Université de Montréal

Changements comportementaux et neuro-anatomiques suite à un entrainement aérobie chez les individus atteints de la maladie de Parkinson

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Résumé

La maladie de Parkinson (MP) est la deuxième maladie neurodégénérative la plus répandue au Canada et dans d'autres pays industrialisés. Cette pathologie se caractérise par des symptômes moteurs tels que les tremblements de repos, la rigidité musculaire, la difficulté à initier les gestes volontaires et la lenteur dans l'exécution des mouvements (i.e., akinésie et bradykinésie). Des symptômes non moteurs, tels que des troubles cognitifs, de sommeil et autres sont également couramment rencontrés.

L'activité physique s'est montrée jusqu'à ce jour un complément intéressant aux traitements pharmacologiques et neurochirurgicaux existants pour soulager les symptômes de la MP. Cependant, malgré les connaissances acquises jusqu'à présent concernant l'impact de l'exercice physique chez les personnes atteintes de cette maladie, il est possible de constater que plusieurs questions demeurent encore sans réponse ou peu élucidées. Le présent travail s'insère donc dans un immense projet de recherche qui a pour but de combler certaines de ces lacunes. Plus précisément, l'objectif principal de cette thèse est d'évaluer les effets d'un entrainement de type aérobie chez une population atteinte de la MP sur les paramètres de marche, la mobilité du membre supérieur et les structures anatomiques cérébrales. Un second objectif est d'observer les relations existantes entre ces trois composantes, et d'autres paramètres tels que l'amélioration des capacités aérobies, les fonctions exécutives et les capacités d'apprentissage d'une nouvelle séquence motrice.

Vingt adultes en bonne santé et 19 personnes atteintes de la MP ont participé à un programme d'entraînement de 3 mois sur vélo stationnaire, à raison de 3 séances par semaine durant lesquelles la durée (20 à 40 minutes) et l'intensité (60% à 80% de la fréquence cardiaque maximale) étaient augmentées de façon progressive. Plusieurs mesures telles que le patron de la

marche, la mobilité du membre supérieur, les fonctions exécutives, l'apprentissage d'une tâche motrice, les capacités aérobies (VO_2 pic), les symptômes moteurs de la MP et quelques métriques provenant de données d'imagerie par résonance magnétique ont été acquises avant et après le programme d'exercice.

Les résultats ont permis de démontrer qu'un entraînement de 3 mois sur vélo stationnaire est bénéfique pour les gens atteints de la MP. En effet, ce type d'exercice permet d'augmenter la cadence et la vitesse marche. Il est également possible de réduire la force antagoniste, en plus d'améliorer la propagation du signal neuromusculaire antagoniste, améliorant globalement la mobilité du membre supérieur. Finalement, un exercice aérobie de 3 mois permettre également d'augmenter le volume de certaines structures cérébrales, tel que le globus pallidus.

Ce projet de recherche est parmi les premiers à démontrer l'efficacité d'un programme d'entraînement aérobie sur vélo stationnaire pour améliorer les paramètres de la marche et la mobilité du membre supérieur. Cette étude est également la première à investiguer les effets de l'exercice sur les structures cérébrales de personnes atteintes de la MP et ainsi essayer de comprendre les mécanismes qui sont sous-jacents aux améliorations des symptômes moteurs et non-moteurs suite à un programme d'activité physique d'intensité modérée à élevée. Nous croyons que les résultats obtenus aideront les spécialistes de l'activité physique à offrir une prescription d'exercice adaptée et variée pour la population de gens atteints de la maladie de Parkinson.

Mots clés : Maladie de Parkinson, exercice aérobie, patron de marche, fonctions exécutives, membre supérieur, neuroimagerie

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease in Canada and other industrialized countries. The pathology is characterized by motor symptoms such as resting tremor, muscle rigidity, difficulty in initiating voluntary gestures and slowness in the execution of movements (i.e. bradykinesia). Non-motor symptoms, such as cognitive impairment, sleep disorders and others are commonly encountered.

To date, physical activity has been an interesting complement to existing pharmacological and neurosurgical treatments to relieve the symptoms of PD. However, despite the knowledge gained so far about the impact of physical exercise in patients with the disease, it is possible to note that many questions remain unanswered or unclear. This work is part of a larger research project that aims to fill some of theses gaps. More specifically, the main objective of this thesis is to evaluate the effects of an aerobic training in a population with PD on walking parameters, upper limb mobility and anatomical brain structures. A second objective is to observe the relationships existing between these three components, and with other parameters such as the improvement of aerobic capacities, the executive functions and the learning capacities of a new motor skill.

20 healthy adults and 19 persons with PD participated in a 3-month stationary recumbent bicycle training program, with 3 sessions per week during which the duration (20 to 40 minutes) and intensity (60 to 80%) were increased gradually. Several measures such as walking pattern, upper limb function, executive functions, learning of a new motor skill, aerobic capacities (VO2 peak), motor symptoms of PD and magnetic resonance imaging were acquired before and after the exercise program.

The results showed that a 3-month training on stationary bike is beneficial for people with PD. Indeed, this type of exercise can increase the cadence and walking speed. It is also possible

to reduce the antagonist force, in addition to improve the propagation of this neuromuscular signal, generally improving the mobility of the upper limb. Finally, an aerobic exercise of 3 months can also increase the volume of certain brain structures, such as globus pallidus.

This research project is among the first to demonstrate the effectiveness of a stationary bicycle aerobic exercise program to improve gait parameters and upper limb function in persons with PD. This study is also the first to investigate the effects of exercise on the brain structures of these patients and to try to understand the mechanisms that underlie improvements in motor and non-motor symptoms following a moderate to high intensity exercise program. We believe that the results obtained will help physical activity specialists to provide a more tailored and varied exercise prescription for people living with Parkinson's disease.

Keywords : Parkinson's disease, aerobic exercise, walking pattern, executive functions, upper limb, neuroimaging

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Liste des abréviations

BAI : *Beck anxiety inventory*
BDI : *Beck depression inventory*
BDNF : *Brain-derived neurotrophic factors*
BOLD : *Blood-oxygen-level dependent*
ECG : Électrocardiogramme
FA : Anisotropie fractionnelle
FCmax : Fréquence cardiaque maximale
H&Y : Hoehn & Yahr
IRM : Imagerie par résonance magnétique
IRMf : Imagerie par résonance magnétique fonctionnelle
MD : Diffusivité moyenne
MoCA : Montreal Cognitive Assessment
MP : Maladie de Parkinson
rpm : révolutions par minute
TBSS : *Tract-based spatial statistics*
TMT : *Trail Making Test*
TUG : *Timed up and go*
UPDRS : *Unified Parkinson's disease rating scale*
VBM : *Voxel-based morphometry*
VO_2pic : Pic du volume d'absorption d'oxygène
W : Watts
6MWT : *6 minutes walking test*

Remerciements

Je tiens à remercier Julien de m'avoir accueillie dans son laboratoire de recherche. Ces quelques années auront été des plus enrichissantes dans mon parcours académique et personnel. Ce séjour m'aura permis de rencontrer des personnes incroyables, qui m'auront été d'un grand support tout au long de mon cheminement. Je ne peux faire autrement que de faire une mention spéciale à Francine, Arnaud et Ovidiu, pour leur grande aide, leur écoute, et le partage de leurs connaissances et sagesse.

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Je remercie maman, cette femme incroyable qui a cru en moi
et qui m'a toujours supportée, mais qui n'aura pas la chance
de voir les fruits de ces efforts.

Avant propos

Le présent travail de thèse s'insère ainsi dans un programme de recherche de grande envergure, lequel vise à mieux comprendre les effets d'un programme de 3 mois d'exercice aérobie chez la clientèle parkinsonienne. Les éléments suivant seront les points centraux de mes analyses :

- la mobilité des membres inférieurs
- le contrôle moteur du membre supérieur
- les changements neuro-anatomiques de matière grise

Aussi, ces éléments seront mis en perspectives avec les changements des fonctions cognitives dites exécutives ainsi que l'apprentissage moteur.

Cette thèse inclue une revue de la littérature couvrant l'épidémiologie, la pathophysiologie de la maladie de Parkinson, ainsi que les symptômes moteurs et non-moteurs et les changements neuro-anatomiques structuraux afin de bien comprendre l'étendue des dommages qui surviennent avec cette dernière et les défis avec lesquels doivent vivre les gens qui en sont atteints. Une seconde section couvre les bienfaits de l'activité physique sur les symptômes moteurs et non-moteurs, ainsi qu'au niveau cérébral. Les mécanismes potentiels sont également discutés.

Après un chapitre détaillant la méthodologie utilisée pour ce travail de recherche, trois articles en tant que première auteure présentent les résultats que j'ai obtenus. Les deux premiers ont été acceptés et publiés précédemment, le troisième et dernier étant prêt à être soumis.

Article 1: Nadeau A, Lungu O, Duchesne C et al. A 12-week cycling training regimen improves gait and executive functions concomitantly in people with Parkinson's disease. Frontiers in Human Neuroscience, 2017, vol 10, doi : 10.3389/fnhum.2016.00690

Article 2 : Nadeau A, Lungu O, Boré et al. A 12-week cycling training regimen improves upper limb functions in people with Parkinson's disease. Frontiers in Human Neuroscience, 2018, vol 12, doi : 10.3389/fnhum.2018.00351.

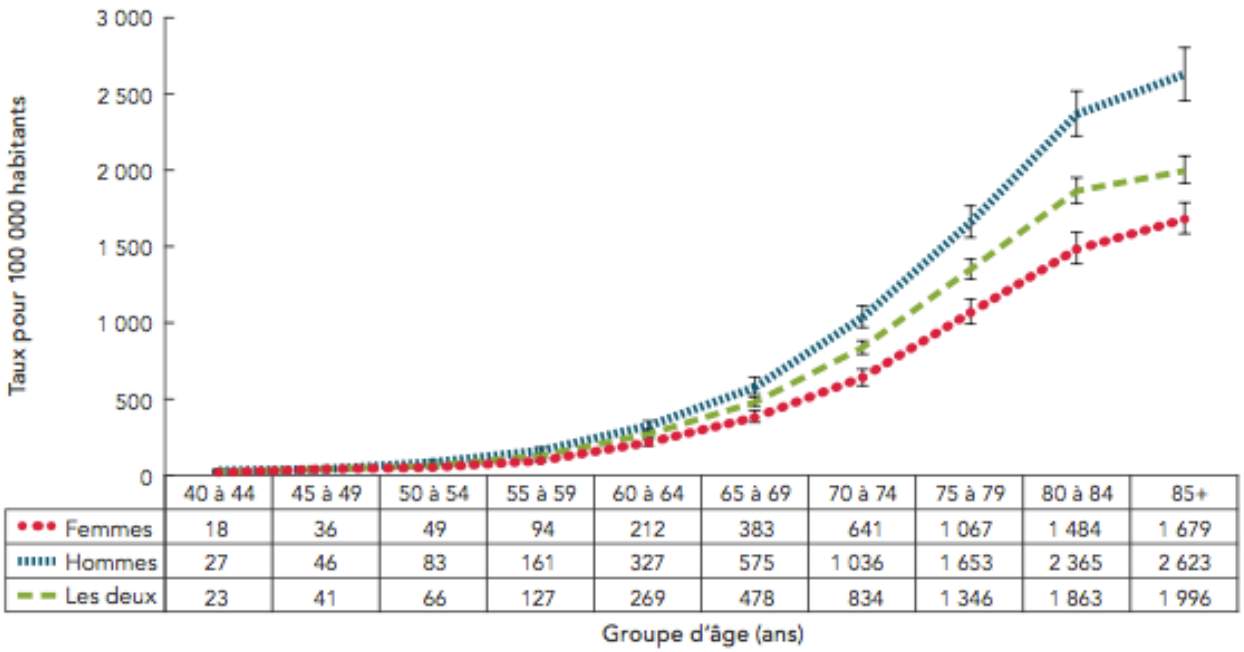
Article 3 : Nadeau A, Lungu O, Boré et al. Effects of aerobic exercise on brain grey matter in people with Parkinson's disease. (En préparation).

La discussion générale permet de mieux situer les résultats du projet de recherche actuel par rapport à la littérature déjà disponible.

CHAPITRE 1 : REVUE DE LA LITTÉRATURE

1.1 Épidémiologie

De nombreuses données démographiques convergentes indiquent que le nombre de personnes atteintes de la maladie de Parkinson dans le monde atteindra 40 millions en 2020 (Ahlskog 2011). En 2011, 84 700 canadiens étaient touchés par la maladie, et il est estimé que nous assisterons à une hausse constante du nombre de cas pour atteindre environ 163 700 malades en 2031 (Agence de la santé publique du Canda et al. 2014), projection établie en considérant seulement les individus âgés de 65 ans et plus. Le début des symptômes se situe en moyenne à l'âge de 63 ans pour les hommes et de 65 ans pour les femmes. La prévalence canadienne moyenne se situait entre 140 et 200 nouveaux cas sur 100 000 habitants pour l'année 2010 à 2011 (Agence de la santé publique du Canda et al. 2014). L'exercice financier de 2009-2010 pour la province de la Colombie-Britannique a montré que la prévalence était 1,5 fois plus élevée chez les hommes que les femmes (voir Figure 1) (Agence de la santé publique du Canda et al. 2014). Bien que la maladie de Parkinson soit principalement liée au vieillissement, dans 5 à 10% des cas, cette maladie neurologique débute entre 30 et 55 ans.



	40 à 44	45 à 49	50 à 54	55 à 59	60 à 64	65 à 69	70 à 74	75 à 79	80 à 84	85+
Femmes	18	36	49	94	212	383	641	1 067	1 484	1 679
Hommes	27	46	83	161	327	575	1 036	1 653	2 365	2 623
Les deux	23	41	66	127	269	478	834	1 346	1 863	1 996

Figure 1 : Prévalence de la maladie de Parkinson selon le sexe et le groupe d'âge

Colombie-Britannique, exercice financier 2009-2010 (tirée du Rapport Mieux comprendre les affections neurologiques au Canada, 2014)

Malgré l'aide reçue et la médication prescrite pour traiter les symptômes, plus de 50% des individus atteints considèrent avoir un état de santé passable, voir mauvais, ce qui affecte la grande majorité des activités de la vie quotidienne (Agence de la santé publique du Canda et al. 2014).

1.2 Pathophysiologie de la maladie de Parkinson

1.2.1 Notions neuro-anatomiques

Profondément au centre du cerveau, on retrouve certaines structures constituées de matières grises, tels que le thalamus et les noyaux gris centraux. Les noyaux gris centraux incluent le striatum (noyau caudé et putamen), le globus pallidus (pallidum externe et interne), le noyau subthalamique et la substance noire (Figure 2). La substance noire tire son nom de la couleur des

cellules qui composent ce noyau, en raison de la présence d'une pigmentation nommée neuromélanine. C'est cette structure qui sécrète le neurotransmetteur de la dopamine.

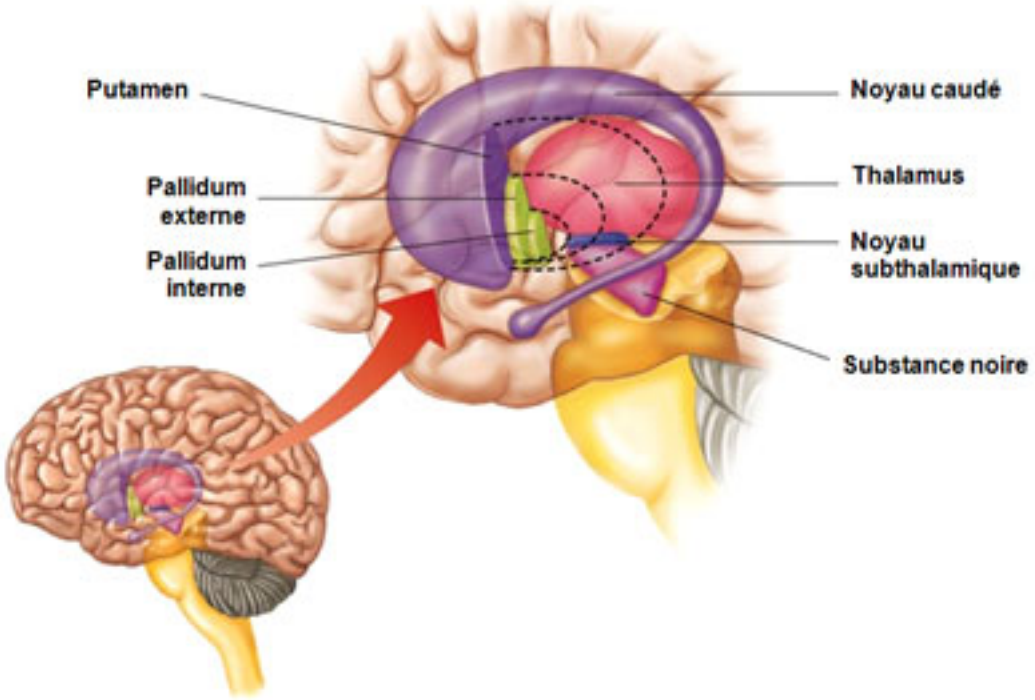


Figure 2 : Représentation des noyaux gris centraux

Les éléments qui composent les noyaux gris centraux communiquent entre eux, pour ensuite envoyer des commandes à différentes régions du cortex. La Figure 3 montre les différentes boucles dans lesquelles les noyaux gris centraux sont impliqués. Le circuit moteur permet de planifier et coordonner les mouvements moteurs volontaires. Le circuit associatif permet les processus cognitifs complexes, tel que le contrôle exécutif (planification, raisonnement, résolution de problème, mémoire de travail). Le système limbique pour sa part regroupe les processus affectifs et émotionnels. Cependant, pour assurer l'harmonie du travail entre les composantes des noyaux gris centraux, la dopamine, sécrétée par la substance noire, est nécessaire.

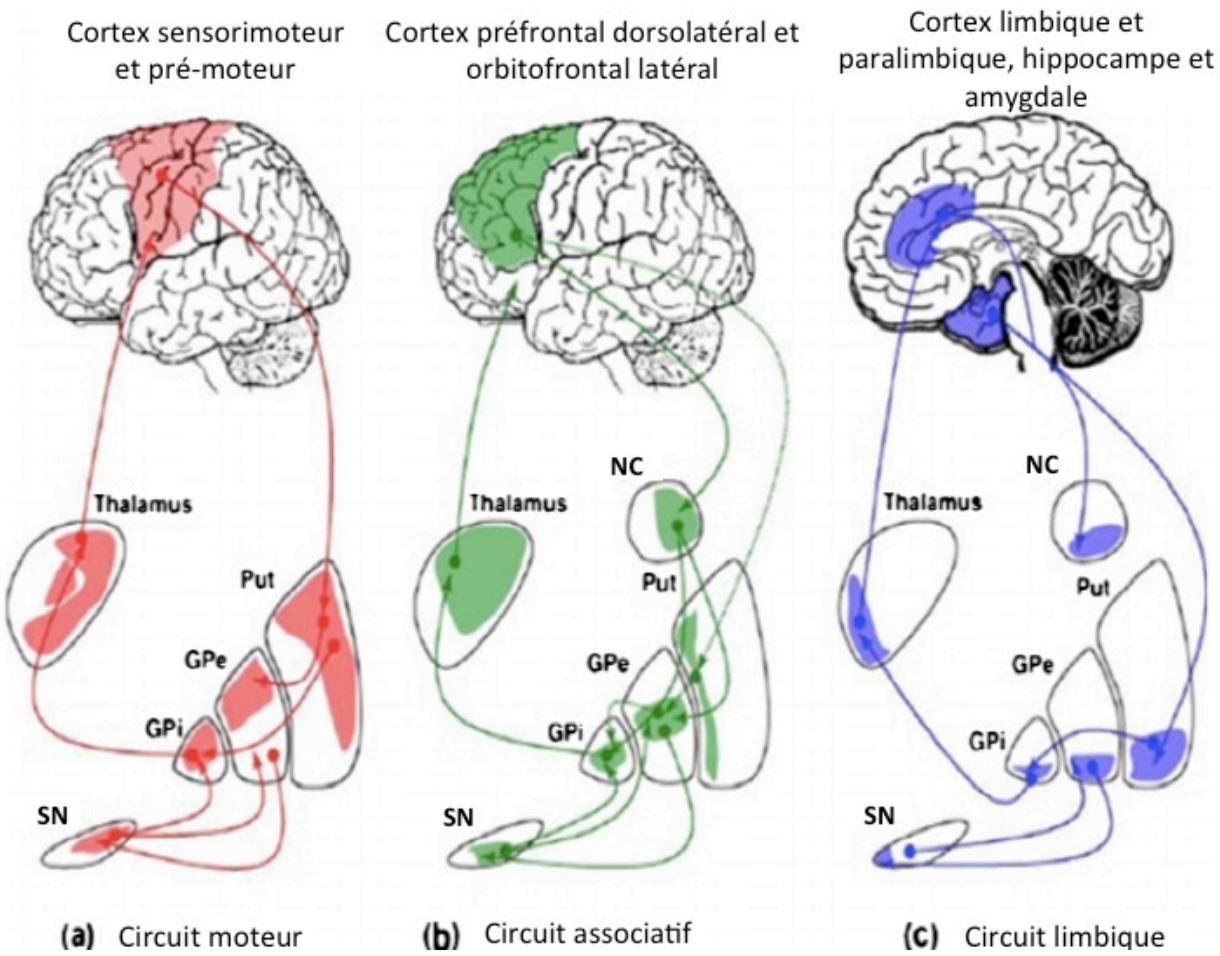


Figure 3 : Circuits impliquant les noyaux gris centraux

(tirée de Obeso et al. 2008)

NC : noyau caudé, Put : putamen, GPe : globus pallidus externe, GPi : globus pallidus interne, SN : substance noire

1.2.2 Physiologie et étiologie de la maladie

Jusqu'à ce jour, la maladie de Parkinson est confirmée de façon officielle que lors de l'examen post-mortem, à l'aide d'une autopsie. En effet, celle-ci peut confirmer la mort des neurones dopaminergiques de la substance noire pars compacta, qui se reflète par une dépigmentation de

cette zone. L'étiologie exacte de cette maladie est encore inconnue (Olanow 2007). Toutefois, l'exposition à différents facteurs environnementaux et certaines modifications génétiques pourraient accroitre les risques de développer cette maladie (Olanow and Tatton 1999). Chez 5 à 10% des cas, la maladie serait due à une mutation sur l'un des 5 gènes identifiés (PARK1, PARK4, PARK5, PARK8, PARK11, PARK13). Il a été suggéré que le dommage observé au niveau de la substance noire pourrait également être causé par une protéine anormale (protéine alpha-synucléide) (Braak et al. 2003). Dans les faits, cet acide aminé se retrouve de façon courante dans le système nerveux, précisément au niveau des terminaisons nerveuses présynaptiques, où son rôle n'est pas clairement établi encore. Plusieurs facteurs contribueraient à générer une mutation de cette protéine qui a alors tendance à s'accumuler au niveau des neurones dopaminergiques, causant leur mort (Breydo et al. 2012). Il a même été proposé que cette accumulation de protéines anormales et leur conséquence destructrice sur les neurones dopaminergiques débuterait au niveau du l'intestin, et s'étendrait ensuite vers le nerf vague, puis vers le bulbe rachidien, le noyau olfactif et le tronc cérébral, L'accumulation se poursuivrait ensuite vers les noyaux gris centraux et le reste du cortex (voir Figure 5, modèle de Braak 2004). Les symptômes moteurs principaux apparaitraient lorsque les dommages neuropathologiques touchent environ 70-80% des neurones dopaminergiques de la substance noire (Yousefi et al. 2009; Vanderheyden 2010).

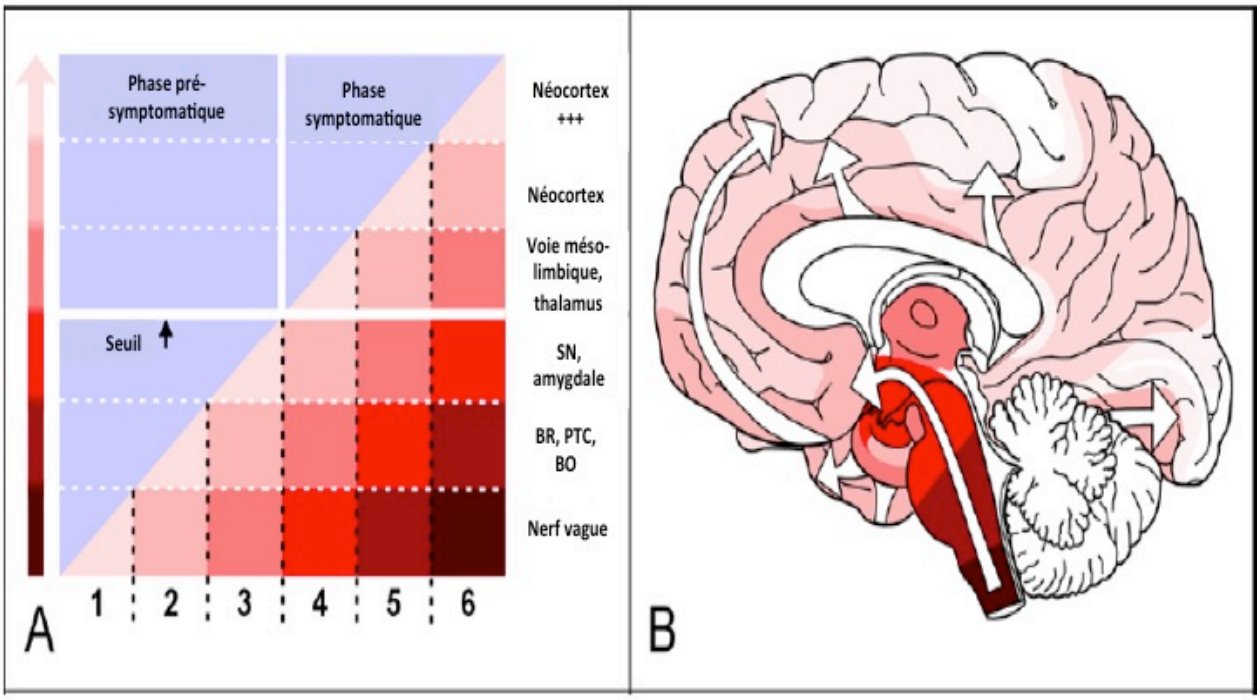


Figure 4 : Progression de la maladie de Parkinson

(adaptée de Braak et al. 2004)
BR : bulbe rachidien, PTC : pont du tronc cérébral, BO : bulbe olfactif, SN : substance noire. L'augmentation de l'intensité des zones colorées sous la diagonale indique la gravité croissante de la pathologie dans les régions vulnérables. Le seuil indique le moment où les symptômes deviennent apparents.

Le mécanisme d'apparition de la maladie de Parkinson au niveau du nerf vague par Braak a été supporté par les résultats d'une étude récente qui s'est intéressée à la protection potentielle contre la maladie offerte par une vagotomie complète (Svensson et al. 2015).

La dégénérescence des neurones dopaminergiques de la substance noire, pars compacta, cause une réduction de la quantité de dopamine disponible. La figure 5 illustre le fonctionnement normal des différentes structures des noyaux gris centraux, versus les changements qui

surviennent avec la maladie de Parkinson. Le manque de dopamine entraîne une augmentation considérable de l'activité de la voie indirecte, ce qui a pour effet une action inhibitrice anormalement élevé de la part du globus pallidus interne sur le thalamus et le noyau pédonculopontin. C'est alors qu'il est possible d'observer un mauvais fonctionnement des circuits impliquant les noyaux gris centraux et l'apparition des symptômes moteurs et non-moteurs propres à la maladie.

