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Aspectos cognitivos na Doença de Parkinson e sua relação com o polimorfismo val158met da catecol-O-metiltransferase

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Dissertação apresentada como requisito para a obtenção do grau e Mestre pelo Programa de Pós-Graduação em Biologia Celular e Molecular da Faculdade de Biociências da Pontifícia Universidade Católica do Rio Grande do Sul.

Orientadora: Dra. Elke Bromberg

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Aos meus pais, Rosa e Edson, por
todo o apoio e carinho dedicados.

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RESUMO

Embora a Doença de Parkinson (DP) seja predominantemente um distúrbio do movimento, a presença de alterações cognitivas relacionadas à função frontal tem sido observada mesmo nos estágios iniciais da doença. Estas alterações incluem déficits atencionais, executivos e de memória. Um estudo usando um paradigma experimental desenvolvido para investigar os efeitos de diferentes instruções codificadoras na memória contextual mostrou que, ao contrário dos idosos, pacientes com DP não são capazes de reverter seus déficits de memória e não tiram nenhuma vantagem das instruções codificadoras. Entretanto, ainda não está claro se estes pacientes têm um déficit de memória ou se as disfunções executivas seriam as responsáveis pelos resultados observados. Déficits atencionais e executivos observados em pacientes com DP têm implicações importantes nas atividades diárias, principalmente quando o paciente desempenha atividades concomitantes cognitivas e motoras que requerem atenção. A catecol- O-metiltransferase (COMT) é uma enzima que degrada a dopamina cortical. Alguns estudos têm examinado a relação entre o polimorfismo val158met da COMT e função executiva em pacientes com DP e têm observado que a atividade reduzida da enzima, relacionada ao polimorfismo, que implica em maiores níveis de dopamina no córtex pré-frontal, está associada a uma pior performance. Entretanto, um estudo recente não demonstrou um efeito direto do genótipo da COMT no desempenho executivo. O presente estudo teve por objetivo caracterizar diferentes parâmetros cognitivos de pacientes com DP e verificar sua relação com o polimorfismo da COMT. Neste estudo participaram 18 pacientes em estágios iniciais da DP e 18 adultos saudáveis, pareados por idade, gênero e nível educacional. Os pacientes foram selecionados de um banco de pacientes genotipados para o polimorfismo da COMT. Todos os participantes completaram o Teste de Classificação de Cartas de Wisconsin, o Teste de Stroop e o paradigma para avaliação da realização de tarefas simultâneas. Adicionalmente, os pacientes com DP completaram o paradigma de memória contextual. Não foi observado efeito do polimorfismo val158met da COMT sobre a função frontal (função executiva e memória contextual) dos pacientes com DP. Os pacientes apresentaram um declínio cognitivo na realização das atividades simultâneas, ao contrário dos

controles. O custo cognitivo associado à realização da tarefa aritmética juntamente à caminhada foi significativamente maior para os pacientes com DP, em relação aos controles. Em conclusão, as dificuldades em realizar uma atividade cognitiva e motora simultaneamente podem ser influenciadas pela carga executiva/atencional da atividade.

Palavras-chave: Doença de Parkinson. déficits cognitivos. catecol-O-metiltransferase.

ABSTRACT

Although Parkinson's Disease (PD) is predominantly a movement disorder, the presence of cognitive problems related to frontal function, even in the earliest stages has been observed. These problems include attentional, executive and memory deficits. A study using an experimental paradigm developed to investigate the effects of different encoding instructions on contextual memory showed that, unlike healthy controls, PD patients could not reverse their contextual memory deficits and take any advantage of encoding instructions. However, it is unclear whether they have a memory deficit or executive dysfunction would be accountable for results. Attentional and executive deficits observed in PD patients have important implications for daily activities, mainly when patient perform concomitant cognitive and motor activities that are attention demanding. Catechol- O-methyltransferase (COMT) is an enzyme that degrades cortical dopamine. Some studies have examined the relationship between the COMT val158met polymorphism and executive function in PD patients and have found low enzyme activity, associated to met/met polymorphism- implying higher prefrontal dopamine levels- is related to worse performance. However, a recent study did not demonstrate a direct effect of COMT genotype on the executive performance. The present study aimed to characterize different cognitive parameters of patients with PD and to assess their relationship with the COMT polymorphism. In this study participated 18 patients with early disease stage PD and 18 healthy adults matched for age, gender and education. Patients were selected from a data bank of patients genotyped for COMT polymorphism. All participants completed the Wisconsin Card Sorting Test (WCST), the Stroop Color and Word Test, and dual tasking paradigm. In addition, patients completed a contextual memory paradigm. No effect of COMT val158met genotype on frontal function in patients with PD (executive function and contextual memory) was observed. A decrease in cognitive task performance under dual-tasking was observed in PD patients, by contrast to healthy controls. Relative dual-task cognitive cost was significantly greater for PD patients compared to controls in the arithmetic-walking condition. In conclusion, difficulties in performing a cognitive task while walking can be influenced by the executive/attentional load of the task.

Keywords: Parkinson's Disease. cognitive deficits. catechol-O-methyltransferase.

SUMÁRIO

1 CAPÍTULO 1

1.1INTRODUÇÃO

A Doença de Parkinson (DP) é a segunda doença neurodegenerativa mais comum no mundo (LAU; BRETELER, 2006) e espera-se que gere um aumento na sobrecarga econômica e social à medida que o padrão demográfico mundial vem se modificando em razão do aumento substancial na população de idosos. Apesar do desenvolvimento tecnológico dos últimos anos, ainda são necessárias investigações básicas a respeito da prevenção, tratamento e manejo de doenças neurodegenerativas, entre as quais está a Doença de Parkinson.

A DP é uma doença neurodegenerativa caracterizada por início insidioso e progressão lenta dos sintomas, os quais são decorrentes da degeneração dos neurônios dopaminérgicos da zona compacta da substância negra (KANDEL; SQUIRE, 2003). Os sintomas clássicos da DP são motores e incluem o tremor de repouso, a bradicinesia, a rigidez e a instabilidade postural (GIBB; LEES, 1988). Entretanto, faz-se necessário considerar também que uma parcela dos pacientes com DP pode apresentar demência com a progressão da doença (DUBOIS; PILLON, 1997; AARSLAND et al., 2003). Mesmo em pacientes com sintomas motores leves, déficits cognitivos têm sido relatados (MUSLIMOVIC et al., 2005), principalmente em testes neuropsicológicos que exigem habilidades relacionadas ao funcionamento do lobo frontal, como funções executivas, atencionais e de memória (OWEN, 2004). Torna-se importante estudar os déficits cognitivos associados à função frontal na DP, uma vez que estes podem gerar um impacto negativo na qualidade de vida, tendo implicações importantes na funcionalidade dos pacientes, no convívio social, aumentando dependência por cuidadores e gerando maior demanda por recursos financeiros.

A partir dos achados de estudos com pacientes com lesões cerebrais e de neuroimagem, um tipo de memória particularmente dependente das funções dos lobos frontais e extremamente importante para uma série de atividades diárias é a memória contextual, a qual se refere aos atributos temporais, espaciais, afetivos, sociais da informação e à fonte da qual ela foi adquirida (JOHNSON; HASHTROUDI; LINDSAY, 1993). Estudos recentes indicam que, além de apresentarem déficit neste tipo de memória, pacientes com DP não são capazes de melhorar seu desempenho quando recebem uma estratégia de codificação para realizar uma tarefa de memória contextual incidental (SANTOS et al,. 2010). Entretanto, ainda não está claro se

estes pacientes têm um déficit de memória específico ou se disfunções em domínios cognitivos gerais, como a função executiva, seriam responsáveis pelos resultados observados. Portanto, a investigação da relação entre função executiva e memória contextual é fundamental para a caracterização dos déficits cognitivos na DP e, consequentemente, para o estabelecimento de estratégias adequadas de reabilitação cognitiva nesta população.

