, 2013). In the present study, the duration of epilepsy and age at onset were correlated ($r=-0.7522$, $p<0.0001$); a post-hoc analysis of residuals failed to find a supplementary contribution of age at onset to the duration of epilepsy. Hence, both the duration of epilepsy and age at onset may be risk factors for impaired affective ToM processes. Regardless of the laterality or type of TLE and the presence of HS, all the patients appear to be at risk of cognitive and affective ToM disorders. In accordance with previous studies, we did not find an effect of seizure frequency on ToM performances (Giovagnoli et al., 2011, 2013; Li et al., 2013). Other parameters may explain ToM network disruptions (Abu-Akel & Shamay-Tsoory, 2011). The frequency and location of interictal abnormalities, and the length and severity of seizures may be involved (as reflected by their associations with other cognitive disturbances) and merit further investigation (for a review, see Badawy, Johnson, Cook, & Harvey, 2012).

One important issue concerning these ToM disorders is what they tell us about how the TLE patients function in everyday life. Impaired empathy in TLE is related to ToM impairments in general and impairments in faux pas tasks in particular. This relationship has been well characterized for a number of neurological and neuropsychiatric diseases (Davis, 1983; Decety & Ickes, 2009). Empathy is defined as a person's reaction to another person's experiences. It is underpinned by the ability to adopt the other person's perspective ("cognitive" empathy) and experience affective reactions to the other person's experiences ("affective" empathy). Broicher et al. did not find a relationship between empathy and ToM abilities (Broicher et al., 2012). However, Broicher et al.'s TLE patients and controls had similar empathy scores. In an additional analysis, we found that self-assessment of empathy by 24 TLE patients did not differ from assessment by family and close friends ($p=0.4931$) and this was also related to ToM performances ($sr^2=0.1498$, $p=0.0617$).

Furthermore, our TLE patients had higher depression and anxiety scores than controls and were more likely to display impaired affective functions (apathy, alexithymia, anhedonia). In agreement with previous studies, depression and anxiety were not related to ToM performances in the faux pas task (Broicher et al., 2012; Giovagnoli et al., 2013). We found a weak positive correlation

between depression and the comprehension of sarcasm (i.e. cognitive ToM processes). Furthermore, physical anhedonia was positively correlated with poor cognitive and affective ToM performances. More specifically, anhedonia predicted the impairment of cognitive ToM processes (comprehension of sarcasm). Anhedonia is a key factor in atypical depressive syndromes or dysthymic-like disorders - a frequent form of interictal depression in epilepsy (Kanner, 2003; Marsh & Rao, 2002).

We also observed that the affective states of TLE patients were less positively valenced and more negatively valenced than controls. In the tripartite model, low positive affectivity and high negative affectivity are closely related to depression and anxiety (Clark & Watson, 1991; Crawford & Henry, 2004; Watson, Clark, & Carey, 1988). It is noteworthy that in epileptic patients, positive affectivity, negative affectivity and self-assessment of coping efficacy are predictive of psychosocial functioning, emotional adjustment and quality of life (Gramstad, Iversen, & Engelsen, 2001). In the present study, we found that positive and negative affectivity were related to ToM disorders in different ways. Low positive affectivity was predictive of greater cognitive and affective ToM impairments in the faux pas task, whereas high negative affectivity was predictive of greater cognitive ToM efficiency in the comprehension of sarcasm task.

In view of our results, the relationships between ToM processes and affective regulation strategies in TLE appear to be complex. Impaired ToM may be related to high anhedonia and low positive affectivity. However, impairment of ToM (and cognitive ToM in particular) may also be related to lower negative affectivity. Accordingly, TLE disrupts the efficiency of ToM processes, which are related to affective regulation strategies. One could hypothesize that a balance between ToM processes and affective regulation strategies is required for appropriate behavior. When studying the relationships between ToM and affective regulation, the atypical features of psychobehavioral disturbances in epilepsy must be taken into account. If there is a causal relationship between ToM and affective regulation, it may act in both directions. On one hand, one could hypothesize that affective dysregulation limits psychosocial functioning and thus have an impact on the ToM development. On the other hand, impaired ToM might limit the understanding of social relationships between the patient and other people and thus worsen affective disorders.

Although social support (a quality of life domain) was positively correlated with the comprehension of faux pas and sarcasm, it did not predict ToM performances. Social support has already been identified as a predictor of mood disorders in epileptic patients (Gandy, Sharpe, & Perry, 2012; Lee, Lee, & No, 2010). Hence, social support may be indirectly related to ToM performances via their common relationships with psychobehavioral disturbances in epileptic patients. As reported by Giovagnoli et al. (2013), the consideration of psychobehavioral aspects of quality of life enables quality of life and ToM to be compared with a greater degree of precision (Giovagnoli et al., 2013).

Conclusion

Our present results suggest that TLE patients exhibit impairments in both cognitive and affective ToM processes, although only one or the other was affected in some patients. The faux pas and sarcasm comprehension tasks appear to be appropriate for detecting this type of impairment. All TLE patients appear to be at risk of ToM disorders; this is especially the case for patients with a long duration of epilepsy and/or younger age at onset. Impaired ToM was also related to psychobehavioral factors - especially anhedonia and affective states - and had a real impact on the TLE patients' empathy abilities. Our results highlight the need to assess ToM abilities and affective regulation in TLE. Further studies are needed to characterize (a) the complex relationships between ToM abilities and affective regulation and (b) the corresponding physiopathological mechanisms.

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Supplementary data

Table 4. Demographic, cognitive, clinical parameters and discriminant ToM scores according to the laterality of epilepsy (right vs. left) for TLE patients, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy		
	Right n=23	**Left** n=27	**p-values**
Demographic characteristics			
Age in years (median; mean (SD))	42.98; 42.67 (13.72)	41.59; 42.17 (10.20)	p=0.8841
Gender (male, %)	47.83	44.44	p=1.00
Educational level (% lacking a high school leaving qualification)	69.57	48.15	p=0.1578
Cognitive characteristics MoCA score (from 0 to 30, median; mean (SD))	26.00; 25.74 (2.34)	24.00; 24.59 (2.42)	p=0.1257
Clinical factors			
Age at onset in years (median; mean (SD))	23.00; 24.00 (16.52)	14.00; 18.56 (13.94)	p=0.2232
Duration of epilepsy in years (median; mean (SD))	17.21; 18.67 (13.72)	21.18; 23.61 (15.18)	p=0.2977
Seizure frequency per day over 3 months (median; mean (SD))	0.10; 0.14 (0.14)	0.10; 0.70 (2.86)	p=0.5429
Type of epilepsy (mesial %)	65.22	59.26	p=0.7733
Presence of HS (with HS/no brain lesions %)	52.17/39.13	40.74/29.63	p=1.00
ToM scores (median; mean (SD))			
Overall faux pas score (out of 60)	50.00; 49.43 (4.18)	50.00; 47.93 (7.99)	p=0.6751
Open questions on direct sarcastic remarks (out of 12)	10.00; 10.17 (1.50)	10.00; 9.85 (2.30)	p=0.9762
Open questions on indirect sarcastic remarks (out of 12)	9.00; 9.39 (1.53)	10.00; 9.11 (2.42)	p=0.9762

Abbreviations: ToM=theory of mind; TLE=temporal lobe epilepsy; SD=standard deviation; MoCA=the Montreal Cognitive Assessment; HS=hippocampal sclerosis

Table 5. Demographic, cognitive, clinical parameters and discriminant ToM scores according to the laterality of epilepsy (right vs. left) and type of epilepsy (mesial vs. lateral) for TLE patients, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy*Type of Epilepsy				
	Right		**Left**		**p-values**
	Mesial n=15	**Lateral** n=8	**Mesial** n=16	**Lateral** n=11	
Demographic characteristics					
Age in years (median; mean (SD))	43.14; 43.80 (15.33)	41.03; 40.54 (10.64)	45.86; 45.30 (11.17)	38.10; 37.61 (6.70)	p=0.3740
Gender (male, %)	46.67	50.00	37.50	54.55	p=0.8392
Educational level (% lacking a high school leaving qualification)	73.33	62.50	56.25	36.36	p=0.3020
Cognitive characteristics					
MoCA score (from 0 to 30, median; mean (SD))	26.00; 25.93 (2.19)	25.50; 25.38 (2.72)	24.00; 24.50 (2.34)	25.00; 24.72 (2.65)	p=0.4588
Clinical factors (median; mean (SD))					
Age at onset in years	21.00; 21.47 (17.38)	33.00; 28.75 (14.63)	16.00; 20.19 (15.93)	14.00; 16.18 (10.69)	p=0.3079
Duration of epilepsy in years	19.34; 22.33 (14.56)	11.84; 11.79 (9.18)	22.79; 25.12 (16.81)	18.59; 21.43 (12.92)	p=0.2355
Seizure frequency per day over 3 months	0.10; 0.12 (.14)	0.12; 0.17 (.14)	0.10; 0.14 (.15)	0.10; 1.52 (4.47)	p=0.4188
ToM scores (median; mean (SD))					
Overall faux pas score (out of 60)	48.00; 48.67 (4.01)	52.00; 50.88 (4.36)	49.50; 48.38 (7.11)	50.00; 47.27 (9.45)	p=0.7490
Open questions on direct sarcastic remarks (out of 12)	10.00; 9.73 (1.39)	11.50; 11.00 (1.41)	10.00; 9.69 (2.12)	11.00; 10.09 (2.63)	p=0.1722
Open questions on indirect sarcastic remarks (out of 12)	9.00; 9.27 (1.39)	10.50; 9.63 (1.85)	10.00; 8.69 (2.85)	10.00; 9.73 (1.56)	p=0.7437

Abbreviations: ToM=theory of mind; TLE=temporal lobe epilepsy; SD=standard deviation; MoCA=the Montreal Cognitive Assessment

Table 6. Demographic, cognitive, clinical parameters and discriminant ToM scores according to the laterality of epilepsy (right vs. left) and presence of HS (with HS vs. No brain lesions) of TLE patients, and the statistical significance (p-values) of intergroup comparisons