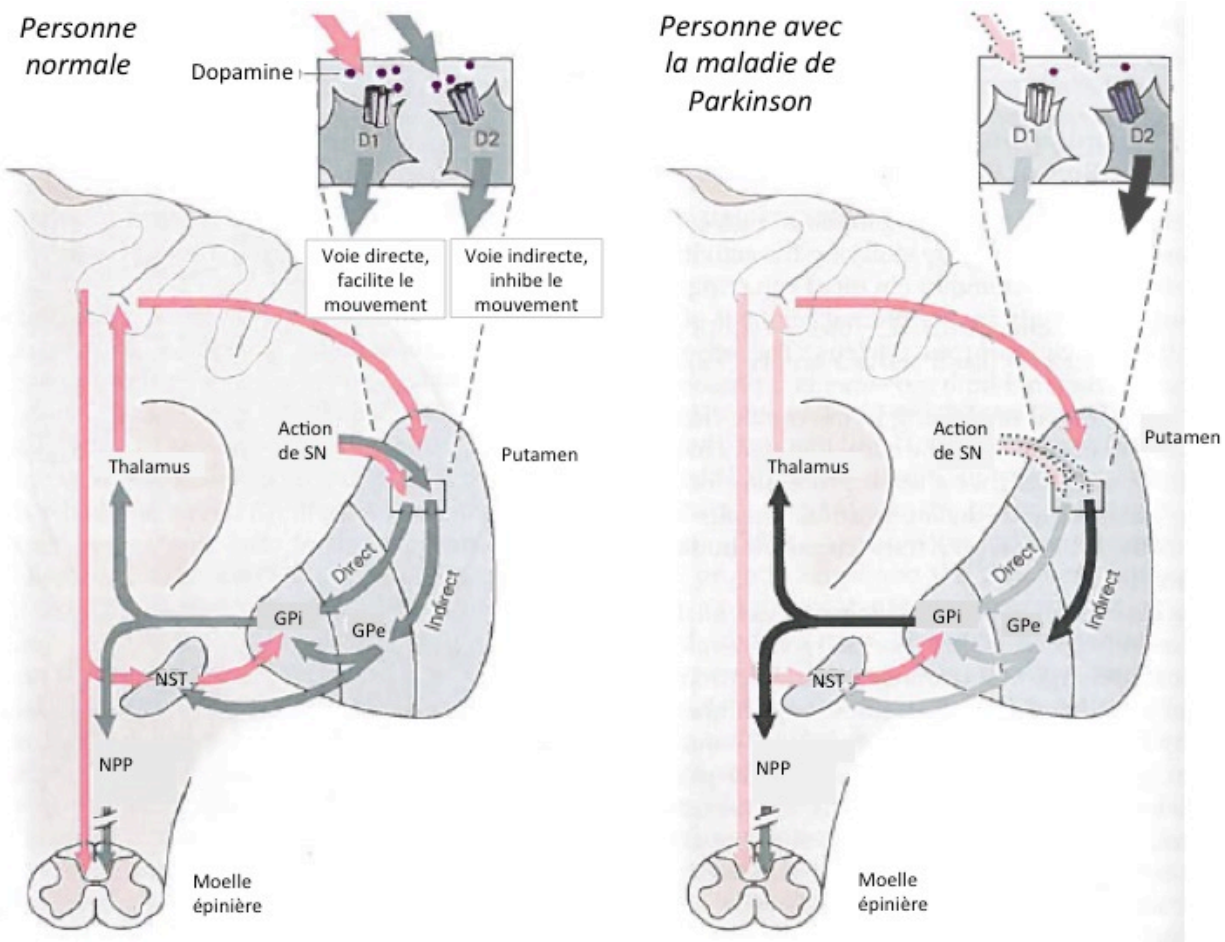


Figure 5 : Interactions entre les structures des noyaux gris centraux

(adaptée de Kandel et al 2000 (Kandel et al. 2000))
SN : substance noire, GPi : globus pallidus interne, GPe : globus pallidus externe, NST : noyau sous-thalamique, NPP : noyau pédonculopontin. Flèches grises indiquent une connexion inhibitrice (noire : augmentation de l'inhibition, gris pâle : diminution de l'inhibition). Flèches roses

indiquent une connexion facilitatrice (rouge : augmentation de l'excitation, rose pâle : diminution de l'excitation)

1.3 Perturbations motrices

Plusieurs changements surviennent sur le plan moteur au fur et à mesure que les neurones dopaminergiques dégénèrent. Les symptômes moteurs sont bien souvent les premiers symptômes qui amènent les patients à consulter un neurologue. Certains changements moteurs sont plus discrets, tels que les changements au niveau de la dextérité motrice, mais apportent aussi leur lot de difficulté dans le quotidien.

1.3.1 Symptômes moteurs

Le manque de dopamine entraine des symptômes moteurs, dont les plus courants sont le tremblement au repos, la rigidité, l'akinésie et la bradykinésie, ainsi qu'une modification de la posture et de la marche. Les tremblements de repos (i.e., mouvements involontaires, rythmiques et de faibles amplitudes) sont principalement présents au niveau des membres supérieurs et des mains et constitue le principal symptôme amenant à 70% des diagnostics (Factor and Weiner 2008). Ils sont amplifiés par la fatigue, le stress et par une activité demandant une concentration accrue de la personne. La rigidité, pour sa part, consiste en une co-contraction pathologique du couple musculaire agoniste-antagoniste des membres en action. Cette raideur se traduit généralement par des à-coups successifs, permettant d'observer un mouvement en roue dentée. L'akinésie, quant à elle, représente une difficulté à initier les mouvements volontaires et une difficulté lors des mouvements d'ajustement postural. La bradykinésie, pour sa part, est une lenteur dans l'exécution de ces mouvements. Cette tendance à l'immobilité est visible au niveau de la marche, du faciès (traits figés et peu expressifs), de la parole (mauvaise articulation et

monotonie) et de l'écriture (micrographie). Finalement, la maladie de Parkinson est associée à une posture caractéristique, où l'individu présente un dos arrondi et fléchi, les bras en extension et légèrement en flexion de chaque côté du corps, avec un léger (voire inexistant) balancement des bras lors de la marche. Il est également possible d'observer une modification du patron de la marche, telle qu'une diminution de la vitesse de marche, une diminution de la longueur des pas, un temps en double support augmenté, ainsi qu'une plus grande variabilité d'une foulée à l'autre (voir Annexe 1 pour descriptif des paramètres de la marche, voir Annexe 2 pour les phases de la marche). L'ensemble de ces modifications a pour effet d'instaurer une instabilité posturale qui accroit le risque de chutes chez cette population, en plus d'avoir un impact considérable sur l'autonomie de façon générale. Les quatre symptômes moteurs principaux (tremblements de repos, rigidité, akinésie/bradykinésie, posture/marche) peuvent être quantifiés grâce à la section trois de l'outil intitulé « *Unified Parkinson Disease Rating Scale* (UPDRS) » (Goetz et al. 2008).

1.3.2 Mobilité du membre supérieur

La rigidité et la bradykinésie peuvent résulter en des troubles affectant les membres supérieurs, notamment par une diminution de la vitesse et de l'amplitude des mouvements, une difficulté à effectuer des tâches séquentielles et une difficulté à exécuter des activités requérant une dextérité fine des mains. Même dans les premiers stades de la maladie, il est possible de noter chez les parkinsoniens une difficulté à contrôler leur force de préhension (Alberts et al. 1998). Ces modifications de leurs aptitudes affectent grandement la réalisation des activités quotidiennes, des soins personnels ainsi que des loisirs.

Bien que les difficultés motrices des membres supérieurs soient un symptôme courant de la maladie de Parkinson, ces déficits sont subtils et peuvent être facilement oubliés lors de

l'examen clinique. Près de la moitié d'une cohorte de physiothérapeutes et de thérapeutes d'Australie n'évaluent pas de façon courante la fonction motrice du membre supérieur de leur clientèle parkinsonienne (Proud et al. 2013). De ce nombre, 20% des répondants ne savent pas quel outil ou quelle mesure utiliser. Parmi les spécialistes qui mesurent cette capacité, 60% utilisent seulement leurs observations. Près du quart utilise une mesure standardisée (échelle d'évaluation motrice (MAS (Carr et al. 1985))). Autant de répondants utilisent l'UPDRS, qui a au moins l'avantage d'être spécialement indiqué pour une population atteinte de la maladie de Parkinson. D'autres outils tels que le test de Purdue Pegboard, le test du Nine Holes Peg, le questionnaire de qualité de vie PDQ-39 ou la tâche de rotation d'une pièce de monnaie sont également parfois utilisés. Une revue de la littérature s'intéressant aux outils disponibles pour évaluer les fonctions du membre supérieur a cependant mis de l'avant la nécessité de développer des tests fiables, adaptés à la réalité des personnes vivant avec la maladie de Parkinson, et qui permettraient d'évaluer avec justesse et objectivité les progrès suite à un traitement (Proud et al. 2015).

Dans les dernières années, des chercheurs ont aussi développé des exercices jumelés à des formules mathématiques afin de permettre l'analyse détaillée du contrôle moteur fin du membre supérieur. Par exemple, l'algorithme de Plamondon et al. (1998) permet de calculer les caractéristiques cinématiques et cinétiques d'un mouvement simple de traçage de lignes. Parmi ces paramètres, certains fournissent des éléments d'information sur le système nerveux central, tels que le temps d'émission de la commande motrice par le système nerveux central ainsi qu'une estimation de l'amplitude des commandes motrices agonistes et antagonistes lors de l'exécution du mouvement de traçage (Plamondon 1998; Plamondon et al. 2003). Cet outil a permis de différencier les sujets sains de ceux présentant au moins un facteur de risque d'accident vasculaire cérébral (Plotnik et al. 2011). Il reste à démontrer, cependant, si cet algorithme

permettrait également de distinguer un sujet parkinsonien d'un sujet sain et vérifier son utilisation permettrait d'évaluer efficacement l'effet d'un traitement.

1.3.3 Apprentissage moteur

L'apprentissage procédural peut être défini par un ensemble de processus cognitifs et moteurs associés à la pratique et à l'expérience qui conduisent à des changements relativement permanents au niveau de la performance d'habiletés motrices (Schmidt and Lee 2011). L'acquisition est implicite et reflète une réduction progressive du temps de réponse et du taux d'erreurs tout au long de la pratique (Dujardin and Laurent 2003). Il a été suggéré que le striatum, et particulièrement le putamen, jouerait un rôle primordial dans l'apprentissage procédural impliquant l'acquisition d'une séquence de mouvements (Dujardin and Laurent 2003; Doyon and Benali 2005; Doyon et al. 2009). Avec l'altération du fonctionnement des noyaux gris centraux dans la maladie de Parkinson, il est donc possible d'observer une modification de la capacité d'apprentissage d'une nouvelle séquence motrice chez les parkinsoniens. En effet, plusieurs auteurs ont démontré que les parkinsoniens sont capables d'apprendre ces nouveaux mouvements, mais que cet apprentissage s'effectuera plus lentement que chez des sujets sains (Krebs et al. 2001; Muslimovic et al. 2007; Stephan et al. 2011). Le degré de sévérité de la maladie et l'avancement de la maladie semble également avoir un impact sur la capacité d'apprentissage procédural, suggérant que cette difficulté n'est pas présente au tout début de la maladie (Muslimovic et al. 2007; Stephan et al. 2011). D'un autre côté, il a aussi été proposé que les phases initiales d'apprentissage reposeraient sur les fonctions cognitives, particulièrement les fonctions exécutives, où l'attention et l'inhibition sont essentielles à une planification adéquate et un contrôle de la réponse (Abrahamse et al. 2013). Ce résultat est appuyé par des études

d'imagerie qui montrent une activation du cortex préfrontal et du cortex cingulaire antérieur pendant l'apprentissage et l'exécution d'une séquence de mouvement (Jueptner et al. 1997; Sakai et al. 1998).

1.4 Symptômes non-moteurs

Bien que moins perceptibles que les symptômes moteurs, les symptômes non-moteurs qui peuvent être engendrés par la pathologie influencent énormément l'autonomie au quotidien et à la qualité de vie des parkinsoniens. De plus, plusieurs d'entre eux peuvent avoir un impact sur une intervention personnalisée en activité physique comme le présent projet de recherche vise.

1.4.1 Les fonctions exécutives

Les problèmes cognitifs sont reconnus comme étant un prédicteur significatif du niveau de qualité de vie chez les parkinsoniens (Leroi et al. 2012). En plus, ces troubles non-moteurs augmentent le fardeau du proche-aidant, accélérant dans un même temps le transfert des personnes atteintes vers des institutions adaptées (Leroi et al. 2012). Un des aspects qui décline de façon notable chez la population parkinsonienne sont les fonctions exécutives. Les fonctions exécutives sont un concept neuropsychologique qui désigne un ensemble de capacités cognitives de haut niveau régulées principalement par le cortex frontal, en lien avec les régions corticales plus postérieures. Elles incluent notamment l'attention, la génération de solutions à de nouveaux problèmes, la planification, l'organisation, l'inhibition cognitive et la flexibilité mentale. La réduction de dopamine disponible en raison de la maladie de Parkinson affecte non seulement le fonctionnement des noyaux gris centraux, mais également les connections de ces noyaux avec la région préfrontale, ce qui résulte en des troubles des fonctions exécutives (Obeso et al. 2011).

Ainsi, les parkinsoniens présentent des difficultés au niveau de l'inhibition, capacité qui permet de résister aux distractions ou de réprimer une réponse automatique au profit d'une réponse contrôlée. Cette capacité est généralement comparée à un filtre. L'inhibition est très souvent mesurée au cours de tâches d'interférence telle que le *Stroop* (Obeso et al. 2011), où les participants doivent inhiber la lecture naturelle des mots et nommer que la couleur de l'encre. Une autre fonction exécutive sur laquelle les parkinsoniens ont démontré des difficultés est la flexibilité cognitive. Cette habileté, quant à elle, fait référence à la capacité de changer de stratégie pendant une tâche, comme dans le *Wisconsin Card Sorting Task* (Monchi et al. 2006) ou alterner entre plusieurs consignes au cours d'une même tâche, comme dans le *Trail Making Test* (TMT) (Sanchez-Cubillo et al. 2009).

Les fonctions exécutives peuvent être associées à certaines performances physiques, telle que la marche, particulièrement lors de situations complexes (double-tâche, marche avec obstacles), mais aussi lors de situations de marche sans difficulté ajoutée si le patron de marche est déjà affecté par une condition neurologique, comme c'est le cas avec la maladie de Parkinson (Yogev-Seligmann et al. 2008). Les personnes présentant des performances cognitives plus faibles que leurs compères au TMT ont montré des vitesses de déplacement inférieures lors d'un parcours à obstacles (Ble et al. 2005) ou lors de tâches complexes de déplacement (parcours à obstacles, marcher en transportant une lourde charge, marcher et parler) (Coppin et al. 2006). Une autre étude ayant évalué des personnes âgées (avec 7 ans de différence entre les deux évaluations) a également conclu qu'une réduction dans les performances cognitives était associée à une perte d'efficacité dans des tâches motrices variées (marche à vitesse préférentielle, marche à vitesse rapide, exercices d'équilibre, levées de chaise, attraper un objet avec une main) (Tabbarah et al. 2002).

1.4.2 Autres changements non-moteurs

Selon une étude récente (Simuni et al. 2017), les symptômes non-moteurs les plus fréquemment rencontrés sont les problèmes de sommeil (53%), les sensations de douleurs (52%), les problèmes urinaires incluant la nycturie ainsi que l'augmentation de l'urgence et de la fréquence des mictions (51%), la fatigue (50%), une somnolence diurne excessive (50%), l'anxiété (36%) et la constipation (33%). Bien que mesuré comme léger au début de la maladie, la cumulation de ces symptômes peut grandement impacter la qualité de vie des parkinsoniens. Les résultats de l'étude de Simuni 2017 suggèrent aussi que la progression des symptômes non-moteurs n'est aucunement associée à celle des symptômes moteurs. En l'espace de deux ans, la sévérité des symptômes non-moteurs peut s'aggraver, et bien que la progression puisse sembler légère, ne fait que renforcer l'impact sur la qualité de vie des gens vivant avec la maladie.

Le nerf vague est une voie très importante de la régulation végétative, avec des actions multiples. Avec la progression de la maladie le long du nerf vague, une dysfonction du système sympathique peut engendrer des dysfonctions autonomes cardiaques. Présents chez environ 50% des parkinsoniens (Amara and Memon 2018), il est possible d'observer une hypotension orthostatique et une augmentation de la fréquence cardiaque de repos. De même, ces changements peuvent expliquer l'altération dans la réponse métabolique et cardiovasculaire, autant en exercice aérobie sous-maximal que maximal (Kanegusuku et al. 2017). Ces changements se traduisent par une difficulté accrue à augmenter sa fréquence cardiaque, à une fréquence cardiaque très instable pendant un exercice, en plus de l'incapacité à atteindre la fréquence cardiaque théorique. Pour ces raisons, l'utilisation de l'échelle de Borg pour évaluer l'intensité de l'effort (plutôt que la fréquence cardiaque) est beaucoup plus adéquate avec la population parkinsonienne (Kanegusuku et al. 2017). Le nerf vague joue également un rôle dans différentes étapes de la digestion. Pour cette raison, il est possible d'observer des symptômes tels

que la sialorrhée, la dysphagies, des troubles de la motilité gastrique, de l'incontinence intestinale, ainsi que de la constipation, ce dernier symptôme étant celui dont les parkinsoniens se plaignent le plus parmi les troubles gastro-intestinaux (Amara and Memon 2018). La sialorrhée correspond à l'écoulement de salive hors de la bouche car les lèvres ne parviennent pas à retenir la salive ou dû à une gêne à la déglutition, à ne pas confondre avec une sécrétion excessive de salive.

La fatigue, les problèmes de sommeil et la somnolence diurne excessive sont d'autres symptômes non-moteurs dont les personnes atteintes de la maladie de Parkinson se plaignent souvent (Amara and Memon 2018).

D'autres symptômes non-moteurs rencontrés avec la maladie de Parkinson incluent des symptômes dépressifs et de l'apathie. Il est cependant difficile de conclure à une prévalence de ces symptômes non-moteurs dû à l'entremêlement de ces symptômes avec de possibles troubles cognitifs, de possibles effets psychiatriques de la médication dopaminergique, et de la présence fluctuante des autres symptômes moteurs et non-moteurs (Gallagher and Schrag 2012).

1.5 Changements structuraux du cerveau avec la maladie de Parkinson

L'imagerie par résonance magnétique (IRM) permet d'observer *in vivo* des images du cerveau qui sont sensibles aux propriétés des tissus scannés, c'est-à-dire les corps cellulaires des neurones (matière grise), leur axone (matière blanche) et liquide céphalo-rachidien. Plusieurs métriques anatomiques et fonctionnelles ont été utilisées jusqu'à présent afin de mieux comprendre la pathophysiologie de la maladie de Parkinson. L'IRM est également de plus en plus utilisée afin d'essayer de distinguer des différences au niveau de la matière grise et de la matière blanche, des

différences qui pourraient permettre de distinguer les gens atteints de la MP, et ainsi tenter de confirmer le diagnostique de la maladie, et ce même lorsque la maladie est encore peu avancée.

1.5.1 La matière grise

Premièrement, la méthode appelée « *Voxel-based Morphometry* (VBM) » est une méthode statistique qui permet de comparer la densité locale de matière grise ou blanche. Plusieurs études ont noté des différences significatives entre des personnes atteintes de la maladie de Parkinson et des sujets sains dans plusieurs zones du lobe frontal (Dagher and Nagano-Saito 2007; Pereira et al. 2009; Agosta et al. 2012; Pan et al. 2012; Lee et al. 2014). Ces dommages s'étendaient jusqu'au lobe pariétal (Pereira et al. 2009; Lee et al. 2013) ou même temporal (Pereira et al. 2009; Pan et al. 2012; Lee et al. 2013). D'autres résultats ont montré une perte de densité de matière grise au sein du système limbique en comparaison à un groupe contrôle (Dagher and Nagano-Saito 2007; Pereira et al. 2009). Une seule étude semble n'avoir trouvé aucune différence dans la densité de matière grise entre sujets parkinsoniens et sujets sains (Lee et al. 2014).

La volumétrie est une autre méthode statistique qui permet d'étudier la variation du volume d'une région d'intérêt. Les différences observées entre les participants atteints de la maladie de Parkinson et les sujets sains étaient présentes au niveau du noyau caudé (Lee et al. 2011), du thalamus (Lee et al. 2011), du putamen (Lee et al. 2011; Lee et al. 2014), du noyau accumbens (Lee et al. 2011; Lee et al. 2014), de l'hypothalamus (Lee et al. 2014) et de la substance noire (Menke et al. 2009). Certaines études ont même observé une perte de matière grise au sein du cervelet, une réduction particulièrement marquée chez les parkinsoniens avec une dominance de tremblements comme symptômes moteurs (Mormina et al. 2017). Une seule étude

ne semble pas avoir observé de différence de volume de matière grise entre les deux groupes (Tinaz et al. 2010).

Finalement, une troisième méthode statistique utilisée pour détecter des changements de matière grise est l'épaisseur corticale. Cette mesure reflète l'épaisseur de la substance grise périphérique des hémisphères cérébraux. Un amincissement cortical est normal avec le vieillissement, et n'implique pas nécessairement une perte neurale, mais plutôt une altération de l'architecture neuronale et dendritique. En comparant des parkinsoniens avec des personnes saines, des réductions ont été notées dans les régions pariétales (Pereira et al. 2011; Madhyastha et al. 2015), temporales (Pellicano et al. 2011; Pereira et al. 2011; Madhyastha et al. 2015), occipitales (Tinaz et al. 2010; Pereira et al. 2011; Hanganu et al. 2014) et également frontales (Tinaz et al. 2010; Pereira et al. 2011; Madhyastha et al. 2015), incluant des différences notables dans les régions prémotrices (Pereira et al. 2011). Certaines études n'ont certes pas observé de différences entre ces deux populations pour l'épaisseur corticales (Jubault et al. 2011; Ibarretxe-Bilbao et al. 2012), mais ont quand même conclu que la réduction s'effectuait à un rythme plus grand chez les personnes atteintes de MP, particulièrement dans la région de l'aire motrice supplémentaire (Jubault et al. 2011). L'apparition de troubles cognitifs augmenterait l'importance de cette détérioration (Hanganu et al. 2014). Plusieurs études ont ainsi conclu qu'il existait une corrélation entre la réduction de l'épaisseur corticale et la durée de la maladie ainsi que l'importance des symptômes moteurs (Jubault et al. 2011; Pereira et al. 2011; Hanganu et al. 2014).

1.5.2 La matière blanche

L'imagerie de diffusion permet d'observer le mouvement des molécules d'eau dans les tissus, plus précisément au niveau de la matière blanche. Le tenseur de diffusion est l'une des méthodes permettant d'estimer le phénomène de diffusion locale de l'eau. Il est possible d'obtenir des informations quantitatives sur l'amplitude (diffusivité moyenne; MD) et la direction (anisotropie fractionnelle; FA) du mouvement d'eau aléatoire le long de ces faisceaux de fibres nerveuses à l'échelle microscopique. Le tenseur peut être décomposé en trois vecteurs propres, correspondant aux principales directions de diffusion du tenseur, auxquels s'associent des valeurs de force de la diffusion dans ces mêmes directions ($\lambda 1$, $\lambda 2$, $\lambda 3$) (voir figure 7). Plusieurs métriques dérivés du tenseur permettent d'extraire de l'information d'isotropie/d'anisotropie au sein d'un voxel (petit volume du cerveau correspondant à un pixel). La diffusivité axiale (AD), représentée par $\lambda 1$, indique la diffusion le long de l'axe principal. La moyenne des deux axes secondaires représente la diffusivité radiale (RD). La diffusivité moyenne (MD) pour sa part correspond à la moyenne des valeurs propres des trois vecteurs. La FA est normalisée entre 0 et 1, où une valeur de 1 signifie la présence d'une anisotropie importante (tenseur en forme de cigare) et une valeur de 0 signifie la présence d'une (tenseur en forme de sphère). Des détails sur les différentes méthodes statistiques pour obtenir ces valeurs se retrouvent à l'Annexe 3 à titre indicatif.

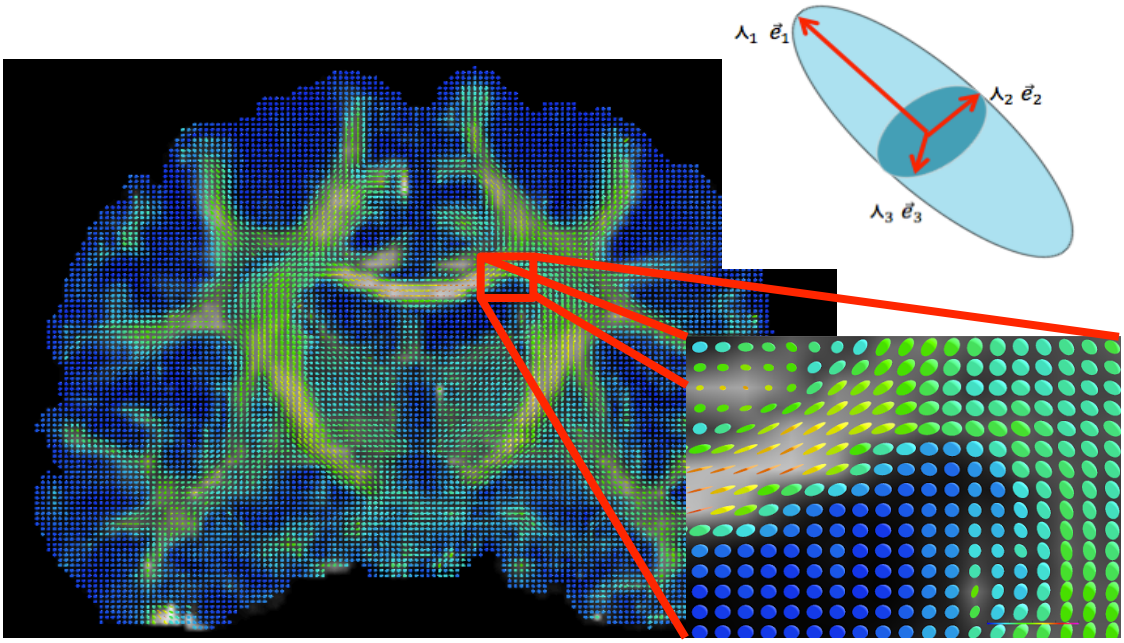


Figure 6 : Visualisation d'un champs de tenseurs

L'analyse de la matière blanche a ainsi permis d'observer que plusieurs faisceaux présentent également un changement avec la maladie de Parkinson. Une étude récente a même suggéré que les changements qui surviennent au niveau de la matière blanche précèderaient les atrophies de matière grise (Rektor et al. 2018). Les travaux de Scherfler (2006) (Scherfler et al. 2005) ont montré grâce à la diffusion une anormalité dans la région du bulbe olfactif chez des patients en début de maladie, ce qui est conforme avec les études histologiques qui ont ciblé cette région comme étant une des premières à être touchée par la maladie (Braak et al. 2004). Plusieurs études ont montré que les valeurs de FA étaient grandement réduites dans la substance noire en comparaison à un groupe de sujets sains (Vaillancourt et al. 2009; Cochrane and Ebmeier 2013; Planetta et al. 2014; Langley et al. 2016; Loane et al. 2016; Qiao et al. 2016; Lehéricy et al. 2017). D'autres régions et structures ont aussi montré une réduction de FA chez les parkinsoniens en comparaison aux participants contrôles, particulièrement au niveau du corps calleux (Gattellaro et al. 2009; Agosta et al. 2012; Rae et al. 2012; Gallagher et al. 2013; Price et al.

2016; Li et al. 2017), du cingulum (Gattellaro et al. 2009; Li et al. 2017), de la capsule interne et externe (Agosta et al. 2012; Gallagher et al. 2013; Li et al. 2017), du cortex frontal (Zhan et al. 2011; Agosta et al. 2012; Gallagher et al. 2013), du cortex pariétal (Agosta et al. 2012; Gallagher et al. 2013), du cervelet (Gallagher et al. 2013; Chiang et al. 2017; Mormina et al. 2017), et plusieurs faisceaux de matière blanche (Chang et al. 2012; Rae et al. 2012; Gallagher et al. 2013; Price et al. 2016).

La plupart des études qui se sont également intéressées à la MD ont observé une augmentation de cette mesure dans sensiblement les mêmes structures où une diminution de FA avait été observée (Gattellaro et al. 2009; Agosta et al. 2012; Rae et al. 2012; Loane et al. 2016; Deng et al. 2018). Quelques études ont noté une augmentation de MD sans conclure à des changements de la FA au niveau de la substance noire (Kim et al. 2013; Schwarz et al. 2013; Lu et al. 2016). Malgré les variations dans les résultats obtenus, plusieurs équipes de recherche ont réussi à démontrer des changements de matière blanche sans pour autant observer de détérioration au sein de la matière grise (Karagulle Kendi et al. 2008; Martin et al. 2009), et ce, même dans un stade précoce de la maladie (Gattellaro et al. 2009; Gallagher et al. 2013; Schwarz et al. 2013; Planetta et al. 2014; Zhang et al. 2015; Price et al. 2016; Qiao et al. 2016; Li et al. 2017).

1.6 Traitements et interventions

Les traitements et interventions qui existent visent à traiter les symptômes moteurs de la maladie puisque celle-ci n'est pas curable. L'approche thérapeutique principale jusqu'à maintenant est de type pharmacologique, bien que la neurochirurgie (stimulation profonde du globus pallidus ou du noyau subthalamique) offre une alternative prometteuse (St George et al. 2015; Koirala et al.

2016; Radhakrishnan and Goyal 2018). Cependant, ces deux méthodes comprennent leur lot de limitations et d'effets secondaires indésirables (St-George et al. 2015; Koirala et al. 2016) et donc, puisque les traitements pharmacologiques et chirurgicaux ne sont pas un point majeur de cette thèse, ces moyens thérapeutiques ne seront pas élaborés plus en détails. Il est possible de retrouver en Annexe 4 un tableau résumant les différents types de médicaments prescrits, leur mode de fonctionnement et indication, ainsi que leurs effets secondaires (Connolly and Lang 2014).