Uma vez que alterações da função frontal, como disfunções executivas e de atenção são bastante comuns em pacientes com DP, é importante também avaliar seu impacto em diferentes atividades diárias dos mesmos. Um conjunto crescente de evidências tem sugerido que o controle da postura e da marcha dependem da função cognitiva (MARQUIS et al., 2002; VERGHESE et al., 2002b; HAUSDORFF et al., 2005) e que mesmo em jovens saudáveis a marcha não é inteiramente automática, dependendo de forma importante de recursos atencionais (WOOLLACOTT; SHUMWAY-COOK, 2002). Como um mecanismo de compensação frente aos déficits dos gânglios da base, responsáveis pelos componentes automáticos da marcha, os pacientes com DP recrutam recursos atencionais na tentativa de gerar uma marcha mais próxima do normal (MORRIS et al., 1996; RUBENSTEIN et al., 2002). Entretanto, ao realizar atividades simultâneas à marcha, como caminhar e participar de uma conversa, as alterações da função frontal (déficits atencionais e executivos) tornam-se ainda mais evidentes (YOGEV et al., 2005). Apesar de muitos estudos (MORRIS et al., 1996; HAUSDORFF et al., 2003; YOGEV et al., 2005) analisarem os efeitos da realização de atividades simultâneas sobre o desempenho na marcha, pouco tem sido investigado a respeito da interferência das atividades simultâneas no desempenho cognitivo dos pacientes com DP.

Um dos mecanismos fisiopatológicos/neuroquímicos que podem estar relacionados com a disfunção frontal na DP refere-se à regulação dos níveis de dopamina no córtex pré-frontal (CPF), que é realizada principalmente pela ação enzimática da catecol-O-metiltransferase (COMT). A COMT apresenta o polimorfismo val158met que leva a alteração da atividade enzimática (CHEN et al., 2004), de forma que o genótipo met/met (COMT de baixa atividade) vem sendo associado a níveis mais elevados de dopamina no CPF (FOLTYNIE et al., 2004). Estudos investigando a interferência deste polimorfismo na DP em tarefas atencionais e executivas são contraditórios, já que alguns têm observado relação

entre desempenho cognitivo e genótipo da COMT (FOLTYNIE et al., 2004; WILLIAMS-GRAY et al., 2007; 2008), e outros não tem encontrado nenhuma associação (HOOGLAND et al, 2010).

Com base no exposto acima sobre as implicações da função frontal sobre a qualidade de vida, pretendemos caracterizar o desempenho dos pacientes com DP em medidas dependentes do funcionamento do CPF incluindo desde testes amplamente utilizados, como o Teste de Stroop (Strauss, Sherman and Spreen, 2006) e o Teste de Classificação de Cartas de Wisconsin (Kongs, Thompsom, Iverson, Heaton, 2000), até paradigmas experimentais que avaliam a realização simultânea de tarefas cognitivo-motoras. Adicionalmente, considerando resultados de estudos prévios, que têm demonstrado associações entre DP, défcits cognitivos e genótipo da COMT, nos propomos a investigar o efeito do polimorfismo val158met da COMT sobre o desempenho cognitivo dos pacientes DP na realização de tarefas dependentes do CPF, como uma tarefa de memória contextual experimental.

Esta dissertação está organizada na forma de capítulos. No primeiro deles, “Introdução” serão apresentados resultados de estudos prévios sobre aspectos cognitivos na DP e sua associação com o polimorfismo val158met da COMT. No capítulo 2 será apresentado o artigo “A preliminary investigation of the effect of COMT val158met genotype on contextual recognition memory in Parkinson’s Disease”. Este artigo científico encontra-se na forma de uma comunicação breve que descreve os resultados de uma investigação preliminar a respeito do efeito do polimorfismo val158met da COMT sobre o desempenho dos pacientes com DP em tarefas dependentes da função frontal, como Teste de Stroop, de Classificação de Cartas de Wisconsin e uma tarefa de memória contextual. No capítulo 3 será apresentado o artigo “Characterization of cognitive and motor performance during dual-tasking in healthy older adults and patients with Parkinson's Disease” no qual investigamos o desempenho cognitivo e motor de pacientes com DP e idosos controles em um paradigma experimental de tarefas duplas (realização de atividades simultâneas). No capítulo final desta dissertação serão apresentadas considerações finais sobre os trabalhos realizados.

1.1.1 Doença de Parkinson

Originalmente descrita em 1817 pelo médico inglês James Parkinson, a DP é comumente presente na clínica neurológica, apresentando distribuição universal e atingindo todos os grupos étnicos e classes socioeconômicas, sendo que sua incidência e prevalência aumentam com a idade (KANDEL; SQUIRE, 2003). Cerca de 2% da população com mais de 65 anos é acometida por esta patologia, sendo esta a segunda doença neurodegenerativa mais freqüente, ficando atrás somente da Doença de Alzheimer (RIJK et al., 1997). Apesar da predominância em indivíduos idosos, esta doença se manifesta também em pacientes mais jovens, principalmente nas formas com herança familiar, contribuindo com 15% do total de casos (CARR et al., 2003).

A etiologia desta doença é ainda pouco conhecida, mas admite-se que vários fatores independentes contribuam para o seu surgimento. Uma interação entre fatores genéticos e ambientais parece ser a explicação mais plausível para o desenvolvimento da DP. Desta forma, os indivíduos herdariam traços determinantes de maior susceptibilidade neuronal a insultos tanto exógenos (toxinas ambientais) como endógenos (estresse oxidativo celular) (LAU; BRETELER, 2006).

Normalmente descreve-se esta patologia como sendo decorrente da morte progressiva de neurônios produtores de dopamina, os neurônios dopaminérgicos, localizados predominantemente na substância negra. A dopamina é um neurotransmissor cuja síntese ocorre nos terminais axonais dos neurônios dopaminérgicos, podendo ter suas ações mediadas por 5 tipos de receptores metabotrópicos: D1, D2, D3, D4, D5. Sua ação na fenda sináptica cessa quando é recaptada por seu transportador (DAT). A dopamina recaptada pela terminação nervosa pode ser internalizada em vesículas sinápticas ou degradada pela ação de enzimas como a monoaminoxidase (MAO) ou a COMT (KANDEL et al., 2000).

Na clínica médica o fármaco mais utilizado para o controle dos sintomas motores da DP é a Levodopa, um precursor da dopamina. Apesar de a meia vida da levodopa ser de apenas 60 a 90 minutos, normalmente, no início do uso da medicação, sua ação estende-se por um maior número de horas na grande maioria dos pacientes, sendo que, em pacientes com formas leves de DP, a ação da Levodopa pode durar até oito ou doze horas (KOLLER, 2000; ROWE et al., 2008; CARDOSO, 1999). No entanto, com o passar do tempo, a duração do efeito da

medicação começa a reduzir-se, e o paciente começa a perceber e distinguir claramente os momentos em que seu desempenho funcional é satisfatório, devido ao efeito da medicação (“período ligado”; ou período *on*) e os momentos em que o desempenho funcional é inferior, devido à interrupção do efeito da Levodopa (“período desligado”; ou período *off*). Estas variações no desempenho funcional são chamadas de flutuações e são consideradas complicações do uso da Levodopa (KOLLER, 2000; CARDOSO, 1999).

1.1.2 Doença de Parkinson e disfunções cognitivas

Estudos realizados em pacientes com DP sugerem que os sintomas clínicos característicos de bradicinesia, rigidez e tremor de repouso estão freqüentemente acompanhados por deficiências na função cognitiva. A prevalência da demência na DP é de 31% em estudos transversais (AARSSLAND et al., 2003) e alterações cognitivas menos graves são comuns mesmo nas fases iniciais da patologia e preditoras importantes da qualidade de vida (KARLSEN et al., 1998; SCHRAG et al., 2000). O padrão de prejuízos cognitivos observados em pacientes nas fases iniciais da DP consiste em déficits na função frontal, assim como ocorre em pacientes com lesões nesta estrutura cerebral (OWEN, 2004). Estes déficits podem ser em relação à função executiva (revisão em OWEN 2004), atenção (METZLER-BADDELEY, 2007) e memória (VINGERHOETS et al., 2005; SANTOS et al., 2010).

Bronnick e colaboradores (2006) observaram que os déficits de atenção de pacientes com DP afetam de forma significativa suas atividades de vida diária. A atenção mostrou-se uma preditora importante do desempenho em atividades motoras cotidianas, como tomar banho, comer e se vestir, e habilidades de interação social, como participar de uma conversa, ver televisão, ler e cumprir compromissos. De acordo com estes autores, a disfunção da atenção seria um dos principais aspectos cognitivos envolvidos nos déficits funcionais e na qualidade de vida de pacientes com DP.

