



HAL
open science

Étude de la vasoréactivité cérébrale par IRM fonctionnelle BOLD dans la maladie de Parkinson avant et après traitement par L-Dopa

Mehmet Ates Sahin

► **To cite this version:**

Mehmet Ates Sahin. Étude de la vasoréactivité cérébrale par IRM fonctionnelle BOLD dans la maladie de Parkinson avant et après traitement par L-Dopa. Human health and pathology. 2012. dumas-00738442

HAL Id: dumas-00738442

<https://dumas.ccsd.cnrs.fr/dumas-00738442v1>

Submitted on 4 Oct 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

AVERTISSEMENT

Ce document est le fruit d'un long travail approuvé par le jury de soutenance et mis à disposition de l'ensemble de la communauté universitaire élargie.

Il n'a pas été réévalué depuis la date de soutenance.

Il est soumis à la propriété intellectuelle de l'auteur. Ceci implique une obligation de citation et de référencement lors de l'utilisation de ce document.

D'autre part, toute contrefaçon, plagiat, reproduction illicite encourt une poursuite pénale.

Contact au SICD1 de Grenoble : thesebum@ujf-grenoble.fr

LIENS

Code de la Propriété Intellectuelle. articles L 122. 4

Code de la Propriété Intellectuelle. articles L 335.2- L 335.10

http://www.cfcopies.com/V2/leg/leg_droi.php

<http://www.culture.gouv.fr/culture/infos-pratiques/droits/protection.htm>

**UNIVERSITÉ JOSEPH FOURIER
FACULTÉ DE MÉDECINE DE GRENOBLE**

Année 2012

N°

**ETUDE DE LA VASOREACTIVITE CEREBRALE PAR IRM
FONCTIONNELLE BOLD DANS LA MALADIE DE PARKINSON
AVANT ET APRES TRAITEMENT PAR L-DOPA**

**THESE
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE
DIPLOME D'ETAT**

SAHIN Mehmet Ates

Né le 04 Mars 1982 à Annonay (07)

**THESE SOUTENUE PUBLIQUEMENT
A LA FACULTE DE MEDECINE DE GRENOBLE**

Le 26 septembre 2012

DEVANT LE JURY COMPOSÉ DE

Président du jury : Pr Paul KRACK

Membres :

Pr Monica BACIU

Pr Maurice DEMATTEIS

Dr Olivier MOREAUD

Pr Alexandre KRAINIK, Directeur de Thèse

La Faculté de Médecine de Grenoble n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ; ces opinions sont considérées comme propres à leurs auteurs.

Professeur des Universités - Praticien Hospitalier
 2011-2012

Nom	Prénom	Intitulé de la discipline universitaire
ALBALADEJO	Pierre	Anesthésiologie-réanimation
ARVIEUX-BARTHELEMY	Catherine	Chirurgie générale
BACONNIER	Pierre	Biostatistiques, informatique médicale et technologies de communication
BAGUET	Jean-Philippe	Cardiologie
BALOSSO	Jacques	Radiothérapie
BARRET	Luc	Médecine légale et droit de la santé
BAUDAIN	Philippe	Radiologie et imagerie médicale
BEANI	Jean-Claude	Dermato-vénérologie
BENHAMOU	Pierre Yves	Endocrinologie, diabète et maladies métaboliques
BERGER	François	Biologie cellulaire
BLIN	Dominique	Chirurgie thoracique et cardio-vasculaire
BOLLA	Michel	Cancérologie; radiothérapie
BONAZ	Bruno	Gastroentérologie; hépatologie; addictologie
BOSSON	Jean-Luc	Biostatistiques, informatique médicale et technologies de communication
BOUGEROL	Thierry	Psychiatrie d'adultes
BRAMBILLA	Elisabeth	Anatomie et cytologie pathologiques
BRAMBILLA	Christian	Pneumologie
BRICAULT	Ivan	Radiologie et imagerie médicale
BRICHON	Pierre-Yves	Chirurgie thoracique et cardio-vasculaire
BRIX	Muriel	Chirurgie maxillo-faciale et stomatologie
CAHN	Jean-Yves	Hématologie
CARPENTIER	Françoise	Thérapeutique; médecine d'urgence
CARPENTIER	Patrick	Chirurgie vasculaire; médecine vasculaire
CESBRON	Jean-Yves	Immunologie
CHABARDES	Stephan	Neurochirurgie
CHABRE	Olivier	Endocrinologie, diabète et maladies métaboliques
CHAFFANJON	Philippe	Anatomie
CHAVANON	Olivier	Chirurgie thoracique et cardio-vasculaire
CHIQUET	Christophe	Ophtalmologie
CHIROSSSEL	Jean-Paul	Anatomie
CINQUIN	Philippe	Biostatistiques, informatique médicale et technologies de communication
COHEN	Olivier	Biostatistiques, informatique médicale et technologies de communication
COUTURIER	Pascal	Gériatrie et biologie du vieillissement
CRACOWSKI	Jean-Luc	Pharmacologie fondamentale; pharmacologie clinique

DE GAUDEMARIS	Régis	Médecine et santé au travail
DEBILLON	Thierry	Pédiatrie
DEMATTEIS	Maurice	Addictologie
DEPONGEOT	Jacques	Biostatistiques, informatique médicale et technologies de communication
DESCOTES	Jean-Luc	Urologie
ESTEVE	François	Biophysique et médecine nucléaire
FAGRET	Daniel	Biophysique et médecine nucléaire
FAUCHERON	Jean-Luc	Chirurgie générale
FERRETTI	Gilbert	Radiologie et imagerie médicale
FEUERSTEIN	Claude	Physiologie
FOUMTAINÉ	Eric	Nutrition
FRANCOIS	Patrice	Epidémiologie, économie de la santé et prévention
GARBAN	Frédéric	Hématologie; transfusion
GAUDIN	Philippe	Rhumatologie
GAVAZZI	Geetan	Gériatrie et biologie du vieillissement
GAY	Emmanuel	Neurochirurgie
GRIFFET	Jacques	Chirurgie infantile
HALIMI	Serge	Nutrition
HCMMEL	Marc	Neurologie
JOUK	Pierre-Simon	Génétique
JUVIN	Robert	Rhumatologie
KRHANE	Philippe	Physiologie
KRACK	Paul	Neurologie
KRAINIK	Alexandre	Radiologie et imagerie médicale
LANTUEJOL	Sylvie	Anatomie et cytologie pathologiques
LEBAS	Jean-François	Biophysique et médecine nucléaire
LEBEAU	Jacques	Chirurgie maxillo-faciale et stomatologie
LECCIA	Marie-Thérèse	Dermato-vénérologie
LEROUX	Dominique	Génétique
LEROY	Vincent	Gastroentérologie; hépatologie; addictologie
LETOUBLON	Christian	Chirurgie générale
LEVY	Patrick	Physiologie
LUNARDI	Joël	Biochimie et biologie moléculaire
MACHECOURT	Jacques	Cardiologie
MAGNE	Jean-Luc	Chirurgie vasculaire
MAITRE	Anne	Médecine et santé au travail
MAJRIN	Max	Bactériologie-virologie
MERLOZ	Philippe	Chirurgie orthopédique et traumatologique