	Laterality of epilepsy * presence/absence of HS				
	Right		**Left**		**p-values**
	With HS n=12	**No brain lesions** n=9	**With HS** n=11	**No brain lesions** n=8	
Demographic characteristics					
Age in years (median; mean (SD))	44.88; 45.40 (13.56)	42.47; 42.76 (13.33)	49.46; 49.10 (8.41)	40.57; 38.15 (5.95)	p=0.2028
Gender (male, %)	50.00	44.44	45.45	37.50	p=0.9591
Educational level (% lacking a high school leaving qualification)	75.00	77.78	63.64	14.29	p=0.0195
Cognitive characteristics					
MoCA score (from 0 to 30, median; mean (SD))	26.5; 26.25 (2.09)	24; 24.67 (2.55)	23; 23.55 (1.86)	25.50; 25.50 (2.51)	p=0.0523
Clinical factors (median; mean (SD))					
Age at onset in years	16.5; 19.50 (14.50)	33; 33.33 (16.45)	10.00; 19.36 (17.93)	20.50; 19.88 (11.69)	p=0.1984
Duration of epilepsy in years	24.31; 25.90 (13.76)	4.65; 9.42 (9.04)	32.44; 29.74 (17.86)	17.12; 18.27 (13.23)	p=0.0176
Seizure frequency per day over 3 months	0.08; 0.10 (0.11)	0.14; 0.20 (0.18)	0.10; 0.15 (0.16)	0.10; 0.12 (0.13)	p=0.4910
ToM scores (median; mean (SD))					
Overall faux pas score (out of 60)	47.00; 47.58 (3.65)	52.00; 50.89 (4.08)	49.00; 48.18 (8.20)	49.00; 47.50 (8.88)	p=0.7585
Open questions on direct sarcastic remarks (out of 12)	10.00; 9.67 (1.30)	11.00; 10.44 (1.59)	10.00; 9.64 (2.34)	10.50; 10.50 (1.51)	p=0.1470
Open questions on indirect sarcastic remarks (out of 12)	9.00; 9.08 (1.31)	11.00; 9.78 (1.79)	8.00; 8.09 (3.27)	10.00; 10.00 (1.07)	p=0.2990

Abbreviations: ToM=theory of mind; TLE=temporal lobe epilepsy; HS=hippocampal sclerosis; SD=standard deviation; MoCA=the Montreal Cognitive Assessment

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Title

A functional magnetic resonance imaging investigation of theory of mind impairments in patients with temporal lobe epilepsy

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Abstract

Although patients with mesial temporal lobe epilepsy (mTLE) are known to have theory of mind (ToM) impairments, the latter's neural functional bases have yet to be explored. We used functional magnetic resonance imaging (fMRI) to gain insights into the neural dysfunction associated with ToM impairments in mTLE.

Twenty-five patients (12 and 13 with right and left mTLE, respectively) and 25 healthy controls performed the "animated shapes" task during fMRI. This complex ToM task requires both explicit reasoning about mental states and implicit processing of information on biological motion and action. The animated shapes evoke both ToM and non-ToM interaction perception, and the corresponding neural activation patterns were compared. Behavioral performance (i.e. categorization of the interactions) was also recorded.

Relative to healthy controls, both right and left mTLE patients were impaired in categorizing ToM interactions. The fMRI results showed that both right and left mTLE patients had less intense neural activation (relative to controls) in regions involved in the implicit component of ToM processes (i.e. the fusiform gyrus in right mTLE patients and the supplementary motor area in left mTLE patients). In right mTLE patients, we also observed more intense activation (relative to controls) in regions involved in the explicit component of ToM processes (i.e. the dorsal medial prefrontal cortex); age at onset of epilepsy also mediated activation in regions involved in the explicit component (i.e. the ventral medial prefrontal cortex and the temporoparietal junction). Left mTLE patients displayed greater activation of the contralateral mesial regions (relative to controls); we speculate that this may correspond to the deployment of a compensatory mechanism.

This study provides insights into the disturbances of the implicit/explicit ToM neural network in mTLE patients. These impairments in the ToM neural network depend on clinical characteristics, such as the laterality (right or left mTLE) and the age at onset of epilepsy.

Keywords: theory of mind - mesial temporal epilepsy - functional imaging - animated shapes

1. Introduction

Epilepsy is a chronic condition characterized by recurrent epileptogenic discharges. In addition to the distress caused by seizures, epilepsy has a negative impact on quality of life and activities of daily living. Indeed, epilepsy is particularly associated with psychosocial difficulties such as poor interpersonal and social relationships, unemployment, and problems in daily life (Hermann et al., 2009; McCagh et al., 2009).

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. It is characterized by recurrent epileptogenic discharges arising from temporal regions, and is frequently associated with lesions and gliosis/atrophy of the medial temporal lobe. Over the last decade, researchers have increasing focused on social cognitive skills in TLE (for reviews, see Bora and Meletti, 2016; Monti and Meletti, 2015; Stewart et al., 2016). Several published studies have evidenced theory of mind (ToM) impairments in a large proportion of patients with TLE (Broicher et al., 2012b; Giovagnoli et al., 2013, 2011; Hennion et al., 2015; Li et al., 2013; Schacher et al., 2006, Shaw et al., 2004). Theory of mind refers to the ability to attribute mental states and thus to explain and predict another person's behavior - a prerequisite for appropriate social skills (Adolphs, 2001). The significant impact of ToM impairments on abnormal psychosocial functioning and poor quality of life in TLE patients has been also recently highlighted (Giovagnoli et al., 2013; Hennion et al., 2015; Wang et al., 2015). However, despite considerable interest, ToM disorders and the latter's physiopathological mechanisms in TLE have yet to be accurately characterized.

It is now well established that TLE is associated with extensive structural and functional alterations not only in mesial regions (such as the hippocampus, rhinal and parahippocampal cortices, and amygdala) but also in extratemporal structures (such as the lateral temporal, temporoparietal, frontal and occipitotemporal neocortices) (Bernhardt et al., 2013; Van Diessen

et al., 2013). These changes encompass the network that is engaged in ToM processing (Giovagnoli, 2014), and might thus account for the ToM impairments observed in patients with TLE (Abu-Akel and Shamay-Tsoory, 2011; Kennedy and Adolphs, 2012). In fact, studies in healthy controls and patients with neuropsychiatric disorders have established that the "social brain" includes both temporal regions (the superior temporal gyrus/sulcus (STS) and the temporoparietal junction (TPJ) as well as the temporal pole), extratemporal cortical regions (the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex, posterior cingulate cortex/precuneus) and subcortical regions (such as the amygdala and striatum). Consistently, Broicher et al. (2012a) observed altered amygdala network activation in mesial TLE (mTLE) patients who were presented with fearful faces, depending on the laterality of epilepsy (right vs. left) (Broicher et al., 2012a). In fact, this network is activated on both sides of the brain in healthy controls but only on the side that is contralateral to the epileptic focus in mTLE patients. Moreover, Broicher et al. found that lower connectivity between the amygdala and other mesial regions (i.e. connectivity to the right insula in left mTLE patients, and connectivity to the left hippocampal formation and the amygdala in right mTLE patients) was positively correlated with performance in the faux pas task (a classic, well-established ToM task) (Stone et al., 1998). The faux pas task assesses the detection and understanding of verbal clumsiness (i.e. faux pas) in stories read to the participant. Other clinical characteristics are also probably associated with ToM impairments. Indeed, several research groups have tried to determine whether the age and the duration of seizure exposure modulate the severity or extent of ToM impairments. It was found that a young age at onset and/or a long duration of epilepsy are risk factors for ToM impairments (Shaw et al., 2004; Giovagnoli et al., 2011, 2013; Hennion et al., 2015). These findings indicate that ToM impairments in TLE patients have at least two potential backgrounds. The effect of age of onset suggests that ToM impairments are developmental in nature. During the development of neural networks, there is a critical period during which ToM

abilities emerge; the age of 12 is the typical threshold for successful completion of the faux pas task. Nevertheless, the observed effect of the duration of epilepsy also implies that ToM impairments in TLE patients are not solely developmental in nature; they might result from brain abnormalities induced by chronic epilepsy well after the end of a critical developmental period. It is noteworthy that both young age at onset and a long duration of epilepsy are associated with brain alterations in neuroimaging studies of TLE patients; these alterations may account for the clinical characteristics' effects on ToM performances (Bernhardt et al., 2013; Van Diessen et al., 2013).

One of the most hotly debated aspects of ToM subcomponents is the supposed dichotomous nature of social inferences (i.e. cognitive vs. affective). Thus, the processes involved in the social inference of cognitive mental states (such as intentions and beliefs, knowledges and intentions) differ from the processes involved in the social inference of affective mental states (such as emotions) (Abu-Akel and Shamay-Tsoory, 2011; Amodio and Frith, 2006). A distinction between cognitive and affective ToM processes is supported by behavioral studies in patients with psychiatric and neurological pathologies (Gregory et al., 2002; Poletti et al., 2011; Roca et al., 2010; Shamay-Tsoory et al., 2002; 2007a; 2077b; Stone et al., 1998; Torralva et al., 2007). Interestingly, lesional and neuroimaging studies suggest that some specific brain regions contribute preferentially to cognitive ToM abilities, whereas other regions are involved in affective ToM abilities. More specifically, the ventral mPFC might be preferentially involved in the inference of emotional mental states, and the dorsal mPFC might be preferentially involved in the inference of cognitive mental states (Abu-Akel et Shamay-Tsoory, S., 2011; Shamay-Tsoory et al., 2005; 2007a; 2077b; Stone et al., 1998; Herold et al., 2009; Hooker et al., 2011). In previous research, we highlighted the presence of ToM impairments in more than 80% of TLE patients by using several ToM tasks to assess the detection and understanding of faux pas, sarcastic remarks and mentalistic actions (Hennion et

al., 2015). In agreement with other studies, our results suggested that both cognitive and affective subcomponents of ToM are impaired in TLE (Giovagnoli et al., 2011, 2013).

The latest research findings also suggest that understanding the minds of others involves a number of interrelated processes (Wolf et al., 2010; Das et al., 2012). On one hand, a more basic, automatic, "implicit" component of ToM processes enables a person to decode facial expression, biological motion and actions as the premises for the explicit attribution of mental states to other people. On the other hand, a more tightly controlled and cognitively demanding component of ToM processes enables a person to reason "explicitly" with regard to other people's mental states.Most of ToM tasks used in behavioral studies in TLE patients involve retrospective, explicit reasoning about another person's mental state (i.e. evaluation of the explicit component of ToM processes). Since ToM processes in everyday life consist of both explicit and implicit components, recent research suggest that the latter should also be probed.

In the "animated shapes" task, the interactions of moving geometric shapes evoke different types of responses. Interactions are usually described as ToM interactions on one hand or non-ToM interactions on the other (i.e. non-specific interactions and physical interactions, corresponding to the control conditions) (Abell et al., 2000). In addition to explicit reasoning about mental states, this ToM task requires the participant to process information on biological motion and action (i.e. the implicit component of ToM processes) (Das et al., 2012; Pedersen et al., 2012). In a behavioral study, Broicher et al. (2012b) found that mTLE patients have impaired performances in the animated shapes task (Broicher et al., 2012b); relative to healthy controls, the mTLE patients had difficulty in accurately interpreting ToM interactions and attributed less intentionality to these interactions.