A atenção pode ser classificada em diferentes componentes, incluindo a atenção seletiva (habilidade de manter a atenção focada em uma tarefa ao longo de determinado período de tempo), a atenção dividida (capacidade de realizar mais de uma tarefa por vez) e atenção alternada (habilidade de mudar rapidamente o foco de atenção de uma tarefa para outra) (LEZAK, 1995; ROGERS, 2006). No presente

estudo avaliaremos o grau de interferência da atenção dividida (realização de atividades simultâneas) sobre a capacidade cognitiva requerida para realizar atividades diárias diversas.

Juntamente às funções cognitivas que se encontram em declínio na DP está a função executiva. O funcionamento executivo é requerido para elaboração de comportamentos adaptativos em resposta a situações ambientais desafiadoras, e inclui processamento de informações relevantes, geração de novos conceitos e habilidades de planejamento e resolução de problemas (DUBOIS; PILLON, 1997). Atribui-se à função executiva os processos cognitivos de integração e controle destinados à execução de um comportamento dirigido a um propósito, necessitando de subcomponentes como atenção, programação e planejamento de seqüências, inibição de informações e processos concorrentes e monitoramento. A estas funções, tem sido relacionado o lobo frontal, mais especificamente, o CPF (KRISTENSEN, 2006). Com base no acima exposto, o presente estudo visou caracterizar os pacientes com DP quanto à função frontal de acordo com seu desempenho em tarefas executivas e investigar a relação deste desempenho com o polimorfismo val158met da COMT.

Dentre as memórias que se encontram prejudicadas na DP encontra-se a memória contextual (SANTOS et al., 2010), que é componente da memória episódica e está relacionada a aspectos contextuais temporais, espaciais, afetivos e sociais de um evento, e à fonte da qual uma informação foi adquirida (de uma pessoa, de um livro ou da televisão). Ela envolve a lembrança de onde, quando e como algo aconteceu (JOHNSON; HASHTROUDI; LINDSAY, 1993) e normalmente é adquirida de forma incidental, através da vinculação automática de um objeto ao seu contexto (HASHER; ZACKS, 1979). A memória contextual tem sido associada ao funcionamento do CPF tanto em condições normais (GLISKY, 1995; MITCHELL, 2009), como patológicas (JOHNSON, 1997; SWICK, 2006), e, além disso, sugere-se que sua performance seja altamente dependente de habilidades do CPF (como por exemplo, função executiva, atenção e memória de trabalho).

Santos e colaboradores (2010) mensuraram a memória contextual através de uma tarefa de memória contextual incidental envolvendo reconhecimento de objeto e de contexto e que poderia ser efetuada sob duas versões: associativa, que fornecia uma estratégia codificadora associativa (instrução facilitadora de vínculo entre objeto e contexto) e não associativa, que não fornecia nenhuma estratégia (BALARDIN et

al., 2009). Os idosos saudáveis do estudo melhoraram seu desempenho na memória contextual com a introdução de uma estratégia associativa. Para pacientes com DP, além de não promover melhora no desempenho da tarefa de memória contextual, a introdução da estratégia codificadora associativa apresentou um efeito deletério no reconhecimento do objeto. Os autores sugeriram que o efeito negativo, e inesperado, da estratégia codificadora sobre a memória de reconhecimento do objeto poderia estar relacionado a disfunções em aspectos atencionais ou executivos relacionadas à DP, já que a estratégia exigiu que os pacientes analisassem dois estímulos simultaneamente: objeto e contexto (ambiente onde o objeto estava). Desta forma, neste estudo, também visamos investigar a relação entre a função frontal na DP, mensurada de acordo com o desempenho dos pacientes na tarefa de memória contextual, e o polimorfismo val158met da COMT, que tem sido relacionado a disfunções em aspectos cognitivos processados pelo CPF (FOLTYNIE et al.,2004; WILLIAMS-GRAY, et al.2007)

1.1.3 Relação entre atenção e marcha na Doença de Parkinson

As disfunções do sistema nigro-estriatal e as alterações funcionais dos gânglios da base estão relacionadas às disfunções motoras características desta patologia (BARBOSA et al., 1997). Entre estas disfunções motoras observam-se as alterações de marcha, que tem um impacto negativo na qualidade de vida devido à dificuldade de mobilidade (e perda de independência) e ao risco aumentado de quedas (BLOEM, 1992; SNIJDERS et al., 2007).

Um conjunto crescente de evidências tem sugerido que o controle da postura e da marcha também dependem da função cognitiva (MARQUIS et al., 2002; VERGHESE et al., 2002b; HAUSDORFF et al., 2005) e que mesmo em jovens saudáveis estes processos não são inteiramente automáticos, dependendo de forma importante de recursos atencionais (WOOLLACOTT; SHUMWAY-COOK, 2002). Paradigmas que analisam a realização simultânea de duas tarefas têm sido utilizados para investigar a relação entre marcha e cognição, ou mais especificamente, marcha e atenção dividida.

O envelhecimento normalmente é acompanhado por alterações estruturais no cérebro, entre elas alterações em áreas do CPF associadas com a atenção. Portanto, é esperado que idosos tenham dificuldades em exercer tarefas

simultâneas em geral, e quando caminham e realizam outra tarefa em particular (WOOLLACOTT; SHUMWAY-COOK, 2002; HOLTZER et al., 2005). Entretanto, a maioria dos estudos com idosos saudáveis observa uma estratégia “normal” em resposta à realização simultânea de caminhada e outra atividade (redução da velocidade da marcha ou do tempo de reação da tarefa secundária), ou seja, sem alterações importantes no padrão da marcha (YOGEV et al., 2008).

A realização simultânea de duas tarefas que demandam atenção não causa somente competição pela atenção, mas também desafia o cérebro a priorizar as duas tarefas. As áreas normalmente envolvidas no estabelecimento da prioridade são o CPF e o córtex cingulado anterior (DREHER; GRAFMAN, 2003; MACDONALD et al., 2000). Acredita-se que o significado e a relevância de informações concorrentes e simultâneas sejam determinados pela motivação de minimizar o perigo e maximizar o prazer (WILLIAMS, 2006). Jovens e idosos saudáveis parecem dar prioridade à estabilidade da marcha enquanto caminham e realizam outra atividade simultânea, provavelmente como forma de evitar lesões e quedas durante a caminhada (BLOEM et al., 2001). Esta hipótese é corroborada por estudos que demonstram que quando adultos jovens realizam uma tarefa cognitiva enquanto caminham, seu desempenho na tarefa cai, mas o padrão e a estabilidade da marcha se mantêm, provavelmente para evitar quedas (LINDENBERGER et al., 2000; SCHRODT et al., 2004; GERIN-LAJOIE et al., 2005).

Em pacientes com DP a situação é bem diferente. Normalmente a dificuldade em realizar tarefas simultâneas é mais evidente que em indivíduos saudáveis. Em pacientes com DP os déficits de marcha e a perda de seu componente automático (dependente do sistema nigro-estriatal) (BALTADJIEVA et al., 2006), são acompanhados pelas disfunções da atenção dividida (DUBOIS; PILLON, 1997; BEDARD et al., 1998). Desta forma, o efeito de uma sobrecarga no sistema de atenção é facilmente demonstrado: quando os recursos atencionais do paciente são exigidos por mais de uma atividade as alterações de marcha são amplificadas (CAMICIOLI et al., 1998; BOND et al., 2000; O’SHEA et al., 2002; HAUSDORFF et al., 2003; GALLETLY; BRAUER, 2005). A sobrecarga do sistema atencional também parece levar estes pacientes a utilizar uma estratégia imprópria de priorização de atividade, colocando a marcha em segundo plano e exacerbando o risco de quedas em situações de atenção dividida (BLOEM et al., 2001).

1.1.4 COMT e cognição

Muitos estudos têm atribuído à dopamina uma função moduladora sobre aspectos cognitivos dependentes do CPF. Sendo assim, vários genes envolvidos na regulação do balanço da dopamina nesta estrutura cerebral têm sido estudados, dentre os quais, encontra-se o gene da catecol-O-metiltransferase (COMT) como o mais amplamente investigado.