Par contre, l'activité physique est reconnue pour ses nombreux bienfaits sur la santé en générale, telle que la prévention des maladies cardiovasculaires, le maintien d'une santé osseuse et musculaire adéquate. De plus, de nombreuses études suggèrent que l'exercice physique constitue un traitement complémentaire sans effets secondaires indésirables dans le traitement des symptômes de la maladie de Parkinson. Jusqu'à ce jour, l'exercice pourrait être le seul moyen d'améliorer les symptômes non-moteurs, en plus de potentiellement permettre de ralentir la progression de la maladie, si pratiqué sur une période prolongée (Ahlskog 2018).

1.7 Effets de l'exercice physique

La présente section sert à démontrer l'étendue des impacts positifs observés jusqu'à présent grâce à des programmes d'exercice structurés sur les symptômes moteurs, les fonctions exécutives, les facteurs neurotrophiques et les structures cérébrales.

1.6.1 Effets de l'exercice sur les symptômes moteurs

Plusieurs modalités d'entraînement ont été utilisées pour évaluer l'effet de l'exercice physique chez la population parkinsonienne. Le Tai chi (Hackney and Earhart 2008; Li et al. 2012; Choi et al. 2013; Gao et al. 2014), la danse (Lötzke et al. 2015; McNeely et al. 2015), le zumba (Delextrat et al. 2016), le renforcement musculaire (Lima et al. 2013; Roeder et al. 2015; Chung et al. 2016) et même la boxe (Combs et al. 2011; Combs et al. 2013) ont tous montré des bénéfices sur les symptômes moteurs de la maladie, tels que mesurés à l'aide de l'UPDRS III. De toutes les modalités, la plus utilisée est certainement la marche sur tapis roulant, qui a permis d'observer des améliorations des capacités aérobies, de la qualité de vie, en plus d'améliorer différentes mesures de marche, telle que la vitesse et la longueur des pas (Mehrholz et al. 2010; Mehrholz et al. 2015).

Des effets immédiats ont été observés après seulement 20 minutes d'exercice sur le tapis roulant au niveau de la vitesse de marche et de la longueur de pas (Bello et al. 2008); les changements persistant jusqu'à 15 minutes après la cessation de l'exercice. Une durée de quatre à douze semaines d'entrainement sur tapis ont aussi montré en moyenne des augmentations de 11,9% et 7,7%, respectivement, pour la vitesse de marche (Miyai et al. 2002; Protas et al. 2005; Toole et al. 2005; Herman et al. 2007; Fisher et al. 2008; Kurtais et al. 2008; Canning et al. 2012; Shulman et al. 2012; Bello et al. 2013) et la longueur de pas (Miyai et al. 2002; Protas et al. 2005; Toole et al. 2005; Herman et al. 2007; Fisher et al. 2008; Bello et al. 2013). Des entraînements de marche à l'extérieur, que ce soit à la marche Nordique (Reuter et al. 2011) ou avec instructions de faire de grands pas (Lehman et al. 2005), ont également montré une certaine efficacité à améliorer la vitesse de marche et la longueur de pas, mais avec des effets moindres en comparaison au tapis roulant (Frenkel-Toledo et al. 2005).

Dû au risque de chute, l'utilisation du tapis roulant, bien qu'ayant démontré son efficacité dans l'amélioration des paramètres de marche, peut être précaire pour une proportion de la population parkinsonienne présentant une incapacité physique importante (c'est-à-dire blocages à la marche, pertes d'équilibre) s'il n'ont pas accès à un système avec harnais. Par conséquent, il a été proposé que la bicyclette stationnaire pourrait représenter une modalité d'entrainement plus sécuritaire pour cette population (Snijders and Bloem 2010), leur permettant de s'exercer à une intensité modérée et intense (Ridgel et al. 2009). Son côté sécuritaire permettrait même un entraînement à la maison sans supervision vu son risque faible de chute (Arcolin et al. 2016).

Des études effectuées sur bicyclette stationnaire chez des parkinsoniens ont montrées que cette modalité d'entraînement permet d'observer des améliorations considérables des fonctions exécutives (Ridgel et al. 2011), des tremblements de repos et de la bradykinésie (Ridgel et al. 2009; Ridgel et al. 2012), des symptômes moteurs généraux (réduction entre 3 et 3,5 points sur l'UPDRS III) (Lauhoff et al. 2013; Uygur et al. 2017), de la séquence de production de forces des mains lors d'une tâche bimanuelle (Ridgel et al. 2009), de la dextérité fine et du temps de réaction (Uygur et al. 2017), suggérant ainsi des adaptations neuronales généralisées au niveau du système nerveux central. Le vélo stationnaire permettrait également d'améliorer l'équilibre (augmentation de 2,1 points sur le test de Berg) (Lauhoff et al. 2013), la mobilité (diminution entre 1,1 et 2,3 secondes au Timed up and go) (Lauhoff et al. 2013; Uygur et al. 2017) ainsi que la vitesse de marche (augmentation de 18,5% au test sur une distance de 10 mètres) (Uygur et al. 2017). Une étude plus récente s'est penchée sur l'effet d'un entraînement sur vélo stationnaire en comparaison à un entraînement sur tapis roulant (Arcolin et al. 2016). Au final, des améliorations significatives ont été notées dans les deux groupes pour l'endurance à la marche (augmentation entre 35,2 et 47,9 mètres au 6MWT), la vitesse de marche (augmentation entre 12,1% et 19%), la cadence de marche (augmentation de 4,3%) et la longueur des pas (augmentation entre 4 et 6,9

cm). L'équilibre (augmentation de 2,3 à 3,3 points sur le *Mini-Balance Evaluation Systems Test*) et les symptômes moteurs (réduction de 6 points sur l'UPDRS III) ont également montré des changements significatifs; le point important de cette étude étant que les deux modalités d'entraînement ont généré des améliorations similaires.

Même si les approches utilisées avec le vélo stationnaire sont différentes d'une étude à l'autre (exercice forcé vs exercice volontaire, haute vélocité vs vélocité plus pondérée, utilisation de la résistance ou non), toutes ont quand même permis d'obtenir des améliorations intéressantes chez la population parkinsonienne.

1.6.2 Effets de l'exercice sur les symptômes non-moteurs

Il a été démontré que la pratique régulière d'exercice aérobie permet d'améliorer les fonctions exécutives chez des adultes sains de tout âge, telles que les capacités d'inhibition cognitive et de flexibilité mentale (Boucard et al. 2012; Guiney and Machado 2012; Predovan et al. 2012). Des résultats similaires ont été observés chez la population parkinsonienne suite à des programmes d'exercices variés (Murray et al. 2014; da Silva et al. 2018), suggérant que la présence de la maladie n'entrave pas les bénéfices possibles au niveau des fonctions cognitives. Ces améliorations ciblaient la mémoire de travail spatiale (Cruise et al. 2010; McKee and Hackney 2013), la fluence verbale (Cruise et al. 2010), mais principalement la flexibilité mentale (mesurée par le Trail Making Test) (Tanaka et al. 2009; Ridgel et al. 2011; Picelli et al. 2016). Puisque ces améliorations ne corrèlent pas avec une augmentation des capacités aérobies, il a été suggéré que le simple fait d'augmenter le flow de sang au cerveau, même pour de si courtes périodes, pourrait engendrer de tels changements (Ridgel et al. 2011).

1.6.3 Effets de l'exercice et de l'apprentissage au niveau des structures cérébrales

Peu d'études ont permis d'examiner les modifications structurelles cérébrales suite à un programme d'exercice chez une population saine. Après plusieurs semaines d'entraînement de type aérobie (entre 24 et 52 semaines), certaines études ont démontré des augmentations de volume de matière grise dans le lobe frontal (incluant l'aire motrice supplémentaire) (Colcombe et al. 2006), et dans le lobe temporal (incluant l'hippocampe) (Colcombe et al. 2006; Erickson et al. 2011). D'autres données ont montré que la densité de matière blanche semble également augmentée au niveau frontal, cette augmentation étant corrélée avec le changement de capacités aérobies des sujets (Colcombe and Kramer 2003; Colcombe et al. 2006). En utilisant la TBSS, il a été observé qu'un entraînement aérobie améliorerait l'intégrité de la matière blanche dans les régions frontales et temporales (Voss et al. 2012). Une étude de moins longue durée (12 semaines), bien qu'utilisant une intensité d'entraînement près de 64% du VO_2max n'a pas réussi à démontrer un effet de ce type d'entraînement sur le volume de matière grise, ni au niveau des capacités aérobies des participants (Matura et al. 2017).

Chez l'humain atteint de la maladie de Parkinson, il ne semble y avoir aucune étude sur l'effet de l'exercice aérobie sur la plasticité des structures cérébrales. Une étude a cependant investigué les effets d'un entraînement à une tâche d'équilibre sur le cerveau de cette population. Cet entraînement de 6 semaines, qui se rapproche plus d'une tâche d'apprentissage motrice qu'un entraînement conventionnel, a démontré des augmentations de la densité de matière grise au niveau des cortex pariétal, frontal (région pré-motrice), temporal et du système limbique (Sehm et al. 2014).

1.6.4 Les mécanismes sous-jacents aux amélioration suite à l'exercice

De nombreuses données scientifiques suggèrent que l'exercice est un excellent complément au traitement pharmacologique car l'augmentation de la fréquence cardiaque et de la tension artérielle aiderait la médication à passer la barrière hémato-encéphalique, où elle pourrait appliquer son action. En d'autres mots, l'activité physique permettrait d'optimiser la médication antiparkinsonienne (Speelman et al. 2011).

Même en début de maladie, l'exercice peut aider à ralentir la progression des dommages, et par conséquent la détérioration motrice (Hirsch and Farley 2009; Frazzitta et al. 2013; Ahlskog 2018). Cependant, il a été suggéré que l'âge, le type d'entraînement (type qui vise à l'apprentissage d'habiletés physiques versus de type aérobie) et la gravité de la lésion seraient quelques facteurs qui pourraient limiter le niveau de protection/restauration attribuable à l'exercice (Tillerson 2003; Al-Jarrah et al. 2007; O'Dell et al. 2007; Pothakos et al. 2009; Thomas et al. 2012).

Un premier mécanisme observé suite à l'exercice est la diminution des transporteurs dopaminergiques, le principal responsable de la recapture de dopamine. Sa présence réduite permet une plus grande disponibilité de la dopamine dans la fente synaptique (Fisher et al. 2004; Churchill et al. 2017). L'exercice permettrait également d'augmenter l'activation des récepteurs D2, qui jouent un rôle important de modulation dans l'activité corticostriatales/glutaminergique (Petzinger et al. 2010). Ces mécanismes contribueraient à améliorer la neurotransmission dopaminergique et glutaminergique, qui permettraient à leur tour de décroitre l'hyperexcitabilité corticale observée chez les personnes vivant avec la MP (Fisher et al. 2004; Petzinger et al. 2010).

Il a cependant été observé que les concentrations plasmatiques de certains facteurs neurotrophiques, ces protéines qui joueraient un rôle central dans le développement, le maintien

et le fonctionnement des neurones du système nerveux central via des processus favorisant la croissance neuronale et la croissance vasculaire, seraient diminuées chez les personnes atteintes de la maladie de Parkinson (Scalzo et al. 2009), diminuant par conséquent leur action protectrice. L'une des principales protéines étudiées à ce jour est la protéine *Brain-Derived Neurotrophic Factor* (BDNF), principalement de par sa grande concentration dans le corps humain, mais aussi car elle a été associée à la plasticité synaptique, à une meilleure capacité cognitive, à l'apprentissage et à la mémoire (Colcombe and Kramer 2003). Dans les récentes années, de plus en plus d'études chez les personnes atteintes de la maladie de Parkinson se sont intéressées aux changements survenus sur les niveaux de facteurs neurotrophiques suite à un programme d'exercice, particulièrement en ce qui concerne le BDNF (Frazzitta et al. 2014; Zoladz et al. 2014; Fontanesi et al. 2015; Marusiak et al. 2015; Angelucci et al. 2016; Sajatovic et al. 2017; Hirsch et al. 2018). Les résultats suggèrent un impact favorable de l'activité physique sur le niveau basal de BDNF plasmatique (Hirsch et al. 2018), sans considération pour le mode d'entraînement, l'intensité atteinte, ou même la durée du programme d'entraînement. Les niveaux plasmatiques de BDNF ont augmenté de 12,6% (Frazzitta et al. 2014) jusqu'à 335,8% (Sajatovic et al. 2017). Plusieurs de ces études ont pu faire des corrélations entre les augmentations de facteurs neurotrophiques et l'amélioration des symptômes moteurs (Fontanesi et al. 2015; Marusiak et al. 2015). Les facteurs neurotrophiques sont reconnus pour stimuler les processus de neurogénèse, d'angiogénèse et de synaptogénèse, ce qui peut changer l'organisation structurelle et fonctionnelle cérébrale. L'amélioration de la neurotransmission glutaminergique pourrait dépendre également des effets du BDNF (Binder and Scharfman 2009). Le BDNF enclencherait des processus favorisant la création de nouveaux récepteurs AMPA post-synaptique, ce qui explique pourquoi les changements persisteraient dans le temps (Frazzitta et al. 2012).

1.7 Objectifs et hypothèses de recherche

Malgré les connaissances que nous avons acquises jusqu'à présent concernant l'impact de l'exercice physique chez les personnes atteintes de la maladie de Parkinson, la recension des écrits ci-dessus a permis de constater que plusieurs questions restent encore sans réponse ou peu élucidée. De fait, seulement trois études ont vérifié l'effet d'un entrainement de type aérobie sur bicyclette stationnaire sur les paramètres de marche de sujets parkinsoniens. Deux études ont permis de vérifier l'effet systémique d'un exercice aérobie sur la dextérité du membre supérieur, mais sans pour autant tenter d'expliquer l'effet d'un tel exercice sur le système nerveux central. De plus, aucune étude n'a vérifié l'effet de l'exercice de type aérobie sur les structures cérébrales de gens atteints de cette maladie.

Le présent travail s'insère donc dans un programme de recherche qui a pour but de combler certaines de ces lacunes. Plus précisément, l'objectif principal de cette thèse est de quantifier les effets d'un entrainement de type aérobie chez une population atteinte de la maladie de Parkinson sur :

1. Le patron de marche;
2. La mobilité du membre supérieur;
3. Les structures anatomiques cérébrales.

Un second objectif est d'observer les relations existantes entre ces trois composantes, et d'autres paramètres tels que l'amélioration des capacités aérobies, les fonctions exécutives et les capacités d'apprentissage d'une nouvelle séquence motrice. De plus, il est pertinent de s'intéresser à la façon dont la maladie et l'âge peuvent influencer les interactions entre la mobilité du membre

inférieur, la mobilité du membre supérieur, les structures anatomiques cérébrales, l'apprentissage moteur et les changements du niveau des capacités aérobies suite à un programme d'exercice.

Nos hypothèses sont les suivantes :

1. Une amélioration de la mobilité, tant au niveau du membre inférieur que supérieur, sera présente chez les personnes atteintes de la maladie de Parkinson suite à un programme d'aérobie de trois mois;
2. Des différences anatomiques au niveau de la matière grise seront observables entre les personnes atteintes de la MP et les sujets sains. Un programme d'exercice de type aérobie permettra d'observer un changement structurel chez les deux groupes;
3. Les améliorations de la mobilité (membres inférieurs et supérieurs) et les changements cérébraux au plan structurel vont corréler avec une amélioration de la capacité aérobie et de la capacité à apprendre une nouvelle séquence motrice;
4. Relations entre les améliorations de la mobilité (membres inférieurs et supérieurs) et les changements cérébraux vont émerger chez les personnes atteintes ou non de la maladie de Parkinson.

CHAPITRE 2: MÉTHODOLOGIE GÉNÉRALE

Il est à noter que cette étude s'inscrit dans le cadre d'un vaste projet dont l'acquisition des données s'est déroulée entre février 2012 et décembre 2013. Pour réaliser cette étude, une approche multimodale a été choisie, à la fois pour l'acquisition des données (mesures comportementales, neuropsychologiques, neuro-imagerie, données biologiques) et l'analyse des données.

Le présent chapitre explique la démarche méthodologique générale employée pour réaliser cette étude. Il est suggéré que le lecteur se réfère à chaque article pour une description spécifique des tests et procédures qui furent utilisés.

2.1 Participants

Les sujets ayant participés à ce programme de recherche devaient être non-fumeurs, droitiers, sédentaires (avec une faible pratique d'activités physiques hebdomadaires selon un questionnaire d'activité physique (≤ niveau 5 sur l'échelle) (Jackson et al. 1990)), et ne devaient pas souffrir de conditions neurologiques (autre que la maladie de Parkinson) ou psychiatriques. Le *Questionnaire sur l'aptitude à l'activité physique* (Q-AAP) a permis de vérifier la présence de problèmes cardiaques ou musculo-squelettiques pouvant nuire à l'adhésion au programme d'exercice et nécessitant l'approbation médicale au préalable (Thomas et al. 1992). Les participants devaient ne présenter également aucun critère de non-compatibilité à la passation d'un scan d'imagerie par résonance magnétique (IRM). Les sujets ne devaient pas présenter de déficit cognitif, tel que mesuré par le *Montreal Cognitive Assessment* (MOCA) (scores≥23)

(Nasreddine et al. 2005). Les musiciens et les professionnels de la dactylographie étaient exclus. Les sujets parkinsoniens ont été recrutés avec l'aide de la neurologue Dre. Anne-Louise Lafontaine, sur la base de l'évaluation neurologique, soit un stade 1 ou 2 sur l'échelle de Hoehn et Yahr et un score des symptômes moteurs inférieur à 35 à la section trois de l'*Unified Parkinson Disease Rating Scale* (UPDRS) (Goetz et al. 2008).

2.2 Évaluation des participants

Tous les instruments brièvement présentés ci-dessous sont des outils qui ont été utilisés lors de l'évaluation des participants, soit avant et après la réalisation du programme d'entrainement physique qui s'est échelonné sur une période de 3 mois. Chaque évaluation débutait avec une prise de sang à jeun effectuée par une infirmière accréditée en vue des analyses de facteurs neurotrophiques. Les échantillons étaient centrifugés puis placés dans des congélateurs à -80°C en vue du dosage de facteurs neurotrophiques. Voir Figure 9 pour un résumé du déroulement du protocole de recherche pour chaque participant.

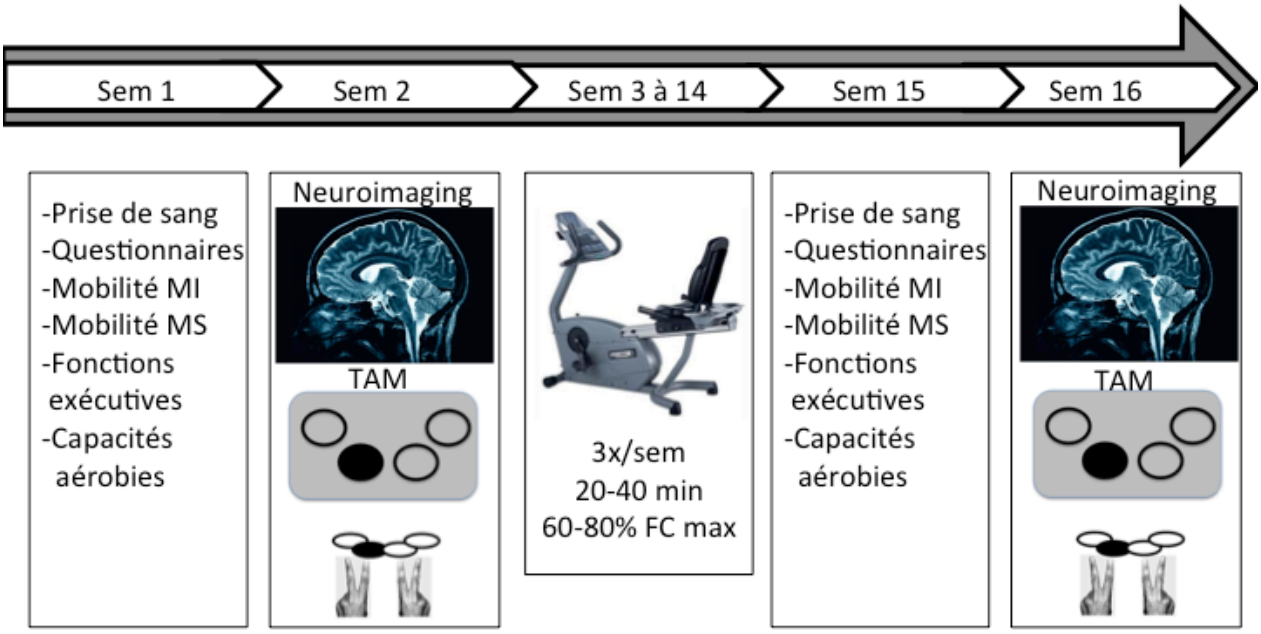


Figure 7 : Déroulement du protocole de recherche

MI : membres inférieurs, MS : membres supérieurs, TAM : tâche d'apprentissage motrice, sem : semaine, min : minutes, FC : fréquence cardiaque

2.2.1 Questionnaires et échelles

L'inventaire de dépression de Beck (BDI) (Beck et al. 1961) et l'inventaire d'anxiété de Beck (BAI) (Beck et al. 1988) ont permis d'évaluer respectivement les niveaux de sentiment de dépression et d'anxiété. La qualité de vie des sujets parkinsoniens a aussi été mesurée avec le *Parkinson Disease Questions-39* (Jenkinson et al. 1997) et avec le SF-36 (Ware and Sherbourne 1992) pour les sujets sains. Les symptômes moteurs des participants parkinsoniens ont été

quantifiés avec la section trois de l'*Unified Parkinson Disease Rating Scale* (UPDRS) (Goetz et al. 2008).

2.2.1 Fonctions exécutives

Le *STROOP color test (Houx et al. 1993)* et le *TMT (Sanchez-Cubillo et al. 2009)* ont été utilisés afin d'évaluer respectivement l'inhibition et la flexibilité mentale de tous les participants.

2.2.2 Paramètres de marche

À une vitesse confortable, les participants avaient comme consigne de marcher sur des plates-formes informatisées (GaitMat II, E.Q. Inc, Chalfont, PA), lesquelles permettent de calculer, entre autres, la vitesse de marche, la longueur des pas, la durée des foulées et autres variables. Trois allers-retours de quatre mètres étaient exigés pour chaque participant. Chaque extrémité possédait une section en bois d'un mètre afin de permettre aux participants d'accélérer et de décélérer leur vitesse de marche.

2.2.3 Tâche de mobilité du membre supérieur

Les participants avaient devant eux une tablette graphique Wacom Intuos2, sur laquelle un plastique transparent délimitant des zones était déposé (Voir Article 2 pour un schéma du matériel), ainsi qu'un écran lumineux. À l'aide d'un crayon électronique positionné sur le point de départ de la tablette, les participants devaient tracer des lignes vers la zone grise située à leur droite. Le mouvement devait s'effectuer le plus rapidement possible, et ce, dès qu'un repère visuel (lumière verte) s'affichait à l'écran devant eux. Trente tracés leur étaient demandés. La

tablette était reliée à un ordinateur, ce dernier permettant l'analyse de la trajectoire et le calcul des différents paramètres cinématiques du mouvement (Plamondon et al. 1993; Plamondon 1995; Plamondon 1995; Plamondon 1998; Plamondon et al. 2003).

2.2.4 Test de consommation d'oxygène

Dans la présente étude, le calcul du pic de consommation d'oxygène (VO_2pic) fût réalisé à l'aide d'un vélo stationnaire horizontal. L'intensité du test débutait avec une résistance du vélo à 50W et augmentait à chaque minute de 25W jusqu'à l'atteinte d'un des critères d'arrêt du test. Quinze participants (11 sujets contrôles et 5 parkinsoniens) ont eu un test sous-maximal pour estimer leur capacité aérobie, ce qui veut dire que le test se déroulait jusqu'à ce que le participant atteigne 85% de leur fréquence cardiaque maximale estimée. Cependant, comme les parkinsoniens présentaient des difficultés importantes à atteindre leur 85% estimé, et que leurs efforts montraient les signes d'atteintes d'un max, le protocole d'évaluation des capacités aérobies a été modifié. Le reste des participants (9 sujets contrôles et 14 parkinsoniens) ont donc effectué un test maximal (VO_2pic) avec mesure des échanges gazeux, c'est-à-dire terminer volontairement l'épreuve en raison de l'épuisement ou si l'un des critères d'atteinte d'un effort maximal était atteint (i.e., un plateau du VO_2 entre deux ou plusieurs charges de travail, un ratio d'échange respiratoire sup. à 1.00, ou un rythme cardiaque maximal prédit (220-âge)). Un électrocardiogramme (ECG) a été ajouté au protocole afin de surveiller l'apparition d'un problème de nature cardiaque pendant le test. De fait, certaines études ont montré qu'une évaluation des capacités aérobies avec un test par paliers sous-maximal permet une estimation acceptable d'un test maximal (Eston et al. 2006; Faulkner et al. 2007; Morris et al. 2010). De plus, ce genre de protocole s'est avéré être bien toléré par les personnes âgées (Puggaard 2003) et

même celles atteintes de la MP (Katzel et al. 2011), suggérant ainsi que ce changement de mesure n'a eu aucune influence sur les données recueillies, sauf sur le confort et la sécurité des participants. Pour les deux types de tests, une prise de la tension artérielle s'effectuait avant le test, lors de l'atteinte du critère d'arrêt, puis 1 minute après le début du retour au calme, alors que la fréquence cardiaque était surveillée tout au long du test grâce à un cardio fréquencemètre.

2.2.5 Tâche de séquence motrice

L'apprentissage moteur a été évalué de façon implicite à l'aide d'une tâche de temps de réaction séquentiel nécessitant l'index et le majeur des deux mains (Nissen and Bullemer 1987) (voir Figure 10). La séquence d'apprentissage implicite était constituée de 12 blocs, chacun d'eux composés de huit éléments répétés à cinq reprises (pour un total de 40 appuis), ainsi que d'une séquence aléatoire de 40 appuis déterminés au hasard. La tâche s'effectuait alors que le participant était couché sur la table du scanner. Deux séquences d'apprentissage furent utilisées dont l'ordre d'exécution entre les deux sessions d'évaluations était déterminé de façon aléatoire. Les deux séquences étaient identiques en terme de fréquence de réponse et de transition. Pour réduire la conscience du participant de la présence d'une séquence, chaque bloc séquentiel débutait à un point aléatoire de la séquence. Pour évaluer l'apprentissage de la séquence, le temps de réaction (c'est à dire, le temps entre le début du stimulus jusqu'à la fin du mouvement) et la précision ont été comparés entre les blocs de séquence et aléatoires. Des temps de réactions plus rapides et une meilleure précision pour la séquence par rapport aux blocs aléatoires pouvait refléter une meilleure capacité d'apprentissage procédural.

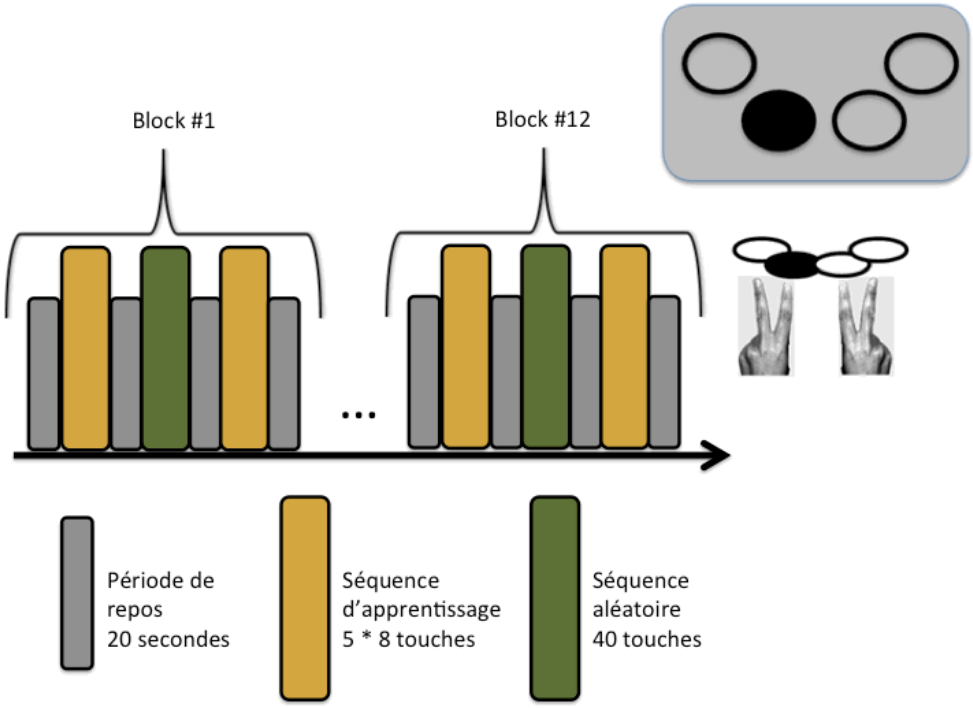


Figure 8 : Schéma de la tâche d'apprentissage moteur

2.2.6 Séquence d'acquisition des données d'imagerie

Les données d'imagerie ont été recueillies à l'aide de l'appareil d'IRM (3.0Tim Trio Siemens) de l'Unité de Neuroimagerie Fonctionnelle (UNF). Une image structurelle de haute résolution de contraste T1 a été acquise pour chaque sujet (Temps de répétition (TR)= 13 ms; Temps d'écho (TE) = 4.92ms; angle d'acquisition= 25 °; champ de vision = 256x256 mm ²; taille de la matrice = 256x256; taille de voxel = 1x1x1 mm³, 176 tranches sagittales).