MORAND	Patrice	Bactériologie-virologie
MORO-SIBILOT	Denis	Pneumologie
MOUSSEAU	Mireille	Cancérologie
MOUTET	François	Chirurgie plastique, reconstructrice et esthétique; brûlogie
PALOMBI	Olivier	Anatomie
PASSAGIA	Jean-Guy	Anatomie
PAYEN DE LA GARANDERIE	Jean-François	Anesthésiologie-réanimation
PELLOUX	Hervé	Parasitologie et mycologie
PEPIN	Jean-Louis	Physiologie
PERENNOU	Dominique	Médecine physique et de réadaptation
PERNOD	Gilles	Médecine vasculaire
PIOLAT	Christian	Chirurgie infantile
PISON	Christophe	Pneumologie
PLANTAZ	Dominique	Pédiatrie
POLACK	Benoît	Hématologie
PONS	Jean-Claude	Gynécologie-obstétrique
RAMBEAUD	Jean-Jacques	Urologie
REYT	Emile	Oto-rhino-laryngologie
RIGHINI	Christian	Oto-rhino-laryngologie
ROMANET	Jean-Paul	Ophthalmologie
SARAGAGLIA	Dominique	Chirurgie orthopédique et traumatologique
SCHMERBER	Sébastien	Oto-rhino-laryngologie
SELE	Bernard	Biologie et médecine du développement et de la reproduction
SERGENT	Fabrice	Gynécologie-obstétrique
SESSA	Carminé	Chirurgie vasculaire
STAHL	Jean-Paul	Maladies infectieuses; maladies tropicales
STANKE	Françoise	Pharmacologie fondamentale
TIMSIT	Jean-François	Réanimation
TONETTI	Jérôme	Chirurgie orthopédique et traumatologique
TOUSSAINT	Bertrand	Biochimie et biologie moléculaire
VANZETTO	Gérald	Cardiologie
VUILLEZ	Jean-Philippe	Biophysique et médecine nucléaire
WEIL	Georges	Epidémiologie, économie de la santé et prévention
ZAOUI	Philippe	Néphrologie
ZARSKI	Jean-Pierre	Gastroentérologie; hépatologie; addictologie

Maître de Conférence des Universités - Praticien Hospitalier
 2011-2012

Nom	Prénom	Intitulé de la discipline universitaire
BONNETERRE	Vincent	Médecine et santé au travail
BOTTARI	Serge	Biologie cellulaire
BOUTONNAT	Jean	Cytologie et histologie
BRENIER-PINCHART	Marie-Pierre	Parasitologie et mycologie
BRIOT	Raphaël	Thérapeutique; médecine d'urgence
CALLANAN-WILSON	Mary	Hématologie; transfusion
CROIZE	Jacques	Bactériologie-virologie
DERANSART	Colin	Physiologie
DETANTE	Olivier	Neurologie
DUMESTRE-PERARD	Chantal	Immunologie
EYSSERIC	Hélène	Médecine légale et droit de la santé
FAURE	Julien	Biochimie et biologie moléculaire
GILLOIS	Pierre	Biostatistiques, informatique médicale et technologies de communication
GRAND	Sylvie	Radiologie et imagerie médicale
HENNEBICQ	Sylviane	Biologie et médecine du développement et de la reproduction
HOFFMANN	Pascale	Gynécologie-obstétrique
LABARERE	José	Epidémiologie, économie de la santé et prévention
LAPORTE	François	Biochimie et biologie moléculaire
LARDY	Bernard	Biochimie et biologie moléculaire
LARRAT	Sylvie	Bactériologie-virologie
LAUNOIS-ROLLINAT	Sandrine	Physiologie
MALLARET	Marie-Reine	Epidémiologie, économie de la santé et prévention
MAUBON	Danièle	Parasitologie et mycologie
MC LEER (FLORIN)	Anne	Cytologie et histologie
MOREAU-GAUDRY	Alexandre	Biostatistiques, informatique médicale et technologies de communication
MOUCHET	Patrick	Physiologie

PACLET	Marie-Hélène	Biochimie et biologie moléculaire
PASQUIER	Dominique	Anatomie et cytologie pathologiques
PAYSANT	François	Médecine légale et droit de la santé
PELLETIER	Laurent	Biologie cellulaire
RAY	Pierre	Génétique
RIALLE	Vincent	Biostatistiques, informatique médicale et technologies de communication
SATRE	Véronique	Génétique
STASIA	Marie-Josée	Biochimie et biologie moléculaire
TAMISIER	Renaud	Physiologie

Remerciements

Au Jury,

Professeur Alexandre Krainik

Merci Alexandre de m'avoir proposé ce sujet et d'avoir tenu le cap quand je divaguais... Ce travail c'est surtout le tien et je te remercie de l'avoir partagé avec moi.

Professeur Paul Krack

Je vous fais part de toute ma reconnaissance pour avoir accepté de présider ce jury.

Merci infiniment.

Professeurs Baciù, Dematteis et Docteur Moreaud

Je vous adresse mes remerciements les plus sincères pour avoir accepté de juger ce travail.

Soyez assurés de mon respect et de toute ma gratitude.

Aileme (à ma Famille),

Bu yaşıma kadar hiç bir fedakarlıktan kaçınmayan, desteğinizi ve sevginizi her zaman hissettiğim, değerli Anneme ve Babama teşekkür ediyorum. Allah sizleri başımızdan eksik etmesin. Ellerinizden öpüyorum.

Birinci senemde beni yalnız bırakmayan ver zor zamanlarda hep yardımcı olan Muhammet abime sonsuz teşekkür ediyorum.

Gurur duyduğum kız kardeşlerim Cihan ve Eşe'ye, özlediğim küçük kardeşim Alpaslan'a teşekkürler.

Bizleri yoktan var eden, herşeyin tek sahibi yüce Allahım, bizlere verdiklerin için sana şükrediyoruz.

Aux services d'Imagerie médicale du CHU de Grenoble,

Aux Médecins

Je vous serai éternellement redevable du savoir que vous m'avez transmis.

Merci pour votre sympathie, votre patience, votre aide, votre disponibilité et aussi votre indulgence...

A mes co-internes

Merci infiniment pour votre camaraderie. Je vous souhaite à tous beaucoup de bonheur et d'épanouissement.

Spéciale dédicace à « ma génération » que je n'oublierai jamais : Julien, Nancy, Thibaut, Aurore, Pierre, Stéphane, Béa, les Marie, Emilie et Jérôme.

A mes Assistants préférés

Pierre Yves, Isabelle et Ömer abi (en iyi sensin, tu es notre modèle à tous).

A nos précieux Manips

Merci à chacun d'entre vous pour votre gentillesse, votre bonne humeur et votre dynamisme : c'est aussi grâce à vous que la radiologie est si plaisante ! Je vous embrasse tous et (surtout) toutes, je vous adore !

Aux ASH :

Merci pour votre travail si discret et pourtant si essentiel.

Gros bisous à ma Popo chérie, merci pour ta joie de vivre, tes kilos de bonbons, tes massages musclés... Et à mon pote Alain Charabie avec son poulet Colombo et son grand sourire.

Merci à Salah et Sonia de la médecine nucléaire pour tous les fous rires.

Merci à Lina, la taulière au grand cœur de l'hôpital Sud.

Aux Infirmières :

Merci à Paulette et Cookie pour leur gentillesse et pour tous les petits thés aux fruits rouges.

Aux secrétaires :

Merci de supporter au quotidien nos dictées et nos comptes rendus interminables.

A ma deuxième Famille : l'Internat de médecine,

Pendant 5 ans j'ai été votre petit Mehmet, vous m'avez choyé, gâté et aimé. Vous êtes à jamais gravés dans mon cœur, MERCI à tous.

Tonton Phiphi : tu es le premier à m'avoir accueilli à l'internat... Tu avais promis à ma mère de bien t'occuper de moi et tu l'as très bien fait. Grand cuisinier, pâtissier, motard, mécanicien, bricoleur et surtout déconneur : ta valeur est inestimable, le plus gros chez toi c'est ton Cœur. MERCI.

Mama Louise : j'ai eu la chance d'avoir une deuxième maman pendant mon internat... Merci pour ta bonté, ta bienveillance, ta complicité et de m'avoir autant chouchouté !

Marie-Anqèle : plein de bisous pour toi ma Marie ;-) Tu es plus qu'une secrétaire en or, tu es une Amie. Les internes ont de la chance de t'avoir. Merci de m'avoir toujours écouté, conseillé et aidé dans mes projets pour l'internat mais aussi concernant tout le reste.