Tem sido descritas duas formas da COMT: uma solúvel, que apresenta o polimorfismo val108met, e uma forma de membrana, que apresenta o polimorfismo val158met (CHEN et al., 2004), o qual será tratado neste estudo.

Após ser liberada na fenda sináptica, a dopamina pode ser inativada pela ação do seu transportador (DAT) ou então ser degradada por enzimas como a COMT (BEAR, 2008). A ação da COMT é dependente de magnésio e envolve a transferência do grupo metil da S-adenosil-L-metionina para um dos grupos hidroxil da dopamina (MATSUMOTO et al., 2003).

Embora seja expressa em todo o cérebro, a COMT parece ter um papel particularmente importante no metabolismo pós-sináptico da dopamina no CPF (MATSUMOTO et al., 2003), já que outros reguladores deste neurotransmissor, como por exemplo, DAT, são expressos em níveis mais baixos nesta estrutura cerebral e não parecem afetar significativamente os níveis deste neurotransmissor (SESACK et al., 1998).

Um estudo que examinou a variação global dos alelos do polimorfismo val158met da COMT em 30 diferentes populações encontrou uma variação significativa na freqüência dos alelos met. Enquanto europeus apresentam freqüências quase equivalentes nos dois alelos, o alelo val é mais comum em outros grupos étnicos (PALMATIER et al., 1999).

O polimorfismo val158met do gene da COMT resulta na substituição de uma valina (val) por uma metionina (met) na posição 158 da seqüência protéica. O alelo met é relacionado à baixa atividade enzimática, sendo os homozigotos associados a uma redução de 3 vezes na atividade da COMT em relação aos homozigotos val (CHEN et al., 2004).

A alteração da atividade enzimática da COMT modifica a eficiência de aspectos cognitivos dependentes do CPF, mais especificamente a função executiva, a memória de trabalho e a atenção (revisão em DICKINSON; ELVEVAG, 2009). Os

dados existentes na literatura relativos à influência do genótipo da COMT e funcionamento frontal na DP são controversos, pois enquanto alguns estudos não têm observado relação entre função executiva e genótipo da COMT (HOOGLAND et al., 2010) outros têm relatado prejuízos na performance executiva (FOLTYNIE et al., 2004) e redução na ativação frontoparietal associados ao genótipo (met/met) de baixa atividade enzimática (WILLIAMS-GRAY et al., 2007).

Embora não existam estudos relacionando especificamente a atenção dividida com este polimorfismo da COMT, Williams-Gray e colaboradores (2008) demonstraram que o genótipo dos pacientes teve um importante impacto na atenção alternada, sendo que os indivíduos com genótipos de baixa atividade da COMT (met/met) adotaram estratégias anormais de transferência de atenção. Adicionalmente, estes pacientes demonstraram uma menor ativação do circuito atencional frontoparietal. No presente estudo investigaremos se existe relação entre o desempenho do pacientes em tarefas relacionadas ao funcionamento do CPF (função executiva e memória contextual) e os genótipos para alta (val/val) e reduzida (met/met) atividade da COMT. Uma vez que se encontre associação entre o genótipo da COMT e função frontal, verificaremos a relação entre o desempenho cognitivo de pacientes com DP na realização de tarefas concomitantes e o polimorfismo val158met da COMT.

1.2 OBJETIVOS

1.2.1 OBJETIVO GERAL

Caracterizar diferentes funções cognitivas associadas ao lobo frontal (função executiva, atenção e memória contextual) de pacientes com DP e verificar sua relação com o polimorfismo val158met da COMT.

1.2.2 Objetivos específicos

- Verificar o efeito do grau de atividade da COMT, expresso pelos genótipos val/val (alta atividade) e met/met (baixa atividade), nas tarefas de função executiva;

- Verificar o efeito do grau de atividade da COMT, expresso pelos genótipos val/val (alta atividade) e met/met (baixa atividade), na memória contextual;

-Caracterizar o desempenho de pacientes com DP em tarefas que avaliam atenção dividida e função executiva;

-Avaliar a relação entre função executiva e realização concomitante de atividade cognitiva e caminhada;

-Avaliar o efeito da atenção dividida (realização simultânea de atividades cognitivas e caminhada) sobre o desempenho cognitivo dos pacientes com DP.

2 CAPÍTULO 2

2.1 ARTIGO CIENTÍFICO

No major effect of COMT val158met genotype on contextual recognition memory in Parkinson´s disease

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(Periódico escolhido*:* Journal of Geriatric Psychiatry and Neurology)

BRIEF COMMUNICATION

No major effect of COMT val158met genotype on contextual recognition memory in Parkinson´s disease

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ABSTRACT

Objectives: The aim of this study was to compare the performance of two matched groups of PD patients with high (val/val) and low (met/met) activity COMT genotypes in a contextual memory paradigm. Methods: Cognitive assessment and COMT genotyping were performed in 18 PD patients with Hoehn and Yahr $\leq$ 3.0. Results: No effect of COMT val158met genotype on recognition memory performance for context was observed. The present findings must be confirmed in future studies with a larger sample size.

Keywords: Parkinson's disease; cognitive deficits; catechol-O-methyltransferase

INTRODUCTION

Besides the classical motor symptoms, Parkinson's disease can be accompanied by cognitive deficits even in its earliest stages.[1] The most well described deficits are observed in tasks requiring executive functions, such as working memory, planning, and attentional set shifting.[2,3] Combined pharmacological and neuroimaging findings support the hyphotesis that some such deficits can be related to dysfunction in dopaminergic frontostriatal networks and may be influenced by a common functional polymorphism (val158met) within the catechol *O*-methyltransferase (COMT) gene.[4-7] COMT is an enzyme that degrades cortical dopamine. Because other regulators of synaptic dopamine (e.g. dopamine transporters) are rare in prefrontal cortex synapses, COMT plays a central role in regulating prefrontal dopamine levels.[8]

Deficits in other cognitive operations that required some degree of attention and executive control, such as binding item and context in episodic memory, [9-11] were previously reported by our group in PD[12] and in other samples of patients with frontal lobe dysfunctions.[13] Santos and collaborators (2011) showed that PD patients, contrary to healthy controls, were not beneficiated from incidental encoding strategies to improve recognition memory for context. In the present study, we conducted a preliminary investigation on the performance in the contextual memory paradigm of two matched groups of PD patients, differing only in whether they possessed high

(val/val) or low (met/met) activity COMT genotypes.

METHODS

Participants

In this study participated 18 adults diagnosed with idiopathic PD under regular medication (ages 53-88; 10 women), selected at the Movement Disorders Clinic of the Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil). Subjects were selected from a data bank of patients genotyped for COMT polymorphism. Inclusion criteria were homozygosity for the COMT val158met polymorphism, clinical diagnostic of PD according to UK Parkinson's Disease Society Brain Bank [14] and a maximum score of 2,5 on the Hoehn and Yahr's classification system.[15] Exclusion criteria comprised the use of psychotropic medication (except to treat PD complications), neurological disorders (other than PD) or injuries known to have significant direct effects on cognitive functioning, major unstable medical illnesses (e.g., metastatic cancer), history of neurosurgical procedure, cognitive deficits as evidenced by the Mini Mental Status Examination (cutoff adjusted for education),[16] scores on the Beck Depression Inventory (BDI)[17] indicating severe depressive symptoms and visual and hearing alterations incompatible with the neuropsychological tests. All PD patients were rated for motor function with the part III of the Unified Parkinson's Disease Rating Scale (UPDRS III)[18] and for functional independence with the Schwab and England Activities of Daily Living Scale.[19] Neuropsychological and memory evaluation were applied during the "on" medication phase.

All patients were taking dopamine precursors either alone (levodopa + carbidopa, n=11 or Levodopa + benserazide chloridrate, n=7), or in combination with amantadine alone (n=2), amantadine and dopaminergic agonists (bromocriptine, n=1; pramipexole, n=1), amantadine and anticholinergic medication (triexifenidil, n=1). Total daily dose of levodopa/carbidopa varied from 500/ 50mg to 1250/125 mg and dose of levodopa/ benserazide chloridrate varied from 300/75mg to 800/200 mg. This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil) and all participants gave informed consent.

Neuropsychological Assessment and Contextual Memory Paradigm

All participants completed neuropsychological tests to compare cognitive ability across experimental groups, including the matrix reasoning subtest of WAIS III, [20] Wisconsin Card Sorting Test- 64 card computer version (WCST) [21] and the Golden version of the Stroop Color and Word Test [22] for executive function assessment.