The animated shapes task has recently been used to explore (i) the neural basis of ToM processes in healthy controls and (ii) potential impairments in patients with neuropsychiatric disorders (such as schizophrenia, euthymic bipolar disorder, and autism) (Castelli et al., 2002,

2000; Das et al., 2012; Malhi et al., 2008; Pedersen et al., 2012; Schultz et al., 2003). In these functional magnetic resonance imaging (fMRI) studies, comparison of the neural activation patterns elicited respectively by ToM and non-ToM interactions provides information on the neural basis of ToM processes (Pedersen et al., 2012). The implicit, automatic component of ToM processes is mediated by the fusiform gyrus, the STS, the inferior frontal gyrus and the premotor areas (Allison et al., 2000; Das et al., 2012; Iacoboni and Dapretto, 2006; Malhi et al., 2008; Pedersen et al., 2012), whereas the more closely controlled, explicit component of ToM processes recruits the mPFC and the TPJ (Amodio and Frith, 2006; Saxe and Kanwisher, 2003). Considering these data as a whole and the task's properties, we considered that the animated shapes task would be an adequate paradigm for investigating ToM impairments in an fMRI study of patients with mTLE.

The present fMRI study sought to investigate the functional neural basis of ToM impairments in patients with mTLE (relative to healthy controls) by using the animated shapes task. We hypothesized that right and left mTLE patients would differ from healthy controls in terms of the neural activation patterns within ToM network components. We further hypothesized that age at onset and the duration of epilepsy would modulate the recruitment of the ToM brain networks in mTLE patients.

2. Materials and methods

2.1. Participants

Twenty-five patients with mTLE were consecutively recruited at Lille University Medical Center's Epilepsy Unit (Lille, France). All patients were candidat to surgery and included in presurgical program. The main inclusion criteria were unilateral mTLE and right-handedness (according to the Edinburgh Handedness Inventory; (Oldfield, 1971)). The

diagnostic criteria for mTLE include a history of complex partial seizures and compatible interictal EEG and ictal video/EEG recordings. All patients had to display unilateral hippocampal abnormalities in a 3.0-Tesla MRI dataset. Hippocampal sclerosis (HS, defined as a volume decrease on T1-weighted images and hyperintensity in fluid-attenuated inversion recovery images) was observed in 16 patients (10 right mTLE patients and 6 left mTLE patients). The lesions other than HS included focal gliosis, focal atrophy, and focal dysplasia. Furthermore, 16 patients (including 11 with HS) presented with hyperintensity in the amygdala in fluid-attenuated inversion recovery images (8 right mTLE patients and 8 left mTLE patients). The main exclusion criteria were: (a) impaired intellectual capacity (an intelligence quotient (IQ) below 75, according to a French adaptation of the National Adult Reading Test (fNART); (Mackinnon and Mulligan, 2005)) or impaired non-verbal reasoning (according to Raven's Coloured Progressive Matrices (PM-47); (Raven, 1965)); (b) significant amnesia or a marked impairment of instrumental capacities (agnosia, aphasia, apraxia, alexia, or agraphia); (c) a history of a neurological disease other than epilepsy; (d) a history of psychiatric disease (other than depression or anxiety disorders, given that these are frequent comorbidities in epilepsy, Lin et al., 2012)) on the basis of a structured patient interview and self-reported estimates of the severity of any symptoms of depressions (according to the Beck Depression Inventory (BDI); Beck et al., 1961) and anxiety (according to the State–Trait Anxiety Inventory (STAI) Spielberger et al., 1983); and (e) a seizure in the 24 hours immediately preceding the experimental session.

The control group included 25 right-handed participants. The exclusion criteria for healthy controls were: (a) impaired intellectual capacity (IQ below 75, fNART) or non-verbal reasoning (PM-47); and (b) a history of neurological or psychiatric disease, on the basis of a structured interview and self-reports of the severity of any symptoms of depression or anxiety (according to the BDI and the STAI, respectively). Each healthy control was matched for

demographic characteristics (age, gender and educational level) with an mTLE patient. All participants underwent the Montreal Cognitive Assessment (MoCA; (Nasreddine et al., 2005)), which probes a number of cognitive domains (attention, executive functions, memory, language, visuoconstructive skills, conceptual thinking, calculation, and orientation). In mTLE patients, clinical characteristics (laterality, age at onset and duration of epilepsy, seizure frequency and the number of antiepileptic drugs taken) were also recorded.

The study protocol was approved by the local independent ethics committee (*CPP Nord Ouest IV*, Lille, France; reference: 2012 A01372 41) and was performed in accordance with the tenets of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/). All participants gave their written, informed consent to participation in the study.

2.2. ToM assessment: the animated shapes task

This ToM task was performed during fMRI. We employed the validated fMRI version adapted from Pedersen et al. (2012) (Pedersen et al., 2012) but based on the original version by Abell et al. (2000) (Abell et al., 2000). Animations lasted 24 s each and depicted a small blue and a large red triangle moving across a framed white background (for examples of animations, see https://sites.google.com/site/utafrith/research). Each animation was preceded by a fixation cross displayed for 3s. The animations were displayed on a projector-mirror system. The animations represented three types of interactions (ToM, goal-directed, and random). The ToM interactions involved perceivable manipulations of mental states by one triangle with regard to the other (e.g. coaxing, see Figure 1 for an illustration). The non-ToM interactions consisted of goal-directed interactions between the triangles and random interactions between the triangles. The goal-directed interactions involved a physical interaction between the triangles (such as one triangle chasing the other) without any consideration of mental states, and thus were likely to evoke direct descriptions of interaction. The random interactions did not involve specific

interactions between the triangles (e.g. drifting and random contacts). For each type of interaction, three different animations were presented twice in pseudo-random order (i.e. no more than two animations of the same type were presented in succession). Before the MRI scan, participants were told about the different types of interactions. They were instructed to categorize each animation during the fMRI scan as a ToM, goal-directed or random interaction immediately after presentation by using a keypad. One point was awarded for each correctly classified animation. Consequently, a score (ranging from 0 to 6) was calculated for each of the three types of interaction (ToM, goal-directed, and random).

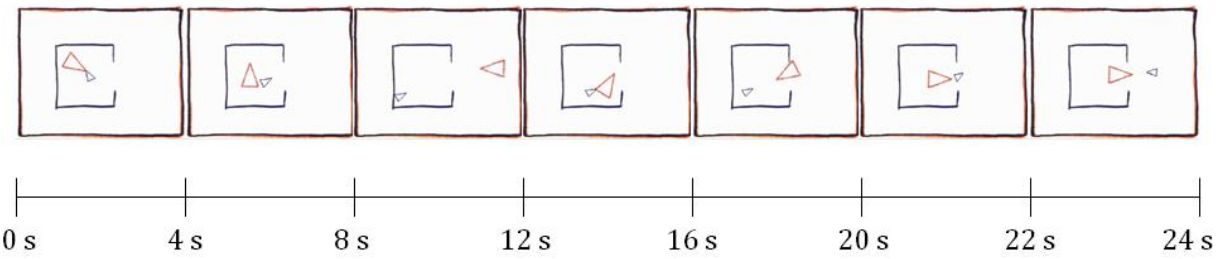


Figure 1. The time course (in seconds) of an animation representing a ToM interaction (coaxing, in this case).

2.3. Image acquisition

The MRI scan was performed on a 3.0-Tesla scanner (Achieva, Philips Medical Imaging, Best, The Netherlands) with an eight-channel head coil. Structural, T1-weighted images were acquired with a magnetization-prepared gradient echo sequence (voxel size: .83 x .83 x 1 mm; repetition time [TR]: 9.83 ms; echo-time [TE]: 4.60 ms; matrix size: 288 x 288; slices: 160). Functional images during the animations were acquired with a T2* weighted echo planar imaging sequence (voxel size: 3 x 3 x 3 mm^3; TR: 2400 ms; TE: 30 ms; matrix size: 64

x 64; slices: 40; flip angle: 90°). Participants were told to stay focused and to remain immobile throughout the acquisition.

2.4. Data analyses

The MRI data were analyzed using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK) and the Freesurfer software package (v5.0, http://surfer.nmr.mgh.harvard.edu/). Preprocessing of the fMRI data included removal of the first three image volumes (to avoid T1 equilibration effects), realignment and slice-timing correction (using the middle slice as the reference frame). The fMRI data were registered against the anatomical images using a boundary-based technique (Greve and Fischl, 2009). This method is more accurate than common registration algorithms (such as the correlation ratio and normalized mutual information). The mid-frame of the preprocessed fMRI data was chosen as the template image. Cross-modality registration was performed by minimizing the misalignment between the cortical grey-white boundaries in the anatomical and fMRI template images with six degrees of freedom. Nuisance signals were removed using a two-step linear regression. The first regression removed linear/quadratic trends (to account for scanner drift) and six motion parameters. The second regression removed five "nuisance" signals obtained by means of a principal component analysis of white matter and ventricle signals using component-based noise correction (Behzadi et al., 2007). Residual data were corrected for high time-domain frequencies by low-pass filtering with a .1 Hz cut-off. The images were spatially normalized against the standard Montreal Neurological Institute space and smoothed using a Gaussian kernel (6 mm full width at half maximum).

Statistical analyses were performed by modeling the different experimental conditions as variables within a fixed-effect, single-participant, general linear model convolved with a Glover standard hemodynamic response function. We included the realignment parameters (six

rigid body transformations) in the design matrix as variables of no interest, in order to control for any movement-related effects. The maps of neural activation data (i.e. the effect map, also referred to as the β-map) were calculated for each participant as a function of the interaction presented (ToM, goal-directed, and random). Next, β-maps for ToM interactions were contrasted with β-maps for non-ToM interactions (i.e. random and goal-directed interactions). One-sample t-tests were used for within-group comparisons (for right mTLE patients, left mTLE patients and healthy controls) of neural activation patterns. A false-discovery-rate (FDR)-corrected significance level of $p < .05$ (with clusters defined by at least 10 contiguous voxels) was chosen. In healthy controls, conjunction analyses of neural activation patterns for ToM interactions vs. goal-directed interactions and for ToM interactions vs. random interactions were performed. Furthermore, two-sample t-tests were used to assess between-group differences (in right and left mTLE patients vs. healthy controls) in neural activation patterns.

For right and left mTLE patients, regression analyses were performed on contrast maps for ToM interactions vs. non-ToM interactions. Age at onset and the duration of epilepsy were included as regressors. An FDR-corrected significance level of $p < .05$ (with clusters defined by at least 10 contiguous voxels) was chosen.

Demographic, cognitive, psychological, clinical and ToM performance data were analyzed for between-group differences using non-parametric tests (Kruskal-Wallis-tests for continuous variables, followed by a pairwise Mann-Whitney U-test if the result was significant; chi -tests were used for categorical variables). Spearman's correlation coefficient was calculated for within-group analyses of continuous variables). All statistical analyses were performed with SPSS software (version 22, IBM, Armonk, NY, USA). The threshold for statistical significance was set to $p < .05$.