Merci à N'Eric, DJ Den's, Kader, Lionel « chevalier », Marie-No, Béatrice, Rabia et tous les autres !

Aux Amis,

Julien

Mon AMI, mon Complice, mon Energie : deux raisins qui se dicavent.

MERCI pour TOUT mon Refré, tu as boosté ma vie.

Molière

Mon grand frère noir... Tu es quelqu'un d'extraordinaire, un exemple d'Humanité : j'aimerais que l'univers entier te connaisse.

Merci pour ta joie de vivre, ton écoute attentive et tes conseils. Tu es mon plus précieux soutien.

Merci à Dedos mon co-pilote de la night, Yannick, Radu, Raed mon Habibi et Romain T. mon Maître.

Merci aux vieux amis de l'internat : Nassira, Grégoire, Clément, Bérénice, Alessandro, Shirley et à la nouvelle génération Loïc, Sultan et Georges.

Merci aux FFI qui m'ont enrichi de leurs cultures : Anas, Timi, Ouattara, Jean Michel, Younes...

Merci à mes co-externes François, Mehdi, Olivier, Pierre Alex et Xavier !

Merci à Jean-Cyril Bourre, Pierre Bessou et à Jean Michel Pellat qui m'a appris à utiliser un stéthoscope et un marteau réflexe (même si ça me sert plus trop...)

Merci à mes anciens médecins traitants, Tarak Bouzaabia et Olivier Peretto.

Merci à mes amis d'Annonay : Yonpé, Touille, Baptiste, Samol, Bass, Teix, Michon, Polo...

A Peter Peter, à New York, au Wokbar, au Cap d'Agde, au Mont Saint Eynard, au Barberousse, aux repas améliorés, aux soirées internat, aux enterrements des assistants, à la Revue des patrons, aux remplas, à Google...

TABLE DES MATIERES

RÉSUMÉ	11
ABSTRACT	12
ARTICLE	14
Introduction	14
Subjects and Methods	16
Subjects	16
MR protocol	17
Statistical analysis	18
Results	19
BOLD response in healthy subjects.....	19
BOLD response in patients.....	19
Comparisons between controls and patients	20
Discussion	21
Acknowledgments	25
References	26
Table	30
Figures	31
CONCLUSION	34
SERMENT D'HIPPOCRATE	35

RESUME

Objectif

La maladie de Parkinson pourrait s'accompagner d'un dysfonctionnement de la perfusion cérébrale partiellement compensé par l'administration de L-Dopa selon certaines études en écho-Doppler transcrânien. Or, il serait intéressant de pouvoir identifier et cartographier de telles anomalies pour mieux comprendre la physiopathologie de la maladie, mieux la diagnostiquer et corriger un éventuel biais de confusion en imagerie fonctionnelle cérébrale basée sur le couplage neurovasculaire, telle que l'IRM fonctionnelle. Nous avons identifié récemment de telles anomalies dans la maladie d'Alzheimer.

L'objectif de ce travail est de cartographier d'éventuelles altérations fonctionnelles de la perfusion par une étude de la vasoréactivité cérébrale à l'hypercapnie en IRM fonctionnelle dans la maladie de Parkinson avant et après administration de L-DOPA.

Méthode

Etude prospective comparative sur 20 patients pris en charge pour une maladie de Parkinson idiopathique avant et après administration de L-Dopa (120% de la dose thérapeutique) et 10 sujets sains appariés, en IRM fonctionnelle BOLD à 3T lors d'un stimulus hypercapnique par inhalation de carbogène, un mélange gazeux de 7% de CO₂ et 93% d'O₂.

Analyse des images par le logiciel SPM8 avec un régresseur dédié et un modèle à effets aléatoires avec correction pour comparaisons multiples.

Résultats

Le stimulus hypercapnique par inhalation de carbogène n'a pas eu d'effet indésirable. Parmi les sujets, 10 patients et 2 volontaires sains ont été exclus à cause d'un protocole incomplet, d'un stimulus inapproprié ou de mouvements excessifs, laissant 10 patients et 8 volontaires sains à analyser.

L'hypercapnie a augmenté le signal BOLD de l'ensemble du cerveau de (moyenne \pm erreur standard) $1,48 \pm 0,06\%$ chez les sujets sains, $1,59 \pm 0,05\%$ chez les patients OFF et $1,62 \pm 0,09\%$ chez les patients ON. Dans la substance grise, le signal a augmenté de $2,60 \pm 0,16\%$ chez les sujets sains, $2,89\% \pm 0,21\%$ chez les patients OFF et $2,87 \pm 0,12 \%$ chez les patients ON.

Aucune différence globale ou régionale significative n'a été détectée en comparant les patients OFF et ON ainsi qu'entre les patients et les sujets sains.

Conclusion

Nos résultats montrent l'absence d'altération de la vasoréactivité cérébrale à l'hypercapnie dans la maladie de Parkinson avant et après administration de L-DOPA.

Ce résultat négatif montre l'absence d'anomalie fonctionnelle de la perfusion cérébrale susceptible de confondre l'interprétation des résultats en IRM fonctionnelle BOLD. Une vasoréactivité cérébrale normale pourrait constituer un élément du diagnostic de la maladie de Parkinson susceptible de la distinguer d'autres syndromes extra-pyramidaux tels que le parkinsonisme vasculaire.

ABSTRACT

Purpose

To study cerebral vasoreactivity to hypercapnia in Parkinson's disease before and after L-DOPA administration.

Methods

The prospective study was conducted in 20 patients presenting with Parkinson's disease, using 3T blood oxygenation level-dependent functional magnetic resonance imaging (fMRI) covering the whole brain. The hypercapnic stimulus was block-designed using carbogen inhalation, a gas mixture of 7% CO₂ and 93% O₂, before (OFF) and 60 minutes after administration of a suprathreshold (120%) therapeutic L-Dopa dose (ON). Ten age-matched controls were enrolled for between-group comparisons. Analyses were conducted with a random effects model and corrected for multiple comparisons.

Results

No adverse reaction to the hypercapnic stimulus was reported. However, 10 patients and 2 controls were excluded because of incomplete protocol realization, inappropriate hypercapnic stimulus, or excessive movements, leaving 10 patients and 8 controls for further analyses. The hypercapnic stimulus increased whole brain BOLD signal of $1.48 \pm 0.06\%$ (mean \pm standard error) in controls, $1.59 \pm 0.05\%$ in patients OFF, and $1.62 \pm 0.09\%$ in patients ON. Regions of interest analyses showed a signal increase in the grey matter of $2.60 \pm 0.16\%$ in controls, $2.89 \pm 0.21\%$ in patients OFF, and $2.87 \pm 0.12\%$ in patients ON. No global or regional significant difference was detected when comparing patients OFF and ON L-Dopa, or between patients and controls.

Conclusion

Contrary to Alzheimer's disease, the vasoreactivity to hypercapnia was normal in Parkinson's disease before and after L-Dopa administration compared to controls. This negative result is an important finding, especially for neuroscientists using fMRI to investigate motricity and cognition, discarding a significant confounding effect.

Mots-clés

Maladie de Parkinson, L-DOPA , vasoréactivité cérébrale, Dioxyde de Carbone, IRMf
BOLD

Key-words

Parkinson's disease, L-DOPA, Cerebral Vasoreactivity, Carbon dioxide, BOLD fMRI

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder responsible for the second cause of motor disability in elderly after stroke. Rare before 50 years-old, the prevalence increases with age from 1 to 4% over 80¹. The disease is responsible of motor disorders such as bradykinesia, rigidity, postural instability, rest tremor, as well as cognitive impairments. The loss of nigro-striatal dopaminergic neurons located in the substantia nigra pars compacta is a widely accepted connection with the motor symptom appearance². Motor symptoms are initially responsive to levodopa (L-Dopa), that enables to increase dopamine levels in the basal ganglia. This drug is used for 40 years in PD therapy and is still the most efficient. However as neuronal loss progresses, the "honey moon" gets over and patients frequently develop drug-induced dyskinesias while treatment fluctuations alternate between ON and OFF motor phases³.