The materials and procedures for the assessment of the recognition memory for context have been described elsewhere (more details at Balardin et al., [23] and Santos et al.,[12]). During the encoding session, photographs of a large number of objects from different semantic categories (household appliances, tools, toys, and clothing) were placed in 2 locations: a living room and an office. Participants made judgments about how well each object fits into the room displayed and were unaware that a test session would follow. After a 5-min interval, a yes-no recognition memory test for objects and locations were carried out.

Data analysis

Chi-square test and independent Student's *t* test were used whenever appropriate to compare the subjects groups with respect to different demographic and neuropsychological characteristics, as well as for performance on memory task. Recognition memory scores for objects were calculated as the proportion of objects correctly identified as previously presented; and scores for context as the proportion of objects attributed to the correct context considering the number of objects correctly identified as previously presented. Results are expressed as mean ± standard error, and $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the demographic and neuropsychological characteristics of PD patients. Groups did not differ in age [t = -0.327, df = 16, p = 0.748], gender [Pearson Chi-Square = 0.90, p = 0.343] or years of education [t = -0.522, df = 16 p =0.523], as well as on the BDI [t =0.986, df =16 , p =0.339] and MMSE [t =-1.928, df =16 , p=0.072] scores.

No significant differences were found between groups on the performance on matrix reasoning wais III [t = 1.344, df =15.91, p =0.198]. There were also no

significant group differences on any of the measures of the Stroop Color and Word Test, as can be seen for the scores on the Color [t =-1.800, df =16, p =0.91], Word [t =-0.897, df = 16, p = 0.383], and Color-Word pages [t =1.853 , df = 16, p=0.082]. Met/met and val/val patients also showed no significant differences on completed categories [t = -0.329, df =16, p =0.747] and perseverative errors on the WCST [t = -0.329, df =16, p =0.717].

Recognition performance for objects and contexts can be found in Figure 1. No significant group differences were found neither for object recognition performance [t = 0.101, df =16, p =0.920], nor for context recognition performance [t = 0.944, df =16, p =0.359].

DISCUSSION

The present preliminary findings did not suggest that COMT val158met genotype could modulate performance in the contextual memory task, neither in the number of categories completed in the WCST nor the Stroop Test. A recent study [24] did not demonstrate a direct effect of COMT functional polymorphism type on the performance of 153 early PD patients in an extensive neuropsychological test battery assessing attention and executive functions. However, patients under medication and with low COMT activity exhibited worse performance on WAIS III Similarities than unmedicated patients with high COMT activity.

These combined findings are contradictory to previous published studies. Foltynie et al. [4] examined the relationship between the COMT val158met polymorphism and executive function in PD patients and found low enzyme activity (met/met)—implying higher prefrontal dopamine levels—related to worse performance. Two functional neuroimaging studies demonstrated that met alleles were associated with reduced activation in a frontoparietal executive network. [6, 25]

There are several factors that may account for discrepancies in the results among studies including differences in sample size and demographics, tasks characteristics, medication and dopamine function in prefrontal cortex. Also, a few studies on the associations between cognition and COMT val158met genotype on PD have considered the influence of gene-gene and gene-environment interactions. In summary, further studies are necessary in order to clarify the role of COMT polymorphism on cognition in PD.

Acknowledgments

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LEGEND OF FIGURES AND TABLES

Table 1. Demographic and Neuropsychological Measures for PD Patients[a]

Abbreviations: MMSE, Mini Mental Status Examination; UPDRS, Unified Parkinson's Disease Rating Scale; ADL, Schwab and England Activities of Daily Living Scale; BDI, Beck Depression Inventory; WCST, Wisconsin Card Sorting Test. [a]

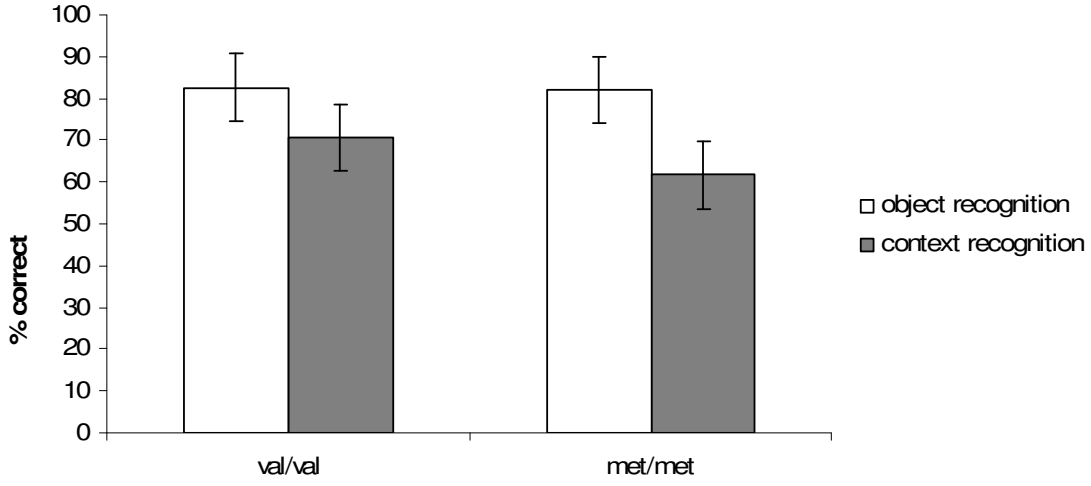
Results are expressed as mean ± standard error (SEM), except for sex (female/male proportion).

Figure 1**.** Object and context recognition performance of Parkinson's disease (PD) patients.

Results are expressed as mean ± standard error (SEM).

Table 1. Demographic and Neuropsychological Measures for PD Patients[a]

	val/val (n = 9)	met/met (n = 9)	P value
Age (years)	68.44 ± 3.26	70.22 ± 4.35	0.748
Gender (female/male)	6/3	4/5	0.34
Education (years)	5.78 ± 0.83	6.67 ± 1.08	0.523
BDI	8.78 ± 3.04	5.11 ± 2.14	0.339
MMSE	25.56 ± 0.50	27.22 ± 0.70	0.072
Hoehn and Yahr stage	1.88 ± 0.13	2.05 ± 0.10	0.345
Disease duration (years)	7.77 ± 0.92	9.00 ± 0.98	0.379
UPDRS (part III)	13.88 + 2.70	18.55 ± 2.45	0.219
ADL	90 ± 2.88	85 ± 2.42	0.255
WCST (categories completed)	0.55 ± 0.17	0.66 ± 0.28	0.747
WCST (perseverative errors)	16.77 ± 1.82	15.11 ± 4.13	0.717
Stroop- Word Page	60.44 ± 5.75	73.56 ± 4.47	0.091
Stroop- Color Page	44.33 ± 4.03	49.44 ± 4.02	0.383
Stroop- Color-Word Page	24.44 ± 2.46	19.22 ± 1.37	0.082



3 CAPÍTULO 3

3.1 ARTIGO CIENTÍFICO

Characterization of cognitive and motor performance during dual-tasking in healthy older adults and patients with Parkinson's Disease

Lucia Bartmann Wild, Daiane Borba de Lima, Joana B Balardin, MS,Luana Rizzi, Bruno Lima Giacobbo, Henrique Bianchi Oliveira, Irani Iracema de Lima Argimon, PhD, Leonardo Alexandre Peyré Tartaruga, PhD, Carlos RM Rieder, PhD, Elke Bromberg, PhD

(Periódico escolhido: Journal of Neurology)

Uma vez que esta dissertação é parte integrante de um estudo maior intitulado “Reabilitação combinada dos déficits motores e atencionais na DP e sua relação com o polimorfismo val158met da COMT” que avaliou tanto aspectos cognitivos como motores na DP, a coleta dos dados referentes à função cognitiva foi de responsabilidade da mestranda Daiane Borba de Lima, enquanto que a avaliação dos aspectos motores dos pacientes foi de responsabilidade da mestranda Lúcia Bartmann Wild.