3. Results

3.1. Demographic, cognitive, psychological and clinical characteristics of the mTLE patients

Patients with mTLE did not differ significantly from healthy controls in terms of their demographic characteristics (see Table 1). The right mTLE patients, left mTLE patients and healthy controls differed significantly in terms of their MoCA, BDI and STAI scores. Pair-wise comparisons showed that the MoCA scores were lower in right and left mTLE patients than in healthy controls ($p = .0105$ and $p = .0017$, respectively). The BDI scores were higher in right and left mTLE patients than in healthy controls ($p = .0051$ and $p = .0076$, respectively). The STAI state and trait scores were higher in right and left mTLE patients than in healthy controls (respectively $p = .0009$ and $p = .0233$ for the STAI state scores, and $p = .0005$ and $p = .0013$ for the STAI trait scores). In mTLE patients, 7 presented with symptoms of depression (3 right mTLE patients and 4 left mTLE patients), and 14 presented with symptoms of anxiety (7 right mTLE patients and 7 left mTLE patients). Right and left mTLE patients did not differ significantly in terms of their respective clinical and psychological characteristics.

Table 1. Demographic, cognitive and psychological characteristics of healthy controls and mTLE patients, clinical characteristics of mTLE patients, and the statistical significance (p-values) of intergroup comparisons

	Controls n=25	**Right mTLE patients** n=12	**Left mTLE patients** n=13	**p-value**
Demographic characteristics				
Age in years (median; mean ± SD)	41.65; 42.50 ± 12.30	42.54; 42.09 ± 12.62	42.12; 42.54 ± 9.60	p = .9584
Gender (male, n)	14	8	6	p = .5870
Educational level in years of full-time education (≥ 12, n)	15	7	8	p = .9867
Cognitive characteristics				
MoCA scores (from 0 to 30, median; mean ± SD)	29.00; 28.44 ± 1.71	27.50; 26.67 ± 2.10	26.00; 26.08 ± 2.14	p = .0018
Psychological characteristics				
BDI scores (from 0 to 63, median; mean ± SD)	4.00; 6.76 ± 6.00	13.50; 14.08 ± 8.83	9; 13.23 ± 9.63	p = .0039
STAI scores (from 20 to 80, median; mean ± SD)				
State	31.00; 32.56 ± 11.83	56.50; 51.17 ± 14.65	45.00; 44.69 ± 14.55	p = .0016
Trait	35.00; 37.28 ± 10.29	50.50; 53.17; 11.08	50.00; 48.92 ± 10.33	p = .0002
Clinical characteristics				
Age at onset in years (median; mean ± SD)		17.00; 17.25 ± 11.24	10.00; 17.85 ± 15.04	p = .8276
Duration of epilepsy in years (median; mean ± SD)		22.50; 24.33 ± 13.96	21.00; 24.23 ± 14.57	p = .9783
Seizure frequency per day over 3 months (median; mean ± SD)		1.17; 3.14 ± 4.34	2.00; 4.10 ± 8.37	p = .7013
Antiepileptic drugs in number (median; mean ± SD)		2.00; 2.00 ± .74	2.00; 2.08 ± .64	p = .7849

Abbreviations: mTLE = mesial temporal lobe epilepsy; SD = standard deviation; HS = hippocampal sclerosis; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory.

1

3.2. Behavioral performances in the ToM task in mTLE patients

A difference between right mTLE patients, left mTLE patients and healthy controls emerged for the categorization scores for ToM interactions (see Table 2). Pair-wise comparisons revealed that the categorization scores were lower in right and left mTLE patients compared with healthy controls ($p = .0016$ and $p = .0434$, respectively) and that there was no significant difference between right and left mTLE patients groups ($p = .7571$). In the mTLE patient groups, the categorization scores for ToM interactions were not correlated with the MoCA, BDI or STAI scores, the duration of epilepsy or the age of onset. Hence, the categorization scores did not differ according to an early onset of epilepsy (at ≤ 12 years of age) vs. late onset (> 12 years), the presence of HS vs. another hippocampal abnormalities, or the presence or absence of hyperintensity in the amygdala. There were no intergroup differences in the categorization scores for goal-directed or random interactions.

Table 2. Scores in the animated shapes task of healthy controls and mTLE patients and the statistical significance (p-values) of intergroup comparisons

	Controls n=25	**Right mTLE patients** n=12	**Left mTLE patients** n=13	**p-value**
ToM interactions (out of 6, median; mean ± SD)	4.00; 3.92 ± 1.38	2.50; 2.42 ± 1.00	2.50; 2.92 ± 1.73	p = .0056
Goal-directed interactions (out of 6, median; mean ± SD)	4.00; 3.88 ± 1.36	3.00; 3.00 ± 1.54	4.00; 3.50 ± 1.38	p = .1457
Random interactions (out of 6, median; mean ± SD)	5.00; 4.84 ± 1.37	3.50; 3.66 ± 1.83	4.00; 4.25 ± 1.36	p = .9434

Abbreviations: mTLE = mesial temporal lobe epilepsy; SD = standard deviation; ToM = theory of mind.

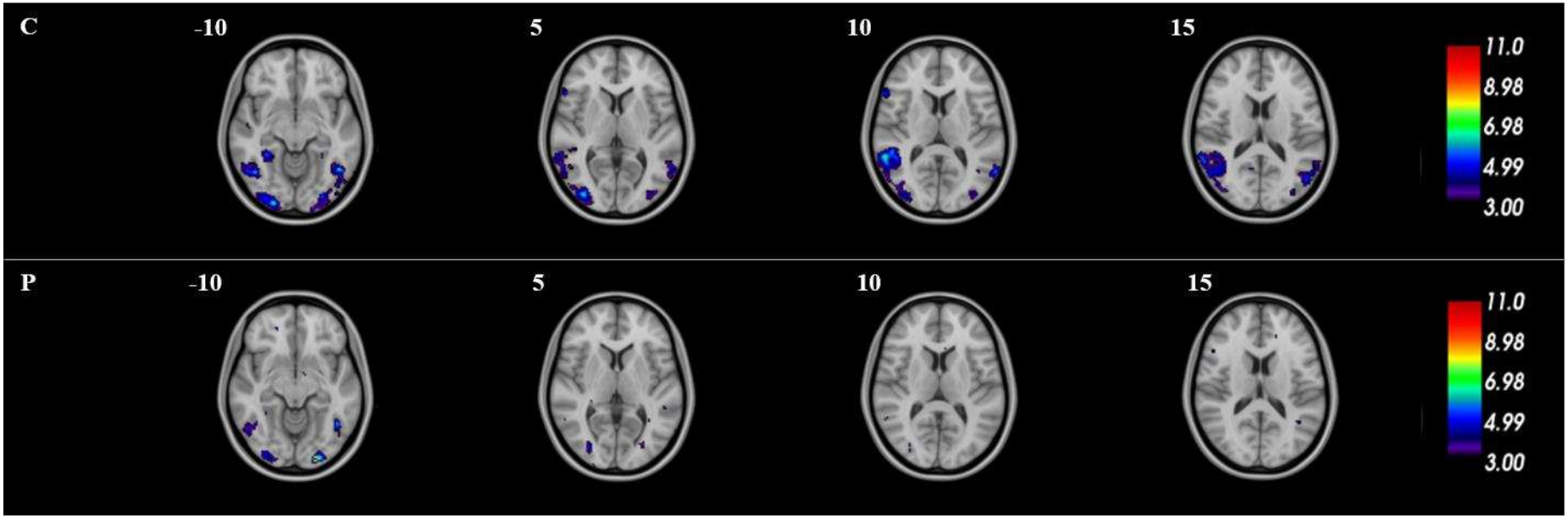
13

3.3. The functional neural basis of ToM impairments in right and left mTLE patients

3.3.1. *Within-group analyses of ToM vs. non-ToM interactions*

Within-group analyses for ToM vs. goal-directed interactions and ToM vs. random interactions revealed that the corresponding brain activation patterns were similar in controls, although the activation pattern was less widespread for ToM vs. goal-directed interactions than for ToM vs. random interactions (Supplementary data, Figure 3). Furthermore, the conjunction analyses revealed a broad, common brain network (Supplementary data, Table 5). Hence, in order to keep the power high enough to detect these effects of interest (and in line with Pedersen et al.'s method (2012)), we decided to perform intergroup brain activation analyses by contrasting ToM vs. non-ToM interactions. The within-group brain activation analyses for ToM vs. non-ToM interactions (Figure 2) revealed widespread bilateral occipitotemporoparietal activation (notably in the inferior and middle occipital gyrus, the left TPJ, the fusiform gyri and the STS) in healthy controls. The within-groups analyses for the two healthy control groups (i.e. participants who were matched for demographic characteristics with either left or right mTLE patients) evidenced similar neural activation patterns. In right mTLE patients, activation was limited to the inferior and middle occipital gyrus. No significant activation was found in left mTLE patients

Figure 2. Activation patterns evidenced by the within-group brain activation analyses in healthy controls (C) and right mTLE patients (P)



Abbreviations: mTLE = mesial temporal lobe epilepsy. The MRI scans (axial slices) shows brain regions with increased neural activity during ToM interactions when compared with non-ToM interactions, in healthy controls (C, top panel) and right mTLE patients (P, bottom panel).

The MRI scans of left mTLE patients are not shown, since no significant activation was found. The number above each photo indicates the plane's z coordinates. The right hemisphere is represented on the left of each picture.

3.3.2. *Between-group analyses of ToM vs. non-ToM interactions*

Given that the MoCA scores were lower in mTLE patients than in healthy controls; this score was used as a covariable in subsequent analyses. As no significant result for the significance level choose was found, it was slightly increased to an uncorrected significance level of $p < .001$ (with clusters defined by at least 10 contiguous voxels). The between-group brain-activation analyses for ToM vs. non-ToM interactions revealed activations in the right precuneus and fusiform gyrus in healthy controls (relative to right mTLE patients) and activations in the dorsal part of the right mPFC and the posterior part of the left cerebellum in right mTLE patients (relative to healthy controls) (see Table 3). When compared with left mTLE patients, healthy controls showed activation in the right supplementary motor area (SMA). Conversely, activations were found in the right entorhinal cortex in left mTLE patients, when compared with healthy controls. In mTLE patients, the categorization scores were not correlated with the neural activation patterns evidenced by the between-groups analyses.

Table 3. Activation patterns evidenced by the between-group analyses (healthy controls and mTLE patients) for ToM vs. non-ToM interactions

Region	Hem	Coordinates			z scores	Voxels
		x	Y	z		
Controls > right mTLE patients						
Precuneus	R	10	-64	18	4.15	23
Fusiform gyrus	R	34	-8	-34	3.69	14
Right mTLE patients > Controls						
Superior frontal gyrus/Dorsal medial prefrontal cortex	R	8	54	40	3.64	11
Cerebellum/Posterior lobe	L	-14	-64	-30	3.58	13
Controls > left mTLE patients						
Superior frontal gyrus/Supplementary motor area	R	28	4	62	3.93	13
Left mTLE patients > Controls						
Parahippocampal gyrus/Entorhinal cortex	R	16	0	-38	3.45	16

Abbreviations: mTLE = mesial temporal lobe epilepsy; Hem = hemisphere; R = right; L = left; Coordinates = coordinates in Montreal Neurological Institute space

3.3.3. *Influence of age at onset and duration of epilepsy on ToM network activations in right and left mTLE patients*

Regression analyses on the ToM vs. non-ToM activation contrasts revealed that age at onset was a predictor of the activation pattern in the ventral part of the mPFC ($r^2 = .6717$, $p = .0011$) and the supramarginal part of the TPJ ($r^2 = .8217$, $p < .001$) in right mTLE patients (see Table 4). No other significant relationships between activation pattern and the duration of epilepsy were found for right mTLE patients. For left mTLE patients, age at onset and the duration of epilepsy were not correlated with the activation patterns.