Although PD pathophysiology has been investigated for years, much remains unclear. Several neurodegenerative diseases, previously considered to result from neuronal defects only, have been linked to structural and functional vascular disorders, such as in Alzheimer's disease (AD)^{4,5} and PD^{6,7}. In patients with PD, comorbid cerebrovascular disease has been advocated on clinical and radiological data^{6,7}. A recent study showed a wide-spread hypoperfusion of the cortex and the caudate nucleus⁸. Animal studies have shown abnormal vessel growth and altered brain-blood barrier permeability in the basal ganglia vasculature⁹. Experimental studies have also shown the direct link between dopamine, cerebrovascular tone, and angiogenic response according to the dopamine receptor class^{10,11}.

In PD and besides basal perfusion changes, orthostatic hypotension and syncope are frequent, suggesting functional disorders of the brain perfusion¹². To investigate vascular function, several stimuli may elicit vasomotricity via 3 main properties: 1) neural activity triggers the neurovascular coupling that increases brain perfusion; 2) perfusion pressure triggers autoregulation to maintain perfusion constant; 3), and circulating gases trigger cerebral vasoreactivity (CVR). In fact, arteriolar hypercapnia induced by apnea, CO₂ inhalation or acetazolamide administration is a powerful cerebral vasodilator¹³. Thus, hypercapnic challenges have been used to estimate cerebrovascular function, although CVR was tested, only. In PD, potential functional cerebrovascular disorders have been recently investigated using transcranial Doppler

(TCD)¹⁴⁻¹⁶. Inconstant results emerged from these studies, although decreased vasomotor responses could be detected, partially improved after L-DOPA administration¹⁵. Such inconsistencies could be due to the methodological limitations of TCD, including a strong dependence on the operator expertise. Moreover, TCD estimates a global parameter and is not a brain imaging technique able to depict potential regional changes such as within the basal ganglia. Contrary to TCD which is restricted to proximal arteries, functional MRI (fMRI) to vasomotor challenges is used to investigate functional changes of parenchymal perfusion.

Based on blood oxygenation level dependent (BOLD) contrast, fMRI has become a popular neuroimaging technique used to map oxygenation and perfusion changes related to neural activity via the neurovascular coupling¹⁷. A fast imaging sequence sensitive to deoxyhemoglobin concentration is performed to measure temporal signal changes while a controlled stimulus is applied. This approach has been further used to monitor BOLD signal changes, and indirectly perfusion, during other vasomotor stimuli such as hypercapnia to study CVR. Initially, this method was used to identify potential neurovascular coupling impairment in false negative results¹⁷⁻²⁰. This technique has been further used to identify CVR abnormalities in steno-occlusive disease^{21,22} and in AD^{23,24}.

Therefore, we aimed at evaluating the cerebral vasoreactivity to hypercapnia before (OFF) and after (ON) L-Dopa administration using fMRI, in order to identify regional impairments of perfusion function in PD patients. Such information could be considered as a potential vasomotor confound in cognitive neuroscience when using fMRI and as a diagnosis marker that could be further tested in clinical practice.

SUBJECTS AND METHODS

Subjects

Twenty right-handed patients with PD were prospectively recruited in the Neurological wards of Grenoble (n = 14) and Lyon (n = 6) University Hospitals. All patients fulfilled the UK Parkinson's disease Brain Bank Criteria²⁵ for the diagnosis of idiopathic PD and presented with predominant akinetic-rigid symptoms, without invalidating motor fluctuations caused by the prolonged use of dopaminergic treatments. Right-handedness was assessed according to the Edinburgh Handedness Inventory²⁶. The study was approved by the Grenoble University Hospital Ethics Committee, and according to the Declaration of Helsinki. Patients were included after providing a written informed consent.

All patients were studied first without medication (OFF), and then with anti-Parkinsonian drugs (ON), during two consecutive sessions of one hour duration each. For the OFF condition, patients were scanned after a whole overnight fast, i.e. at least 12 hours of PD treatment withdrawal. The ON medication fMRI session was carried out 60 minutes after administration of a suprathreshold dose of L-dopa (120% of the usual morning dose). The patients' global motor disability was assessed before each fMRI session, using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS, part III). Only patients with mild to moderate symptoms (without or with little tremor in the OFF state, and without any dyskinesia in the ON state) were included in this study, in order to make sure that their symptoms would not compromise image quality. All patients were free of stroke history.

For the purpose of a comparison between PD patients and a normal state, 10 age- and-sex matched right-handed healthy controls were also enrolled in the study.

MR imaging protocol

Image acquisitions were performed on a 3T whole-body MR scanner (Bruker® Medspec S300) equipped with an emitting/receiving head coil. MR images were acquired parallel to the anterior commissure–posterior commissure (AC–PC) plane.

Anatomical imaging

T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MP-RAGE) images of the whole brain were acquired (time of repetition (TR)/time of echo (TE)/time of inversion (TI)/flip angle (α): 2500ms/3.89ms/900ms/8°; field of view (FOV)=256x224x176mm³; voxel size=1.33x1.75x1.375 mm³).

Functional imaging

Data acquisition was performed using single-shot gradient-echo echo-planar-imaging (GE/EPI) T2* weighted-images (WI), covering the whole brain (TR/TE/ α : 3000ms/30ms/77°; FOV: 216x216 mm²; matrix size 72 x 72, voxel size=3x3x3,2 mm³; 40 slices; no gap; number of dynamic scans: 240).

Cerebral vasoreactivity was estimated using the BOLD response to carbogen inhalation, a gas mixture of CO₂ (7%) and O₂ (93%). This task was block-designed and consisted of 3 cycles of alternating inhalation of air (60s), carbogen (120s), and air (60 s) for a total duration of 12 min. Gas administration was achieved using a nasal canula at 6 l/min (Jiang et al., 2010).

Functional data analysis

The data was processed offline in MATLAB® with SPM8 software (Wellcome Department of Cognitive Neurology, UK). Preprocessing steps included in-plane motion correction, realignment, spatial normalization to the Montreal Neurologic Institute T1-weighted template, and spatial smoothing with a 12-mm Gaussian kernel. Gray and white matters were segmented and a gray matter mask was constructed by thresholding the individual smoothed gray matter maps.

First level analyses were conducted on BOLD responses to hypercapnia using the general linear model with a dedicated regressor¹⁸. This stimulus increases the arterial PCO₂ by 4.8 mm Hg, and arterial PO₂ increased by 51.2 mm Hg, without significant change of heart pulse and respiratory frequency.

Contrasts between the air and carbogen conditions were then introduced within second-level analyses using t-tests. Only cerebral areas whose probabilities survived to the $p_{\text{FWE-corrected}} < 0.05$ statistical threshold, at the voxel level, were retained. Only activation foci for which the number of voxels was equal or superior at $k=10$ were considered. The regional BOLD signal amplitudes were further analyzed using regions of interest (ROI) in the frontal, parietal, temporal and occipital lobes, the cingulum, the insula, the striatum and the thalamus. ROIs were chosen by combining the regions from the AAL package in SPM.

Statistical analyses

Statistical analyses were processed using SPSS 18.0®. Statistical significance was set at $p < 0.05$. In patients, pairwise comparison between OFF and ON medication UPDRS scores was carried out using a paired t-test to evaluate the clinical impact of the treatment.

ROIs analyses were conducted using ANOVAs with repeated measures. In controls, an ANOVA was carried out to test for main effects of the ROI location (factor "ROI"), the hemispheric side (factor "SIDE"), and the interaction "ROIxSIDE". In patients, an ANOVA was conducted to test for the main effects of the L-DOPA administration (factor "DOPA"), ROI, and SIDE with all interactions. Intergroup comparisons between controls and patients OFF and ON conditions were conducted separately to identify a main effect of the pathological condition. Post-hoc tests corrected for multiple comparisons were conducted when a main effect or an interaction was detected. Correlations between ROI values and clinical parameters were studied by Pearson tests.