Characterization of cognitive and motor performance during dual-tasking in healthy older adults and patients with Parkinson's Disease

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Abstract

Background: The primary purpose of this study was to investigate the effect of dual-tasking on cognitive performance and gait parameters in patients with idiopathic Parkinson's disease (PD) without dementia. The impact of cognitive task complexity on cognition and walking was also examined.

Methods: Eighteen patients with PD (ages 53-88, 10 women; Hoehn and Yahr stage I-II) and 18 older adults (ages 61-84; 10 women) completed two neuropsychological measures of executive function/attention (the Stroop Test and Wisconsin Card Sorting Test). Cognitive performance and gait parameters related to functional mobility of stride were measured under single (cognitive task only) and dual-task (cognitive task during walking) conditions with different levels of difficulty and different types of stimuli. In addition, dual-task cognitive costs were calculated.

Results: Although cognitive performance showed no significant difference between controls and PD patients during single or dual-tasking conditions, only
patients had a decrease in cognitive performance during walking. Gait parameters of patients differed significantly from controls at single and dual-task conditions, indicating that patients gave priority to gait while cognitive performance suffered. Dual-task cognitive costs of patients increased with task complexity, reaching significantly higher values then controls in the arithmetic task , which was correlated with scores on executive function/attention (Stroop Color-Word Page).

Conclusions: Baseline motor functioning and task executive/attentional load affect the performance of cognitive tasks of PD patients while walking. These findings provide insight into the functional strategies used by PD patients in the initial phases of the disease to manage dual-task interference.

Key Words: Parkinson's Disease. Dual-task. Cognition. Gait

Introduction

In addition to classical motor symptoms, Parkinson's disease (PD) is associated with a variety of cognitive deficits that begin to appear in the earliest stages of the disease. These deficits encompass executive function, attention, memory, language, and visuospatial aspects [1-3] which can significantly interfere with occupational and social functioning. Tasks that require the simultaneous performance of two or more cognitive functions along with motor activities (e.g. walking and talking on the phone or walking while rehearsing a shopping list) can be particularly affected. Specific cognitive features, such as set shifting, divided or alternating attention and executive function have been specifically associated with impairments in "dual-tasking" ability in PD patients [4-6]. While dual-tasking deficits do not independently predict the likelihood of falls, they are linked to gait parameters associated with falling [7]. Deficits in performing a cognitive task while walking may uncover problems not apparent under single task conditions, and may be a more sensitive assessment of everyday cognitive impairments in patients in the initial stages of PD, with mild symptom severity and discrete neuropsychological deficits.

The ability to walk while performing another task can have a significant influence on cognition, gait and mobility. Dual-task impairments in PD patients have been observed during standing [8, 9] and gait tasks. Both PD patients and elderly controls demonstrate shorter strides, less time in the swing phase, and lower functional ambulation values than healthy younger controls [10]. Decrements in performance from single-task to dual-task cognitive scores have been related to "prioritization" of gait in a system that has limited processing capacity [11]. However, the majority of previous studies on motor–cognition dual-task performance were primarily designed to investigated dual-task interference on gait parameters, resulting in a scanty characterization of dual-task interference on cognition in PD.

The current study characterized changes in cognitive performance under single- and dual-task conditions with different levels of task difficulty and different types of stimuli (i.e. text comprehension, phoneme monitoring and mathematical subtractions) in PD patients in the initial phases of the disease and in elderly healthy controls. In addition, motor performance of participants was determined by means of stride-related measures (speed, average swing time and relative stance time). Associations between two specific neuropsychological measures (executive function

and divided attention) previously demonstrated to be related to dual-task performance were also tested. It was hypothesized that PD patients would not only alter gait parameters to a greater extent, but would also perform worse on cognitive tasks during dual-task conditions and that such dual-task interference would be greater for tasks demanding greater attention. Additionally, whether cognitive-motor performance during dual-task conditions was affected to a greater extent in PD patients than in controls was investigated.

Methods

Participants

In this study participated 18 older adults diagnosed with idiopathic PD (ages 53-88; 10 women) from the Movement Disorders Clinic at the Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil) and 18 adult controls (ages 61-84; 10 women) recruited from the community. Inclusion criteria for patients comprised a clinical diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank [12] and the absence of balance alterations (indicated by scores below 3 in Hoehn and Yahr's classification system [13]). Thus, advanced PD patients were not included.

All patients were taking dopamine precursors either alone (levodopa + carbidopa, n = 8 or Levodopa + benserazide chloridrate, n = 5), or in combination with amantadine alone (levodopa +carbidopa plus amantadine n=1, Levodopa + benserazide chloridrate plus amantadine, n = 1), amantadine and dopaminergic agonists (levodopa + carbidopa plus amantadine plus bromocriptine, n =1; levodopa + carbidopa plus amantadine plus pramipexole dihydrochloride, n = 1) or amantadine and anticholinergic drugs (levodopa + carbidopa plus amantadine plus trihexyphenidyl hydrochloride, n = 1). Patients were not required to abstain from medication prior to testing.

Exclusion criteria for PD patients and controls included the use of psychotropic medication (except for treatment of PD complications), neurological disorders (other than PD) and injuries with known significant effects on cognitive functioning (e.g. traumatic brain injury, multiple sclerosis, stroke), major unstable medical illnesses (e.g., metastatic cancer), history of neurosurgical procedure, inability to ambulate independently, past history of disorders affecting gait or posture (except PD),

cognitive deficits as evidenced by the Mini Mental Status Examination (cut-off adjusted for education) [14], scores on the Beck Depression Inventory (BDI) [15] indicating severe depressive symptoms and visual and hearing impairment incompatible with the neuropsychological tests.

Motor functioning of PD patients was rated with the Unified Parkinson's Disease Rating Scale part III (UPDRS III) [16]. Neuropsychological and gait assessments were made only during the "on" medication phase.

The current study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil) and have therefore been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All participants gave informed consent.

Neuropsychological Assessment

Participants completed neuropsychological tests to compare cognitive ability across experimental groups. Tests included the Wisconsin Card Sorting Test-64 card computer version (WCST) [17] and the Golden version of the Stroop Color and Word Test [18] for executive function assessment. Previous studies have demonstrated that executive functioning (e.g. inhibition processes, the capacity to divide attention and shift between two concurrent tasks) [19] is involved in dual-task performance [20].

The Wisconsin Card Sorting Test requires participants to use trial and feedback to determine how to sort a deck of cards on the basis of four stimulus cards that vary on such parameters as number, colour and shape of symbol [17]. Scores were tallied along several dimensions. The number of categories performed correctly (ranging from 0 to 6) is one of the most commonly reported measures [21] and is a good general measure of executive function [22].

The Stroop Color and Word Test measures the ability to shift perceptual set to conform to changing demands and to suppress a habitual response in favor of an unusual one [23]. In brief, the test consists of a Word Page with color words (e.g. "pink", "green", "blue") printed in black ink, a Color Page with Xs printed in either pink, green, or blue ink, and a Color-Word Page with words from the first page ("pink", "green", "blue") printed in colors from the second page such that the color and the word do not match. For example, the word "pink" may be printed in blue ink. The test

yields three scores based on the number of correct responses on each of the three stimulus sheets [18].

Dual-task Assessment

Three cognitive tasks adapted from the protocol developed by Yogev et al. (2005) [20] were performed: (1) text comprehension: the subject listened to a story through earphones; (2) phoneme counting: the subject listened to a different story through earphones and counted the number of times a predetermined phoneme was heard; (3) arithmetic task: subjects were asked to perform serial 7 subtractions aloud. Text comprehension was scored as a percent of correct responses on a multiple-choice questionnaire. Phoneme counting performance was measured as the percent of total phonemes in the text counted by the subject. Performance on the arithmetic task was measured by the total correct serial subtractions. Each of the cognitive tasks was performed while sitting (baseline cognition) and while walking (dual-task cognition), as described below.

The effects of dual-tasking (performing a cognitive task during walking) on cognition were analyzed under three walking conditions: 1) text comprehension during walking; 2) phoneme counting during walking and 3) arithmetic task during walking. The only instruction participants received was to walk at a comfortable rhythm while performing the cognitive tasks. The texts presented at baseline and dual-task conditions were different and the serial subtractions were initiated with different numbers in the two conditions (300 while sitting and 234 while walking).