Table 4. Significant regression analyses for the contrast in neural activation patterns in response to ToM interactions vs. non-ToM interactions, with age at onset of epilepsy in right mTLE patients

Region	Hem	Coordinates			z scores	Voxels
		x	Y	z		
Middle frontal gyrus/Ventral medial prefrontal cortex	L	-8	30	-14	5.20	142
	*	0	36	-18	4.37	_
	L	-14	48	-14	3.46	_
Supramarginal gyrus/ Temporoparietal junction	L	-64	-42	34	3.99	98
	L	-62	-50	34	3.60	_

Abbreviations: ToM = theory of mind; mTLE = mesial temporal lobe epilepsy; Hem = hemisphere; R = right; L = left; Coordinates = coordinates in Montreal Neurological Institute space. Data for left mTLE patients are not shown because there were no significant results.

4. Discussion

By using an animated shapes task, our study sought to provide the first insights into the functional neural basis of ToM disorders in mTLE patients. We evidenced different neural activation patterns within the neural networks of the two ToM components in mTLE patients compared with healthy controls (i.e. explicit reasoning about mental states and implicit processing of information on biological motion and action). These activation patterns were influenced by the laterality of epilepsy (right vs. left) and the age at onset of epilepsy.

On the behavioral level, mTLE patients showed impairments (relative to healthy controls) in the categorization of ToM interactions. The mTLE patients were more likely to categorize ToM interactions as non-ToM interactions than healthy controls. This supports Broicher et al.'s (2012b) finding that mTLE patients ascribe less intentionality to mental state interactions than healthy controls do (Broicher et al., 2012b). In contrast to the literature data, we did not observe an association between clinical characteristics (such the age of onset and the duration of epilepsy) and ToM performance scores (Shaw et al., 2004; Giovagnoli et al., 2011, 2013; Hennion et al., 2015). However, the categorization scores for ToM interactions had a low dispersion (0 to 6). Furthermore, the included mTLE patients had relatively homogeneous clinical profiles, with hippocampal abnormalities and, in general, an early age of onset and a long disease duration. Taken together, these methodological factors might have limited the ability to evidence the effects of clinical risk factors for ToM impairments in the mTLE patients. Concerning the potential impact of symptoms of depression and anxiety on ToM impairments, we did not observe an association between the ToM scores on one hand and the BDI and STAI scores on the other. It is noteworthy that the potential existence of this association in TLE patients has been probed by several behavioral studies (Broicher et al., 2012b; Giovagnoli et

al., 2013; Hennion et al., 2015; Wang et al., 2015). However, none of the latter studies identified symptoms of depression and anxiety as predictive factors for ToM performances.

On the neural level, our within-group analyses showed that healthy controls activated a more widespread network in response to the ToM interactions than they did in response to non-ToM interactions. This confirms the results of previous studies of healthy controls using the same ToM task (Castelli et al., 2002, 2000; Das et al., 2012; Malhi et al., 2008; Pedersen et al., 2012; Schultz et al., 2003). Indeed, our results showed greater activation associated with mental state attribution in four main regions: the inferior and middle occipital gyrus, the TPJ, the fusiform gyrus and the STS. However, the level of activation of the prefrontal cortex reported in the literature was not statistically significant in the present study.

In contrast, the neural activation in response to ToM interactions (compared with non-ToM interactions) was extremely limited in mTLE patients. No significant activation was found in left mTLE patients and only the inferior and middle occipital gyrus was activated in right mTLE patients. Previously, Castelli et al.'s (2002) positron emission tomography study found that this extrastriatal region was the only part of the brain to be frequently activated in both autistic patients and healthy controls in response to ToM interactions (compared with random interactions) (Castelli et al., 2002). As suggested by Castelli et al., this neural activation pattern could reflect the greater visual complexity of the ToM interactions, which results in a more complex activation pattern. More recently, it was also found that neural activation of this occipital area might be more specific for the attribution of physical states (Mason and Just, 2011). This region of the brain could be of relevance for understanding biological motion and action, which is considered to be an important component of elementary ToM processes (i.e. the implicit component of ToM) (Wolf et al., 2010).

Our between-group analyses revealed that several regions of the brain were recruited in healthy controls (relative to mTLE patients) for ToM interactions (relative to non-ToM

interactions). Compared with right mTLE patients, healthy controls activated the right precuneus and fusiform gyrus. Compared with left mTLE patients, healthy controls activated the right SMA. Interestingly, the fusiform gyrus and the SMA are both involved in the implicit component of ToM processes (Das et al., 2012; Pedersen et al., 2012). Hypo-activation of the fusiform gyrus and the SMA has been associated with difficulties in interpreting biological motion and action in autism (Marsh and Hamilton, 2011). Positron emission tomography and fMRI studies of the animated shapes task in autistic patients have also highlighted a role of the fusiform gyrus in ToM impairments (Castelli et al., 2002; Schultz et al., 2003). Moreover, the precuneus is currently thought to be an important area for high-level cognitive functions (including visuospatial mental imagery and self-processing operations) and is considered to be a nodal structure that forms and processes self-representations (Cavanna and Trimble, 2006).

Conversely, several regions of the brain were more activated in the mTLE patients (relative to healthy controls) in response to ToM interactions (relative to non-ToM interactions). Compared with healthy controls, right mTLE patients activated the left posterior cerebellum and the right dorsal mPFC. The left posterior cerebellum is known to be a modulator of affect and cognition (Stoodley and Schmahmann, 2010) and has been implicated in social interaction and visual ToM task processing through reciprocal connectivity with the right STS (Sokolov et al., 2012). It is noteworthy that impairments in the faux pas task in a patient with cerebellar atrophy have also recently been described (Parente et al., 2013). Thus, over-activation of the left posterior cerebellum in right mTLE patients might reflect the use of a compensatory mechanism involved in ToM processes. In turn, the dorsal mPFC is involved in the explicit component of ToM processes, and specifically in cognitive ToM processes (such as social inferences of intentions and beliefs) (Abu-Akel and Shamay-Tsoory, 2011; Amodio and Frith, 2006). Interestingly, hyperactivation of the dorsal mPFC has been demonstrated in patients with schizophrenia performing the animated shapes task (Pedersen et al., 2012). In contrast, left

mTLE patients activated the right entorhinal cortex (relative to healthy controls). The entorhinal cortex receives the terminal afferent of the visual pathway and is strongly connected with the hippocampus. Both structures are involved in binding processes (Diana et al., 2007). As described above, Broicher et al. (2012a) found that the connectivity between amygdala and the left hippocampal formation in right mTLE patients was positively correlated with ToM performance in the faux pas task - suggesting the presence of a compensatory mechanism in contralateral mesial regions (Bettus et al., 2009). Thus, our observation of hyper-activation of the right mesial regions in left mTLE patients during a ToM task prompts us to speculatively suggest the presence of a mechanism that compensates for left mesial dysfunction in the implicit component of ToM processes. However, we did not find a significant correlation between the categorization of ToM interactions on one hand and neural activation patterns in this region on the other. It should be noted that the low dispersion of the categorization scores for ToM interactions (0 to 6) may have affected our ability to detect this type of association. A potential effect of stimulus type (a verbal stimulus in the faux pas task vs. a visuospatial stimulus in the animated triangles task) on the differential recruitment of the left vs. right hippocampal formation can also be considered. Interestingly, Cohn et al. (2015) recently reported that structural damage to the temporal regions impairs ToM performances in TLE patients. Indeed, by applying a voxel-based morphometry (VBM) analysis, the researchers demonstrated that the grey matter volumes of left hippocampus and left anterior neocortex are correlated with both basic and advanced social inference abilities in left TLE patients.

The patients' clinical characteristics appeared to have a direct association with the recruitment of specific regions of the ToM network. When compared with healthy controls, right and left mTLE patients differed in the nature of the impairments in the ToM network, suggesting an influence of laterality. Age at onset of epilepsy was also found to have an impact on neural activation patterns within the ToM neural network. In right mTLE patients, a young

age at onset of epilepsy was predictive of hypo-activation in the TPJ and the ventral mPFC, which form part of the network involved in the explicit component of ToM processes (Amodio and Frith, 2006; Saxe and Kanwisher, 2003). Hypo-activation of the TPJ (a key region for the formation of mental states (Abu-Akel and Shamay-Tsoory, 2011)) has been associated with ToM impairments in the animated triangles task in patients with schizophrenia or autism (Castelli et al., 2002; Das et al., 2012). The ventral mPFC is also thought to be involved in affective ToM processes, such as social inferences of emotional states (Abu-Akel and Shamay-Tsoory, 2011).

Taken as a whole, our data show that both right and left mTLE patients have similar levels of behavioral impairments in a task that encompasses the implicit and explicit components of ToM processes. However, these ToM impairments are mediated by distinct neural abnormalities. Both right mTLE and left mTLE patients present less intense neural activation patterns in regions of the brain involved in the implicit component of ToM processes. However, the impaired regions differ according to the laterality of mTLE (i.e. posterior regions in right mTLE patients, and anterior regions in left mTLE patients). Furthermore, we found an increased pattern of activation in regions involved in the explicit component of ToM processes (including social inferences of intentions and beliefs) in right mTLE patients. Age at onset also mediated these processes (including the formation of mental states and social inferences of emotional states). In left mTLE patients, there were no differences in neural activation patterns related to the explicit component of ToM processes. However, we speculatively hypothesize that greater activation of contralateral mesial regions is a compensatory mechanism in left mTLE patients. The neural abnormalities of the ToM network seen in mTLE patients have been also outlined in other neuropsychiatric disorders, such as autism and schizophrenia. It would be interesting to perform a transdiagnostic fMRI study of ToM processes, with a view to understanding similarities in and differences between the underlying mechanisms.

Our study had two main limitations. Firstly, we chose a relatively undemanding significance threshold for the between-group analyses (uncorrected $p < .001$, with 10 voxels). However, this threshold is known to produce a balance between type I and II errors (Lieberman and Cunningham, 2009). Secondly, the fact that there were fewer mTLE patients (n = 12 right and 13 left mTLE patients, respectively) than healthy controls (n = 25) means that we cannot rule out low statistical power in the between-groups MRI analyses. However, the within-groups analyses for the two smaller healthy control groups (which were matched for demographic characteristics to the left or right mTLE patient groups) evidenced similar neural activation patterns. Furthermore, the patient vs. control neural activation patterns observed here were similar to those reported in studies with comparable or larger numbers of participants.