RESULTS

Among the 20 enrolled patients, 10 patients were excluded because of: 1° excessive movements (n=7), inappropriate hypercapnic stimulus (n=2), 2° sleeping during examination (n=1), leaving 10 patients for further analyses (2 women, 8 men; age range: 44–67 years, mean: 58.2 ± 7.0 years). Mean disease duration was 7.8 ± 3.6 years. L-Dopa administration improved the motor score of the UPDRS significantly ($p < 0.001$) (Table 1).

Among the 10 healthy controls recruited in the study, 2 subjects were excluded because of excessive movements or inappropriate hypercapnic stimulus, leaving 8 controls for further analyses (2 women, 6 men; age range: 48–69 years, mean: 61.9 ± 6.4 years). No significant age difference was detected among the selected subjects.

No side effect, including anxiety, was reported during and after hypercapnia.

Seven patients out of 20 were excluded because of excessive head motion with a movement amplitude superior to half of the voxel dimension. Because patients were scanned twice (OFF and ON conditions), the exclusion rate was 17.5% (7 out of 40 examinations). This rate was similar to controls' rate of 20 % (2 out of 10 examinations). Thus, the pathological condition did not increase the exclusion rate.

BOLD response in healthy subjects

Carbogen inhalation elicited a whole brain BOLD response, predominant in gray matter in all subjects. The mean amplitude of the BOLD signal detected in the brain and calculated by comparing steady states of air and hypercapnic inhalation during the last minute of the stimuli was $\text{mean} \pm \text{standard error} = 1.48 \pm 0.06\%$ (Figure 1). In segmented gray matter, BOLD signal increase was $2.60 \pm 0.16\%$. The ANOVA detected a main effect of ROI ($p < 0.001$), mostly due to significant increase of CVR in the thalamus and the occipital lobes compared to the striatum and the insula (Figures 2,3). No main effect of SIDE and no interaction $\text{ROI} \times \text{SIDE}$ were detected.

BOLD response in patients

In patients, mean amplitudes of whole brain BOLD signal change were $1.59 \pm 0.05\%$ and $1.62 \pm 0.09\%$ before and after L-Dopa administration, respectively. Time courses of the whole brain BOLD signal were similar to the controls under OFF and ON conditions (Figure 1). In segmented gray matter, BOLD signal increases were

2.89±0.21% in patients OFF, and 2.87±0.12% in patients ON. The ANOVA detected a main effect of ROI ($p<0.001$) with similar regional differences to controls (Figures 2 and 3). No main effect of SIDE or DOPA was detected. No interaction between ROI, SIDE, and DOPA was detected.

No correlation between the BOLD signal amplitude and the UPDRS, the age, or the disease duration was detected OFF and ON medication. No correlation was found between the same previous parameters and the L-Dopa equivalent dose.

Comparisons between controls and patients

No main effect of the pathological condition could be identified, neither interaction between groups, SIDE or ROI. Although, CVR was higher in patients in the thalamus and the occipital lobes, no significant change between groups could be detected because of the interindividual variability (Figure 2).

DISCUSSION

In order to identify functional impairment of cerebral vasoreactivity (CVR) in PD before and after L-Dopa administration, we conducted a BOLD fMRI study using a hypercapnic challenge. Although no adverse reaction to the stimulus was detected, excessive head movements or inappropriate stimulus led to exclude half of the patients and a quarter of the controls. No difference of CVR was detected between controls and patients before or after L-Dopa, even in the basal ganglia. Despite methodological limitations, this is the first study to our knowledge that used fMRI to investigate CVR in PD and the potential effect of L-Dopa on the BOLD signal.

The negative results are in line with a previous study using transcranial Doppler (TCD) after acetazolamide in PD patients (3 hours OFF medication)¹⁴. In a TCD study, abnormal CVR to hypercapnia was detected in 34% of patients only (3h OFF medication), without any relationship with the occurrence of orthostatic hypotension¹⁶. However, a TCD study on cerebral autoregulation to perfusion pressure using a thigh cuff release test showed decrease responses in PD, without any difference between OFF and ON medications¹⁵. This discrepancy could be explained by a 9 years older population although no correlation neither with the age nor the disease duration could be detected and a weaker improvement of the UPDRS after medication. In our study, no patient had a stroke history, silent infarct, or severe microangiopathy on MRI. In fact, TCD and fMRI explore different vascular compartments with different parameters. Whereas TCD records the velocity of proximal portion of major intracranial arteries regulated by the extrinsic innervation under sympathetic/parasympathetic balance, fMRI measures changes of the parenchyma arterioles and the neurovascular units regulated by the intrinsic innervation, including dopaminergic innervation¹³. TCD provides quantitative measures and remains operator dependent whereas fMRI to hypercapnia provides a semi-quantitative measure correlated to the cerebral blood flow²⁷ and remains mostly dependent of the subject cooperation. Thus, fMRI may allow testing parenchymal vasomotor properties more directly than TCD, and especially potential dopamine effects.

Because dopamine modulates the vascular tone, perfusion changes have been detected in animals experimentally. Dopamine receptors have opposite effects. In rats, the activation of D1/D5 receptors located in the frontoparietal cortex, striatum, and thalamus elicits vasodilation and hyperperfusion. In contrast, the activation of D2/D3 receptors located in the striatum elicits vasoconstriction and hypoperfusion¹⁰. In patients, dopamine depletion might explain wide-spread cortical hypoperfusion in prefrontal areas, dorsal premotor cortex, pre-SMA, posterior parietal cortex, and occipitoparietal areas although no change was detected in the basal ganglia nuclei and the thalamus⁸. After L-Dopa administration, CBF increases in the putamen/globus pallidus, dorsal midbrain/pons, subthalamic nucleus and ventral thalamus, revealing the vasodilator effect of treatment in these regions²⁸.

The basal perfusion influences the magnitude and the dynamics of the BOLD signal. In the case of basal hypoperfusion, the amplitude of the BOLD response increases and the slope is steep. In case of basal hyperperfusion, the amplitude of the BOLD response decreases and the slope dampened²⁹. Thus, we might have expected increased BOLD response in most cortical area in patients OFF medication, and then normalization after L-Dopa administration. In such case, regional disorders could have been a potential imaging biomarker for PD diagnosis. This negative result may suggest the little effect of small basal perfusion changes of the BOLD response to hypercapnia. Indeed, global vasodilatation may account for a decrease of 0.15% of a neural-related BOLD response³⁰. Although the neurovascular coupling is a different functional property of the arterioles that relies on different biomolecular interactions, the amplitude of both BOLD responses is roughly similar³⁰. This similarity has been previously used to identify hemodynamics confounds in stroke fMRI^{19,20} and presurgical mapping in neurooncology^{17,18}. The main difference between these two stimuli is the dynamics of the BOLD response with a plateau reached after 5-10 seconds after a neural stimulus, and after 30-60 seconds after hypercapnia^{18,23}.

Although we could not measure cerebral perfusion simultaneously in this experiment, the potential basal perfusion modulation might have not significantly change the results, mainly because of the important variability of the CVR measure using fMRI. Considering the physiological differences between neurovascular coupling and

vasoreactivity, this negative result would argue for the absence of major hemodynamic confounds in fMRI studies conducted in patients with PD, before and after L-Dopa administration³¹⁻³³. However, one may not exclude that our negative results might be due to a potential long duration response to L-Dopa of the vascular system. Then, the reproducibility of our findings should advantageously be estimated using an additional group of truly unmedicated patients after a washout delay of several days instead of an overnight to avoid long duration response to L-Dopa³⁴. This approach has been previously used in cognitive fMRI study to better estimate BOLD signal changes to the ON and OFF conditions³⁵.