La capacité d'apprentissage d'une séquence motrice a été évaluée en même temps que les changements du signal BOLD étaient acquis grâce à la technique d'imagerie par résonance magnétique fonctionnelle (IRMf). Puisque les données recueillies par cette méthode ne font pas partie intégrante du présent projet de thèse, les détails de l'acquisition fonctionnelle, ainsi que de

celle des données anatomiques, se retrouvent à l'Annexe 5 mais ne seront pas discutés plus en détails ici.

2.3 Protocole d'entrainement

Le programme d'exercice cardiorespiratoire impliquait un entrainement sur vélo stationnaire horizontal, à raison de trois séances par semaine d'une heure chacune. La prescription de l'intensité de l'exercice était basée sur la fréquence cardiaque maximale (FC_{max}) et de la puissance aérobie maximale atteinte lors du test de consommation maximale d'oxygène (VO_2pic) réalisé le jour du pré-test (Heil 2006). Pour chaque participant, la durée de l'exercice était de 20 minutes lors la première semaine, et ce à 60% de la FC_{max}. Les semaines suivantes, la durée était augmentée de 5 minutes et de 5% de l'intensité à chaque semaine jusqu'à ce que les participants aient atteint 40 minutes à 80%. Les participants devaient maintenir le plus possible une vitesse de pédalage de 60 révolutions par minute (rpm). Une augmentation de la puissance de la résistance du vélo (Watts) était visée afin de favoriser l'atteinte de l'intensité ciblée. En outre, la perception de l'effort (échelle modifiée de Borg (Boone et al. 1990)) était demandée à chaque séance d'entrainement afin de s'assurer de l'atteinte de l'intensité. Le programme était conçu pour atteindre et maintenir l'objectif jusqu'à ce que les trois mois d'entraînement à vélo soient atteints. Un taux de participation de 75% ou moins aux séances d'entrainement était considéré comme un taux de participation trop faible, de sorte que le sujet était alors retiré de l'étude. Un ratio de quatre participants par superviseur fut respecté, et un kinésiologue formé supervisait le programme.

CHAPITRE 3 : PRÉSENTATION DES RÉSULTATS

Contributions et rôle de chaque co-auteurs pour les articles présentés dans la présente thèse:

Alexandra Nadeau : acquisition des données, analyses et interprétation des données, écriture des manuscrits;

Ovidiu Lungu : conception de l'étude, analyses et interprétation des données, révision des articles;

Catherine Duchesne : conception de l'étude, acquisition des données, révision des articles;

Marie-Ève Robillard : acquisition des données, révision des articles;

Arnaud Boré : acquisition des données, analyses et interprétation des données, révision des articles;

Florian Bobeuf : acquisition des données, révision des articles;

Réjean Plamondon : interprétation des données, révision des articles;

Anne-Louise Lafontaine : révision de l'article;

Freja Gheysen : révision de l'article;

Louis Bherer : révision de l'article;

Julien Doyon : Directeur des travaux. Conception de l'étude, interprétation des données, révisons des articles.

ARTICLE 1:

A 12-week cycling training regimen improves gait and executive functions concomitantly in people with Parkinson's disease

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Running title: Cycling training in Parkinson
Key words: Parkinson's disease, exercise, gait, aerobic, stationary bicycle
Conflict of Interest: The authors have no conflict of interest to declare.

Words count for abstract: 291
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Abstract

Background: There is increasing evidence that executive functions and attention are associated with gait and balance, and that this link is especially prominent in older individuals or those who are afflicted by neurodegenerative diseases that affect cognition and/or motor functions. People with Parkinson's disease (PD) often present gait disturbances, which can be reduced when PD patients engage in different types of physical exercise (PE), such as walking on a treadmill. Similarly, PE has also been found to improve executive functions in this population. Yet, no exercise intervention investigated simultaneously gait and nonmotor symptoms (executive functions, motor learning) in PD patients. **Objective**: To assess the impact of aerobic exercise training (AET) using a stationary bicycle on a set of gait parameters (walking speed, cadence, step length, step width, single and double support time, as well as variability of step length, step width and double support time) and executive functions (cognitive inhibition and flexibility) in sedentary PD patients and healthy controls. **Methods**: Two groups, 19 PD patients (Hoehn & Yahr $\leq$2) and 20 healthy adults, matched on age and sedentary level, followed a 3-month stationary bicycle AET regimen. **Results**: Aerobic capacity, as well as performance of motor learning and on cognitive inhibition, increased significantly in both groups after the training regimen, but only PD patients improved their walking speed and cadence (all $p<0.05$) (with no change in the step length). Moreover, in PD patients, training-related improvements in aerobic capacity correlated positively with improvements in walking speed ($r=0.461$, $p<0.05$). **Conclusion**: AET using stationary bicycle can independently improve gait and cognitive inhibition in sedentary PD patients. Given that increases in walking speed were obtained through increases in cadence, with no change in step length, our findings suggest that gait improvements are specific to the type of motor activity practiced during exercise (i.e., pedaling). In contrast, the improvements seen in cognitive inhibition were, most likely, not specific to the type of training

and they could be due to indirect action mechanisms (i.e. improvement of cardiovascular capacity). These results are also relevant for the development of targeted AET interventions to improve functional autonomy in PD patients.

Introduction

Parkinson's disease (PD) is a neurodegenerative pathology characterized by progressive motor symptoms, including gait modifications leading to balance instability (Bello et al. 2010). Patients can also develop several nonmotor complications, such as depression, sleep disturbances and cognitive impairments like executive dysfunctions (Speelman et al. 2011) and deficits in procedural learning (Clark et al. 2014; Ruitenberg et al. 2015). Despite advances in pharmacological agents and surgical procedures that could be employed in PD patients to alleviate the primary motor signs of the disease, these treatment options often fail to improve the whole range of symptoms observed in PD and side effects are common (Bloem et al. 2004). Recently, exercise has been proposed as an adjuvant therapy that may help in alleviating multiple symptoms, but very little is know about the impact and the mechanisms of such alternatives.

Despite the fact that the link between gait and cognitive functions, especially executive functions, is well documented in aging research (Springer et al. 2006; Yogev-Seligmann et al. 2008; Liu-Ambrose et al. 2010; Martin et al. 2013), to date, only a few studies have investigated the same relationship in PD patients. In contrast, there is growing evidence documenting the association between standing balance and gait initiation with cognition in PD population, but in a dual-tasking context (Fernandes et al. 2015; Fernandes et al. 2016). The latter have shown that some cognitive processes, such as executive functions, processing speed and semantic fluency (Smulders et al. 2013; Stegemoller et al. 2014) are associated with some gait parameters and functional mobility in PD. In addition, several studies have shown independently that non-pharmacological treatment approaches, such as physical exercise, do improve various gait parameters in PD (Mehrholz et al. 2010; Li et al. 2012; Shu et al. 2014; Arcolin et al. 2015), on the one hand, and executive functions, on the other hand (Tanaka et al. 2009). Yet, evidence that this type of intervention can simultaneously improve motor (such gait) and nonmotor symptoms

(executive functions, motor learning) in PD is non-existent and the mechanisms by which training produces changes in both of these components remain unknown.

We have recently reported that an aerobic exercise training (AET) regimen using a stationary bicycle is not only safe for PD patients in early stages of the disease, but that it has also improved aerobic capacity as well as cognitive inhibition and motor sequence learning (Duchesne et al. 2015). In the current study, our main objective was to assess the effects of an AET regimen using stationary bicycling on gait parameters in sedentary people with PD (not reported in the previous study). As a second objective, we set out to compare these effects to those observed in healthy adults (HA) in order to determine whether this type of intervention has a different impact depending on the participant's health status. In addition, as a third objective, we intended to evaluate the associations between exercise-related changes in gait (not reported in the previous study) with those seen in cardiovascular capacity, executive functions and motor sequence capacity (Duchesne et al. 2015). We hypothesized that: (1) bicycle training would improve gait parameters in all participants (especially speed and cadence based on the specificity of the bicycle training), but especially those diagnosed with PD, (2) such improvements in gait parameters would correlate with other AET-related improvements, such as cardiovascular capacity, cognitive inhibition and the capacity to learn a new sequence of movements, and that (3) these relations would be moderated by disease.

Methods

Participants

In order to be eligible for the study, all participants (healthy adults and those with PD) had to be right-handed, sedentary, and aged between 40 and 80 years old. They were screened for the presence of possible dementia (score of 24 or more on the Mini Mental State Evaluation)

(Folstein et al. 1975) or on the Montreal Cognitive Assessment (Marinus et al. 2011) and appropriateness for testing in an MRI environment (e.g., no metallic implants that could interfere with testing, no claustrophobia). The Physical Activity Readiness Questionnaire (PAR-Q) was used to verify the participant's safety in participating in a physical program. Exclusion criteria included other neurological disorders, and comorbidities likely to affect gait, smoking or heart diseases. Importantly, HA were matched with PD patients with respect to sex distribution, age, education as well as cognitive and fitness levels. PD patients had to be classified as stage 1 or 2 according to Hoehn and Yahr's scale based upon evaluation of a certified neurologist (A-LL). Participants who were under medication continued their treatment all throughout the study (testing and training). This study was carried out in accordance with the recommendations of the research ethics committees' guidelines of the Research Center of the University Institute of Geriatrics of Montreal, which approved the protocol. Written and informed consent was obtained from each participant in this study. Demographic characteristics of the samples are presented in Table 1.

Exercise Intervention Protocol

Prior to engaging in the training regimen, all participants were cleared by a physician, who analysed the electrocardiogram (ECG) at rest in order to rule out any cardiac anomalies. The aerobic exercise intervention was designed to improve cardiorespiratory fitness with an exercise intensity prescription based on each participant's maximal aerobic power output achieved at maximum volume of oxygen (VO_2peak) uptake assessed on the pre-test day (ACMS 2006). Recumbent bicycles were used to train participants. Duration of the exercise program started at 20 minutes and 60% of intensity per session, and was then increased by steps of 5 minutes and 5% of intensity every week, until participants reached 40 minutes of training at 80% intensity.

Bike speed was maintained at 60 revolutions per minute (RPM). As such, to achieve the desired bike resistance power and adjust intensity level (if needed), the work intensity was based on power output (Watt), controlling for participant's heart rate. In addition, rate of perceived exertion (Borg scale) (Borg 2012) was assessed during each training session. The program lasted 12 weeks, with three training sessions per week. A participation rate equivalent to 75% of the sessions was achieved by each participant included in the data analyzes. Trained kinesiologists supervised all sessions.

Assessments

Participants were evaluated on a variety of outcome measures before the intervention and immediately after completion of the 3-month exercise program.

Lower limb capacities were assessed with the GaitMat II (E.Q. Inc., Chalfont, PA) (Barker et al. 2006). The GaitMat II consists of a 7.8-m long walkway and its computer software, which controls the mat sensors and calculates different metrics of gait. The mat is also equipped with initial and final 1 m inactive sections that allow acceleration and deceleration of the participant locomotion. One trial consisted of participants walking the full length of the Mat at their self-selected walking speed. After a practice of 2 trials, participants completed four more trials for data collection and measurements (walking speed, cadence, step length, step width, single and double support time, as well as variability of step length, step width and double support time).

To evaluate the patient's mood, the Beck Depression Inventory (BDI) (Beck et al. 1961) and the Beck Anxiety Inventory (BAI) (Beck et al. 1988) were used. Also, executive functions were assessed, precisely cognitive inhibition and flexibility. Participants' inhibitory aptitude was assessed using a version of the Stroop test with three different conditions (naming, reading,

interference). Each condition contained 100 stimuli (i.e., words, coloured rectangles, words in colours) printed on a 21.5 x 28 cm sheet of paper. In the reading condition, participants had to read the words (red, green, blue, and yellow) printed in black. In the naming condition, subjects had to name of the rectangles. In the third condition (interference), individuals needed to name the colour of the ink in which the words were written. In the latter condition, the meaning of each word had to be ignored, as it was incongruent with the colour to name (i.e., the word "blue" written in yellow). The trail Making Test (TMT) was used to assess subjects' flexibility functions. The first part of the test (TMT A) included numbers from 1 to 25, circled and written on a 21.5 x 28 cm sheet of paper. Participants were asked to connect with a pencil, as fast as possible, the numbers in numerical order. In contrast, the second part (TMT B) included numbers from 1 to 13 and letters from A to L. Subjects were asked to connect, as fast as possible, a number followed by a letter in numerical and alphabetic order respectively (i.e. 1-A-2-B-etc.). The participants' capacity in motor sequence learning (MSL) was evaluated during a functional magnetic resonance imaging session, where they had to perform an implicit serial reaction time task (Nissen and Bullemer 1987). More details of the complete fitness, psychological, neuropsychological and motor learning evaluations can be found in our previous study by Duchesne and collaborators (Duchesne et al. 2015).

Statistical analysis

A repeated model ANOVA was used to test the effect of AET on primary and secondary outcomes in PD participants. In addition, a mixed model ANCOVA was carried out to assess group differences pre-post AET, as well as the effect of training within each group and group differences at baseline and after AET for all gait parameters. BDI scores and age were used as covariates for all analyses to account for group differences in sentiments of depression and age, two factors that may impact gait parameters such walking speed (Rochester et al. 2008). In order

to account for the effect of multiple comparisons, the statistical significance was adjusted using the Bonferroni method. All results were expressed as means ± standard deviations for descriptive statistics. Pearson linear correlations between walking speed, cadence and step length with aerobic capacity, executive functions (inhibition and flexibility) and MSL (performance and learning scores) were tested to figure out if there is a link between gait and these factors among PD participants only. We then employed Andrew F. Hayes's free add-on SPSS macro (Hayes 2009) to test whether the disease (present/absent) moderated the relationship between gait parameters and other variables of interest, i.e. if the relation between variables in PD is in the same direction than the group of reference. Training-related changes in cognitive scores, MSL, and aerobic capacity constituted the independent variables in the moderation model, while gait parameters that changed significantly as a result of training corresponded to the outcome variable. Analyses were conducted using SPSS 21.0 (IBM, Armonk, NY). The level of statistical significance for all tests was set at $p<0.05$.

Results

Forty-four participants (21 PD patients and 23 HA) were deemed eligible to enrol in the study after the completion of the first evaluation. However, between the evaluation and the beginning of the exercise program, two HA decided to withdraw from the project for personal reasons. One PD participant and one HA were excluded after the beginning of the training regimen for health security reasons. Only one PD patient was excluded from analysis after AET regimen completion because of extreme results on several outcomes, even if this person respected all inclusion criteria. In the end, a total of 39 persons (19 PD patients and 20 HA) were analysed. All demographic characteristics and initial values of the study participants are described in Table 1. There was no difference between groups for any of the gait parameters at baseline.

Table 1: Demographic data

Characteristics	HA			PD			Group differences
Demographic information							
Age (years)	64	±	8	59	±	7	p=0.06
Ratio men/women		8/12			13/6		p=0.07
Education (years)	15.7	±	2.4	15.1	±	2.8	p=0.43
Overall cognitive level							
Cognition (MMSE/MoCA)	29.2	±	1.3	28.4	±	1.3	p=0.28
	29.6	±	1.5	27.2	±	1.9	p=0.08
Psychological well-being							
Depression (BDI)	4.8	±	4.5	10.5	±	8.3	p<0.01
Anxiety (BAI)	2.1	±	2.7	8.6	±	9.4	p<0.01
Executive functions							
Inhibition (Stroop, in s)	115.4	±	4.7	128.5	±	6.7	p=0.12
Flexibility (TMT, in s)	75.0	±	6.4	85.5	±	10.5	p=0.39
Clinical variables							
UPDRS III		N/A		21.8	±	6.2	N/A
Duration of disease (years)		N/A		8.1	±	9.1	N/A
H & Y		N/A		2.1	±	0.2	N/A
Gait parameters							
Walking speed (m/s)	1.14	±	0.03	1.10	±	0.04	0.39
Cadence (steps/min)	115.49	±	2.00	110.05	±	2.72	0.12
Step length (m)	0.593	±	0.064	0.598	±	0.080	0.83
Step width (m)	0.207	±	0.032	0.215	±	0.035	0.46
Single support time (s)	0.401	±	0.006	0.417	±	0.009	0.15
Double support time (s)	0.12	±	0.01	0.13	±	0.01	0.34
Step length variability	0.012	±	0.009	0.011	±	0.006	0.74
Step width variability	0.009	±	0.007	0.011	±	0.007	0.59
Double support time variability	0.009	±	0.002	0.007	±	0.001	0.91

Means ± SD.
HA: healthy adults; PD: Parkinson's diseases individuals; N/A: non applicable; s: seconds; m: meters; min:minute

Following the 12-week AET, repeated measures ANOVA indicated that PD participants showed significant improvements for the walking speed ($F_{1,18}$=6.154, p<0.05), the step length ($F_{1,18}$=5.828, p<0.05) and the single support time ($F_{1,18}$=4.771, p<0.05), with a trend for cadence ($F_{1,18}$=4.211, p=0.055). When using the mixed ANCOVA model, the effect observed in PD for walking speed and single support time remained the same while the one obtained for step length disappeared (see Figure 9).

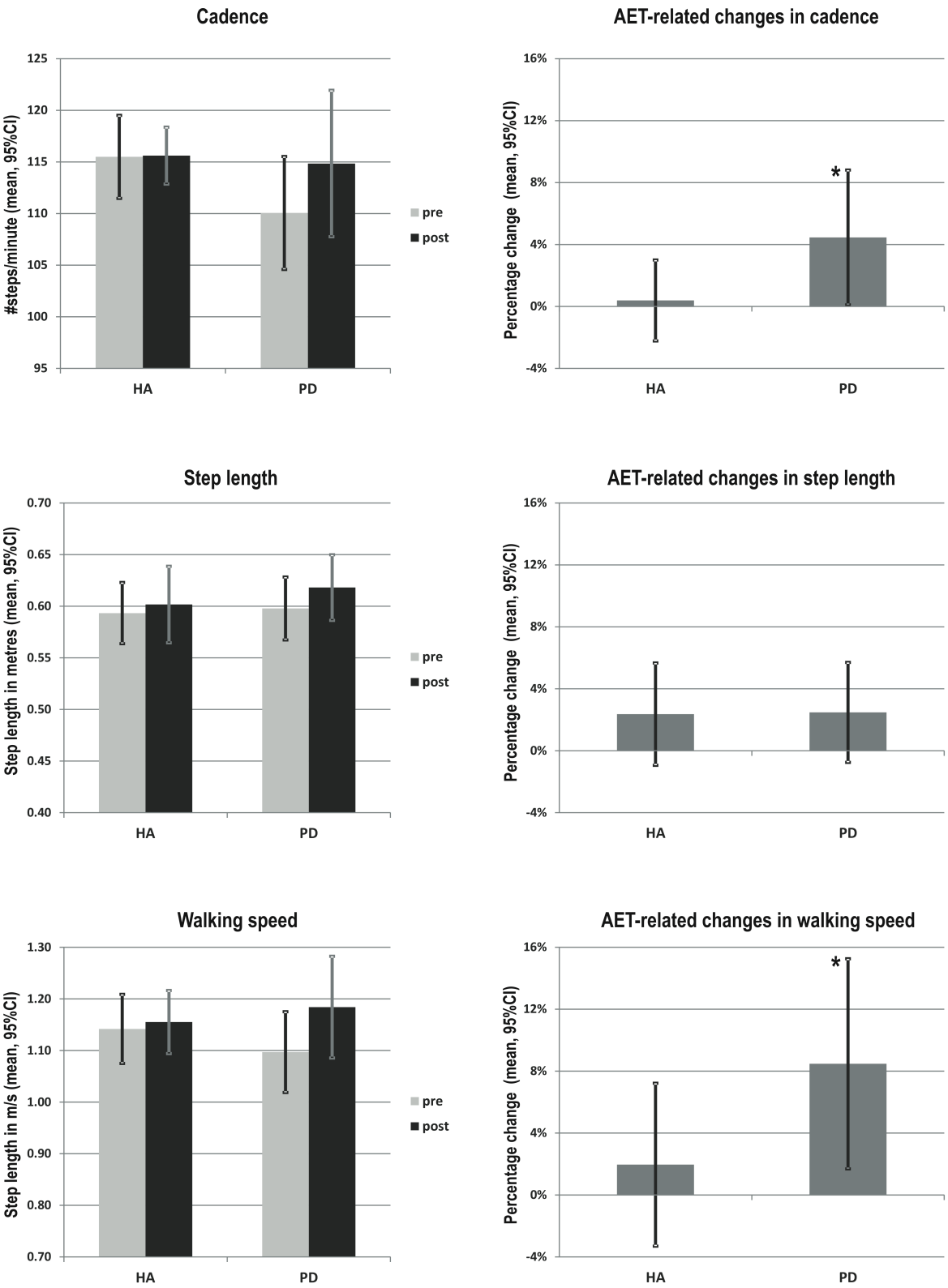

Figure 9: AET-related changes in walking speed, cadence and step length in PD patients and healthy adults

* Indicate statistically significant differences pre- to post- training ($p < 0.05$). AET: aerobic exercise training, HA: healthy adults, PD: Parkinson's diseases patients.

However, the trend observed for the cadence became significant when using covariates such the age and the BDI ($p<0.05$). In addition, the groups did not differ significantly neither in pre- or post- comparisons, nor in regards to AET-related changes. All other gait parameters did not change significantly following the aerobic training ($ps>0.05$) (Table 2).

Table 2: Spatiotemporal gait parameters during self-selected speed condition

Gait variables	HC		PD		Statistical significance for the independent variables		
	Pre-AET	Post-AET	Pre-AET	Post-AET	AET	Group	Interaction
Walking speed (m/sec)	1.14 ± 0.03	1.16 ± 0.03	1.10 ± 0.04	1.18 ± 0.05 †	p=0.28	p=0.91	p=0.27
Cadence (steps/min)	115.49 ± 2.00	115.61 ± 1.37	110.05 ± 2.72	114.84 ± 3.53 †	p=0.15	p=0.70	p=0.10
Step length (m)	0.593 ± 0.064	0.602 ± 0.066	0.598 ± 0.08	0.618 ± 0.069	p=0.71	p=0.73	p=0.98
Step width (m)	0.207 ± 0.032	0.213 ± 0.028	0.215 ± 0.035	0.222 ± 0.037	p=0.381	p=0.727	p=0.962
Single support time (s)	0.401 ± 0.006	0.398 ± 0.004	0.417 ± 0.009	0.384 ± 0.015 †	**p<0.05***	p=0.83	**p<0.05***
Double support time (s)	0.120 ± 0.010	0.117 ± 0.004	0.130 ± 0.010	0.136 ± 0.013	p=0.25	p=0.24	p=0.21
Step length variability	0.52 ± 0.01	0.52 ± 0.01	0.55 ± 0.01	0.53 ± 0.02	p=0.15	p=0.41	p=0.17
Step width variability	0.010 ± 0.007	0.011 ± 0.008	0.011 ± 0.007	0.008 ± 0.010	p=0.166	p=0.983	p=0.509
Double support time variability	0.009 ± 0.010	0.006 ± 0.003	0.007 ± 0.004	0.033 ± 0.077	p=0.417	p=0.160	p=0.087

No significant differences between groups at baseline were found. Means ± SD. †: a significant within-group difference from baseline
HA: Healthy adults; PD: Parkinson's disease patients; m: meters; s: second(s); min: minute; AET: aerobic exercise training. Bolded terms emphasize statistical differences.

Significant between-sessions differences were found in both groups for outcomes related to aerobic capacity (VO2 peak), MSL capacity and cognitive inhibition (all $p < 0.05$), indicating that the training improved participants' fitness, procedural learning and cognitive inhibition, regardless of the health status. Given that these results were analyzed in detail and reported elsewhere (Duchesne et al. 2015), they are presented here only for reader's convenience in the Supplementary material (see Figure S1, online). However, these data were used to test the correlation with gait parameters among PD participants. We observed a significant association only between the walking speed at the post-test and the aerobic capacity after the AET ($r=0.461$, $p<0.05$, $N=19$). No correlation was observed between other gait parameters and cognition or MSL.

A multiple regression model was then employed to investigate whether the association between pre-post change in walking speed and change in fitness depended upon the presence of disease (i.e., moderation). The relationship between change in fitness and change in walking speed was significantly moderated by the presence of the disease (R-square increase due to the interaction: $F_{1,32}= 4.34$, $p< 0.05$; conditional effect of change in fitness on change in walking speed: HA $t= -1.08$, $p=0.29$, PD $t=1.79$, $p=0.08$). Specifically, patients with PD who increased their cardiorespiratory capacities the most also showed the best improvement in walking speed (Figure 10). By contrast, there was no significant relationship between these variables in HA (HA group: $\beta = -0.162$, $p= 0.505$; PD group: $\beta = 0.596$, $p= 0.027$). Also, no relationship between gait parameters and motor skill learning or executive functions was found alone or when investigating the moderation of these relationships by the presence of the disease.

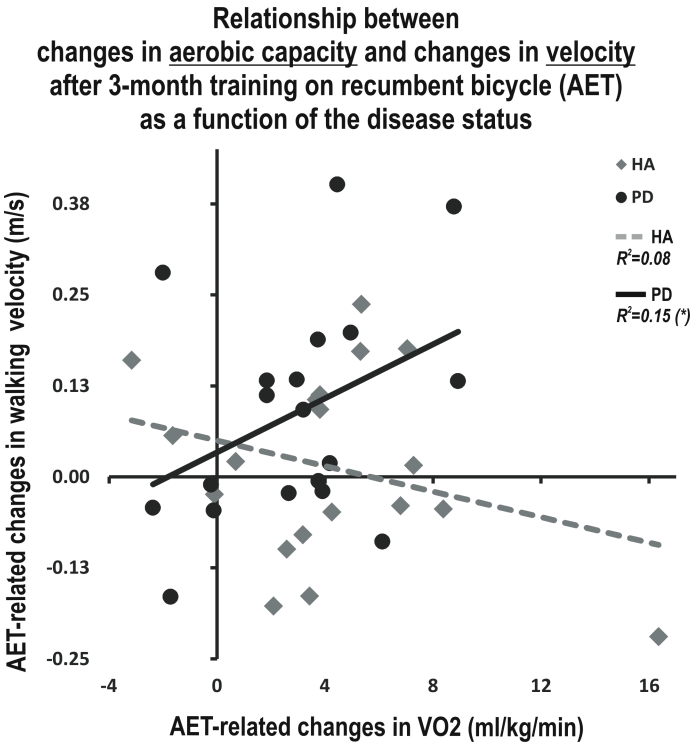

Figure 10: Moderating effect of the disease on the relationship between AET-related changes in walking speed and aerobic capacity

* Indicate statistically significant differences pre- to post- training ($p < 0.05$). HA: healthy adults; PD: Parkinson's disease; AET: aerobic exercise training; m: meters, sec: second, ml: millilitres, kg: kilogram, min: minute.

Discussion

In the current study, we investigated the effects of an AET regimen using stationary bicycling on gait parameters in sedentary healthy adults and in Parkinson's disease patients. As reported previously by our group (Duchesne et al. 2015), such training regimen improved cardiovascular capacity, executive functions and motor learning capacities in both groups. Here, we report that AET also had a significant positive impact on cadence and walking speed in the PD group. Moreover, the presence of the disease mediated the relationship between aerobic capacity and walking speed, as the improvement in fitness correlated positively with that in walking speed of PD patients only. Contrary to our expectations, we did not find significant relationships between

AET-related changes in gait parameters and cognition.

Importantly and as predicted, however, the present study yielded significant increases in walking speed and cadence in the PD group. The latter findings are consistent with previous studies indicating that 4 to 12 weeks of treadmill training improved walking speed, step length and step-to-step variability (Herman et al. 2009). This is also in accordance with other reports that resistance training, tai chi and physical therapy lead to improvements in walking speed and step length (Pellecchia et al. 2004; Li et al. 2012). Until now, studies on stationary bicycle training used forced exercise paradigm and observed improvements of dexterity, tremor and bradykinesia (Burini et al. 2006; Ridgel et al. 2009; Alberts et al. 2011). Finally, the fact that we did not find significant improvements in step length in PD patients, but observed significant increases in walking speed and cadence, may be due to the nature of our AET program. Indeed, the pedalling rhythm during exercising has a built-in cadence, and thus, it is expected that training-specific effect of bicycling would be more pronounced in terms of cadence, as compared to other gait parameters. This is similar to the mechanism by which treadmill training will impact more step length and walking speed, rather than other gait variables (Fisher et al. 2008; Herman et al. 2009).