In conclusion, the present study generated novel, useful data on social cognitive disorders in TLE - the most common form of focal epilepsy. Even though several behavioral studies have evidenced the frequent presence of ToM disorders in TLE, the neural basis of these impairment has not been extensively characterized. Our use of a novel fMRI paradigm in mTLE patients showed that their poor ToM performance is probably due to the impairment of several sub-components in ToM brain networks, depending on the exact clinical profile. Our results also indicate that sociocognitive impairments in mTLE result from a brain network pathology; in fact, anomalies outside the temporal lobe may have a negative impact on outcomes in mTLE patients. A better understanding of the neurocognitive processes of ToM is particularly important in mTLE, given that ToM impairments are risk factors for abnormal psychosocial functioning and poor quality of life (Giovagnoli et al., 2013; Hennion et al., 2015; Wang et al., 2015).

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Disclosure of Conflicts of Interest

None. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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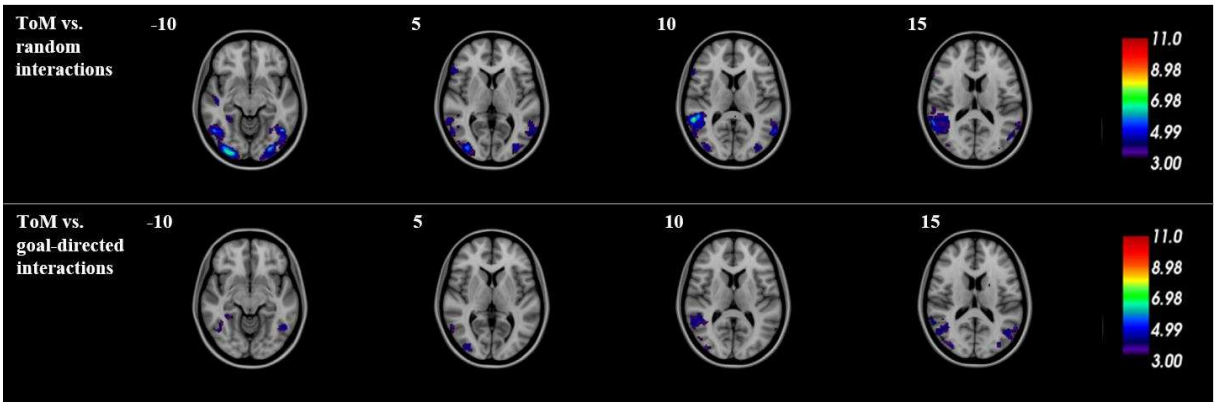
Supplementary data

Figure 3. Activation patterns evidenced by the within-group brain activation analyses for ToM vs. random interactions and ToM vs. goal-directed interactions in healthy controls



The MRI scans (axial slices) shows brain regions with increased neural activity during ToM interactions when compared with non-ToM interactions in healthy controls. The number above each photo indicates the plane's z coordinates. The right hemisphere is represented on the left of each picture.

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Table 5. Activation patterns evidenced by the conjunction analyses for ToM vs. random interactions and ToM vs. goal-directed interactions in healthy controls

Region	Hem	Coordinates			z scores	Voxels
		x	y	z		
Superior temporal gyrus	R	58	-50	12	4.8	339
Cerebellum/Anterior lobe	R	28	-40	-16	5.61	257
Middle occipital gyrus	R	36	-84	4	4.86	74
Temporoparietal junction	L	-44	-70	20	4.16	46
Fusiform gyrus	L	-40	-48	-14	4.3	41
Inferior occipital gyrus	R	30	-92	-4	4.07	30
Fusiform gyrus	L	-46	-60	-10	5	25
Cerebellum/Posterior lobe	L	-32	-76	22	4.5	14
Middle occipital gyrus	R	42	-78	14	3.72	10

Abbreviations: Hem = hemisphere; R = right; L = left; Coordinates = coordinates in Montreal Neurological Institute space

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Experiences of self-conscious emotions in temporal lobe epilepsy

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Abstract

Self-conscious emotions (SCEs) with a negative valence (such as shame and guilt) or a positive valence (such as pride) are moral emotions that emerge from self-reflection and self-evaluation processes in social contexts. In some neurologic and psychiatric disorders, experiences of SCEs are dysregulated. The objectives of the present study were to (i) evaluate whether patients with temporal lobe epilepsy (TLE) experience SCEs in the same way as non-clinical (control) participants, and (ii) probe the relationships between experiences of SCEs on one hand and the psychological symptoms frequently diagnosed in patients with TLE (anxiety and depression), the patients' clinical characteristics, and their functional outcomes in everyday life.

Sixty-one patients with TLE and 61 matched controls completed a self-questionnaire (the Positive and Negative Affect Schedule) that enabled us to evaluate the extent to which they experienced

shame, guilt and pride. Demographic data, cognitive data, the severity of anxiety symptoms, and the severity of depressive symptoms were recorded for all participants. In patients with TLE epilepsy, data of clinical characteristics and quality of life were also evaluated.

Relative to controls, patients with TLE were more likely to experience negative-valence SCEs to a higher extent and positive SCEs to a lesser extent. The patients who experienced negative-valence SCEs to a higher extent (rather than to a lesser extent) had a higher frequency of seizures, more severe anxiety and depressive symptoms, and a greater prevalence of anxiety and depressive disorders. Furthermore, patients who experienced positive-valence SCEs to a lesser extent (rather than to a higher extent) displayed a higher level of anxiety. Lastly, differences in experiences of SCEs by patients with TLE were associated with a lower quality of life.

In conclusion, experiences of SCEs can be dysregulated in patients with TLE. This dysregulation is linked to the patients' clinical and psychological symptoms and quality of life. In this context, SCEs might be a target of interest in the management of epilepsy.

Keywords: self-conscious emotion, temporal lobe epilepsy, depression, anxiety, quality of life

1. Introduction

Shame, guilt, embarrassment, and pride are referred to as self-conscious emotions (SCEs, a subset of moral emotions) [1]. An individual’s experience of SCEs emerges from self-reflection and self-evaluation processes [2]. Self-conscious emotions motivate individuals to defend and enhance their self-representations, produce behaviors that are socially valued, and inhibit those that are socially disapproved [3]. In this respect, SCEs differ from nonmoral emotions (e.g., basic emotions like joy, fear, anger, and disgust). This difference might also explain why experiences of SCEs are thought to appear later in a child's development than experiences of nonmoral emotions (for an example of an experiment on the developmental trajectory of pride, see[4]). However, the link between SCEs and nonmoral emotions remains poorly understood and requires further exploration. On a behavioral level, experiences of SCEs and experiences of basic emotions may differ in their neural basis; Gilead et al.

(2016) showed that SCEs recruited more frontal areas (such as the medial prefrontal cortex), whereas basic emotions recruited "relatively phylogenetically-ancient" areas of the cortex [5].

The dysregulation of experiences of SCEs has been documented in some psychiatric disorders [6]. Perturbed experiences of negative-valence SCEs (such as shame and guilt) are frequently observed; for example, exaggerated feelings of shame have been observed in anxiety disorders in general [7] and social anxiety in particular [8]. It may also be the case that people suffering from depression are more prone to experiences of shame [9]. Moreover, combinations of contrasting changes in experiences of SCEs have also been described; people with borderline personality disorders may experience shame to a higher extent but guilt to a lesser extent [10]. Nevertheless, more intense experiences of positive-valence SCEs (such as pride) might also be associated with psychopathology, just as more intense experiences of pride might be observed in narcissism [11] or schizophrenia [12]. Although neurologic conditions have been studied less extensively, differences in modifications of experiences of SCEs have also been highlighted in neurologic conditions. For example, diminished experiences of SCEs have been reported following an orbitofrontal lesion [13], and in patients with frontotemporal dementia[14,15]. It is noteworthy that both of these neurologic disorders are known to have an impact on the patients' social behavior. It is now well established that patients with TLE are exposed to a risk of extensive structural and functional alterations in both temporal regions and extratemporal structures (such as the lateral temporal, temporoparietal, frontal and occipitotemporal neocortices) [16,17]. These changes encompass regions involved in SCE processing and might thus, account for disturbances in patients with TLE.

A growing number of studies of patients with temporal lobe epilepsy (TLE) have highlighted emotional processing disorders, with a current focus on the ability to recognize basic emotional stimuli on the basis of facial and vocal emotional expressions[18,19]. However, some aspects of emotional processing have not been extensively explored in patients with TLE; one such aspect is emotional experience [20–22]. In previous work, we found that experiencing the emotional valence of pictures (ranging from very unpleasant to very pleasant) might be – in contrast to the arousal experience – unaffected in patients with TLE [22]. However, the way in which patients with TLE experience SCEs has not previously been investigated. We therefore decided to establish whether or not patients with

TLE report differences in experiences of SCEs. To this end, we applied the Positive and Negative Affect Schedule (PANAS), a self-questionnaire that enables an individual to rate the extent to which he/she experiences a number of SCEs, including shame, guilt, and pride [23]. We focused on TLE because psychological symptoms have been described in this context. Indeed, depressive disorders are frequently encountered in TLE [24], and are often associated with anxiety disorders [25]. Furthermore, the relationship between epilepsy and psychological symptoms is thought to be bidirectional, since the presence of depression and anxiety appears to be a risk factor for certain clinical characteristics of TLE [26], and is predictive of the patients' quality of life [27]. Consequently, a better understanding of psychiatric disorders in TLE might have major clinical implications.

2. Material and methods

2.1 Participants

Sixty-one patients with TLE consulting at Lille University Medical Center's Epilepsy Unit (Lille, France) were consecutively recruited on the basis of a clinical evaluation, a video-electroencephalographic recording, neuropsychological data, and neuroimaging results. The inclusion criteria were (i) unilateral TLE and (ii) right-handedness (according to the Edinburgh Handedness Inventory) [28]. The main exclusion criteria were (i) impaired intellectual capacity (an intellectual quotient below 75, according to a French adaptation of the National Adult Reading Test: fNART) [29] or impaired non-verbal reasoning (according to Raven's Coloured Progressive Matrices: PM-47) [30]; (ii) significant amnesia or a marked impairment of instrumental capacities (agnosia, aphasia, apraxia, alexia or agraphia); (iii) a history of neurologic disease other than epilepsy; (iv) a history of psychiatric disorders (other than depression or anxiety); and (v) a seizure in the 24 hours preceding the experimental session.

The control group included 61 right-handed participants (according to the Edinburgh Handedness Inventory), each of whom was matched for demographic characteristics (age, gender and educational level) with a patient. The exclusion criteria for controls were (i) impaired intellectual

capacity (an intellectual quotient below 75, according to the fNART) or impaired non-verbal reasoning (according to the PM-47), and (ii) a history of neurologic or psychiatric disorders.

The study protocol had been approved by the local investigational review board (CPP Nord Ouest IV, Lille, France) and was performed in accordance with the tenets of the Declaration of Helsinki. All participants gave their written, informed consent to participation in the study.