Despite pathophysiological and clinical differences, Alzheimer's and Parkinson's diseases are both considered as neurodegenerative disorders. Using a similar method to estimate CVR with BOLD fMRI to hypercapnia, we identified a broad impaired CVR in AD and in patients with mild cognitive impairment²³. In AD, the CVR was correlated with the cognitive status and the hippocampal atrophy. The effect of the Alzheimer's disease was so significant, that individual maps of patients were easily distinguishable from matched controls. Here, no difference could help to identify the effect of the Parkinson's disease or of the L-Dopa administration. Thus, a normal parenchymal CVR could be a radiological marker of idiopathic PD when compared to other parkinsonisms, such as vascular parkinsonism (VP). Indeed, VP is an ill-defined disease without generally accepted diagnostic criteria. Besides gait disturbance and less responsiveness to L-Dopa, vascular lesions of the brain were almost constant¹². However, such microangiopathy is so common in elderly, AD and even in PD, that it could hardly be used as a diagnosis marker without further specification. In VP, the severity and the location of the vascular lesions may suggest a causal relationship with basal ganglia disorders and clinical symptoms. Then, impaired perfusion function or basal perfusion might affect the metabolism and the anatomical integrity of particular neuronal populations. It could be interesting for diagnostic and pathophysiological purposes to investigate regional difference of basal brain perfusion and CVR in patients with PD, patients with VP, and patients with similar micrangiopathy without parkinsonism.

These negative results suggest the absence of significant functional vascular disorder that may confound BOLD fMRI results in PD, even after L-Dopa administration contrary to stroke, brain tumor, and Alzheimer's disease. Indeed, these results emphasize the importance of the cerebrovascular dysfunction in Alzheimer's disease as previously reported. It could also be suggested that CVR fMRI may provide imaging information to distinguish Parkinson's disease from vascular parkinsonism.

ACKNOWLEDGMENTS

We acknowledge the financial support of the University Hospital of Grenoble and the France Parkinson association, and the precious help of Chistelle Henry-Lagrange for the organization of the project and Patrice Jousse for the artwork preparation.

REFERENCES

1. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol.* 2006; 5: 525-35
2. Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E, et al. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. *Lancet Neurol.* 2009; 8: 1128-39
3. Abbott A. Levodopa: the story so far. *Nature.* 2010; 466: S6-7
4. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol.* 2009; 118: 103-13
5. Iadecola C. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol.* 2010; 120: 287-96
6. Patel M, Coutinho C, Emsley HC. Prevalence of radiological and clinical cerebrovascular disease in idiopathic Parkinson's disease. *Clinical neurology and neurosurgery.* 2011; 113: 830-4
7. Nanhoe-Mahabier W, de Laat KF, Visser JE, Zijlmans J, de Leeuw FE, Bloem BR. Parkinson disease and comorbid cerebrovascular disease. *Nature reviews Neurology.* 2009; 5: 533-41
8. Fernandez-Seara MA, Mengual E, Vidorreta M, Aznarez-Sanado M, Loayza FR, Villagra F, et al. Cortical hypoperfusion in Parkinson's disease assessed using arterial spin labeled perfusion MRI. *Neuroimage.* 2012; 59: 2743-50
9. Westin JE, Lindgren HS, Gardi J, Nyengaard JR, Brundin P, Mohapel P, et al. Endothelial proliferation and increased blood-brain barrier permeability in the basal ganglia in a rat model of 3,4-dihydroxyphenyl-L-alanine-induced dyskinesia. *J Neurosci.* 2006; 26: 9448-61
10. Choi JK, Chen YI, Hamel E, Jenkins BG. Brain hemodynamic changes mediated by dopamine receptors: Role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. *Neuroimage.* 2006; 30: 700-12
11. Lindgren HS, Ohlin KE, Cenci MA. Differential involvement of D1 and D2 dopamine receptors in L-DOPA-induced angiogenic activity in a rat model of Parkinson's disease. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2009; 34: 2477-88

12. Kalra S, Grosset DG, Benamer HT. Differentiating vascular parkinsonism from idiopathic Parkinson's disease: a systematic review. *Mov Disord*. 2010; 25: 149-56
13. Edvinsson L, Krause D. Cerebral blood flow and metabolism. 2nd ed. Edvinsson L, Krause D, editors. Philadelphia: Lippincott Williams & Wilkins; 2002.
14. Gurevich T, Gur AY, Bornstein NM, Giladi N, Korczyn AD. Cerebral vasomotor reactivity in Parkinson's disease, multiple system atrophy and pure autonomic failure. *J Neurol Sci*. 2006; 243: 57-60
15. Vokatch N, Grotzsch H, Mermillod B, Burkhard PR, Sztajzel R. Is cerebral autoregulation impaired in Parkinson's disease? A transcranial Doppler study. *J Neurol Sci*. 2007; 254: 49-53
16. Zamani B, Mehrabani M, Fereshtehnejad SM, Rohani M. Evaluation of cerebral vasomotor reactivity in Parkinson's disease: is there any association with orthostatic hypotension? *Clinical neurology and neurosurgery*. 2011; 113: 368-72
17. Krainik A. Functional MRI. In: Duffau H, ed. *Brain mapping: from neural basis of cognition to surgical applications*. Wien: Springer-Verlag; 2011. p. 45-59.
18. Jiang Z, Krainik A, David O, Salon C, Tropes I, Hoffmann D, et al. Impaired fMRI activation in patients with primary brain tumors. *Neuroimage*. 2010; 52: 538-48
19. Krainik A, Hund-Georgiadis M, Zysset S, von Cramon DY. Regional impairment of cerebrovascular reactivity and BOLD signal in adults after stroke. *Stroke*. 2005; 36: 1146-52
20. Hamzei F, Knab R, Weiller C, Rother J. The influence of extra- and intracranial artery disease on the BOLD signal in FMRI. *Neuroimage*. 2003; 20: 1393-9
21. Haller S, Bonati LH, Rick J, Klarhofer M, Speck O, Lyrer PA, et al. Reduced cerebrovascular reserve at CO₂ BOLD MR imaging is associated with increased risk of periinterventional ischemic lesions during carotid endarterectomy or stent placement: preliminary results. *Radiology*. 2008; 249: 251-8
22. Han JS, Abou-Hamden A, Mandell DM, Poublanc J, Crawley AP, Fisher JA, et al. Impact of extracranial-intracranial bypass on cerebrovascular reactivity and clinical outcome in patients with symptomatic moyamoya vasculopathy. *Stroke*. 2011; 42: 3047-54

23. Cantin S, Villien M, Moreaud O, Tropres I, Keignart S, Chipon E, et al. Impaired cerebral vasoreactivity to CO₂ in Alzheimer's disease using BOLD fMRI. *Neuroimage*. 2011; 58: 579-87
24. Yezhuvath US, Uh J, Cheng Y, Martin-Cook K, Weiner M, Diaz-Arrastia R, et al. Forebrain-dominant deficit in cerebrovascular reactivity in Alzheimer's disease. *Neurobiol Aging*. 2012; 33: 75-82
25. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1988; 51: 745-52
26. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971; 9: 97-113
27. Mandell DM, Han JS, Poublanc J, Crawley AP, Stainsby JA, Fisher JA, et al. Mapping cerebrovascular reactivity using blood oxygen level-dependent MRI in Patients with arterial steno-occlusive disease: comparison with arterial spin labeling MRI. *Stroke*. 2008; 39: 2021-8
28. Hirano S, Asanuma K, Ma Y, Tang C, Feigin A, Dhawan V, et al. Dissociation of metabolic and neurovascular responses to levodopa in the treatment of Parkinson's disease. *J Neurosci*. 2008; 28: 4201-9
29. Cohen ER, Ugurbil K, Kim SG. Effect of basal conditions on the magnitude and dynamics of the blood oxygenation level-dependent fMRI response. *J Cereb Blood Flow Metab*. 2002; 22: 1042-53
30. Stefanovic B, Warnking JM, Rylander KM, Pike GB. The effect of global cerebral vasodilation on focal activation hemodynamics. *Neuroimage*. 2006; 30: 726-34
31. Buhmann C, Glauche V, Sturenburg HJ, Oechsner M, Weiller C, Buchel C. Pharmacologically modulated fMRI--cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients. *Brain*. 2003; 126: 451-61
32. Haslinger B, Erhard P, Kampfe N, Boecker H, Rummeny E, Schwaiger M, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain*. 2001; 124: 558-70
33. Ng B, Palmer S, Abugharbieh R, McKeown MJ. Focusing effects of L-dopa in Parkinson's disease. *Hum Brain Mapp*. 2010; 31: 88-97