Contrary to our expectations, there was no significant relationship between changes in PD participants' executive functions, MSL, cardiovascular capacity and gait parameters. We had hypothesized that we would find a positive and significant relation between executive functions and gait in the PD group, mostly because previous evidence suggested that some elements of cognition such as working memory and attention capacities, were associated with gait abnormalities in PD (Smulders et al. 2013). Our hypothesis was based on the fact that in a recent

study, Sohmiya and colleagues (2012) found significant correlation between frontal assessment battery scores and changes in gait following physical therapy (Sohmiya et al. 2012). Yet it is important to note that in that study, PD patients with high, but not low, executive functioning scores improved walking speed, stride and step length after physical training. Furthermore, unlike in our sample, PD participants in these studies were in more advanced stages of the disease. Thus this suggests that the relationship between gait and executive functions may be more evident as the disease progresses, hence possibly explaining why we did not observe any relation between gait parameters and other cognitive and learning functions. The fact that AET improved certain gait parameters and cognitive functions, but that these changes did not correlate with each other suggest that independent action mechanisms underlie this therapeutic improvements, at least at this stage of the disease.

We used moderation analyses to investigate the extent to which age influenced the relationship between changes in participants' fitness levels as well as their executive functioning and motor learning capacities on the one hand, and gait parameters, on the other hand. Using such an approach, we found a significant moderation effect for the disease variable only, regarding the relationship between AET-related improvements in aerobic capacity and those in walking speed. It has previously been suggested that motor abilities in the PD population, such as gait, could be affected by various health conditions. For example, a decrease in cardiorespiratory capacity has been shown to affect walking speed (Skidmore et al. 2008). Therefore, our results, especially the positive correlation between improvements in VO2 peak and those in walking speed in PD patients only, seem to support this hypothesis. In addition, they suggest that motor abilities may be improved in PD via non-pharmacological means, such as aerobic physical exercise.

The main objective of our study was to assess of AET in PD patients. We used the HA group to explore the possibility that AET may have a differential impact as a function of disease. However, we found no significant differences between these two groups in regards to any of the primary and secondary outcomes, neither in pre-, post- or AET-related changes. This is in contrast with the few studies that compared gait parameters in these two populations (Frenkel-Toledo et al. 2005; Bello et al. 2008). Thus, although conjectural, the reason why we did not observe any group differences may be that we recruited PD patients that were in the early phase of the disease (i.e., Hoehn and Yahr stage 1 or 2), compared to previous reports which included patients in more advanced stages (Frenkel-Toledo et al. 2005; Bello et al. 2008).

Several mechanisms have been proposed to explain physical training-related improvements similar to those seen in the present study. Some of these include direct effects on the central nervous system based upon an optimisation of the medication intake by easing its absorption (Speelman et al. 2011) or through increased corticomotor excitability (Fisher et al. 2008) and dopaminergic neurotransmission (Petzinger et al. 2010). Other proposed mechanisms have been more indirect and include increased cortical vascularisation, synaptic plasticity and neurogenesis (Speelman et al. 2011). These processes, which could be mediated by neurotrophic factors, would lead to structural and functional brain changes. Although the present study does not allow identifying the mechanism(s) that could explain the effects of AET on gait measures reported here, one can nevertheless assume that some brain structural and functional changes could be at the origin of such clinical outcomes. For example, in rodents, regional grey matter volume in a region equivalent to supplementary motor area (SMA) in humans has shown to be correlated positively with the total distance run by the animal following 7 days of exercise (Sumiyoshi et al. 2014). Similar increases, in both white and grey matter, have been reported in a

group of older sedentary human adults after participation in a 6-month aerobic training regimen (Colcombe et al. 2006). Furthermore, a recent study using resting state functional magnetic resonance imaging found significant changes in activity in sensorimotor areas in a group of young individuals after 20 minutes of aerobic exercise (Rajab et al. 2014), while a couple of studies demonstrated that functional brain activity in motor areas increased proportional to the movement rate on a pedaling task executed during scanning (Mehta et al. 2012). Finally, increased SMA activation was observed during motor imagery of locomotor-related tasks (Malouin et al. 2003) as well as during real locomotion as measured by electrophysiological studies showing SMA modulation during walking (Petersen et al. 2012; Wagner et al. 2012; Wagner et al. 2014; Seeber et al. 2015). Thus despite the scarcity of studies assessing cerebral structural and functional changes in relation to gait parameters and aerobic training in humans, the above mentioned studies provide basic evidence that AET can have a direct impact on the brain. Given the lack of neuroimaging studies looking at the effect of physical exercise in PD, further investigations are needed to directly assess these mechanisms in PD patients using neuroimaging techniques.

An issue that merits discussion would be the role of medication. There is evidence that medication itself may have a differential effect on movement rate and amplitude, as demonstrated by past research (Espay et al. 2009; Stegemöller et al. 2009; Espay et al. 2010; Espay et al. 2011; Teo et al. 2013; Teo et al. 2014). In the current study, we believed that medication did not play a major role influencing the outcomes for PD patients. The reason is that patients were always on their medication during both pre and post evaluations, their medication did not change and more importantly, assessments always took place at the same time of the day.

Although our findings help increasing our knowledge base about the effects of AET on gait, the current study has some limitations. A limitation of the present study was the lack of an additional training condition controlling for the type and intensity of exercise that PD patients performed over the 3-month period. However, despite this shortcoming, we believe that the results of the current study are theoretically and clinically relevant as they suggest that the use of AET using stationary bicycle can have a beneficial impact in persons suffering from PD. Another limitation is the fact that we only assessed two cognitive functions, inhibition and flexibility, which are the most commonly used in the PD literature. Therefore, one cannot exclude the possibility that other cognitive domains may show correlations with gait parameters following physical training.

From a clinical perspective, the use of high-intensity exercise is now a common rehabilitation method in PD. It is important to note that the AET effects in the current study were observed after a moderate to a high intensity exercise regimen (half of the program was performed at 80% of maximal intensity). Thus, with its stable and comfortable sitting posture, our results suggest that AET with a stationary bicycle is not only a viable, but also a safe training procedure for PD patients in stage 1 and 2 of the disease. Further studies are still needed in order to assess the safety and feasibility of a training regimen on stationary bicycle in patients in more advanced stages of the disease who are showing greater physical limitations such as balance impairments, as well as to evaluate the long-term benefits of this training method. Yet, despite such limitations, our study shows that stationary bicycle can be successfully used to improve gait functions in PD patients. The main contribution of the current study thus stems from the fact that our findings are showing AET-related improvements in a gait parameter (walking speed) is crucial for the daily functioning of sedentary patients who are in the initial stages of the disease.

Therefore, we believe that this result is another step closer to developing a reliable strategy to stimulate an active lifestyle in patients with PD, taking into account safety issues and each patient's individual capacities.

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Disclosures

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ARTICLE 2 :

A 12-week cycling training regimen improves upper limb functions in people with Parkinson's disease

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Abstract

Background: It has been proposed that physical exercise can help improve upper limb functions in Parkinson's disease (PD) patients; yet evidence for this hypothesis is limited **Objective**: To assess the effects of aerobic exercise training (AET) on general upper limb functions in sedentary people with PD and healthy adults (HA). **Methods**: Two groups, 19 PD patients (Hoehn & Yahr ≤2) and 20 HA, matched on age and sedentary level, followed a 3-month stationary bicycle AET regimen. We used the kinematic theory framework to characterize and quantify the different motor control commands involved in performing simple upper-limb movements as drawing lines. Repeated measures ANCOVA models were used to assess the effect of AET in each group, as well as the difference between groups following the training regimen. **Results**: At baseline, PD individuals had a larger antagonist response, a longer elapsed time between the visual stimulus and the end of the movement, and a longer time of displacement of the stylus than the HA. Following the 12-week AET, PD participants showed significant decreases of the agonist and antagonist commands, as well as the antagonist response spread. A significant group*session interaction effect was observed for the agonist command and the response spread of the antagonist command, suggesting a significant change for these two parameters only in PD patients following the AET. Among the differences observed at baseline, only the difference for the time of movement remained after AET. **Conclusion**: A 3-month AET has a significant positive impact on the capacity to draw lines in a more efficient way, in PD patients, indicating an improvement in the upper limb motor function.

1.1 Introduction

Parkinson's disease (PD) is a neurodegenerative condition characterized by cardinal motor symptoms, such as tremor, rigidity and bradykinesia (Goetz et al. 2008). These symptoms impact the movement and function of the upper limbs during everyday activities such as writing, self-care, and fine object manipulation. Past studies have also shown that PD patients present difficulties in force control, as well as in coordinating and controlling multiple tasks (Alberts et al. 1998). For example, they are impaired in modulating muscles activity, as reflected by an antagonist activation occurring earlier than normal, hence overlapping with actions from the agonist muscle (Pfann et al. 2001). Such disease-related functional alterations may thus explain the difficulties observed in fine motor skills and general upper movements in PD, hence leading to restrictions in autonomy and quality of life.

PD is usually treated using medication (levodopa, dopamine agonists) and surgical intervention (deep brain stimulation). While these treatments are very effective upon initiation, their effectiveness diminishes over time and a range of side effects emerges. Physical exercise has been proposed as an adjuvant therapy and a complementary approach that could improve both motor and non-motor symptoms in PD (Goodwin et al. 2008; Speelman et al. 2011). Among the motor benefits, a few studies have suggested that exercise could be a good alternative intervention to improve upper limb function (Ridgel et al. 2009; Muller and Muhlack 2010; Alberts et al. 2011; Ridgel et al. 2012). However, it is imperative to understand the mechanisms underlying its therapeutic impacts. In addition, the present study intends to investigate the association between upper limb function and other domains such as executive functioning and motor sequence learning known to be impaired in PD patients and sensitive physical exercise.

To date, several studies have aimed to better understand the role of exercise on neurophysiological mechanisms regulating upper limb functions in PD population (Ridgel et al. 2009; Alberts et al. 2011; David et al. 2016). In Alberts et al. (2011), the Opening Container Task was used in PD participants before and after an 8-week forced exercise (FE) intervention that used a lower limb tandem cycling apparatus (Alberts et al. 2011). In comparison to a voluntary exercise group, the FE group showed an improvement in grip-load coupling and an increased rate of grip force production. The authors concluded that such training modality could be efficient in improving global motor functioning in people with PD. However, the specific mechanisms underlying such improvements are still unknown. In another study, David et al. (2016) showed that not only a 24-month of progressive resistance exercise did result in faster elbow movement velocity in PD participants, but also that such exercising program led to a normalized magnitude of agonist burst and an increased antagonist muscle activity, as measured with electromyography (EMG) (David et al. 2016).

The efficacy of exercise in improving upper limb functions in PD cannot be properly assessed unless we use appropriate and specific measurements of this function. To date, several tests have been developed to assess fine upper limb functioning. For instance, tasks requiring object manipulation such as coin flipping or spinning, changing a combination lock, transferring small objects from point A to point B (Stewart et al. 2009), simple tapping tasks or the Purdue pegboard test, have all been used to measure motoric functions in PD patients (Alberts et al. 2011). Even tasks simulating real-life activities, such as opening a container, have been tested (Alberts et al. 2011) and shown to be sensitive to coordination and motor control problems seen in PD patients, hence being a good indicator of the global upper limb function in this clinical population. Yet, these motor tasks focus mostly on speed of execution, and few of them actually

assess the underlying neurophysiological mechanisms mediating motor functioning in this population. An ideal test would allow the characterization of the temporal activation pattern of muscles during a task involving the upper limb (David et al. 2016), such as electromyography (EMG). However, this technique is not user-friendly in clinical settings as it requires EMG expertise and significant time to install electrodes on the different muscle groups required to carry out the array of motor tasks needed to measure motoric functions in PD.

In this paper, we sought to test whether an aerobic exercise training (AET) regimen could bring similar improvements on upper limb motor control using another movement velocity task, a line drawing task, and whether the effects of AET on the neurophysiological level could be inferred using the kinematic theory of human movements. This theory offers an alternative way to indirectly characterize and quantify the different motor control commands involved in performing simple upper-limb movements (Plamondon 1995; Plamondon 1995; Plamondon and Alimi 1997; Plamondon 1998; Feng and Plamondon 2003; Plamondon et al. 2003; Djioua and Plamondon 2008). According to this model, the very large number of coupled neural and muscular cells constituting a given neuromuscular network generate an impulse response that converge toward a lognormal profile. The central nervous system then takes advantage of this emerging behavior in other to control the velocity of an end effector in simple and complex tasks.

Figure 11C illustrates, for example, how the Kinematic Theory describes a rapid pointing movement. Such a movement requires the activation of an agonist and an antagonist neuromuscular systems. Each of these systems is thought to produce a lognormal velocity profile, an asymetric bellshaped curve, (dotted line: agonist; solid line: antagonist in the Figure 11C) and the resulting velocity is the subtraction of these two curves, as depicted in Figure 11B, which is refered to as a delta-lognormal curve. Each delta-lognormal equation is described by seven

parameters: t_0, the time occurrence of the two input commands activating the pair of neuromuscular systems; D_1 and D_2, the agonist and antagonist commands; μ_1 and μ_2, the time delay of the agonist and antagonist systems (on a logarithmic scale); σ_1 and: σ_2 the time response of the agonist and antagonist systems (on a logarithmic scale). In other word, t_0, D_1 and D_2 describe the central action plan and μ_1, μ_2, σ_1 and σ_2 the timing properties of the peripheral synergy reacting to it. Thus, according to the kinematic theory, the experimental delta-lognormal velocity profile (Figure 11B) can be used to reconstruct the given movement with its corresponding agonist and antagonist components, the seven parameters estimated during the reconstruction process allowing researchers to indirectly infer the properties of the central controller and the agonist and antagonist peripheral systems involved in such a movement.

The lognormality of the asymmetric bellshaped velocity profile has been validated in many comparative studies and under numerous experimental conditions (Plamondon et al. 1993; Djioua and Plamondon 2008; Woch et al. 2011; O'Reilly et al. 2013). Moreover, it has even been mathematically demonstrated that the lognormal profile was the optimal output that a perfectly controlled neuromuscular system could produce (Djioua and Plamondon 2010), and the basic hypotheses of this model have also been supported using electroencephalography (EEG) (O'Reilly et al. 2013) and EMG (Plamondon et al. 2013) experiments, which have confirmed its physiological plausibility. Indeed it has been shown, using EEG, that a specific motor event related potential (ERP) was happening at t_0, the time occurrence of the neuromuscular commands, as predicted by the theory (O'Reilly et al. 2013). Additionally, the proportionality of the cumulative time delays between different muscles involved in a given movement have also been observed, as expected, from EMG measurements. Over the years, exploiting lognormal functions of the synergistic action of neuromuscular networks in numerous pointing tasks has

proven to be a reliable way to describe the velocity profile of simple human movements (Plamondon et al. 1993; Plamondon 1995; Plamondon 1995; Plamondon and Alimi 1997; Plamondon 1998; Djioua and Plamondon 2008). In doing so, the parameters extracted in the signal reconstruction provided a global evaluation, albeit indirect, of a subject fine motricity, in terms of a central representation of his action plans and the timing properties of the peripheral processes reacting to it. In other words, without any EMG or EEG data capturing devices, the kinematic theory provides a consistent and non-invasive estimation of the global motor control behaviour of a subject.

In response to the knowledge gap described above, the main objective of the current study was to assess the effects of AET on general upper limb functions in sedentary people with Parkinson's disease and healthy adults. Although the exercise program aimed especially the lower limbs, we relied on the global effect of aerobic training to drive changes in upper limb function. In order to infer the central nervous system (CNS) mechanisms underlying AET-related changes in upper-limb functions, we used a fast simple reaction time task (FSRTT) based upon the delta-lognormal model of the kinematic theory (O'Reilly and Plamondon 2011; Plamondon et al. 2013; O'Reilly et al. 2014). Indeed, in a straight line drawing task to a target, the delta-lognormal model is the simplest one to use. It can reproduce a given velocity profile by subtracting two lognormal curves, one representing the agonist activity toward this target and the other, the antagonist breaking at this target. We assumed that the kinematic theory (Plamondon 1995; Plamondon 1995), with its delta-lognormal model, involving both agonist and antagonist activations during a simple line drawing task, would offer an efficient framework not only to assess the effect of exercise on upper limb function in PD patients, but also to simultaneously inform us, indirectly, on the mechanisms underlying its therapeutic impact. For example, if the

AET had an impact on either t_0, D_1 and D2, this would mean that the training affected the central motor controller, whereas if AET had an impact on the μ_1, μ_2, σ_1 and σ_2, this would indicate that the peripheral system would be involved. Moreover, the present methodology allowed us to explore the agonist and antagonist systems separately. The data presented here are part of a larger research program that investigated the effects of this type of exercise training on several outcome measures such as cardiorespiratory capacities, executive functions and motor sequence learning capacity (measured behaviourally and with functional imaging); the results of which have been presented elsewhere (Duchesne et al. 2015; Duchesne et al. 2016). Given that other types of outcome measures were collected before and after the intervention, the second objective of the current study was to investigate the possibility of correlations between exercise-related changes in upper limb function and other metrics related to motor symptoms, cardiovascular capacity, executive functions and motor sequence learning capacity. We hypothesized that: (1) there would be differences at baseline between PD and their healthy counterparts regarding the kinematic properties of their agonist and antagonist neuromuscular systems (2) these differences would diminish as a result of training, an effect driven specifically by changes in the PD group, who were expected to improve the kinematic parameters of their movements, (3) these improvements in upper limb movements would correlate with exercise-related changes in motor symptoms, cardiovascular capacity, executive functions and motor sequence learning capacity.

1.2 Material and methods

1.2.1 Participants

Eighteen PD patients and 20 healthy adults subjects (HA), between 40 and 80 years of age, took part in the study. They were right-handed, sedentary (score of 5 or lower on the

Jackson's Questionnaire (Jackson et al. 1990), neurologically intact (i.e. score of 24 or more on the Mini Mental State Evaluation (Folstein et al. 1975) or the Montreal Cognitive Assessment (Nasreddine et al. 2005; Marinus et al. 2011). HA participants were matched with PD patients at the group level with respect to sex distribution, age, number of years of education as well as cognitive and fitness levels. Exclusion criteria included other neurological disorders, comorbidities likely to affect gait, smoking or heart diseases, and participation to less than 75% of the AET sessions during the study. PD patients had to be classified as stage 1 or 2 according to Hoehn and Yahr's scale (Hoehn and Yahr 1967) based upon evaluation of a certified neurologist (A-LL), and had to score below 35 on motor functions assessed with the third section of the United Parkinson's Disease Rating Scale (UPDRS III) (Goetz et al. 2008). The target of 75% or more participation rate in the fitness training program had to be achieved by all participants to be retained in the analysis. This study was carried out in accordance with the recommendations of the research ethics committee's guidelines of the Research Center of the "Institut Universitaire de Gériatrie de Montréal", which approved the protocol. A written and informed consent was obtained from participants prior to their inclusion in this study.

1.2.2 Exercise Intervention Protocol

Prior to engaging in the training regimen, all participants were cleared by a medical doctor, who analysed the electrocardiogram (ECG) at rest and ruled out any cardiac anomalies that could put participants at risk during exercising. At the same time, all participants completed a graded exercise test with the stationary bicycle to obtain their peak oxygen uptake (VO_2peak) (ACMS 2006). The result at this test was used for personalized exercise prescription. The duration and frequency of AET was of 12 weeks, 3 times per week. Duration of the exercise sessions started at 20 minutes and 60% of intensity, and was then increased by steps of 5 minutes

and 5% of intensity every week, until participants reached 40 minutes of training at 80% intensity. To reach a high-intensity level, bike speed was maintained at 60 revolutions per minute (RPM). As such, to achieve the desired bike resistance power and adjust intensity level (if needed), the work intensity was based on power output (Watt), controlling for subject's heart rate. In addition, rate of perceived exertion (Borg scale) (Borg 1982) was assessed during each training session. Even if some studies showed good results using forced exercise (FE) (Ridgel et al. 2009; Alberts et al. 2011; Ridgel et al. 2012; Beall et al. 2013; Ridgel et al. 2015; Alberts et al. 2016) to improve upper limb functions, we chose to use voluntary exercise (VE) instead, because from a clinical and practical perspective, FE devices are not easily accessible to the general public, and because we wanted to test an easily accessible type of workout for this population. Trained kinesiologists supervised all training sessions.

1.2.3 Assessments

Participants were evaluated on a set of outcome measures before the intervention (at baseline), and immediately after completion of the 3-month exercise program (post-intervention).

Main outcome. Kinematic properties of the upper limb movement were assessed with a target directed FSRTT using the kinematic theory (Plamondon et al. 1993; Plamondon 1995; Plamondon 1995; Plamondon 1998; Plamondon et al. 2003). This task employs an electronic drawing board (a graphic tablet), an electronic pen (stylus) and an electronic display to present visual stimuli. The tablet displays a dot in the center (starting position) and target zones on either side (See Figure 11A). On each trial, participants are required to draw straight lines on the graphic tablet by executing simple arm movements in response to a visual stimulus. Figure 11A depicts the task and its phases: (1) A LED screen alternating from red to black indicates to the

participants that the system is ready for acquisition. At this moment, the participant is asked to position the tip of the stylus on the starting position. (2) Once the stylus hits the digitizer, the LED screen stops blinking, turns black and a green screen appears after a random delay, signalling the subject to start drawing a straight line towards the target zone as fast as possible. This delay is exponentially distributed, the parameters of the corresponding flat hazard distribution have been chosen such that the delay is between 0 and 10s. Thus, regardless of the duration the subject has waited for the stimulus, the probability that it will be emitted during the next millisecond is always the same (Luce 1986). During line drawing, and once in the target zone, the pen has to be in contact with the tablet. (3) Once the stylus is in the target zone, the participants are required to keep it immobile and in contact with the tablet for a three to five seconds to allow for a better delimitation of the movement. After completing a trial, participants are asked to raise the stylus and wait for the screen to start alternating from black to red again signalling the onset of a new trial. Participants are informed that neither the precision, nor the direction of the movement are important, only the speed of execution. A speed curve is then obtained for each line drawn (See Figure 11B). Trials in which participants did not reach the target zone or needed two segments to reach it were not counted and analyzed. Thirty successful trials, or a maximum of forty trials, were required of all participants, whichever criterion was reached first. The mean of each kinematic parameter was calculated from successful trials and used as dependent variables (see section 1.2.4).

Secondary outcomes. As secondary outcomes for the current study, we included the patient's motor symptoms evaluation, assessed with the UPDRS (Goetz et al. 2008), sub-divided in scores for rigidity, tremor, motor symptoms for the right upper limb (including the following items: tremor at rest, postural tremor, rigidity of arm, finger taps, hand movements, rapid

alternating movements of hands) in addition to a total score for this section of the questionnaire. Participants' cardiovascular fitness level (VO_2peak) was evaluated using a recumbent bike, either by a submaximal aerobic test (11 HA, 5 PD) or by a medically supervised maximal oxygen uptake test (9 HA, 14 PD). Mood was also evaluated using the Beck Depression Inventory (Beck et al. 1961) and the Beck Anxiety Inventory (Beck et al. 1988). The Stroop Test (naming, reading, interference) (Stroop 1935) and the Trail Making Test (TMT A & B) (Sanchez-Cubillo et al. 2009) were used to evaluate inhibition and cognitive flexibility, respectively, two components of executive neuropsychological functions. In addition, participants' motor sequence learning (MSL) capacity was evaluated behaviourally using an implicit serial reaction time task performed during functional MRI acquisition. For more details regarding those evaluations, please refer to our previous published work (Duchesne et al. 2015; Duchesne et al. 2016).

1.2.4 Extraction of the kinematic parameters of the movements

Participants' trials were used to extract several kinematic parameters of the movement based on the kinematic model (See Figure 11C).

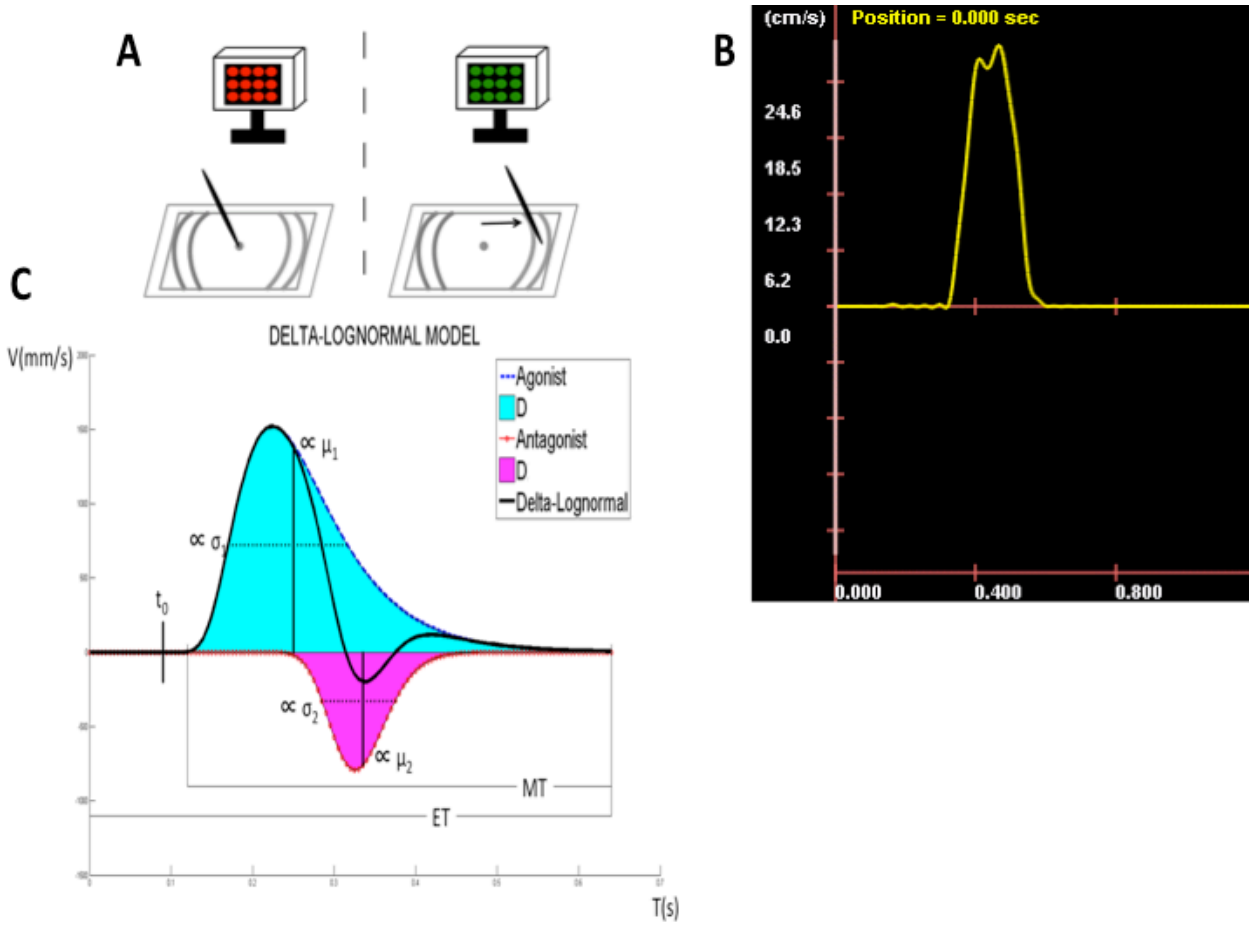

Figure 11: Description of the target directed fast simple reaction time task

1A: tablet display and target zone; 1B: Speed curve obtained for each line drawn; 1C: Kinematic parameters (t0: time occurrence of the input commands to the neuromuscular system; D1: agonist component; μ1: time delay of D1; σ1: response spread of D1; D2: antagonist component; μ2: time delay of D2; σ2: response spread of D2; ET: time between visual stimulus and the immobilization of the stylus; RT: reaction time; MT: movement time).