2.2 Measures

2.2.1 Experiences of SCEs

The participants' experiences of SCEs were measured using items from the PANAS, which has been found to have good item validity [23,31]. Participants were requested to respectively report on the extent to which they experienced ten negative affects (including shame and guilt) and ten positive affects (including pride) during the past few weeks, on a 5-point Likert scale (1: "very slightly or not at all"; 2: "a little"; 3: "moderately"; 4: "quite a bit"; 5: "very much"). Only the data on shame, guilt and pride were specifically analyzed.

2.2.2 Clinical characteristics

The following characteristics of patients with TLE were recorded: age at onset of epilepsy, duration of epilepsy, seizure frequency (per month, over the previous three months), and laterality of epilepsy (right, left). The presence or absence of a brain lesion was established from structural neuroimaging results (3 Tesla MRI), and classified as "hippocampal sclerosis", "no lesion" or "other temporal lesions" (focal gliosis, focal atrophy or focal dysplasia). The diagnosis of hippocampal sclerosis was based on a volume decrease on T1-weighted images and a high signal intensity on fluid-attenuated inversion recovery images.

2.2.3 Cognitive function

The patients with TLE and the controls underwent the Montreal Cognitive Assessment (MoCA) [32], which assesses a number of cognitive domains (attention, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculation, and orientation).

2.2.4 Psychological symptoms

Self-reports by the patients with TLE and the controls were used to estimate the severity of depressive symptoms (according to the Beck Depression Inventory (BDI)) [33] and anxiety symptoms (according to the trait version of the State-Trait Anxiety Inventory (STAI-T)) [34].

2.2.5 Functional outcomes

In patients with TLE, quality of life was estimated using the Quality of Life Inventory in Epilepsy (QOLIE-89) [35].

2.3 Data analysis

All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC). The threshold for statistical significance was set to $p<.05$. Quantitative variables were expressed as the median and the mean ± standard deviation (SD), and qualitative variables were expressed as the frequency (%). Parametric tests were used for normally distributed datasets; otherwise, non-parametric tests were applied.

Patients with TLE and controls were compared in terms of their cognitive functioning (MoCA score) and psychological symptoms (STAI-T and BDI scores), using the Mann–Whitney U test or Student's t test. To estimate the prevalence of depression and anxiety disorders, we considered the corresponding cut-off scores (i.e. a BDI score $\geq$ 12, and a STAI-T score $\geq$ 39) and the results of a structured interview.

Based on the PANAS score, the participants (i.e. both patients with TLE and controls) were classified according to the extent ("high" or "low") to which they experienced each SCE. Participants with a self-reported PANAS item score of 3, 4 or 5 for the SCE were considered to have experienced

that SCE to a high extent. Conversely, participants with a self-reported PANAS item score of 1 or 2 for the SCE were considered to have experienced that SCE to a low extent. Comparisons of the proportion of individuals experiencing each SCE (for patients with TLE vs. controls) were performed using a chi-squared test or (when the expected cell frequency was <5) Fisher's exact test.

To better characterize the experiences of each SCE in patients with TLE, patients experiencing the SCE to a high extent and those experiencing the SCE to a low extent were compared in terms of demographic, cognitive and clinical characteristics and psychological symptoms. These comparisons were performed by using the Mann–Whitney U test or Student's t test for quantitative variables and a chi-squared test or Fisher's test for qualitative variables.

Lastly, patients in the "high" and "low" groups for each SCE were compared in terms of the functional outcome (quality of life, according to the QOLIE-89), using Student's t test.

3. Results

3.1 Demographic, cognitive and psychological characteristics of patients with TLE

The mean MoCA score was lower in patients with TLE than in controls (Table 1). Relative to controls, patients with TLE had higher scores for depression (according to the BDI) and anxiety (according to the STAI-T). Among the patients with TLE, 60.66% (n=37) met the clinical criteria for depression, and 85.25% (n=52) met the clinical criteria for anxiety.

3.2 Experiences of SCEs in patients with TLE

Relative to controls, the proportion of patients experiencing shame and guilt to a high extent was greater, and the rate of patients experiencing pride to a high extent was lower (Table 2).

3.3 Characterization of the experiences of SCEs in patients with TLE

3.3.1 Relationships with demographic characteristics

There were no differences in demographic characteristics between patients experiencing SCEs to a high extent and those experiencing SCEs to a low extent (Table 3).

3.3.2 Relationships with clinical characteristics

Seizures were more frequent in patients experiencing shame to a high extent than in patients experiencing shame to a low extent (Table 3). There were no other differences in clinical characteristics with regard to the extent to which SCEs were experienced.

3.3.3 Relationships with cognitive characteristics

There were no differences in cognitive characteristics between patients experiencing SCEs to a high vs. a low extent (Table 3).

3.3.4 Relationships with psychological symptoms

When compared with patients who experienced shame to a low extent, patients who experienced shame to a high extent had higher depression scores (according to the BDI score) and were more likely to meet the clinical criteria for depression (48.78% vs. 85%, respectively; $p = .0066$). Likewise, patients who experienced shame to a high extent had higher anxiety scores (according to the STAI-T), and were more likely to meet the clinical criteria for anxiety (100%, vs. 78.05% of the patients who experienced shame to a low extent; $p = .0242$).

Relative to patients who experienced guilt to a low extent, patients who experienced guilt to a high extent had higher depression scores (according to the BDI), and were more likely to meet the clinical criteria for depression (48.72% vs. 81.82%, respectively; $p = .0110$). Likewise, patients who experienced guilt to a high extent had higher anxiety scores (according to the STAI-T), and were more likely to meet the clinical criteria for anxiety (100%, vs. 76.92% of the patients who experienced guilt to a low extent; $p = .0203$).

When we compared patients who experienced pride to a low vs. high extent, there were no significant differences in terms of depression (according to the BDI scores and the prevalence of

depression, 70.59% and 48.15%, respectively; p = .0748). Relative to patients who experienced pride to a high extent, patients who experienced pride to a low extent had higher anxiety scores (according to the STAI-T); however, there was no significant difference between these "high" and "low" groups in terms of the proportion of participants meeting the clinical criteria for anxiety (74.07% vs. 94.12%, respectively, p = .0646).

3.3.5 Relationships with functional outcomes

Relative to patients who experienced shame and guilt to a low extent, patients who experienced shame and guilt to a high extent had a worse quality of life (according to the QOLIE-89, Table 3). Relative to patients who experienced pride to a low extent, patients who experienced pride to a high extent had a better quality of life.

4. Discussion

Our study provided insights into how patients with TLE experience SCEs, relative to nonclinical controls. More specifically, patients with TLE showed specific patterns of change in their experience of SCEs; they were more likely than controls to experience the negative-valence SCEs of shame and guilt and less likely to experience the positive-valence SCE of pride. Our observation of this specific pattern suggests that experiences of moral emotions can be dysregulated in patients with TLE[22, 36].

From a developmental perspective, one can also hypothesize that SCEs are experienced to a lesser extent by patients with TLE because experiences of these emotions (e.g. pride) develop later in childhood than experiences of non-moral emotions (e.g. joy) [4]. However, we found that experiences of SCEs were not associated with the clinical characteristics of TLE, such as the age of onset and even the duration of epilepsy. Furthermore, a relationship between age of onset and experiences of SCEs would have not explained why our patients with TLE experienced negative-valence SCEs to a higher extent than controls did.

However, on the clinical level, we observed a specific, positive relationship between experiences of shame and the frequency of seizures in patients with TLE. This relationship might be

linked to a direct (i.e., neurophysiological) effect of seizures on experiences of SCEs. As indicated in the Introduction, it has been well established that patients with TLE are at risk of alterations in the temporal and extratemporal structures involved in SCE processing (such as the temporal and frontal neocortices, [16,17] These alterations might therefore, account for disturbances of SCE experiences in patients with TLE.

Nevertheless, an indirect effect of seizures (such as stigma) can also be envisaged [37]. Indeed, patients with TLE might feel more shame in daily life because they may experience seizures in social contexts. This uncertainty about having a seizure in the presence of other people and the latter's reactions to these seizures might be involved in the higher extent to which the patient in the present study experienced feelings of shame. A longitudinal study might be needed to explore these hypotheses; in particular, it could explore the relationships between seizure frequency, the feeling of stigma, and experiences of SCEs, as well as changes over time in these relationships. Other ictal and interictal clinical parameters (such as the frequency and location of interictal abnormalities, and seizure length and severity) also merit further investigation. Indeed, these parameters are already known to be associated with cognitive impairments and might therefore, also be linked to disturbances in SCE processing [38,39].

Dysregulated experiences of SCEs might be also result from the psychological symptoms frequently encountered in patients with TLE. Depression and anxiety were highly prevalent in our group of patients with TLE. A high prevalence of psychiatric disorders has been documented by many other studies of epilepsy [40], suggesting that this co-occurrence warrants further investigation. In our patients with TLE, experiencing negative-valence SCEs to a high extent (vs. a low extent) was found to be associated with higher levels of anxiety and depressive symptoms, and a higher prevalence of anxiety and depressive disorders. Shame and guilt have been frequently associated with psychiatric conditions [41], and might thus be potential targets for psychotherapy [6]. Longitudinal studies might be of great interest to establish whether changes in the psychological status of patients with TLE have repercussions on their experiences of SCEs. It might be worth testing specific therapies aimed at working on the exacerbated feelings of shame and guilt experienced by patients with TLE. It would also be interesting

to observe whether therapeutic interventions (whether pharmacological or not) for anxiety and depression in TLE are associated with changes in the expression of shame and guilt.

The relationship between our patients' experiences of positive-valence SCEs on one hand and depressive and anxious symptoms on the other was less clear. Indeed, only the anxiety score (and not the prevalence of a clinical anxiety disorder) was significantly associated with the extent to which the positive-valence SCE pride was experienced. However, it is possible that the extent to which pride is experienced has a less direct impact on the psychopathological status of patients with TLE more. Relationships between some aspects of pride and self-esteem have been observed [11], whereas low self-esteem is associated with depression and anxiety [42].

Focusing on experiences of SCEs in TLE might not only provide a better understanding of anxiety and depressive symptoms but could also have consequences on the epilepsy itself and associated manifestations. The relationship between depression and epilepsy is thought to be valid in both directions [43]: patient with epilepsy have a greater risk of developing depression, and people suffering from depression are more at risk of developing epilepsy [44]. Moreover, the presence of depression in patients with epilepsy in TLE affects the clinical symptoms by increasing the subsequent risk of generalized seizures [45]. It is noteworthy that in the present study, the patients' experience of shame was associated with the frequency of seizures. Thus, it would be interesting to explore the bidirectional nature of the relationships between experiences of SCEs and clinical symptoms in epilepsy - as already suggested above.

Lastly, experiences of SCEs were also related to our patients' quality of life. Patients who experienced negative-valence SCEs to a high extent and/or positive-valence SCEs to a low extent had a lower quality of life. This finding is in line with literature data showing that elevated negative affectivity of valence and decreased positive affectivity were predictive of a worse quality of life and emotional and psychosocial maladjustments in patients with epilepsy [27]. Moreover, relationships between quality of life and the extent to which SCEs are experienced have been documented in populations with psychiatric disorders [12].