The ability of controls and PD patients to execute two tasks concurrently was further analyzed to investigate the effect of gait on cognitive performance. For this purpose dual task cost (DTC) was calculated for each subject and condition as follows: DTC (%) = 100 * (single-task cognitive score - dual-task cognitive score)/single-task cognitive score [24].

Gait Assessment

Gait was assessed under baseline conditions (walking only) and dual-tasking conditions (walking while performing each of the cognitive tasks) in order to identify possible relationships between cognitive performance during dual-tasking and gait

parameters (stride length and frequency, average swing time, average support phase, speed and relative stance time). Participants walked down a nine-meter corridor and gait parameters were obtained by kinemetry with a fixed camera (JVC GR-DVL 9800 – JVC Company of America, Wayne, New Jersey, USA – 50Hz) positioned laterally to the corridor at a distance of four meters from where the individual passed, a spotlight and a two-dimensional gauge. Reflective markers were placed on the following anatomical landmarks: fifth metatarsal, calcaneus, lateral malleolus, lateral femoral epicondyle, greater trochanter and acromion.

The movement analysis system Dvideow (Digital Video for Biomechanics, developed by Instrumentation Laboratory for Biomechanics, Faculty of Physical Education, UNICAMP, Campinas, Brazil, Version 5.0) was used for two-dimensional analysis (2D) of a stride cycle (first touch from the right foot on the ground until the next touch of the same foot on the ground). Coordinate evaluation was made point by point on the digitalized images and the movement analysis system calculated and monitored the bidimensional positions of the reflective markers. The data processing was carried out with Labview 85 software.

For simplicity, only average swing time, gait speed (stride length multiplied by the stride frequency) and relative stance time (support time divided by stride time) are reported and discussed. These parameters were chosen due to their prior proven validity as predictors of gait automaticity, stability and protective adjustments during dual-tasks [25-28].

Statistical Analysis

Independent Student's t-tests and chi-square tests were used to compare demographic and neuropsychological characteristics of the PD patients and control subjects. Between-group performance on cognitive tasks was analyzed with independent Student's t-tests and comparisons of dual-tasking effects on cognitive performances of controls and PD patients were analyzed with dependent sample t-tests. Between-group differences in performance on cognitive tasks at baseline and during each of the dual-tasking conditions (text comprehension, phoneme monitoring and mathematical subtractions) were examined by independent *t*-tests. Repeated measures. analysis of variance (ANOVA) was used to examine differences between groups (healthy older adults versus PD patients) and type of task (baseline walking,

walking + text comprehension, walking + phoneme monitoring, walking + mathematical subtractions) on stride parameters (relative stance time, speed, average swing time). Multiple comparisons among group mean differences were checked with Tukey post hoc tests. Independent and paired samples *t* tests were used whenever appropriate. (confidence interval adjustments with Bonferroni corrections). Results are expressed as mean ± standard error, and $P < 0.05$ was considered statistically significant.

Results

Table 1 summarizes the demographic and neuropsychological characteristics of all participants. Groups did not significantly differ in age [t = -0.037 , df = 25.940, p = 0.971], gender [Pearson Chi-Square = 0, p = 1,00], years of education [t =-0.522, df =34 p =0.605], as well as on the BDI score [t =1.596, df =34 , p =0.120] and MMSE [t =-1.195, df =34 , p=0.240] scores. However, PD patients scored lower than controls on completed categories on the WCST [t = -2.043, df =34, p = 0.049]. PD patients also scored significantly lower than controls on the Stroop Color-Word Page [t = -2.365, df = 34, p = 0.024]. However, groups did not significantly differ in performance on the Stroop Word [t = -0.433, df = 34, p = 0.688] or Color [t = -1.157, df = 34, p = 0.255] pages.

Performance on cognitive tasks during baseline (sitting) and dual-tasking (during walking) is displayed in table 2. There were no significant differences between PD patients and controls in baseline text comprehension [t =0.887, df = 34, p =0.381], phoneme counting [t = 0.856, df = 34, p= 0.398] and arithmetic task [t = 0.277, df = 34, p =0.783]. Controls and PD patients also showed similar cognitive performances during dual tasking, since no significant differences were found between groups during walking in text comprehension [t =-1.204, df = 34, p= 0.234], phoneme counting [t = -0.891, df = 34, p = 0.379] and arithmetic task [t = -0.825, df = 34, p = 0.415]. However, performance on text comprehension [t = 2.997, df = 17, p = 0.008], phoneme counting [t = 2.870, df = 17, p = 0.011] and the arithmetic task [t = 2.596, df = 17, p = 0.019] was significantly decreased in the dual-tasking condition compared to the baseline condition in PD patients, although the effect sizes were small. Control participants, on the other hand, showed no significant alterations in cognitive performance during dual-tasking as compared to baseline. While there were

no significant differences in cognitive performance between controls and PD patients during baseline or dual-tasking conditions, these results indicate a greater difficulty for PD patients to perform dual-tasks, since cognitive performance decreased with walking (all p values < 0.05). PD is associated with gait alterations [29, 30] and a growing body of evidence suggests that gait requires attention resources during dual-tasking [31-33] and therefore this issue was further investigated.

Gait parameters during baseline (walking only) and dual-tasking (walking while performing cognitive tasks) are displayed in table 3. There were significant differences between PD patients and controls in relative stance time [$F(1,34) = 14.74$, $p = 0.01$] and gait speed [$F(1,34) = 10.39$, $p = 0.03$]. Independent sample t-tests found PD patients to have a longer relative stance time and slower speed than controls during both baseline and all dual-task conditions (all p values < 0.05). PD patients and controls did not significantly differ in swing time [$F(1,34) = 0.45$, $p = 0.5$], indicating the absence of differences in this gait parameter between controls and PD patients at the different walking conditions, as confirmed with independent t tests [all p values > 0.05].

Relative stance time [$F(3,102) = 12.57$, $p < 0.01$], speed [$F(3,102) = 46.02$, $p = 0.003$] and average swing time [$F(3,102) = 8.64$, $p < 0.01$] were all significantly affected by condition. Bonferroni confidence interval adjustments of paired t-tests confirm the greatest dual-task gait alteration in the control group relative to baseline values occurred under the arithmetic task condition, in which the relative stance time ($p = 0.012$) and average swing time ($p = 0.009$) significantly increased and the gait speed significantly decreased ($p < 0.001$) (Figure 1a). A similar increase of relative stance time also occurred in the phoneme counting condition ($p = 0.03$ in relation to baseline and $p = 1$ in relation to the arithmetic task condition) and smaller speed alterations were found in the text comprehension task ($p = 0.005$ in relation to baseline and $p = 0.027$ in relation to arithmetic task conditions) and the phoneme counting conditions ($p = 0.003$ in relation to the baseline condition and $p = 0.036$ in relation to arithmetic task conditions). PD patients showed gait adjustments only in the arithmetic task condition, in which a decrease in speed ($p < 0.001$) and an increase in relative stance time ($p = 0.014$) were found, as shown by Bonferroni confidence interval adjustments (Figure 1b).

PD patients significantly differed from controls in gait at baseline and throughout the different dual-task conditions. To further investigate the effect of gait

on PD patient cognitive performance the ability to execute two tasks concurrently was quantified. Thus, the dual task cost (DTC) was calculated. Overall, PD patients had larger DTCs than control participants. However, only the arithmetic DTC differed significantly between the groups ($p = 0.031$) (Figure 2). We next analyzed whether DTCs and the decrease in cognitive performance of PD patients during the dual-task conditions were related to executive and attention dysfunctions (since PD patients scored lower on the WCST and Stroop Color-Word Page relative to controls) and/or to gait alterations (PD patients demonstrated greater effort than controls in maintaining stability in all experimental conditions). We thus performed correlation analyses exploring relationships between performance on different cognitive tasks during walking and neuropsychological test scores (WCST and Stroop Color-Word Page) and gait parameters. A correlation analysis was also performed for DTC and neuropsychological test scores (scores of WCST and Stroop Color-Word Page) or gait parameters. The gait parameters introduced in the correlation analysis were relative stance time and speed, since they were significantly different between groups in all experimental conditions.