Reconstruction of the velocity profile using two lognormal models was used to reveal the agonist and antagonist components of the profile. The upper curve (dotted line) represents a measure of the agonist activity, which corresponds to the velocity of the pen tip toward its target. By contrast, the lower curve (solid line) depicts the antagonist activity, which has a direct opposite contribution and is mainly used to break the motion, although it can also be useful in

stabilizing the movement and in increasing its precision. The obtained velocity profile obeys the following delta-lognormal law (Plamondon et al. 1993; Plamondon 1995; Plamondon 1995; Plamondon 1998; Plamondon et al. 2003):

$$v(t) = D_1\Lambda_1(t; t_0, \mu_1, \sigma_1^2) - D_2\Lambda_2(t; t_0, \mu_2, \sigma_2^2)$$

where

$$\Lambda(t; t_0, \mu_i, \sigma_i^2) = \frac{1}{\sigma_i \sqrt{2\pi}\,(t - t_0)} exp - \left(\frac{(\ln(t - t_0) - \mu_i)^2}{2{\sigma_i}^2}\right)$$

and where t_0 represents the time occurrence of the simultaneous input commands D_1 and D_2 to the neuromuscular system. The time between the occurrence of the stimulus (t=0) and t_0 is, in fact, the period needed for the perception of the stimulus and the command preparation. The delay between the stimulus onset (t=0) and the beginning of the movement (beginning of the velocity increase) corresponds to the classical reaction time (RT). The time between t_0 and the reaction time RT corresponds to the command propagation time. In the upper curve, the area under the curve, correspond exactly to the agonist response (D1), while the μ1 and the σ1 represent, respectively, the time delay and the response spread of the agonist activation on a logarithmic scale. The equivalent is presented with the lower curve for the antagonist response (D2, μ2, σ2). In other words, t_0, D1 and D2 reflect command processes, often referred to the action plan, in terms of amplitude and time occurrence, while μ1, σ1, μ2 and σ2 reflect the distributed timing properties of the system. The elapsed time (ET) corresponds to the delay between the moment where the visual stimulus is sent until the immobilization of the stylus on the digitizer, while the moment where the movement is started (beginning of the curve), until the immobilization of the stylus on the tablet is considered as the movement time (MT). Signal-to-noise ratio (SNR)

between the original and the reconstructed velocity profile can be considered like a cue of the reconstruction's quality. As suggested in O'Reilly et al (2013), a SNR of 20 dB minimum is required to use the trial in the analysis, without that, the reconstruction was considered of too low quality. Also, trials with a negative t_0 were rejected from analyzes. This situation may occur when the protocol is not respected in a given trial and a movement is anticipated, that is the commands are initiated before the onset of the stimulus. This might also seldom happen when the parameter extraction algorithm fails. Indeed, t_0 is computed from the curve fitting process using a seven parameter optimization algorithm that minimize the error between the original velocity curve and the reconstructed one, using the delta-lognormal equation. Given that there is no guarantee that the process will always lead to a global optimum, there are instances where the algorithm might get trapped in a local inconsistent minimum with a negative t_0.

1.2.5 Statistical analysis

As our main interest is to verify whether each group reacted to the 3-month AET, we first carried out simple repeated-measures ANOVA, separately for each group. The dependent variables were the kinematic parameters and the independent variable was the time of the assessment (pre- vs. post-AET). Whenever we observed significant changes in a single group, a repeated-measure ANCOVA model (the same dependent variables, but with group and time of assessment as independent variables) was used to test the effect of AET on primary and secondary outcomes in PD participants compared to HA subjects. Given that there were significant differences between the groups in terms of depression level and age at baseline, we used these variables as covariates in the model to statistically control for their effect when assessing group differences. The ANCOVA aimed to test for group differences across assessments (group*assessment interaction), as well as the effect of training within each group

after AET, for all kinematic movement parameters. In order to account for the effect of multiple comparisons, the statistical significance was adjusted using the Bonferroni method. Paired t-test were used to evaluate AET-related changes in UPDRS subscores in PD participants alone. In addition, the associations between exercise-related changes in upper-limb functioning, cardiovascular capacity, executive functions and MSL in PD patients were tested using Pearson's partial correlation (controlling for age and depression level). All results were expressed as means ± standard deviations for descriptive statistics. Analyses were conducted using SPSS 21.0 (IBM, Armonk, NY: IBM Corp.). The level of statistical significance for all tests was set at $p<0.05$.

1.3 Results

Forty-four participants (21 PD patients and 23 HA) were eligible after the completion of the first evaluation. Two HA decided to withdraw from the project prior to commencing the AET regimen, for personal reasons. Two participants (1 HA and 1 PD) did not complete the program because of medical conditions external to the research project. One PD patient completed the AET, but was excluded from analysis because of unusually low levels of physical and cognitive performances (outlier: mean >2 SD). Another PD patient was excluded from the analyses for technical reasons given that his drawing trials were not saved during one of the evaluations. A total of 38 persons (18 PD patients and 20 HA) were thus included in the final analysis. Demographic characteristics and initial values of the study participants are described in Table 3. The 3-month AET did not permit to observe any change in the UPDRS III in PD participants, whether in total, at the level of tremor, rigidity or the right upper limb (see Table 4).

Table 3: Demographic data

Characteristics	HA	PD	Group differences
Age (years)	64 ± 8.19	59 ± 7.11	p=0.06
Ratio men/women	8/12	13/6	p=0.07
Education (years)	15.7 ± 2.36	15.05 ± 2.78	p=0.43
Cognition (MMSE/MoCA)	29.18 ± 1.25 29.56 ± 1.51	28.4 ± 1.34 27.21 ± 1.85	p=0.28 p=0.08
Depression (BDI)	4.8 ± 4.5	10.5 ± 8.3	p<0.01
Anxiety (BAI)	2.1 ± 2.7	8.6 ± 9.4	p<0.01
Inhibition (Stroop, in s)	115.4 ± 4.7	128.5 ± 6.7	p=0.12
Flexibility (TMT, in s)	75.0 ± 6.4	85.5 ± 10.5	p=0.39
UPDRS III	N/A	21.84 ± 6.16	N/A
Duration of disease (years)	N/A	8.1 ± 9.12	N/A
H & Y	N/A	2.1 ± 0.2	N/A

Means ± SD, HA: healthy adults, PD: Parkinson's diseases patients, N/A: non applicable, s: seconds

We observed significant difference between PD and HA groups at baseline in regards to three variables: D2 ($p<0.05$), ET ($p<0.05$) and MT ($p<0.01$), suggesting that PD individuals had a larger antagonist response, a longer elapsed time between the visual stimulus and the end of the movement, and longer time of displacement of the stylus before the exercise training program began.

Table 4: Kinetic parameters of the a fast simple reaction time task and motor symptoms examination

	HA		PD		Statistical significance		
Kinematic variables	Pre-AET	Post-AET	Pre-AET	Post-AET	Interaction	AET	Group
SNR	25.6 ± 4.3	26.3 ± 4.7	24.1 ± 3.9	23.5 ± 2.7	0.151	0.503	0.116
Nb of trials	23.4 ± 5.2	21.7 ± 7.2	17.8 ± 8.1	20.6 ± 5.3	0.119	0.606	0.442
t0	0.17 ± 0.08	0.17 ± 0.08	0.15 ± 0.07	0.16 ± 0.06	0.555	0.306	0.706
D1	119.4 ± 11.2	122.8 ± 9.9	126.6 ± 15.8	115.1 ± 7.3†	0.006*	0.719	0.965
μ1	-1.17 ± 0.34	-1.19 ± 0.42	-0.86 ± 0.37	-0.95 ± 0.37	0.675	0.283	0.055
σ1	0.29 ± 0.06	0.27 ± 0.05	0.28 ± 0.05	0.28 ± 0.05	0.957	0.207	0.934
D2	22.1 ± 6.5	22.6 ± 6.9	30.8 ± 14.1	22.8 ± 5.0†	0.052	0.683	0.064
μ2	-0.81 ± 0.32	-0.84 ± 0.39	-0.57 ± 0.33	-0.64 ± 0.32	0.824	0.324	0.128
σ2	0.12 ± 0.02	0.11 ± 0.02	0.13 ± 0.03	0.11 ± 0.01†	0.027*	0.236	0.226
ET	0.72 ± 0.15	0.70 ± 0.19	0.88 ± 0.23	0.83 ± 0.19	0.489	0.490	0.027*
RT	0.33 ± 0.10	0.34 ± 0.13	0.37 ± 0.11	0.37 ± 0.10	0.487	0.064	0.512
MT	0.35 ± 0.10	0.33 ± 0.10	0.48 ± 0.17	0.42 ± 0.12†	0.133	0.671	0.007*
UPDRS III							
Tremor	N/A	N/A	1.08 ± 1.26	1.08 ± 1.56		1.000	
Rigidity	N/A	N/A	4.72 ± 2.65	3.81 ± 2.43		0.124	
Right UL	N/A	N/A	4.61 ± 1.53	4.58 ± 1.78		0.923	
Total	N/A	N/A	21.92 ± 6.32	21.53 ± 6.38		0.765	

Means ± SD. †: a significant within-group difference from baseline, *: a significant effect for interaction or mean effects; HA: Healthy adults; PD: Parkinson's disease patients; AET: aerobic exercise training; SNR: signal-to-noise ratio (in decibels); Nb of trials: number of successful trials; t0: time occurrence of the input commands to the neuromuscular system; D1: agonist component; μ1: time delay of D1; σ1: response spread of D1; D2: antagonist component; μ2: time delay of D2; σ2: response spread of D2; ET: time between visual stimulus and the immobilization of the stylus; RT: reaction time; MT: movement time; UL: upper limb, includes the following items: tremor at rest, postural tremor, rigidity of arm, finger taps, hand movements, rapid alternating movements of hands.

Following the 12-week AET, the repeated measures ANOVA revealed that PD participants showed significant decreases of the D1 ($F_{1,17}$=8.916, p<0.01), D2 ($F_{1,17}$=5.039, p<0.05) and σ2 ($F_{1,17}$=6.553, p<0.05), the agonist command, the antagonist command and its response spread, respectively. The mixed ANCOVA model revealed a significant group*session interaction effect for D1 ($F_{1,34}$=8.679, partial R^2=0.203, p<0.01) and σ2 ($F_{1,34}$=5.359, partial R^2=0.136, p<0.05) (Table 2), suggesting a significant change for these two parameters only in PD patients following AET (Figure 12). While differences were observed at baseline for D2, ET and MT, the groups did not differ significantly in post-AET comparisons for D2 and ET (Figure 13).

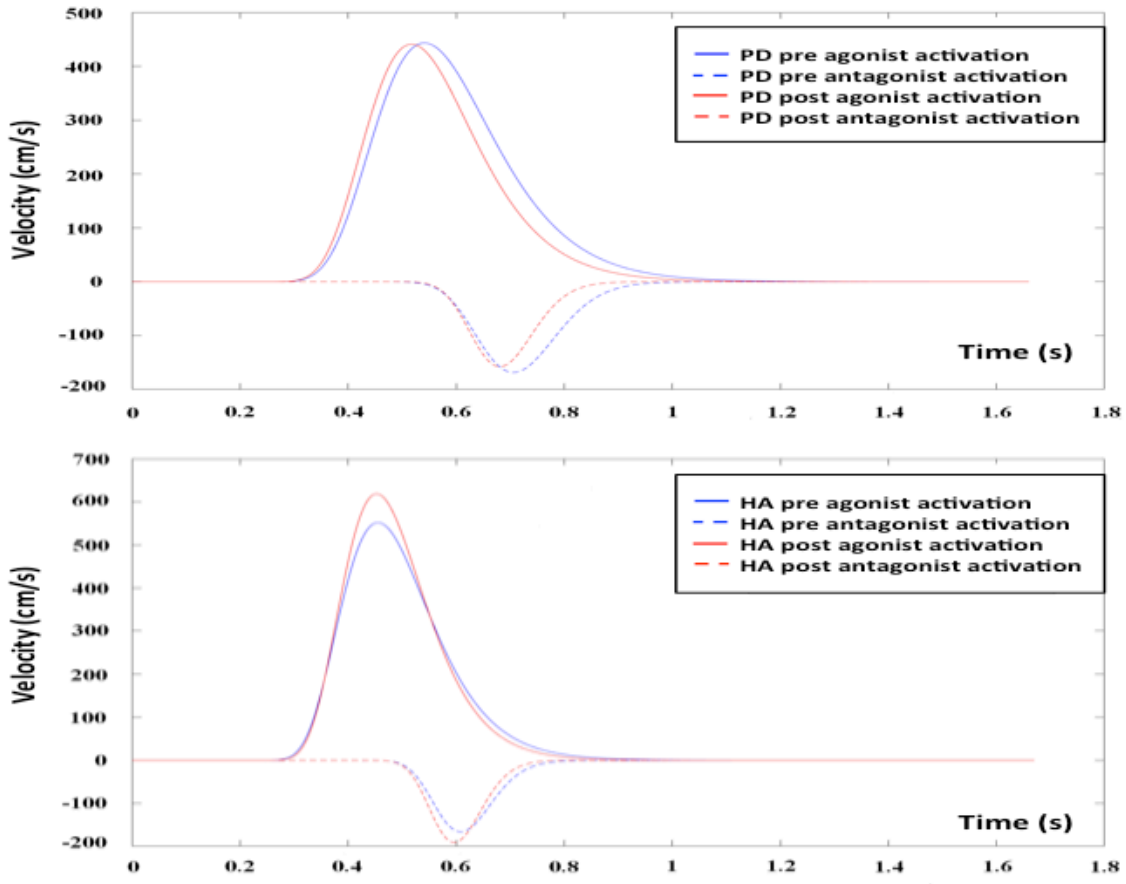

Figure 12: Agonist and antagonist responses before and after AET for PD and HE groups

AET: aerobic exercise training; PD: Parkinson's disease patients, HA: healthy adults.

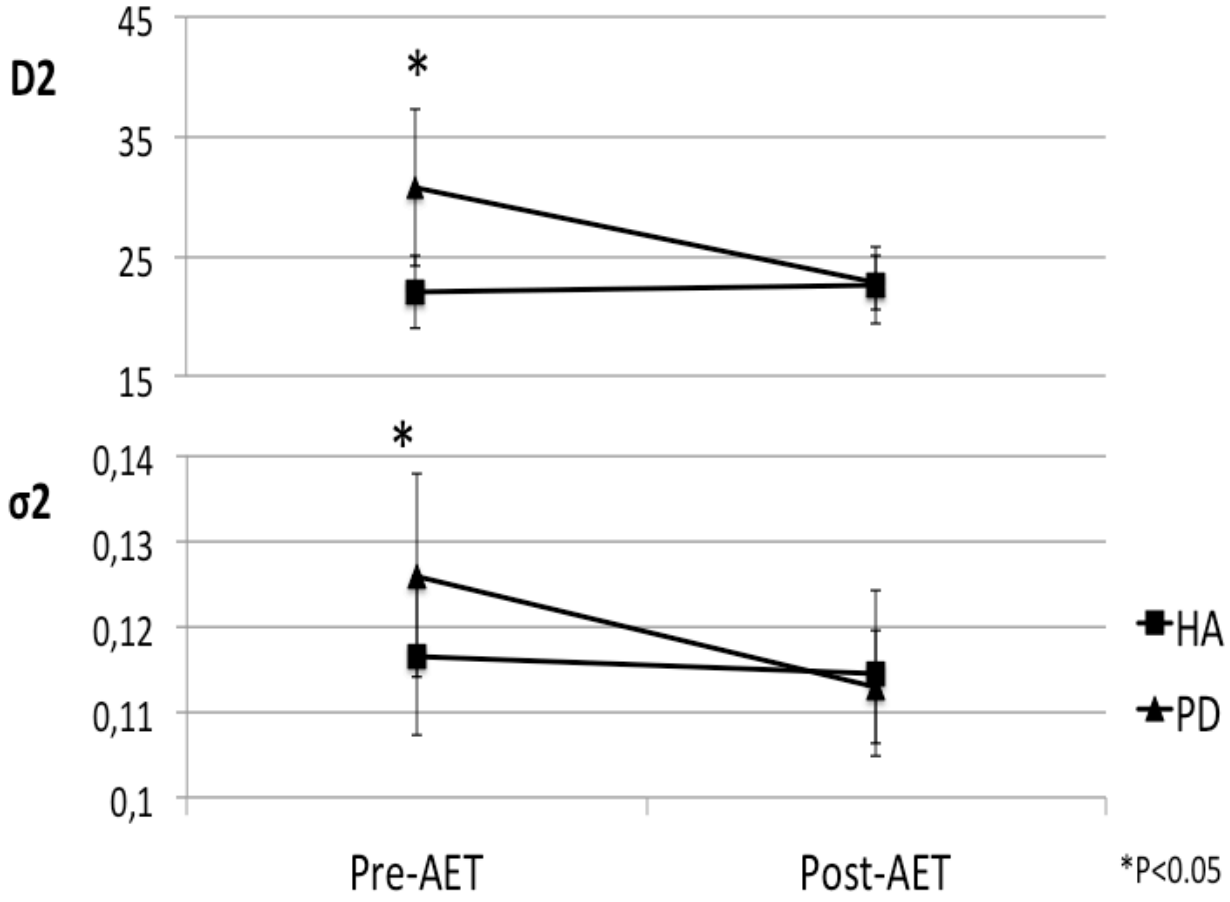

Figure 13: Normalization of antagonist parameters in PD group after AET

AET: aerobic exercise training; PD: Parkinson's disease patients, HA: healthy adults, D2: antagonist component, σ2: response spread of D2.

As reported previously by our research group (Duchesne et al. 2015; Duchesne et al. 2016), significant between-sessions differences were found in both groups for outcomes related to aerobic capacity (VO2 peak), motor sequence learning (MSL) capacity and cognitive inhibition (all ps < 0.05), indicating that the training improved participants' fitness, procedural learning and cognitive inhibition, regardless of the health status. These results are only presented here as supplementary material (see Supplementary Materials (Nadeau et al. 2017), AET-related changes in various domains). However, in the current study, we tested for correlations between

these variables and kinematic parameters that showed significant AET-related changes (D1, D2, σ2, MT), among PD participants. We observed a significant association between the change in cognitive inhibition and σ2 ($r=-0.560$, $p<0.05$, $df=14$), as well as between AET-related change in inhibition and the change in MT ($r=-0.531$, $p<0.05$, $df=14$). These results indicate that an increase in response spread of the antagonist component or in movement time are associated with a decrease in inhibition effect. No correlation was observed between any of the kinematic parameters and the patients' aerobic or MSL capacities.

1.4 Discussion

In the current study, we investigated the effects of an AET regimen using stationary bicycling on kinematic parameters of an arm movement in sedentary healthy adults and in Parkinson's disease patients. As reported previously by our group (Duchesne et al. 2015; Duchesne et al. 2016), such training regimen improved cardiovascular capacity, executive functions and motor learning capacities in both groups. Here, we report that AET also had a significant positive impact on the capacity to draw lines in a more efficient way, in PD patients, indicating an improvement in the upper limb motor function. Specifically, after AET there was a significant decrease of the antagonist response of the movement (D2), an amelioration that can be interpreted as an improvement in the control of the motor command in PD patients. Other AET-related changes included a better response spread of the antagonist activation (σ2), which may reflect a more global modification of the central nervous system in improving its response time. The significant improvement in MT in the context of no change in the RT also demonstrates AET-related improvements in the capacity to execute a faster movement, while the time needed from the brain to process the information of the visual stimulus remained the same in PD patients. Although we did not observe any changes in motor symptoms (UPDRS III), this last result suggest that the

improvements measured while drawing lines are not due to a decrease in rigidity, for example. By contrast to the changes observed in the PD group, no significant AET-related changes in the kinematic parameters were observed in the HA group.

Initial group differences for ET and D2 variables disappeared after AET, suggesting an effect of "normalization" due to improvements in PD patients. For the MT, even if there was a significant AET-related change in PD patients, the difference between the two groups was still present after AET. To our knowledge, this is the first time a "normalization" effect is reported following AET in PD patients in regards to the upper limb motor function.

We found a significant negative relationship between changes in cognitive inhibition of PD participants and their change in the MT or response spread of the antagonist activation ($\sigma 2$), indicating that individuals who improved on one variable showed a decrease in the other after AET. Although conjectural, these results suggest that in this specific population, there may be a trade-off between improving motor function and executive function. It may also indicate the presence of two clinical sub-populations in our sample, a mixture of patients who are more impaired on either executive or motor functions hence responding differently to the intervention and making the correlation spurious. Further studies should explore this issue.

To date, studies on physical exercise training have proposed several action mechanisms underlying this type of intervention. The simplest one is that increase of heart rate and blood pressure during exercise could help to increase effectiveness of PD medication by making it more easily pass the blood-brain barrier (Speelman et al. 2011). Also, some studies have reported an increase in brain derived neurotrophic factors (BDNFs) and glia cell line-derived neurotrophic factor (GDNF), neurotrophins known to regulate survival and activity of dopaminergic neurons, following short bouts of aerobic exercise in PD patients (Frazzitta et al. 2014; Zoladz et al. 2014;

Marusiak et al. 2015). Moreover, Marusiak et al. (2015) reported that this increase in BDNF levels correlated with improvements in PD rigidity. Another proposed action mechanism has been related to neurotransmitters, as that progressive aerobic exercise could lead to an increase in dopamine D2 receptor density within the regional boundaries of the dorsal striatum (observed with PET imaging, (Fisher et al. 2013)). Similarly, there is evidence for an increase in corticomotor excitability (observed via transcranial magnetic stimulation) in parkinsonian individuals (Fisher et al. 2008), It is important to highlight the fact that our participants used primarily the lower limbs during AET; yet we observed changes in the upper limb. This would suggest that functional changes in corticospinal pathways may occur at multiple levels, not only at those directly involved in generating and controlling the limbs performing the movements. In support of such mechanisms are the findings of a work performed by Zhou and colleagues (Zhou et al. 2017) that demonstrate changes in the motor evoked potentials in the lower limb in neurologically intact individuals and patients with incomplete spinal cord injury following arm cycling alone or simultaneous arm and leg cycling, respectively. Our study adds to this body of knowledge, by providing evidence that AET can improve the synergistic action of an agonist and antagonist neuromuscular networks in PD. Whether this improvement in motor control is achieved via one or some of these neurophysiological mechanisms remains to be explored in future research.

A third possible mechanism of action could be that AET may lead directly to structural and/or functional changes in the brain. Indeed, many neuroimaging studies have already reported differences in gray and white matter between healthy adults and PD subjects (Lehéricy et al. 2012; Meijer et al. 2013; Agosta et al. 2016; Al-Radaideh and Rababah 2016), as well as in functional activity at rest or during various tasks (Mallol et al. 2007; Sharman et al. 2012; Caproni et al. 2013; Skidmore et al. 2013; Nigro et al. 2016). However, to date, only one study

reported the effect of exercise training on the neural correlates of motor sequence learning in PD (Duchesne et al. 2016).

Contrary to other studies using forced exercise (FE) to improve upper limb, we chose to use voluntary exercise (VE) instead. FE is described as an aerobic exercise in which the rate is augmented mechanically to assist the participant, hence allowing the achievement and maintenance of an exercise rate greater than the preferred voluntary rate of exercise (VE). Consequently, it has been hypothesized that the magnitude of intrinsic feedback provided in FE could permit the release of a greater amount of dopamine than VE, which could then have a greater positive impact on the brain structure and function in PD (Alberts et al. 2011). In fact, it has been proposed that lower-extremity FE could produce global improvements in motor symptoms using the same pathways through which anti-PD medication acts to produce symptomatic relief in individuals with PD (Alberts et al. 2016). For this reason, it has also been suggested that FE could be a better way to exercise for people affected by PD. However, from a clinical and practical perspective, FE devices are not easily accessible to the general public, including people suffering from PD. Furthermore, given that our study shows that there are significant beneficial effects when using VE, we thus believe that this latter type of training is more feasible in clinical settings.

The fact that we observed improvements in kinematic parameters, but not in the UPDRS scores, after AET suggests that our task using the delta-lognormal model (Plamondon et al. 1993; Plamondon 1995; Plamondon 1995; Plamondon 1998; Plamondon et al. 2003) may be a more sensitive mean to assess changes in motor function (and indirectly, motor symptoms) following treatment in PD. Even though accelerometers and gyroscopes could be used to record 3-dimentional motions and to quantify more objectively tremor and bradykinesia during the

different tasks composing the motor examination of the UPDRS (Heldman et al. 2014), such a setup does not offer any insight into the neurophysiological mechanisms underlying the motor symptoms (i.e. agonist and antagonist muscle activity during motor task performance). The original contribution of the current study is thus the use of a relatively simple kinematic task, which can be easily performed by PD patients and, most importantly, does offer an indirect and objective clinical measure of the state of the global neurophysiological mechanisms involved in controlling the upper limb. Indeed, it must be remembered that the lognormal impulse response predicted by the kinematic theory is the optimal function describing the neuromuscular system of human subjects in perfect control of their movements (Djioua and Plamondon 2010). As a person get old, he/she will depart from this ideal behaviour more or less severely, depending on his/her health status (Plamondon et al. 2013). In this context, the SNR can be seen as an objective parameter that characterizes the global motor behaviour of a subject. The higher it is the better is the motor control. Moreover, the delta-lognormal model proposes a complementary and new window to analyse and interpret a movement kinematics in terms of agonist (D_1) and antagonist (D_2) input commands, which reflects the intention of a subject, as D_1-D_2 is equal to the physical distance covered by a given movement. Similarly, the occurrence of these commands at t_0 has been shown to be directly correlated to a specific ERP potential occurring at t_0 (O'Reilly et al. 2013). Similarly, the timing parameters μ and σ indirectly reflect the muscle coupling through the proportionality of their cumulative time delays, as observed via EMG data (Plamondon et al. 2013). In other words, reconstructing each velocity profile with the delta lognormal model, a neuroscientist get access to physiologically meaningful global parameters describing the status of the agonist and antagonist neuromuscular system of a subject, can monitor its time evolution and estimate if he or she is improving, stays stable or deteriorates.

One limitation of the current study was the lack of a PD control group for the type and

intensity of exercise (e.g. a PD group undertaking another type of training regimen). Also, having more than the two pre- and post-AET assessments would have allowed the mapping of the trajectory of changes during training. Another limitation stems from the use of a mathematical model (kinematic theory) to infer the neurophysiological changes in the motor system; even though this model has been found to have some physiological plausibility, supported previously with EEG and EMG, it remains nevertheless an indirect assessment of these mechanisms. EEG or EMG would have to be used in future research to corroborate the findings of the present study. Despite these constraints, however, our findings indicate that using VE and a typical stationary bicycle can still lead to great improvements in the upper limb movement fluidity, in addition to aerobic capacity, executive function, motor sequence learning and in gait. Finally, we believe that our study results contribute to the field and may inspire future research about how exercise could help to improve activities of daily living relying on the motor function of the upper limb in people with PD.

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ARTICLE 3:

Effects of aerobic exercise on brain grey matter in people with Parkinson's disease

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Key words: Parkinson's disease, exercise, grey matter, VBM, volumetry, cortical thickness

Authors' contributions: JD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He was responsible for design, funding, conduct of the study. AN and CD managed the study. AN, OL and AB led the statistical analyses. AN wrote the manuscript. AN, OL, AB and JD were involved in data interpretation. OL, LDB, AB, CD, MER, FB, FG, ALL, LB and JD reviewed and approved the manuscript.

Abstract

Background: Despite evidence that physical exercise in general, and aerobic training in particular, may benefit PD patients, no study has investigated the effects of aerobic training on structural brain changes in this population. We aimed to determine whether aerobic exercise training (AET) regimen could be associated with changes in grey matter (GM) structure to the same extent or differently in PD patients and healthy adults.

Methods: Two groups, 19 PD patients (Hoehn & Yahr ≤2) and 20 HA, matched on age and sedentary level, followed a 3-month stationary bicycle AET regimen. Measures of GM (VBM, cortical thickness and volumetry) were obtained via MRI processing and analysis. VBM was measured with a GLM model in FSL, cortical thickness used also a GLM model in the FreeSurfer software, and volumetry was measured using an ANCOVA in SPSS. All analyses used age and gender as covariates to correct for confounding effects.

Results: No GM intensity or cortical thickness differences were found at baseline between PD patients and HA participants, nor were there any significant reductions or increases in PD or HA participants following the aerobic training regimen. At baseline, compared to HA, PD patients had a significant smaller volume of the left hippocampus. Following the AET, PD patients showed a significant increase in the right globus pallidus volume. For the HA group, an AET-related volumetric increase was found in the left VIIIA cerebellar lobule. In both groups, there was no significant AET-related volumetric changes that were significantly associated with changes in aerobic capacity, MSL or cognitive inhibition.

Conclusion: Even though changes obtained were limited and they did not correlate significantly with other parameters that were sensitive to AET, we believe that we provide evidence for

exercise-related brain structural plasticity and the potential benefits of using aerobic training as a non-pharmacological intervention in sedentary individuals, both healthy and with PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a wide variety of motor and non-motors symptoms, attributable to the degeneration of dopaminergic neurons, initially in the basal ganglia and later in other parts of the brain, as disease progresses (Braak et al. 2004). Notwithstanding a substantial heterogeneity among PD patients regarding the clinical manifestation of the disease, there is evidence that there are specific structural changes in the brain that either correlate with disease progression or are apparent when comparing patients with their healthy counterparts. For instance, several studies have reported a decrease or reduction in neural density and in cortical thickness in the frontal cortex (Dagher and Nagano-Saito 2007; Tinaz et al. 2010; Pereira et al. 2011; Agosta et al. 2012; Ibarretxe-Bilbao et al. 2012; Pan et al. 2012; Lee et al. 2013; Madhyastha et al. 2015) including the premotor region (Pereira et al. 2011), as well as in the parietal (Pereira et al. 2011; Lee et al. 2013; Madhyastha et al. 2015), temporal (Pereira et al. 2009; Pellicano et al. 2011; Pereira et al. 2011; Pan et al. 2012; Madhyastha et al. 2015) and occipital cortices (Tinaz et al. 2010; Pereira et al. 2011) in PD patients. Other studies have shown a decrease in grey matter density in some subcortical regions, such as cerebellum (Camicioli et al. 2009; Pereira et al. 2009) and the limbic system (Dagher and Nagano-Saito 2007; Pereira et al. 2009). Despite reports that PD patients and healthy controls do not present differences regarding the overall brain volume (or overall white or gray matter volumes), there is evidence of significant regional volumetric or shape differences in the basal ganglia,

amygdala, thalamus and hippocampus (Menke et al. 2009; Lee et al. 2011; Ibarretxe-Bilbao et al. 2012; Lee et al. 2014).