34. Quattrone A, Zappia M, Aguglia U, Branca D, Colao R, Montesanti R, et al. The subacute levodopa test for evaluating long-duration response in Parkinson's disease. *Ann Neurol.* 1995; 38: 389-95
35. Fera F, Nicoletti G, Cerasa A, Romeo N, Gallo O, Gioia MC, et al. Dopaminergic modulation of cognitive interference after pharmacological washout in Parkinson's disease. *Brain research bulletin.* 2007; 74: 75-83

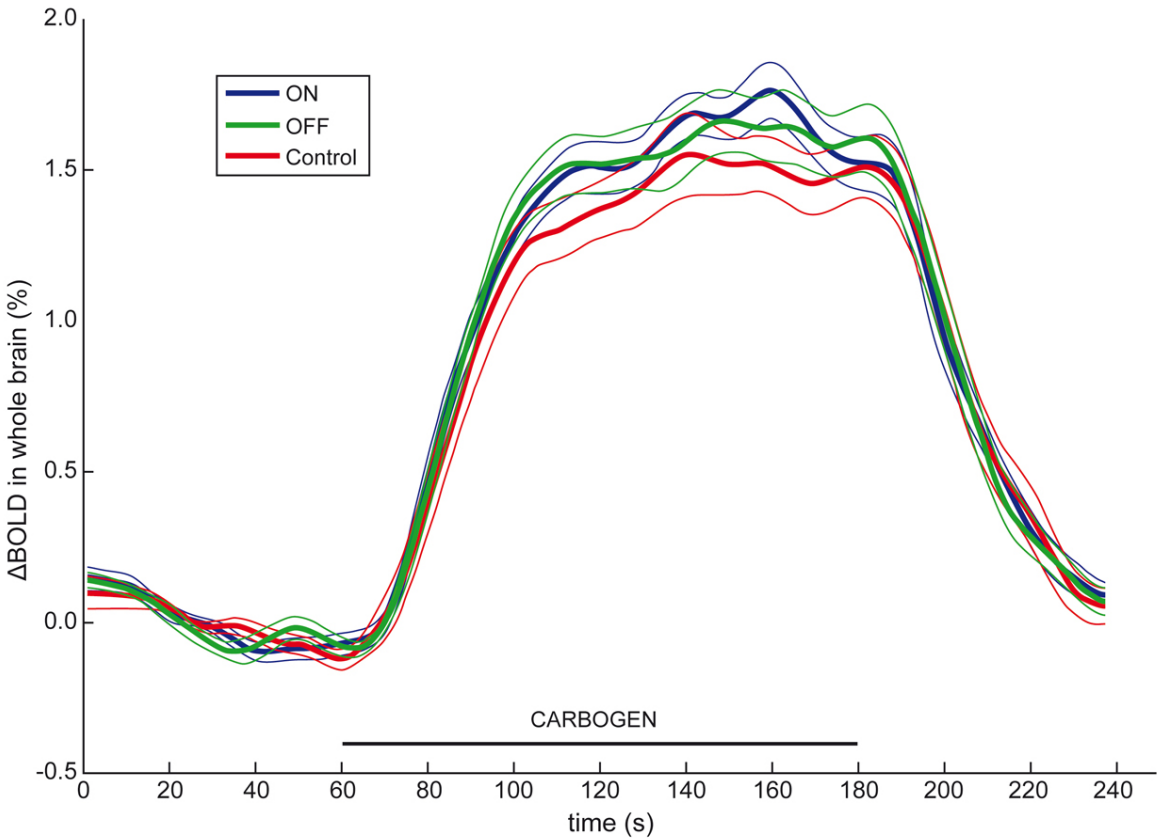
TABLE

Table 1 Patients characteristics

Patient number	Gender M/F	Age (years)	Disease duration (years)	UPDRS OFF/ON (score/108)	L-DOPA equivalent dose (mg)
1	F	44	2	13/5	550
2	M	61	4	43/14	2000
3	M	58	8	28/11	910
4	F	58	14	28/10	600
5	M	66	8	25/7	500
6	M	67	5	36/7	300
7	M	55	8	32/5	400
8	M	51	8	37/3	350
9	M	58	9	40/8	200
10	M	64	12	36/10	350
mean		58.2	7.8	31.8/8.0	616