The present study had several limitations. Firstly, we documented SCE experiences by asking participants to report (via the PANAS) the extent to which they had experienced a given emotion over the past few weeks, without contextualization. Thus, despite the PANAS' good item validity [23,31], this was a subjective evaluation of SCE experiences. In future studies, it would be interesting to consider whether experiences of SCEs change when a patient with TLE is faced with specific situations. For example, the patient could be asked to state what he/she would feel in particular scenarios [46]. Another avenue of investigation would be to identify a more objective marker of SCE experiences, such as changes in neurophysiological variables like (for example) the autonomic activity reflected by the skin conductance response. The latter is reportedly a reliable indicator of arousal experience [47]. Lastly, the present work focused on patients with TLE; we cannot say whether the changes observed here are specific to this epileptic syndrome or are applicable to all kinds of epileptic disorder.

In conclusion, our present results suggest that experiences of SCEs can be dysregulated in patients with TLE; more specifically, patients can experience negative-valence SCEs to a higher extent and positive-valence SCEs to a lower extent (relative to nonclinical subjects). These dysregulations appear to be associated with the patients' clinical and psychological status, i.e. the frequency of seizures, and the severity and prevalence of depressive and anxious disorders. Importantly, these dysregulations of experiences of SCEs appear to have a functional impact on the patients' daily life by significantly influencing the quality of life. Consequently, experiences of SCEs in epilepsy should be investigated more extensively because this aspect might be worth considering in the management of patients.

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Disclosure of conflicts of interest

None.

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Table 1. Characterization of TLE patients and the statistical significance of intergroup comparisons (p-values)			
	Controls n = 61	**TLE patients** n = 61	**p-values**
Demographic characteristics			
Age[1] in years	41.53; 42.81±12.15	42.40; 42.19±11.30	p=.7697
Gender (% male)	49.18	49.18	p=1.00
Educational level (≥ 12 years %)	47.54	47.54	p=1.00
Clinical characteristics			
Age of onset[1] in years		20.00; 21.10±14.55	
Duration of epilepsy[1] in years		18.59; 21.00±13.68	
Seizure frequency[1] per month		2.96; 4.33±4.40	
Laterality (right/left %)		49.18/50.82	
Brain lesion (HS/no lesion %)		49.18/27.87	
Cognitive functioning			
MoCA score[1] (from 0 to 30)	28.00; 28.20±1.38	26.00; 25.52±2.41	p<.0001
Psychological symptomatology			
BDI score[1] (from 0 to 63)	3.00; 5.20±6.31	14.00; 15.59±10.10	p<.0001
STAI-trait score[1] (from 20 to 80)	34.00; 35.11±8.94	48.00; 49.26±11.00	p<.0001
Functional outcomes			
QOLIE-89 score[1] (from 0 to 100)		61.59; 60.08±13.84	

Abbreviations: TLE = temporal lobe epilepsy; [1] = expressed in median; mean±standard deviation; HS = hippocampal sclerosis; MoCA = Montreal Cognitive Assessment; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; QOLIE-89 = Quality of Life Inventory in Epilepsy-89

1 Data are expressed as the median; mean ± standard deviation.

Table 2. Prevalence (%) of experiencing self-conscious emotions to a high extent among controls and patients with TLE and the statistical significance of intergroup comparisons (p-values).

Type of self-conscious emotion	Controls n = 61	Patients with TLE n = 61	p-Value
Shame (negative affect)	4.92	32.79	$p < .0001$
Guilt (negative affect)	18.03	36.07	$p = .0250$
Pride (positive affect)	80.33	44.26	$p < .0001$

Table 3. Demographic, cognitive and clinical characterization of patients with TLE with a high or with a low extend of self-conscious emotions' experience (of shame, guilt or pride),									
Dependent variables	**Type of self-conscious emotion*extend of experience**								
	Shame			**Guilt**			**Pride**		
	Low n=41	**High n=20**	**p-values**	**Low n=39**	**High n=22**	**p-values**	**Low n=34**	**High n=27**	**p-values**
Demographic characteristics									
Age[1] in years	41.80; 43.86±10.81	38.10; 38.77±11.80	p=.0994	41.80; 43.10±11.39	41.53; 40.58±11.23	p=.4086	44.78; 42.81±9.15	41.33; 41.40±13.69	p=.6477
Gender (% male)	46.34	55.00	p=.5254	48.72	50.00	p=.9234	41.18	59.26	p=.1606
Educational level (≥ 12 years %)	51.22	40.00	p=.4101	45.45	48.72	p=.8064	44.12	51.85	p=.5480
Clinical characteristics									
Age of onset[1] in years	20.00; 21.32±14.57	20.50; 20.65±14.88	p=.8536	14.00; 20.33±15.47	23.00; 22.45±13.00	p=.4212	22.50; 20.68±12.80	14.00; 21.63±16.75	p=.8959
Duration of epilepsy[1] in years	18.59; 22.51±14.73	17.03; 17.90±10.93	p=.3217	21.18; 22.66±14.18	14.97; 18.05±12.53	p=.1913	20.16; 22.04±13.72	16.49; 19.69±13.78	p=.4120
Seizure frequency[1] per month	2.96; 2.68±2.35	8.57; 7.72±5.62	p=.0010	2.96; 3.29±3.09	2.98; 6.17±5.70	p=.0751	2.96; 4.49±4.64	2.96; 4.13±4.16	p=.9825
Laterality (right/left %)	43.90/56.10	60.00/40.00	p=.2378	51.28/48.72	45.45/54.55	p=.6620	50.00/50.00	48.15/51.85	p=.8857
Brain lesion (HS/no lesion % (n^2)	63.64/36.36 (33)	64.29/35.71 (14)	p=.9662	71.88/28.12 (32)	46.67/53.33 (15)	p=.0936	66.67/33.33 (27)	57.89/42.11 (19)	p=.6381

Cognitive functioning									
MoCA score[1] (from 0 to 30)	26.00; 25.44±2.41	26.50; 25.70±2.45	p=.6082	25.00; 25.49±2.34	26.50; 25.59±2.58	p=.7042	25.00; 25.18±2.44	26.00; 25.96±2.33	p=.2431
Psychological symptomatology									
BDI score[1] (from 0 to 63)	11.00; 12.63±8.52	20.50; 21.65±10.58	p=.0014	11.00; 12.59±8.22	18.50; 20.91±11.09	p=.0040	15.50; 17.53±10.79	11.00; 13.15±8.75	p=.0926
STAI-trait score[1] (from 20 to 80)	44.00; 46.41±10.55	54.00; 55.10±9.72	p=.0030	43.00; 46.03±11.23	57.00; 55.00±7.96	p=.0008	51.00; 52.91±11.21	43.00; 44.67±10.37	p=.0029
Functional outcomes									
QOLIE-89 score[1] (from 0 to 100)	63.45; 63.64±13.01	46.69; 52.78±12.87	p=.0032	63.45; 63.34±13.04	54.54; 54.30±13.61	p=.0130	55.45; 56.67±13.34	67.21; 64.37±13.49	p=.0297

Abbreviations: TLE = temporal lobe epilepsy; [1] = expressed in median; mean±standard deviation; HS = hippocampal sclerosis; ; [2] = patients considering for this analyze; MoCA = Montreal Cognitive Assessment; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; QOLIE-89 = Quality of Life Inventory in Epilepsy-89

TITRE DE LA THESE :

L'évaluation de la cognition sociale dans la pratique clinique

RESUME :

L'évaluation de la cognition sociale fait désormais partie intégrante des bilans d'évaluation des fonctions cognitives. Pour être pertinente, cette évaluation nécessite une bonne compréhension des outils utilisés et de leur pertinence dans la prise en charge des patients. Par ailleurs, il est également important de pouvoir cerner au mieux les changements de comportement pouvant résulter de déficits de ces capacités de cognition sociale. Ces questions ont été au cœur de mes recherches sur la cognition sociale ces dernières années. Mes travaux se sont, dans un premier temps, focalisés sur l'intérêt du test des faux pas dans la pratique clinique. Les objectifs étaient, d'une part, de déterminer les prédicteurs cognitifs et comportementaux des performances à ce test chez le volontaire sain et, d'autre part, d'en évaluer l'intérêt pour la prise en charge de patients atteints de démence fronto-temporale et de patients souffrant d'épilepsie du lobe temporal. Ces travaux ont souligné la nécessité d'aborder plus finement ces compétences de cognition sociale dans la pratique clinique. Dans cette perspective, mes projets en cours se sont progressivement orientés vers de nouveaux outils d'évaluation pour une approche plus qualitative. Cette approche est actuellement en cours auprès de patients présentant une dystrophie myotonique de type 1 (maladie de Steinert) afin de caractériser leurs compétences dans ce domaine et d'appréhender les conséquences de potentiels dysfonctionnements de la cognition sociale sur leur vie quotidienne. Dans la même optique, le projet développé dans ce document met, quant à lui, l'accent sur l'intérêt d'une évaluation de la cognition sociale à la première personne (impliquant l'individu en tant qu'acteur des interactions sociales) dans les populations neurologiques. Ce projet se base sur l'étude de l'expression d'émotions à forte valeur sociale, que sont les émotions auto-conscientes (fierté, honte ou culpabilité, entre autres). Les résultats attendus sont de mieux caractériser le fonctionnement socio-émotionnel de différentes populations cliniques et de pouvoir déterminer la spécificité de certains profils d'expression émotionnelle. Une meilleure compréhension des bases neuronales de ces émotions auto-conscientes devrait également être rendue possible par l'adoption d'une approche transnosologique.

ABSTRACT :

The assessment of social cognition is now classically included as part of the assessment of cognitive functions. To be relevant, this assessment requires a good understanding of the used tools and their relevance in the care of patients. Furthermore, it is also important to be able to identify, as well as possible, changes in behavior related to deficits in these social cognition capacities. These topics have been central to my research in recent years. First of all, my work initially focused on the interest of the faux pas test for clinical practice. On the one hand, the objectives were to determine the cognitive and behavioral predictors of performance to this test in healthy volunteers and, on the other hand, to assess its interest in the management of patients with frontotemporal dementia and patients with temporal lobe epilepsy. These works highlighted the need for a more detailed approach to these social cognition skills in clinical practice. From this perspective, my current projects have gradually turned towards new assessment tools for a more qualitative approach. This approach is currently underway with patients suffering from myotonic dystrophy type 1 (Steinert's disease) in order to characterize their skills in this area and to understand the consequences of potential dysfunctions of social cognition on their daily life. In the same vein, the research project developed in this document emphasizes the value of an assessment of social cognition at the first person (involving the individual as an actor of social interactions) in neurological populations. This project is based on the study of the emotions expression with high social value, which are self-conscious emotions (pride, shame or guilt, among others). The expected results could help to characterize more precisely the socio-emotional functioning of different clinical populations and to be able to determine the specificity of certain profiles of emotional expression. A better understanding of the neural basis of these cognitive processes (self-conscious emotions) should also be made possible by our transnosological approach.