In recent years, emerging evidence suggests that specific changes in brain structure in PD patients also correlate with symptoms that are often comorbid with the disease, such as depression (Hanganu et al. 2017), as well as cognitive (Mak et al. 2015; Caspell-Garcia et al. 2017) or visuospatial and visuoperceptual impairments (Garcia-Diaz et al. 2017). In all of these studies, there was a larger cortical thinning or volume reduction in PD patients having these symptoms as compared to those who did not. These results indicate that structural brain changes in PD may be modifiable and subject to external interventions. Among the types of non-pharmacological interventions that could have an impact on brain structural integrity in PD is the aerobic training. In healthy individuals, it has been shown that after 24-52 weeks of aerobic training there were significant increases in grey matter volumes in the frontal lobe (including the supplementary motor area) (Colcombe et al. 2006) and in the temporal lobe (including the hippocampus) (Colcombe et al. 2006; Erickson et al. 2011). Yet, despite evidence that physical exercise in general, and aerobic training in particular, may benefit PD patients (Goodwin et al. 2008; Petzinger et al. 2010; Speelman et al. 2011; Mehrholz et al. 2015; Ahlskog 2018), no study has investigated the effects of aerobic training on structural brain changes in this population.

In this paper, we aimed to determine whether aerobic exercise training (AET) regimen could be associated with changes in gray matter structure using three different metrics (VBM, cortical thickness and volumetry) to the same extent or differently in PD patients and healthy adults. Finally, we planed to assess the correlations between AET-

related behavioural changes and variations in brain structural metrics. The data presented here are part of a larger research program that observed the benefits of this type of exercise training on several outcome measures such as cardiorespiratory capacities, executive functions, motor sequence learning capacity, gait parameters and upper limb functions; the results of which have been presented elsewhere (Duchesne et al. 2015; Duchesne et al. 2016; Nadeau et al. 2017; Nadeau et al. 2018).

2. Material and methods

2.1 Participants

Twenty-one PD patients and 23 healthy adults took part in the study. Participants were aged between 40 and 80 years, were right-handed, sedentary (≤5 on the Jackson's Questionnaire (Jackson et al. 1990), without significant cognitive impairment (i.e. ≥24 or more on the Mini Mental State Evaluation (Folstein et al. 1975) or the Montreal Cognitive Assessment (Nasreddine et al. 2005; Marinus et al. 2011). The two groups were matched with regards to sex distribution, age, education, as well as on cognitive and fitness levels. Exclusion criteria for the patients included the presence of other neurological disorders or comorbidities likely to affect gait or practice of exercise. PD patients had to be classified as stage 1 or 2 according to Hoehn and Yahr's scale (Hoehn and Yahr 1967) based upon medical evaluation performed by a certified neurologist (A-LL), and had to score below 35 on motor functions as assessed by the third section of the United Parkinson's Disease Rating Scale (UPDRS III) (Goetz et al. 2008). This study was carried out in accordance

with the recommendations of the research ethics committee's guidelines of the Research Center of the Institut Universitaire de Gériatrie de Montréal, which approved the protocol. A written and informed consent was obtained from participants prior to their inclusion in this study.

2.2 Exercise intervention protocol

Following the baseline assessment, participants were assigned to a 3-month, supervised AET in small groups of four participants per trained kinesiologist. AET intensity prescription was based on each participant's maximal aerobic power output achieved during the VO_2 peak test. The AET used recumbent bicycles. Duration of the exercise started at 20 minutes and 60% of intensity per session, and then was increased by steps of 5 minutes and 5% of intensity every week, until participants reached 40 minutes of exercise at 80% of intensity, after which this intensity level was maintained for the rest of the AET program. Bike speed was maintained at 60 revolutions per minute. Rate of perceived exertion (measured with the Borg scale (Borg 1998)) and heart rate were assessed during each training session to ensure participants' tolerance of the prescribed effort. The program lasted 12 weeks, including 3 sessions per week.

2.3 Assessments

Participants underwent a thorough evaluation including a variety of outcome measures, at baseline, before the AET, as well as immediately after the completion of the 3-

month training regimen. These evaluations are described in the 'secondary outcomes' section.

2.3.1 Main outcomes

Measures of grey matter (VBM, cortical thickness and volumetry) were obtained via MRI processing and analysis detailed below.

MRI acquisition

T1 images were acquired with a 12-channel head coil and a 3.0 Tesla Siemens TIM TRIO magnetic resonance imaging system (T1: repetition time = 13 ms, echo time = 4.92 ms, inversion time = 900 ms, flip angle = 25°, 176 slices, field of view = 256 x 256 mm^2, matrix size = 256 x 256 x 176, voxel size = 1 x 1 x 1 mm^3.

MRI preprocessing

VBM

Structural data was analysed with FSL-VBM (Douaud et al. 2007), an optimised VBM protocol (Good 2001) carried out using FSL tools (Smith et al. 2004). First, the brain was extracted from structural images by stripping the skull and grey matter was segmented before being registered to the MNI 152 standard space using a non-linear registration approach (Andersson et al. 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. In a second step, all native grey matter images were non-linearly registered to this study-specific

template and 'modulated' to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed using a 3D isotropic Gaussian kernel of 3 mm full width at half maximum (FWHM).

Cortical thickness

Cortical thickness was measured from the whole-brain T1-weighted images using FreeSurfer 6.0 software package (https://surfer.nmr.mgh.harvard.edu). The preprocessing pipeline included motion correction and averaging of multiple volumetric T1-weighted images, removal of non-brain tissue using a hybrid surface deformation procedure (Ségonne et al. 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (Fischl et al. 2004), intensity normalization (Sled et al. 1998), tessellation of the grey/white matter boundary, automated topology correction (Ségonne et al. 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Fischl and Dale 2000). To extract reliable volume and thickness estimates for both time points (pre- and post-AET), images where automatically processed using a longitudinal procedure (Reuter et al. 2012). Specifically, an unbiased within-subject template space and image was created using a robust, inverse consistent registration (Reuter et al. 2010). Skull stripping, Talairach transformation, atlas registration, as well as spherical surface maps and parcellations, were then initialized with common information from the within-subject

template (Reuter et al. 2012). Cortical thickness was calculated as the closest distance from the grey/white matter boundary to the grey/cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl and Dale 2000). These procedures for the measurement of cortical thickness have been previously validated and used (Salat 2004; Hanganu et al. 2014). A smoothing Gaussian kernel of 10 mm FWHM was used.

Volumetry

Volumes were measured based on the whole-brain T1-weighted images using FreeSurfer 6 software package (https://surfer.nmr.mgh.harvard.edu). The subcortical structures were segmented in order to obtain their volumes. The volumes were then normalized to the estimated total intracranial volume ([volume/eTIV]*100).

2.3.2 Secondary outcomes

Peak volume of oxygen uptake (VO_2 peak) was estimated by a submaximal aerobic test (11 HA, 5 PD) or by a medically supervised maximal oxygen uptake test (9 HA, 14 PD), both during a graded exercise test on stationary bicycle (ACSM 2006), after a physician analyzed an electrocardiogram to rule out any cardiac anomalies. The Stroop Test (naming, reading, interference) (Stroop 1935) and the Trail Making Test (TMT A & B) (Sanchez-Cubillo et al. 2009) were used to evaluate inhibition and cognitive flexibility, respectively, two components of executive neuropsychological functions. The participants' capacity in motor sequence learning (MSL) was evaluated during a functional magnetic resonance imaging session, where they had to perform an implicit serial reaction time task

(Nissen and Bullemer 1987). Mood was also evaluated using the Beck Depression Inventory (Beck et al. 1961) and the Beck Anxiety Inventory (Beck et al. 1988). The patient's motor symptoms were assessed using the third section of the UPDRS (Goetz et al. 2008). Other motor symptoms were assessed, such as the kinematic properties of the agonist and antagonist neuromuscular systems of the right upper limb during a fast simple reaction time task and lower limb capacities during walking. More details of the complete fitness, neuropsychological and motor evaluations can be found in our previous studies (Duchesne et al. 2015; Duchesne et al. 2016; Nadeau et al. 2017; Nadeau et al. 2018).

2.4 Statistical analysis.

To assess voxel-wise group differences in grey matter (GM) intensities between PD patients and healthy controls, we used a GLM model where the modulated GM images represented the dependent variable. Group differences between PD patients and healthy controls (at baseline or in regards to the post-AET vs pre-AET differences) were assessed using two-tailed t-statistics, with age and gender as covariates to correct for confounding effects. The GLM analysis was used in conjunction with the 'randomise' procedure in FSL that controls the false positive rate by conducting a permutation-based non-parametric testing of the statistical estimates. To correct for multiple comparisons with family wise error, the Threshold-Free Cluster Enhancement (TFCE) technique was used (Smith and Nichols 2009), with a significant threshold p-value of < 0.05.

Group and group*time differences in cortical thickness were assessed using the GLM model with different offsets and slopes and the Monte Carlo simulations (n=5000) to

correct for multiple comparisons, as implemented by the mri_glmfit procedure in FreeSurfer software.

Volumetric differences between groups at baseline and over time were analyzed using an ANCOVA model (dependent variable: volumes, independent variable: groups, covariates used: age, gender). Analyses were conducted using SPSS 21.0 (IBM, Armonk, NY: IBM Corp). The level of statistical significance for all tests was set at $p<0.05$.

A repeated-measure ANCOVA model (the same dependent variables, but with group and time of assessment as independent variables) was used to test the effect of AET on secondary outcomes in PD participants compared to HA subjects. In addition, the association between exercise-related changes in structural brain changes and cardiovascular capacity was tested using Pearson's partial correlation. All results were expressed as means ± standard deviations for descriptive statistics. These analyses were conducted using SPSS 21.0 (IBM, Armonk, NY: IBM Corp.). The level of statistical significance for all tests was also set at $p<0.05$.

3. Results

Of all 44 participants who were recruited initially, two HA subjects withdrew voluntarily, whereas one PD and one HA participants were excluded prior to AET onset for health security reasons, based on their cardiogram. Furthermore, one PD subject who completed the AET was excluded from analysis due to extreme results on several outcomes. Demographic characteristics of the final sample are presented in Table 5. The

two groups did not show significant differences in age, sex distribution, years of education, cognitive status or the total estimated intracranial volume (all ps > 0.05).

Table 5: Demographic data

Characteristics	HA	PD	Group differences
Age (years)	64 ± 8.19	59 ± 7.11	p=0.06
Ratio men/women	8/12	13/6	p=0.07
Education (years)	15.7 ± 2.36	15.05 ± 2.78	p=0.43
Cognition (MMSE/MoCA)	29.18 ± 1.25 29.56 ± 1.51	28.40 ± 1.34 27.21 ± 1.85	p=0.28 p=0.08
Depression (BDI)	4.8 ± 4.5	10.5 ± 8.3	p<0.01
Anxiety (BAI)	2.1 ± 2.7	8.6 ± 9.4	p<0.01
Inhibition (Stroop, in s)	115.4 ± 4.7	128.5 ± 6.7	p=0.12
Flexibility (TMT, in s)	75.0 ± 6.4	85.5 ± 10.5	p=0.39
Estimated total intracranial volume (mm^3)	1433069 ± 134788,5	1598814 ± 144951,9	p=0.86
UPDRS III	N/A	21.84 ± 6.16	N/A
Duration of disease (years)	N/A	8.1 ± 9.12	N/A
H & Y	N/A	2.1 ± 0.2	N/A

Means ± SD, HA: healthy adults, PD: Parkinson's diseases individuals, N/A: non applicable, s: seconds

As reported previously by our research group (Duchesne et al. 2015; Duchesne et al. 2016), significant between-sessions differences were found in both groups for outcomes related to aerobic capacity (VO2 peak), motor sequence learning (MSL) and cognitive inhibition (all ps < 0.05), indicating that the training had a global effect, improving these

outcomes regardless of the health status. Nevertheless, we did not observe any significant change in the UPDRS III parameters in PD participants after the 3-month AET, whether in total score, or the sub-scores related to the level of tremor, rigidity or the right upper limb (Nadeau et al. 2018).

No morphometric differences were found at baseline between PD patients and HA participants, nor were there any significant reductions or increases in grey matter intensity in PD or HA participants following the aerobic training regimen. Similarly, we found no differences in cortical thickness between the two groups at baseline, nor were there any significant regional reductions or increases in cortical thickness following AET in either group.

Adjusted volumes for the subcortical grey matter structures and statistical results are summarized in Table 6. At baseline, compared to HA, PD patients had a significant smaller volume of the left hippocampus ($p=0.003$). We also observed a significant negative association between the left hippocampus volume and the disease duration in the PD group ($r= -0.775$, $p=0.000$, $N=19$).

Table 6: Normalized cerebral grey volumes at baseline for PD patients and HA

	PD		HC		
	mean (mm^3)	SD	mean (mm^3)	SD	p value
Left side					
Cerebellum					
I-II	0,0518	0,0122	0,0439	0,009	0,061
III	0,6642	0,1039	0,6541	0,0566	0,781
IV	1,7453	0,2309	1,8213	0,232	0,129
V	3,0829	0,2707	2,9478	0,2653	0,769
VI	5,9123	0,7324	5,7625	0,495	0,952
Crus I	8,8106	0,7847	9,0916	0,8517	0,185
Crus II	6,0982	0,8527	6,0095	0,8901	0,825
VIIB	3,0183	0,3205	3,0883	0,2557	0,1
VIIIA	3,9926	0,4136	3,9182	0,3206	0,704
VIIIB	2,7747	0,4084	2,6871	0,2948	0,97
IX	2,7165	0,316	2,6818	0,3009	0,629
X	0,4974	0,0305	0,4897	0,0554	0,705
CM	6,142	0,3423	5,9762	0,4166	0,948
Striatum	0,5659	0,0483	0,5906	0,0477	0,117
Globus Pallidus	0,0886	0,015	0,0924	0,0136	0,412
Thalamus	0,3151	0,0324	0,3198	0,0282	0,631
Hippocampus	0,2374	0,0247	0,259	0,0183	0,003*
Right side					
Cerebellum					
I-II	0,0712	0,0133	0,0638	0,0106	0,197
III	0,7428	0,1115	0,7002	0,0745	0,492
IV	1,4444	0,2353	1,3835	0,1332	0,787
V	3,1954	0,3377	3,1123	0,2191	0,921
VI	6,2596	0,6394	6,2147	0,5646	0,618
Crus I	8,9362	0,8291	9,1148	0,7951	0,261
Crus II	6,6362	0,7097	6,5477	0,5678	0,693
VIIB	3,4827	0,3636	3,5403	0,3064	0,218
VIIIA	3,3516	0,3298	3,4012	0,253	0,205
VIIIB	2,6971	0,2878	2,649	0,2865	0,684
IX	2,6869	0,2789	2,7061	0,2852	0,283
X	0,5146	0,0322	0,517	0,042	0,289
CM	6,2432	0,3329	6,0811	0,4465	0,966
Striatum	0,5716	0,0502	0,5881	0,0479	0,3
Globus Pallidus	0,0832	0,0135	0,0866	0,011	0,393
Thalamus	0,339	0,0325	0,3443	0,0344	0,624
Hippocampus	0,2374	0,0262	0,252	0,0248	0,058

HA: healthy adults; PD: Parkinson's diseases individuals, mm: millimetres

Moreover, following the AET, PD patients showed a significant increase in the right globus pallidus volume (p=0.04) and a decrease in the volumes of the left I-II (p=0.02) and the right VIIIB lobules (p=0.001) of the cerebellum (see Table 3). For the HA group, an AET-related volumetric increase was found in the left VIIIA cerebellar lobule (p=0.01), and a significant decrease in the right I-II (0.03) and the left VIIB lobules (p=0.005) (see Table 7). In both groups, there was no significant AET-related volumetric changes that were significantly associated with changes in aerobic capacity, MSL or cognitive inhibition.

Table 7: AET-related changes in normalized cerebral grey volumes

PD	Change mean (mm^3)	p value		Change mean (mm^3)	p value
Left side			Right side		
Cerebellum			**Cerebellum**		
I-II	-0.0011	0,02*	I-II	0.00208	0.51
III	0.006	0.46	III	0.0035	0.81
IV	-0.0128	0.16	IV	-0.0077	0.60
V	0.0145	0.25	V	-0.0141	0.56
VI	-0.0167	0.68	VI	-0.0043	0.54
Crus I	0.016	0.62	Crus I	-0.05	0.28
Crus II	0.0138	0.43	Crus II	0.0179	0.19
VIIB	0.014	0.43	VIIB	-0.0058	0.95
VIIIA	-0.0098	0.17	VIIIA	0.0052	0.43
VIIIB	-0.0019	0.23	VIIIB	-0.0073	0.001*
IX	-0.0127	0.27	IX	-0.0151	0.10
X	-0.0009	0.13	X	0.0022	0.23
CM	0.04	0.57	CM	0.0121	0.20
Striatum	-0.0042	0.16	**Striatum**	-0.0045	0.60
Globus Pallidus	0.0014	0.23	**Globus Pallidus**	0.0008	0.04*
Thalamus	0.0006	0.38	**Thalamus**	0.0002	0.95
Hippocampus	-0.0027	0.23	**Hippocampus**	-0.0027	0.46
HC	Change mean (mm^3)	p value		Change mean (mm^3)	p value
Left side			Right side		
Cerebellum			**Cerebellum**		
I-II	0.0017	0.24	I-II	-0.0013	0.03*
III	0.003	0.67	III	0.0094	0.99
IV	0.0049	0.31	IV	0.0152	0.65
V	0.009	0.46	V	0.0354	0.28
VI	-0.0191	0.70	VI	-0.0023	0.11
Crus I	0.0299	0.40	Crus I	-0.03	0.13
Crus II	-0.0179	0.24	Crus II	0.0003	0.18
VIIB	-0.019	0.005*	VIIB	-0.0305	0.65
VIIIA	0.0108	0.01*	VIIIA	-0.0089	0.18
VIIIB	-0.0245	0.84	VIIIB	0.0249	0.75
IX	-0.0087	0.43	IX	0.0044	0.28
X	0	0.59	X	0.0116	0.29
CM	0.0336	0.31	CM	0.0221	0.31
Striatum	-0.0004	0.11	**Striatum**	0.0005	0.79
Globus Pallidus	-0.0017	0.48	**Globus Pallidus**	-0.0009	0.51
Thalamus	0.0016	0.67	**Thalamus**	0.001	0.34
Hippocampus	-0.002	0.61	**Hippocampus**	-0.003	0.54

HA: healthy adults; PD: Parkinson's diseases individuals, mm: millimetres

4. Discussion

In the current study, we investigated the effects of an AET regimen using stationary bicycling on cerebral grey matter structures in sedentary healthy adults and patients with PD. As reported previously by our group, this 3-month AET regimen was found to improve cardiovascular capacity, executive functions and motor learning capacities in both groups (Duchesne et al. 2015; Duchesne et al. 2016). Such exercise program was also associated with improvements in several gait and upper limb function parameters in PD patients (Nadeau et al. 2017; Nadeau et al. 2018). Here, we report that the same 3-month AET had an impact on grey matter volumes in both populations. Specifically, after AET there was a significant increase of the right globus pallidus volume in PD patients and a significant increase of the left VIIIA lobule volume in HA. In addition, we observed decreases in grey matter volumes in the cerebellum in both groups following the 3-month AET (left lobules I-II in PD, as well as the right I-II and left VIIB cerebellar lobules in HA). However, these changes did not correlate with any behavioural improvements previously observed in this study.

Baseline comparisons

Comparisons of MRI structural data between healthy elderly and patients with PD have revealed inconsistent results. In fact, despite the fact that several studies previously reported VBM differences between PD patients and healthy controls (Dagher and Nagano-Saito 2007; Pereira et al. 2009; Agosta et al. 2012; Pan et al. 2012; Lee et al. 2013), the present study, like others (Ibarretxe-Bilbao et al. 2012; Lee et al. 2014), did not replicate such pattern of findings. Likewise, we did not observe any difference in cortical thickness

between the two groups at baseline; the latter findings being in accord with previous studies such as Ibarretze-Bilboa et al (2012) and Jubault et al (2011) (Jubault et al. 2011; Ibarretxe-Bilbao et al. 2012) but not with other reports (Tinaz et al. 2010; Pellicano et al. 2011; Pereira et al. 2011; Hanganu et al. 2014; Madhyastha et al. 2015). Yet, the volumetric analyses revealed the existence of a smaller left hippocampal volume seen in PD patients as compared to HA, a difference that was previously reported elsewhere ((Duncan et al. 2013) for a review), and interestingly, this difference was correlated with the disease duration, hence suggesting a larger atrophy of the left hippocampus with longer disease duration.

Several reasons could explain the heterogeneity of the brain structural differences reported in the literature when comparing PD and HA, including our own study. The most obvious explanation would be the within- and between-studies heterogeneity regarding the characteristics of the recruited PD patients, such as differences in stage and disease duration, presence of comorbid factors, age and sex distribution, cognitive and educational levels, as well as the ON/OFF status of the dopaminergic medication at the time of assessment. Another reason could be that, as it was previously suggested, PD patients may display very little GM atrophy despite their functional deterioration, even in more advanced stages of the disease (Agosta et al. 2012). This assertion is in line with a recently conducted systematic literature review, which concluded that there is no specific pattern of grey matter atrophy in PD patients (Minkova et al. 2017).

The effect of AET

The results did not show any VBM nor any cortical thickness changes in either group following AET. Using volumetry, however, we observed some significant changes in both groups following the aerobic training program, despite the short duration of the

intervention in our study. Indeed, our results show that AET produces an increase in volume of the right globus pallidus in PD patients, the latter being paralleled by an increase in motor sequence learning capacity seen at the behavioral level in the same subjects. Although activity in globus pallidus is known to be associated with some behavioral correlates (e.g. speed of execution) over the course of motor learning (Lehéricy et al. 2005), the fact that we did not observe a significant correlation between the volumetric changes and those in motor sequence learning capacity seems to indicate that different mechanisms underpin the AET effects on brain structure versus those on behavior. The interpretation of these results is made more difficult by the lack of studies assessing the AET-related grey matter changes after an AET regimen in PD patients.

In HA, several studies have investigated the effects of exercise on brain structures. Studies that employed longer interventions (24- or 52-week AET regimen) have reported increases in grey matter intensity in the cingulate cortex, the supplementary motor cortex, the frontal and temporal cortices (Colcombe et al. 2006) as well as an in the hippocampus (Erickson et al. 2011). In contrast, a study with an AET duration comparable to ours (12 weeks) did not report any change in grey matter(Matura et al. 2017). Thus, the duration of the exercise program could also explain the fact that we found very few structural changes in our study, as compared with those using an AET of 6 months and over (Colcombe et al. 2006; Erickson et al. 2011).

As reported in one of our previous studies (Duchesne et al. 2015), the 3-month AET regimen led to significant improvements in aerobic capacity in both groups, similar in magnitude as those reported by Colcombe et al 2006, Erickson et al 2011 and Voss et al 2012 (Colcombe et al. 2006; Erickson et al. 2011; Voss et al. 2012) who employed AET of longer duration. Given that we used the same type of exercise and intensity as in these

studies, with the only difference being the duration of the intervention, our results suggest that functional changes (i.e. aerobic capacity, upper limb function, motor learning capacity etc.) are more sensitive to this type of intervention than the neuroanatomical changes. Although it is plausible that these functional changes may be parallel by micro-structural changes that are not detectable using the traditional VBM, volumetric and cortical thickness methods, it is also conceivable that a longer AET regiment duration is needed to observe structural changes using these techniques. Thus, although significantly more challenging from an operational viewpoint, in retrospect, an AET intervention of at least 6-months would have been better suited for detection of structural brain changes.

It was previously suggested that AET-related changes in brain volume could be due to improvements in synaptic interconnections, axonal integrity, and capillary bed growth by processes as neurogenesis, angiogenesis and synaptogenesis (Colcombe et al. 2006). These modifications are likely to be promoted by increases in circulating levels of brain-derived neurotrophic factors (BDNF), as proposed by Erickson et al (2011) based on the results of their clinical trial (Erickson et al. 2011). The above-mentioned evidence was collected in healthy older adults and these volumetric changes were the result of longer training regimen. Yet, despite the fact that – to our knowledge – there is no study investigating the effect of exercising on both brain structure and BDNF in PD, it is conceivable that a similar mechanism could underlie the AET-related changes in brain structure in PD. Indeed, a recent systematic review and a meta-analysis of studies investigating exercise-induced changes in BDNF in people with PD has found an increase in this indicator as a results of physical exercising (Hirsch et al. 2018) and two of the studies included in this meta-analysis have also reported positive correlations between increases in this neurotrophic factor and improvements in motor symptoms (Fontanesi et al. 2015; Marusiak et al. 2015).

From a clinical perspective, our findings indicate that using a high-intensity 3-month AET regiment on a typical stationary bicycle is feasible, and that it can lead to great improvements in several outcomes, such as aerobic capacity, cognitive function, motor sequence learning, gait and upper limb movement fluidity in patients with early stages of PD, and even grey matter changes. Functional changes seem to be more sensitive to AET, indicating that they tend to precede the structural changes. However, this may be due to the nature of our investigation techniques, which, by themselves, may be more sensitive to these types of outcomes (i.e. behavioural and functional). All those behavioural changes can lead to significant improvement in daily functioning, and this aspect should be prioritized when planning a long-term exercise intervention with person with PD.

5. Conclusion

To our knowledge, the current study is the first to investigate and report changes in grey matter following a 3-month AET regimen in PD patients. Even though these changes were limited and they did not correlate significantly with other parameters that were sensitive to AET, we believe that the latte findings provide evidence for exercise-related brain structural plasticity and the potential benefits of using aerobic training as a non-pharmacological intervention in sedentary individuals, both healthy and with PD.

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CHAPITRE 4 : DISCUSSION GÉNÉRALE

Dans les dernières années, les études concernant la maladie de Parkinson ont grandement proliférées. Grâce à cet intérêt grandissant et à la productivité scientifique qui en a découlée, nous comprenons mieux l'évolution de la maladie (Braak et al. 2004), de même que des nouvelles pistes étiologiques (Svensson et al. 2015). De plus, ces récents progrès ont permis aux chercheurs de poursuivre de nouvelles investigations qui permettront un diagnostic précoce de la maladie (ex : à l'aide des techniques d'imagerie in vivo) et une prise en charge rapide et efficace.

Le premier chapitre de cette thèse avait pour but de bien faire ressortir les éléments peu étudiés jusqu'à ce jour en lien avec la motricité du membre inférieur et du membre supérieur, ainsi que les structures cérébrales chez la population parkinsonienne, d'autant plus concernant l'effet de l'exercice sur ces paramètres. Le chapitre 2 pour sa part présentait la méthodologie du projet de recherche utilisé pour tenter de répondre à ces lacunes. Le chapitre 3 présente les résultats obtenus, et ce via 3 articles scientifiques dont 2 ont déjà été publiés. Finalement, le présent chapitre fera tout d'abord un survol des résultats, où ceux-ci se situent par rapport à la littérature existante. Finalement, en considérant les limitations de l'étude, des pistes de recherches futures sont proposées.

4.1 Sommaire des résultats obtenus

L'objectif de ce projet de recherche était de quantifier les effets d'un entrainement de type aérobie sur plusieurs aspects touchés par la maladie de Parkinson, en plus de tenter de mieux comprendre comment ces changements surviennent. Vingt sujets en bonne santé et 19

parkinsoniens ont complété le programme d'entraînement qui consistait à pédaler sur un vélo stationnaire horizontal trois fois par semaine, pour une durée de trois mois. La durée et l'intensité étaient progressives (20 à 40 minutes, 60 à 80% du VO2pic).

Malgré l'utilisation de critères stricts d'inclusion et d'exclusion, le groupe de parkinsoniens se démarquait du groupe sain par un sentiment dépressif et anxieux plus grand. L'âge moyen des parkinsoniens était légèrement plus jeune que celui des contrôles ($p=0.06$). De plus, les résultats de ce programme de recherche ont montré que l'entraînement offert a permis d'améliorer les capacités aérobies, l'inhibition cognitive et la capacité d'apprentissage moteur, autant chez les sujets sains que ceux parkinsoniens (Duchesne et al. 2015).

Dans le cadre de mon projet de thèse, je me suis intéressée aux effets d'un entraînement aérobie sur le patron de marche, la mobilité du membre supérieur et les structures anatomiques cérébrales, ce qui aura résulté en 3 différents articles.