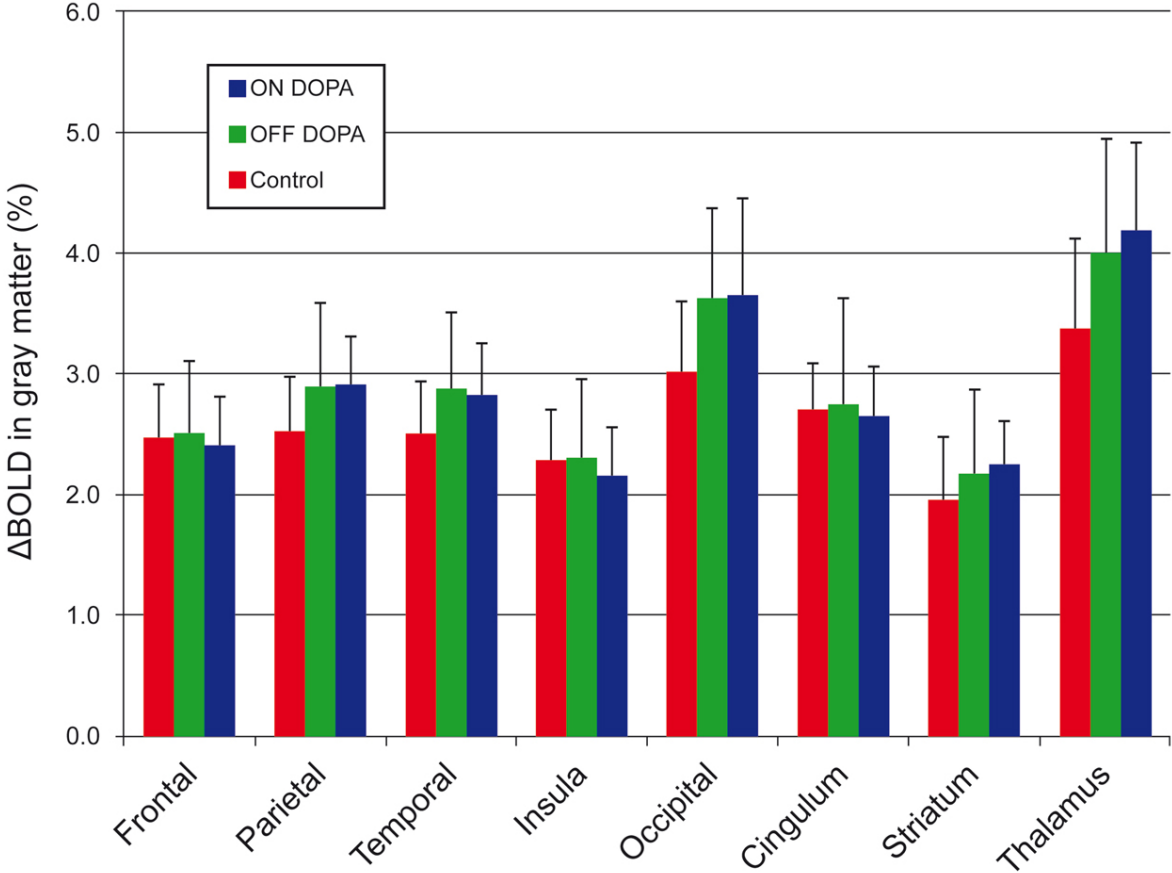
FIGURES

Figure 1



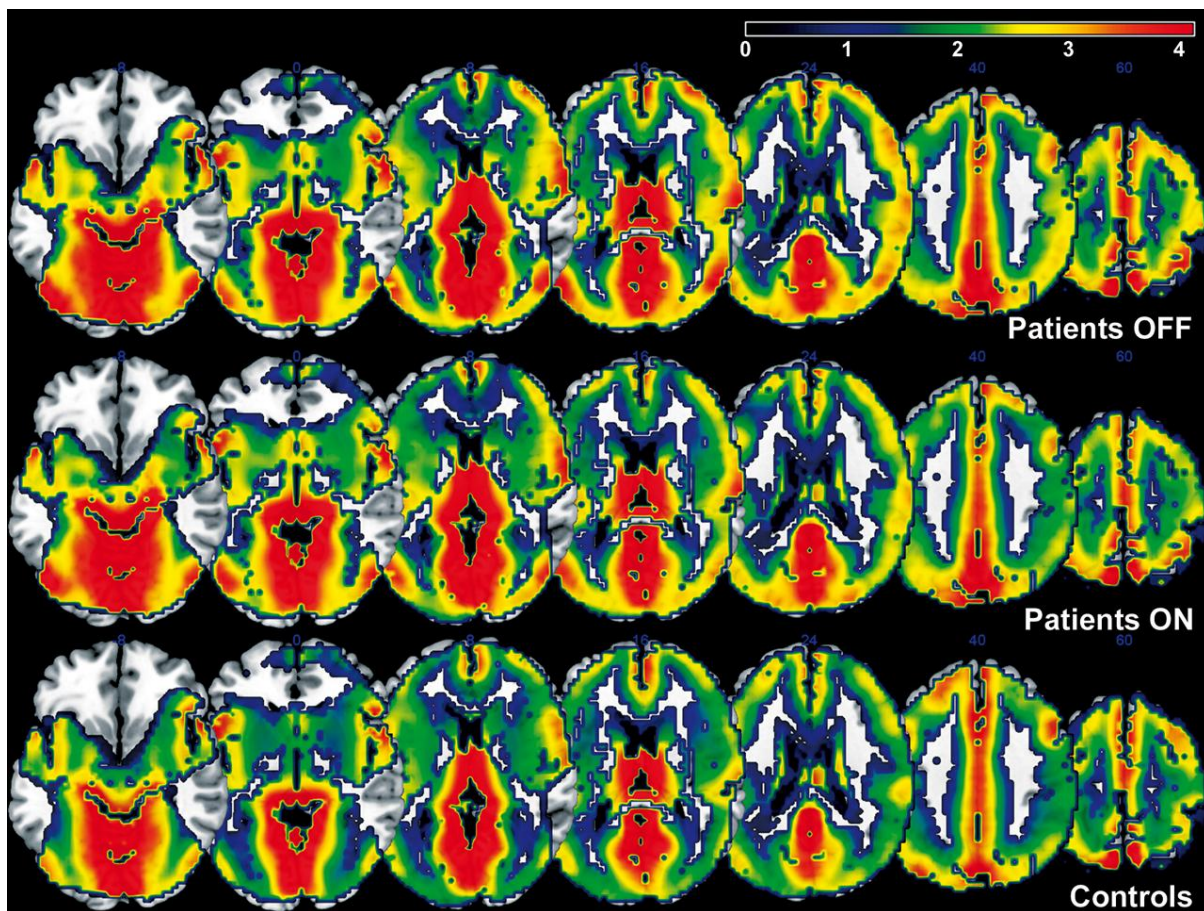
Mean whole-brain BOLD signal changes (bold lines) ± standard error (thin lines) during carbogen inhalation in controls (red line), patients before (green line) and after L-Dopa administration (blue line). The three-block paradigm was averaged over one-block. No significant difference in signal amplitude and dynamics could be detected across groups.

Figure 2



Mean regional amplitude of the BOLD signal changes in the grey matter \pm standard deviation during carbogen inhalation in controls (red bar), patients before (green bar) and after L-Dopa administration (blue bar). Despite CVR was higher in patients in the thalamus and the occipital lobes, no significant change could be detected because of the interindividual variability.

Figure 3



Maps of mean amplitude of the BOLD signal increase during hypercapnia (% color bar) across groups show similar regional changes.

Ce travail a été soumis à publication sous le titre : "Cerebral vasoreactivity is normal in Parkinson's disease before and after L-Dopa" par A. Krainik, A. Maillet, V. Fleury, M. Sahin, I. Tropres, L. Lamalle, S. Thobois, V. Fraix, M. Villien, J. Warnking, P. Pollak, S. Pinto, P. Krack

Il est actuellement en cours de révision dans la revue Movement Disorders.

THESE SOUTENUE PAR : SAHIN Mehmet

TITRE :

Etude de la vasoréactivité cérébrale par IRM fonctionnelle BOLD dans la maladie de Parkinson avant et après traitement par L-Dopa.

CONCLUSION

Il s'agit de la première étude sur la vasoréactivité cérébrale à l'hypercapnie dans la maladie de Parkinson et sur l'effet de la L-DOPA en IRM fonctionnelle BOLD.

Vingt patients suivis pour une maladie de Parkinson idiopathique avant (OFF) et après administration de L-Dopa (ON) et dix volontaires sains appariés pour l'âge et le sexe ont été examinés en IRM fonctionnelle BOLD lors d'un stimulus hypercapnique par inhalation de carbogène à 7% de CO₂. Dix patients et deux sujets sains ont été exclus des analyses à cause de protocoles incomplets ou de mouvements excessifs, illustrant les difficultés techniques rencontrées lors de la réalisation de ce type d'étude.

Le stimulus hypercapnique n'a pas entraîné d'effet indésirable.

Aucune modification globale ou régionale de la vasoréactivité cérébrale n'a été identifiée chez les patients aussi bien avant qu'après administration de L-Dopa.

Avec l'absence d'altération de la vasoréactivité cérébrale dans la maladie de Parkinson, ce résultat négatif présente :

- 1°) un intérêt physiopathologique qui contraste avec les anomalies diffuses identifiées dans la maladie d'Alzheimer ;
- 2°) un intérêt méthodologique en neurosciences cognitives qui suggère l'absence d'altération du couplage neurovasculaire susceptible de biaiser l'analyse des résultats en imagerie fonctionnelle et en particulier en IRM fonctionnelle BOLD lors de tâches motrices ou cognitives
- 3°) un intérêt clinique, qui pourrait constituer un élément du diagnostic différentiel avec d'autres pathologies neurodégénératives responsables de syndromes extra-pyramidaux tels que le parkinsonisme vasculaire, ce qui nécessiterait des études complémentaires dédiées.

VU ET PERMIS D'IMPRIMER

Grenoble, le *05/09/12*

LE DOYEN

LE PRESIDENT DE THESE

J.P ROMANET

PROFESSEUR PAUL KRACK



A handwritten signature in black ink, appearing to be 'P. Krack', written below the name 'PROFESSEUR PAUL KRACK'.



Qui diis memorem laudes, repetimque fideles
 Ingenij dotes, Hippocraticae decus.
 Democriti auditor Phœbea, ô, Coë propago,
 Certius an quis te tradidit ante opes?

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.