Dans mon premier article (Nadeau et al. 2017), nous avons démontré que ce type d'entraînement physique a été en mesure d'améliorer les paramètres de la marche chez les sujets atteints de la MP, malgré l'absence de différence entre nos deux groupes en début de programme. Plus spécifiquement, ce groupe a démontré une nette amélioration de la vitesse de marche ainsi que de la cadence, sans que la longueur des pas soit changée. De plus, les personnes atteintes de la MP ayant le plus amélioré leur capacité aérobie sont ceux ayant démontré une plus grande augmentation de leur vitesse de marche. Toutefois, les sujets sains n'ont pas démontré de changement significatif au niveau de leurs paramètres de marche.

Vu les améliorations obtenues, nous avons proposé que les changements mesurés sont spécifiques à la modalité d'entraînement utilisée dans la présente étude, c'est-à-dire l'augmentation de la cadence, pour expliquer l'amélioration de la vitesse de marche.

Dans mon second article (Nadeau et al. 2018), nous avons vérifié si l'impact de l'entrainement physique sur les membres inférieurs pouvait également se généraliser aux membres supérieurs. Pour ce faire, nous avons utilisé une tâche simple de tracés de crayon et un algorithme qui découle du modèle kinématique, qui permet de caractériser les commandes motrices agonistes et antagonistes de la force nécessaire à cette tâche de traçage. Tout d'abord, cela nous a permis de constater plusieurs différences entre les sujets sains et parkinsoniens. Ces derniers étaient en effet plus lents à effectuer les tracés, ce qui peut être expliqué par le fait qu'ils ont également une plus grande réponse antagoniste lors du mouvement. Suite au programme d'exercice, les gens atteints de la MP ont montré une réduction des composantes agonistes et antagonistes, en plus d'améliorer la propagation du signal antagoniste, ce qui se traduit par un mouvement plus rapide. Ces changements démontrent les bénéfices globaux d'un exercice de type aérobie. Après les 3 mois d'exercice, le groupe de parkinsoniens reste peut-être plus lent que celui des sujets sains, mais les résultats ont montré que les mouvements effectués étaient plus efficaces. Ces améliorations associées aux paramètres neuromusculaires ont montré une association négative avec les améliorations mesurées pour au test mesurant l'inhibition, suggérant ainsi un effet de compensation chez les sujets atteints de la maladie de Parkinson. Aucun changement n'est survenu après l'exercice pour le groupe de sujets sains. Il est à noter que nous n'avons pas observé de changements pour les symptômes moteurs de la maladie, tel que mesuré par l'UPDRS III.

Toutefois, nous nous attendions à obtenir une association entre une amélioration des fonctions exécutives et celle reliées aux paramètres de la marche. Bien que cette corrélation ait été surtout observée lors de situations complexes de marche (double-tâche, marche avec obstacles), il avait été suggéré que ce genre de relation pouvait aussi être observée lors d'une tâche de marche sans difficulté ajoutée si le patron de marche est déjà affecté par une condition neurologique, comme c'est le cas avec la maladie de Parkinson (Yogev-Seligmann et al. 2008). Cependant, dans notre cohorte, les sujets parkinsoniens n'ont pas montré de différences au niveau des paramètres de la marche avec les sujets sains. Ceci laisse suggérer que leur patron n'était peut-être pas suffisamment altéré pour observer une association avec les changements au niveau de l'inhibition cognitive. D'un autre côté, nous avons mesuré des différences entre les deux groupes pour la mobilité du membre supérieur via la tâche de traçage couplée au modèle kinématique. Contre toutes attentes, une corrélation fut observée entre les changements de ces composantes et ceux observés lors de la tâche d'inhibition cognitive. Toutefois, cette relation était négative, signifiant que les sujets parkinsoniens amélioraient les caractéristiques de leur contrôle moteur, mais au détriment de leurs capacités cognitives. Une récente étude a rapporté que la dextérité manuelle corrélait fortement et positivement avec les performances des fonctions exécutives chez des sujets âgés sains (Kobayashi-Cuya et al. 2018). Il est donc possible que cette association entre la mobilité du membre supérieur et les fonctions exécutives diffère chez les patients atteints d'un trouble neurologique. Peu d'études sont disponibles pour le moment concernant la relation entre ces deux composantes. Il faudra certainement d'autres recherches pour mieux comprendre la corrélation qui existe entre elles, autant avec une population saine qu'avec celle atteinte d'une pathologie neurologique.

Dans mon troisième et dernier article, nous avons examiné si un programme d'exercice aérobie pouvait apporter des changements au niveau des structures cérébrales, plus précisément en termes de matière grise. En comparant nos deux groupes avant le début du programme d'aérobie, nous avons trouvé une différence importante entre les sujets parkinsoniens et les sujets sains au niveau du volume de la partie gauche de l'hippocampe. Les résultats ont révélé une corrélation positive significative suggérant que plus la durée de maladie est élevée, plus cette structure s'en trouve réduite chez les personnes atteintes de la MP. Suite à l'exercice, nous avons mesuré des changements de volume de matière grise non seulement chez les sujets sains mais aussi chez les sujets parkinsoniens suite à l'entraînement. Chez le groupe avec la MP, le changement est survenu au niveau de la partie droite du globus pallidus, alors que chez les contrôles, ce changement touchait un lobe du cervelet, la partie gauche du lobule VIIIA précisément. Cependant, ces deux augmentations de volume n'ont montré aucune corrélation avec les changements comportementaux préalablement observés dans cette étude. Les analyses d'intensité de MG (VBM) et les analyses d'épaisseur corticale pour leur part n'ont montré aucune différence entre nos deux groupes, ni aucun changement suite au programme d'exercice.

La littérature est contradictoire en ce qui concerne les différences structurelles présentes au niveau des métriques de matière grise entre les gens atteins de la MP et les sujets sains. Nous ne sommes pas les seuls à avoir observé aucune différence à l'aide de la VBM et de l'épaisseur entre ces deux groupes (Jubault et al. 2011; Ibarretxe-Bilbao et al. 2012; Lee et al. 2014). Pour la différence que nous avons notée au niveau de l'hippocampe, d'autres études avaient reporté ce même résultat ((Duncan et al. 2013) pour une revue systématique). L'hétérogénéité (par exemple, âge, durée de maladie, stades inclus, etc.) entre les patients et dans les protocoles d'acquisition des images des différentes études, incluant la nôtre, peut expliquer en grande partie les fluctuations observées au niveau des résultats. Cependant, il avait déjà été proposé qu'il n'y

aurait pas vraiment de schéma précis de perte de matière grise chez les parkinsoniens (Minkova et al. 2017), alors que d'autres ont carrément suggérer que les personnes atteintes de la MP pourraient présenter peu de changement de matière grise malgré la progression des symptômes de la maladie (Agosta et al. 2012). Considérant les changements suite à l'exercice, faute d'études avec les parkinsoniens comme groupe contrôle, nous considérons que le peu de résultats obtenus avec les métriques de matière grise donne son lot d'informations sur la chronologie potentielle des évènements au niveau cortical. Plus précisément, il est possible que des changements de matière blanche surviennent en premier lieu, et même avant les changements sur le plan fonctionnel, comme suggéré par des travaux publiés en lien avec la présente étude (Duchesne et al. 2016).

Somme toute, les résultats obtenus via ces analyses renforcent l'idée que l'exercice est un excellent complément au traitement pharmacologique pour traiter les symptômes de la maladie de Parkinson, et ce même dans les premiers stades.

4.2 Contribution au domaine scientifique

Paramètres de la marche

À notre connaissance, seulement deux études ont investigué les effets d'un entraînement de vélo stationnaire sur les paramètres de la marche chez la population parkinsonienne (Arcolin et al. 2016; Chang et al. 2018). Nos résultats concordent avec ceux de ces deux études, suggérant qu'un programme sur vélo stationnaire peut aider à augmenter la vitesse de marche, et ce malgré le manque de spécificité de ce type d'entraînement. Il est difficile cependant de comparer nos résultats avec ceux de Chang et al (2018) et Arcolin et al (2016) puisque plusieurs différences sont présentes entre nos protocoles et nos participants parkinsoniens. Ces disparités incluent la

durée du programme (3 et 8 semaines pour les deux autres, 12 pour nous) et l'importance des symptômes moteurs (UPDRS III à 15,5 pour Chang et al 2018 alors que nous, UPDRS III à 21,8). De plus, dans l'étude d'Arcolin et al 2016, des exercices multimodaux étaient utilisés, il est donc difficile de conclure si les changements sont réellement dus à l'exercice aérobie, à la musculation ou à une interaction entre ces deux composantes. Un point majeur apporté par notre étude est l'utilisation d'un groupe de sujets non atteints de la maladie pour comparer en parallèle avec les sujets parkinsoniens les changements suite à un programme de vélo stationnaire. Les sujets atteints de la MP semblent plus bénéficier de l'entraînement reçu que les adultes sains, tel que démontré par les changements spécifiques à leur groupe pour la fonction motrice des membres inférieurs et supérieurs. D'autres études devraient donc viser à confirmer cette conclusion. Des études futures devraient vérifier si ce type d'exercice pourrait être tout aussi bénéfique pour une clientèle parkinsonienne présentant de plus grandes difficultés à la marche.

Mobilité du membre supérieur

Quelques études avaient déjà préalablement utilisé l'exercice aérobie sur vélo stationnaire pour mesurer l'impact d'un tel exercice sur la mobilité du membre supérieur (Ridgel et al. 2009; Alberts et al. 2011). Les résultats de ces études ont alors montré une amélioration des symptômes moteurs de la maladie en plus d'une amélioration du couplage des forces nécessaires à l'accomplissement d'une tâche de dextérité bi-manuelle. Or, nous sommes les premiers, à notre connaissance, à utiliser un algorithme basé sur le modèle kinématique (Plamondon et al. 1993; Plamondon 1995; Plamondon 1995; Plamondon 1998; Plamondon et al. 2003) pour caractériser les commandes agonistes et antagonistes du contrôle moteur nécessaire à la réalisation d'une simple tâche de traçage de lignes chez des sujets parkinsoniens. L'utilisation de l'algorithme provenant du modèle kinématique semble plus objective et plus sensible pour mesurer l'impact

d'un traitement. Il serait donc intéressant qu'une application soit développée sur tablette pour pouvoir facilement administrer la tâche de traçage que nous avons utilisée, en plus de permettre une analyse rapide des performances et une interprétation plus appropriée de la performance. Un tel outil serait certainement moins encombrant et moins coûteux que ce qui est majoritairement utilisé en recherche actuellement pour obtenir un descriptif des forces du membre supérieur nécessaires lors d'une tâche de mobilité.

Changements cérébraux

Nous sommes les premiers à mesurer les changements de matière grise chez les sujets parkinsoniens suite à un programme d'exercice. Même chez une population saine et âgée, de telles études sont rares (Colcombe et al. 2006; Erickson et al. 2011; Voss et al. 2012; Matura et al. 2017). L'étude de Matura est celle qui a utilisé une durée d'entraînement le plus similaire à la nôtre (12 semaines versus 6 et 12 mois pour les autres) sans obtenir, pour leur part, de changement au niveau de la matière grise. Cependant, plusieurs différences sont présentes dans leur protocole. Outre le fait que leur population ait été plus âgée que la nôtre ou celle des autres études, l'intensité de leur entraînement était inférieure d'environ 10% à l'intensité utilisée par Colcombe, Erickson et Voss, et inférieure de 15% à celle que nous avons utilisée. La durée du programme d'entraînement semble donc être importante pour observer des changements au niveau de la matière grise, mais l'âge des participants et l'intensité utilisée peuvent également avoir un impact dans les résultats attendus. D'autres études seront nécessaires afin d'isoler l'effet de ces paramètres. En bref, les quelques résultats que nous avons obtenus s'ajoutent donc à ce petit nombre de recherche concernant la population saine et âgée. En ce qui a attrait aux sujets parkinsoniens, nous sommes à notre connaissance les premiers à mesurer les changements cérébraux suite à un programme d'exercice. Nous croyons que nous ouvrons ainsi la porte à un

plus grand nombre d'investigations sur ce sujet. Nous avons pu observer une augmentation du volume du globus pallidus chez les personnes atteintes de la MP suite au programme d'exercice, une structure clé dans la pathologie. Cette augmentation n'a néanmoins pas montré de corrélation avec les améliorations motrices ou cognitives démontrées. D'autres études seront nécessaires pour mieux comprendre l'impact de l'exercice sur la structure et le fonctionnement des noyaux gris centraux suite à un entraînement aérobie.

Mécanismes

Plusieurs mécanismes ont été proposés pour expliquer les changements moteurs et non-moteurs similaires à ceux observés dans nos études (Duchesne et al. 2015; Duchesne et al. 2016; Nadeau et al. 2017; Nadeau et al. 2018) chez les sujets parkinsoniens suite au programme d'entraînement. La première classe de mécanismes est basée sur l'idée que l'entraînement aérobie a un impact direct sur le système nerveux central. Par exemple, grâce à l'augmentation de la fréquence cardiaque et de la pression artérielle suite à l'exercice, la prise de la médication anti-parkinsonienne pourrait être optimisée via le passage plus facile à travers la barrière hémato-encéphalique par les médicaments (Speelman et al. 2011). D'autres impacts directs sur le système nerveux central peuvent inclure une amélioration de la neurotransmission dopaminergique (Petzinger et al. 2010) ou de l'excitabilité corticomotrice (Fisher et al. 2008). L'autre classe considère les mécanismes qui agissent indirectement. Dans cette catégorie, nous retrouvons l'augmentation de la vascularisation corticale, de la plasticité synaptique et de la neurogénèse, des changements attribuables aux facteurs neurotrophiques (Speelman et al. 2011). Ces altérations pourraient elles-mêmes êtres les précurseurs de changements structuraux et fonctionnels dans le cerveau. Vu les résultats peu nombreux que nous avons obtenus avec les métriques de matière grise cérébrale et l'absence d'association avec les améliorations

comportementales, et considérant qu'au niveau fonctionnel, plusieurs changements avaient été notés (Duchesne et al. 2016), il semble plausible que les améliorations comportementales (i.e. au niveau de l'apprentissage moteur, des fonctions exécutives, des paramètres de la mobilité des membres inférieurs et supérieurs) soient plutôt le fruit d'une amélioration de la neurotransmission dopaminergique, et peut-être dans une deuxième mesure, de changements au niveau de la matière blanche.

Certains pourraient se surprendre qu'une partie des améliorations n'aient affecté que les sujets parkinsoniens (i.e. les paramètres de mobilité des membres supérieurs et inférieurs) alors que d'autres ont touché les deux groupes de participants (i.e. l'inhibition cognitive, l'apprentissage moteur). Il a été proposé que certaines régions du cerveau pourraient être plus sensibles que d'autres aux micro-changements locaux stimulés par l'effet d'un exercice aérobie, tels que le cervelet, le cortex moteur et le lobe frontal ((Thomas et al. 2012), pour une revue de la littérature), ce qui pourrait expliquer les améliorations communes à notre groupe sain et notre groupe de parkinsoniens. Il est possible que certains effets de l'exercice soient plus spécifiques encore, tel que l'augmentation de la neurotransmission dopaminergique. Considérant que les sujets sains n'ont pas de problématique sur ce point, cette hypothèse pourrait peut-être expliquer les changements au niveau des paramètres de la marche et de la mobilité du membre supérieur, améliorations propres aux sujets atteints de la maladie de Parkinson dans l'étude actuelle. Cependant, de plus amples études, avec des outils de mesure ciblant les changements de matière blanche (diffusion cérébrale) et la neurotransmission dopaminergique (tomographie par émission de positrons), seront nécessaires afin de confirmer le tout.

Perspectives cliniques

Le présent projet de recherche a permis de conclure qu'un entraînement aérobie sur vélo stationnaire peut apporter des améliorations considérables pour une personne atteinte de la MP, même après une période aussi courte que trois mois d'exercice (Duchesne et al. 2015; Duchesne et al. 2016; Nadeau et al. 2017; Nadeau et al. 2018). Les bienfaits incluent des changements importants d'ordre moteur, malgré le manque de spécificité du type d'exercice, sur le plan du patron de marche et aussi sur la mobilité du membre supérieur. Ces améliorations sont importantes puisqu'elles peuvent se refléter dans la vie de tous les jours, avec un impact majeur sur l'autonomie et la qualité de vie des sujets parkinsoniens. D'autres changements ont touché l'aspect non-moteur des participants, tel que leur capacité d'apprendre de nouvelles séquences motrices et leurs fonctions exécutives, deux habiletés également utiles dans le quotidien.

Sur un plan clinique, en comparaison avec les autres recherches utilisant le vélo stationnaire comme modalité d'exercice, le protocole d'entraînement que nous proposions est de loin le plus proche des recommandations de l'American College of Sports Medicine (ACSM) en ce qui concerne la prescription d'exercice aérobie pour cette population (ACSM 2006). Ces derniers recommandent de viser un entraînement aérobie 3 fois par semaine, jusqu'à une durée maximale de 60 minutes, de 60 à 80% de la fréquence cardiaque maximale, et de viser un minimum de 3 mois d'exercice. Chang et al 2018 ont proposé une intensité faible pendant seulement 8 semaines, à raison de 2 séances par semaine (Chang et al. 2018) alors que Arcolin et al 2016 ont offert un programme intensif (5 jours par semaine, pendant 3 semaines) et de grand volume (2 heures d'exercice par jour, dont 1 heure d'exercices de renforcement musculaire et des étirements) (Arcolin et al. 2016). Quelques études sur vélo stationnaire (Ridgel et al. 2009; Ridgel et al. 2012) avaient utilisé un exercice forcé pour obtenir leurs résultats, ce qui est peu accessible en dehors d'un contexte de recherche. Considérant le fait que les résultats obtenus dans ces études

étaient similaires à ceux que nous avons pu observer mesurer, notre protocole représente encore une fois un plus grand réalisme et une meilleure portée clinique pour les spécialistes de l'exercice qui travaillent avec cette population dans la vie de tous les jours.

4.3 Futures avenues de recherche

Une des principales limitations de cette étude était l'absence d'un groupe de comparaison qui incluait des individus atteints de la maladie de Parkinson et qui auraient été soit exposés à un exercice de type aérobie utilisant une autre modalité ou une autre intensité, soit en ne participant à aucun exercice. Un tel groupe (précisément, un groupe de parkinsoniens avec exercices d'étirement) était prévu dans le protocole original de ce projet de recherche de grande envergure. Cependant, la difficulté à recruter des participants atteints de la maladie a fait en sorte que nous nous sommes principalement concentrés sur seulement deux groupes d'intervention (sujets sains et gens parkinsoniens). Or, avec les études qui montrent les bénéfices qu'il est possible de retirer avec de nouvelles et différentes modalités d'entrainement (boxe (Combs et al. 2011; Combs et al. 2013), zumba (Delextrat et al. 2016), yoga (Hall et al. 2011)), il y a maintenant plus d'intérêt à comparer ces modalités entre elles et peut-être de pouvoir faire émerger certains types d'entraînements plus bénéfiques que d'autres selon les symptômes rencontrés.

Les résultats des analyses de neuroimagerie n'ont malheureusement pas rencontrés nos attentes. L'ajout d'un groupe avec une durée d'exercice atteignant au moins 6 mois d'exercice aurait certainement pu permettre de mieux comparer nos résultats avec les quelques études disponibles. Plusieurs autres métriques provenant de l'imagerie in vivo par résonance magnétique et analyses de données pourraient permettre de mieux comprendre les impacts d'un programme d'exercice sur le cerveau. Pour ne nommer que quelques exemples, analyser les fibres de matière blanche,

ou même utiliser une imagerie telle que la Tomographie par Émission de Positron (TEP scan) afin de pouvoir observer les changements au niveau des neurotransmetteurs, et de la transmission dopaminergique en particulier.

4.4 Conclusion

Dans les dernières années, le nombre d'études qui s'est intéressé aux bienfaits de l'exercice n'a fait que croître, particulièrement chez les populations présentant des troubles neurologiques telle que la maladie de Parkinson. Nos résultats, jumelés avec ceux présents jusqu'à maintenant dans la littérature concernant la maladie de Parkinson, permettent de suggérer que l'exercice, particulièrement de type aérobie, pourrait offrir des améliorations comparables et même meilleures que les traitements pharmacologiques et ce, avec moins d'effets secondaires négatifs. En effet, l'exercice pourrait permettre d'optimiser la médication, de traiter les symptômes moteurs et non-moteurs de la maladie, en plus de potentiellement ralentir la progression de la maladie.

Ce projet de recherche a permis de démontrer qu'un entraînement de vélo stationnaire avec une haute intensité est sécuritaire et peut bénéficier à ceux qui sont dans les premiers stades de la maladie de Parkinson. Qui plus est, le protocole que nous avons mis en place reflète une prescription réaliste pour un contexte hors recherche, et suit les recommandations que des organisations reconnues ont pu faire en lien avec cette problématique de santé. En prenant en charge tôt les personnes qui reçoivent un diagnostique de la MP, il est certain qu'il est possible de les aider à conserver une autonomie et une qualité de vie, plus longtemps.

Ce projet de thèse répond donc à certaines questions peu étudiées jusqu'à ce jour. Il reste beaucoup encore à comprendre sur la progression de la maladie, son étiologie, son diagnostic précoce, comment optimiser les traitements, mais je crois qu'il est possible de conclure que les résultats présentés dans le cadre de ce projet de thèse ont apporté leur lot de contributions au domaine scientifique.

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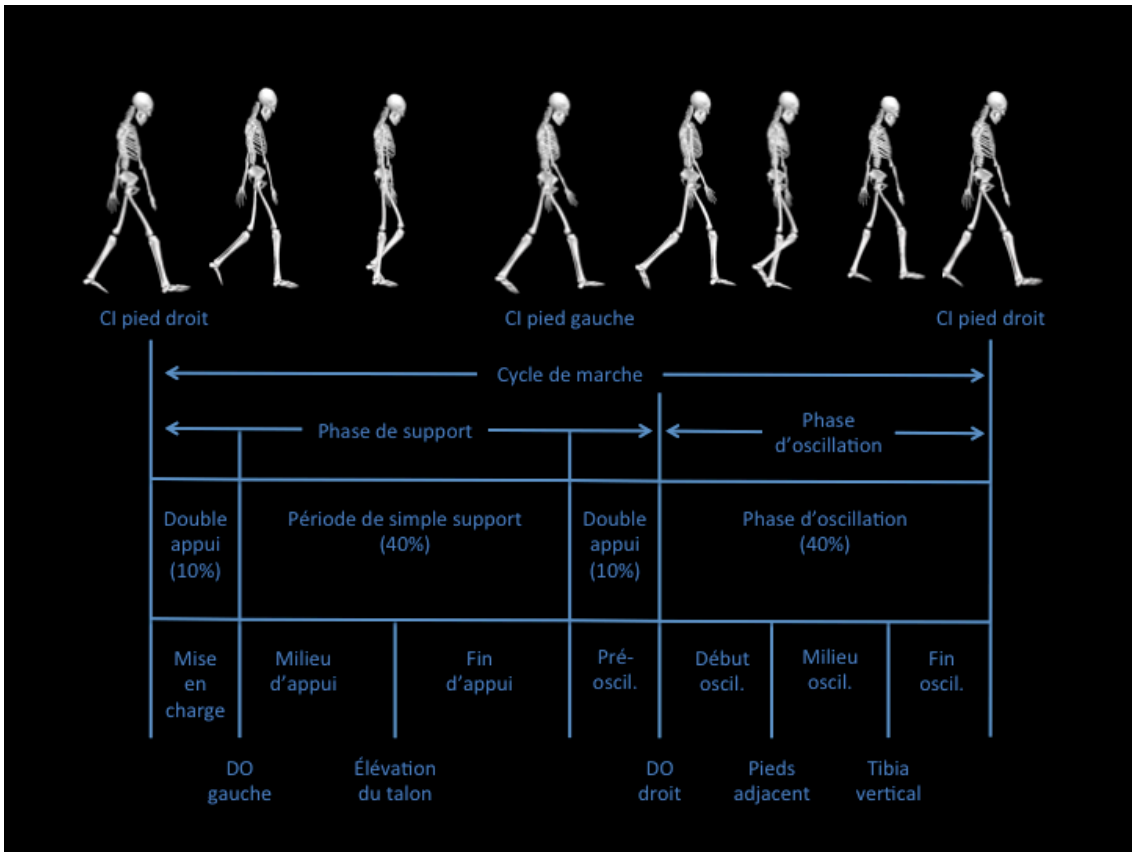
ANNEXE 1 : DESCRIPTION DES DIFFÉRENTS PARAMÈTRES DE LA MARCHE

Appui en double-support	Correspond au moment où les deux pieds sont en contact simultanément avec le sol
Appui en simple-support	Correspond au moment où un seul pied est en contact avec le sol alors que le second pied est en déplacement entre un point A et un point B
Pas	Un pas correspond à la distance, par exemple de talon à talon, entre les deux pieds (Figure 5)
Foulée	La foulée correspond à la distance, par exemple de talon à talon, entre deux contacts successifs avec le sol du même pied (Figure 5)
Durée de balancement	Correspond à la durée de l'appui en simple-support
Vitesse de marche	La vitesse de marche correspond à la durée nécessaire pour parcourir une certaine distance
Cadence	La cadence (nombre de pas/minute) est la résultante de la vitesse (mètres/seconde) et de la longueur du pas (mètres) : Cadence = vitesse x longueur du pas
Cycle de marche	Intervalle de temps entre deux répétitions successives d'un des évènements de la marche

ANNEXE 2 : LES DIFFÉRENTES ÉTAPES DE LA MARCHE



ANNEXE 3 : EXPLICATION DES MÉTHODES STATISTIQUES D'ANALYSE DE MATIÈRE BLANCHE

La *Tract-Based Spatial Statistics* (TBSS) est une méthode statistique couramment utilisée pour l'analyse des caractéristiques de la matière blanche (Smith et al. 2006). Le principe est de créer un squelette à partir des valeurs de FA (la valeur maximale de FA dans un voxel), sensé représenter le centre des faisceaux communs à tous les participants. Par la suite, les valeurs individuelles sont projetées sur ce squelette pour en faire ressortir les écarts par rapport à la moyenne des sujets.

La tractographie est une méthode qui permet d'avoir un portrait plus global du 'câblage' de la matière blanche. En effet, la tractographie permet de reconstruire les faisceaux de matière blanche à partir des informations locales données par les tenseurs de diffusion. Son approche est très différente de la TBSS. Un masque sera utilisé afin de classer la matière cérébrale en liquide céphalo-rachidien, en matière grise ou en matière blanche. Par la suite, c'est un peu comme relier les tenseurs les uns aux autres tout en suivant la direction principale de chacun afin d'obtenir les fibres. Il est possible de faire la tractographie au travers du cerveau en entier ou de suivre une fibre à partir d'une région ou d'une structure d'intérêt. Il est possible alors d'obtenir les valeurs de FA à différents points précis le long du faisceau de matière blanche qui nous intéresse, valeurs qu'il est possible de comparer entre 2 groupes par la suite.

ANNEXE 4 : MÉDICAMENTS PRESCRITS ET LEURS CARACTÉRISTIQUES

Classe	Mode de fonctionnement	Indication	Effets secondaires
Lévodopa-Inhibiteurs de la dopamine décarboxylase	La dopamine décarboxylase convertie normalement la L-Dopa en dopamine, mais avant la barrière hémato-encéphalique (et elle ne peut plus traverser). L'inhibiteur de la dopamine décarboxylase fait donc que plus de L-Dopa traverse la barrière pour être transformé.	Symptômes moteurs	Nausées, hypotension orthostatique, dyskinésies, hallucinations
Agonistes dopami-nergiques	Stimulent les récepteurs dopaminergiques	Symptômes moteurs	Nausées, hypotension orthostatique, œdème, hallucinations, troubles du contrôle des impulsions, somnolence diurne
Anticholi-nergiques	Rééquilibre le ratio dopamine-acétylcholine en bloquant les récepteurs cholinergiques	Tremblements	Hallucinations, troubles cognitifs, nausées, bouche sèche, vision brouillée, rétention urinaire, constipation
Amantadine	Bloquent les récepteurs NMDA glutamergiques	Troubles de la marche, dyskinésies	Hallucinations, confusion, vision brouillée, œdème, nausées, bouche sèche, constipation
Inhibiteurs de la mono-aminine-oxydase B	MAOBIs est responsable de la dégradation de la dopamine, donc en l'inhibant, augmente la disponibilité de la dopamine	Début de maladie, symptômes modérés, fluctuations motrices	Effet stimulant, étourdissements, maux de tête, confusion, exacerbation des effets secondaires de la Lévodopa, douleurs articulaires, troubles digestifs, symptômes qui s'apparentent à ceux de la grippe, constipation.
Inhibiteurs de la catéchol-O-méthyltransfér ase	La COMTIs est responsable de la dégradation de la dopamine, donc en l'inhibant, augmente la disponibilité de la dopamine	Fluctuations motrices	Exacerbation des effets secondaires de la Lévodopa, coloration de l'urine, dommage au foie

ANNEXE 5 : SCHÉMA DES ACQUISITIONS D'IMAGERIE PAR RÉSONANCE MAGNÉTIQUE