No significant correlations were found for the different cognitive parameters (text comprehension, phoneme counting, arithmetic task) during walking and WCST scores (all p values > 0.05). Performance on the Stroop Color-Word Page was significantly correlated with the serial subtractions dual-task ($r = 0.35$, $p = 0.036$). No significant correlations were found for relative stance time and cognitive parameters during walking (all p values > 0.05), or for gait speed and cognitive performance in dual-tasks (all p values > 0.05). There were no significant correlations between DTCs for the different cognitive tasks and scores on WCST (all p values > 0.05) nor between DTCs and performance on the Stroop Color-Word Page (all p values > 0.05) or between gait parameters (relative stance time and gait speed) and DTCs for the different cognitive tasks during walking (all p values > 0.05).

Discussion

The aim of the present study was to compare the ability of performing cognitive tasks while walking in PD patients and healthy elderly controls under different combinations of a cognitive-only and a cognitive-walking task. We sought to determine which task characteristics contribute to impairments in cognitive

performance and to identify associations between cognitive performance, general motor parameters and cognitive measures.

Cognitive performance was decreased in PD patients during all dual-tasking conditions (i.e. phoneme monitoring, text comprehension and arithmetic test) compared to baseline cognitive-only testing. Alternatively, cognitive performance of healthy controls did not significantly differ between baseline and dual-tasking conditions. Relative dual-task cognitive costs were greater for PD patients compared to controls in all dual-tasking conditions, however statistical significance was reached only in the arithmetic-walking condition. Changes in gait parameters under dual-tasking conditions were affected by task complexity to a greater extent in healthy controls than in PD patients. Control participants exhibited a progressive decrease in gait speed and increase in average swing time from baseline, to text comprehension and phoneme monitoring, to the arithmetic task. Gait adjustment was only significantly affected under the arithmetic-walking condition in patients with PD.

Significant between group differences in the single-task walking condition confirm previous findings that PD patients demonstrate single-task walking deficits, even during the “on” cycle of medication. Poor performance on single-task measures of balance and functional mobility have previously been associated with increased axial rigidity in patients with Hoehn and Yahr scores of 2 or 3, [34] along with reduced movement amplitude across all lower limb joints, in all movement planes [35]. In addition, the current findings are consistent with prior studies showing that under dual-tasking conditions healthy older adults and PD patients demonstrate alterations in several gait parameters, such as reduced gait velocity and step length, [25,36-39] increased stride to stride variability [40] and more freezing episodes [41] when compared to walking alone. Multiple mechanisms may be responsible for interference between walking and concurrent cognitive or motor tasks in people with PD (for a review see Kelly et al., 2012 [11]). Nonspecific mechanisms include theoretical information processing frameworks, such as the capacity theory [42] and the bottleneck theory [43]. These theories postulate that dual-task interference occurs when two tasks compete for attention from the same system leading to deterioration in performance of one or both tasks. PD-specific deficits include reduced movement automaticity, dopamine-mediated dysfunction of the basal ganglia and the presence of nondopaminergic pathology, which may affect both gait and cognition.

The current results indicate that healthy controls adjust gait under dual-tasking

in order to maintain cognitive performance while adjusting gait according to increasing executive load. PD patients, on the other hand, gave priority to gait while cognitive performance suffered. There were no significant differences between PD patients and healthy controls in cognitive task performance at baseline indicating that both groups were equally capable of performing the tasks and hence emphasizing the disrupting effect of motor deficits on dual-tasking specific to PD patients. In the present study, it is possible that PD patients concentrated on gait even during the baseline walking-only condition, and thus demonstrated less gait adjustment during dual-tasking than the healthy controls. The lower performance on gait parameters of PD patients in relation to controls may not necessarily be indicative of postural instability or pathologically impaired central processing capacity, but rather as a form of "prudent" behavior intended to maintain balance over execution of the "secondary" mental task [44].

The greater DTC observed in PD patients was not associated with all tasks, and was specifically influenced by task nature and difficulty. Previous research in frail older adults has indicated that mathematical subtraction (which relies more on working memory) generates a greater cognitive load than, for example, verbal fluency (which relies more on semantic memory) [45]. Furthermore, language tasks impact gait performance in PD patients differently than mathematics tasks [46], and PD patients are more severely affected by more demanding cognitive tasks than healthy controls [39], as the arithmetic task in our study.

Previous studies have demonstrated that walking deficits during dual-tasking in PD patients have been associated with impairments in specific cognitive functions such as set-shifting, attention, and executive functions [4-6]. PD patients in the current study performed worse than controls on the Stroop Color-Word Page and on the WCST. However, only scores on the Stroop Color-Word Page were correlated with performance during the arithmetic dual-tasking condition. The marginal statistical difference between PD patients and healthy controls on the WCST my explain the absence of a significant correlation between WCST scores and arithmetic dual-tasking. Specifically, the response inhibition necessary for Stroop Color-Word Page performance is an ability closely related to selective attention, which is critical when walking in complex, everyday environments, allowing subjects to focus on gait and give it the appropriate attention and priority, despite numerous distractions [7].

There are limitations to the current study that should be considered in result

interpretations. While kinemetry is a well-established method in the evaluation of gait [26, 27], we assessed only one stride, excluding the evaluation of other gait parameters, including gait variability. Another limitation in the current study is the small number of subjects in each group. Our inclusion criteria (i.e. patients classified as mild Hoehn & Yahr stage and in the “on” medication cycle) restricted patient recruitment. Moreover, we did not take into account the possible contribution of clinical symptoms (such as fatigue) on the cognitive and motor dual-task impairments in PD [6].

In conclusion, the present findings demonstrate that baseline motor functioning and task executive/attentional load affect the performance of cognitive tasks while walking. These findings provide important insight into the different functional strategies used by PD patients in the initial phases of the disease and by healthy older adults in the adjustment of gait under dual-tasking conditions. Recent studies have begun to examine the effects of training on directed motor behaviors (i.e walk with larger steps) [47] to improve dual-tasking. Further studies are necessary to investigate the effects of cognitive training focused on attentional/executive strategies on the ability to perform concomitant tasks in patients with different severities of PD.

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Conflict of Interest

The authors declare that they have no financial relationship with the organization that sponsored the research. The authors also declare that they have no conflict of interest.

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LEGEND OF FIGURES AND TABLES

Table 1. Demographic and Neuropsychological Measures for Healthy Controls and PD Patients[a]
Abbreviations: MMSE, Mini Mental Status Examination; UPDRS, Unified Parkinson's Disease Rating Scale; BDI, Beck Depression Inventory; DTQ, Dual- tasking questionnaire; WCST, Wisconsin Card Sorting Test.
[a] Results are expressed as mean ± standard error (SEM), except for sex (female/male proportion).

Table 2. Subjects performance for cognitive tasks in baseline (sitting) and dual tasking (during walking) conditions.
Comparison between patients and control were performed with independent Student's t test. Comparisons between single and dual task conditions for each cognitive task and group were performed with dependent Student's t test.
Results are expressed as mean ± standard error.

Table 3. Gait parameters at baseline and dual tasking conditions in controls and PD patients.
Results are expressed as mean ± standard error.

Figure 1. Effect of simultaneous activities on relative stance time (s), average swing time (s) and speed (Km/h) of controls (a) and PD patients (b). Results are expressed as mean ± standard error. * $p < 0.05$ and ** $p < 0.001$ in relation to the baseline gait. + $p < 0.05$, ++ $p < 0.001$ and # $p = 1$ in relation to arithmetic task condition .

Figure 2. Dual task cost. DTC values ranged from negative values in controls (indicating that gait did not impose any additional cost to cognitive performance) to positive values in PD patients (suggesting that walking can impair concurrent cognitive tasks). Although PD patients showed larger DTCs than control participants, only arithmetic DTC reached statistical significance. Results are expressed as mean ± standard error. * $p=0.031$ compare arithmetic DTC in patients and controls.

Table 1

	Controls (n = 18)	PD (n = 18)	P value
Age (years)	69.44 ± 1.41	69.33 ± 2.65	0.971
Gender (female/male)	10/8	10/8	-
Education (years)	6.72 ± 0.68	6.22 ± 0.67	0.605
BDI	3.72 ±0.83	6.94 ± 1.86	0.122
MMSE	27.06 ± 0.31	26.39 ± 0.46	0.242
Hoehn and Yahr stage	-	1.97 ± 0.36	-
Disease duration (years)	-	8.39 ± 2.85	-
UPDRS (part III)	-	16.22 ± 7.88	-
WCST (categories completed)	1.22 ± 0.25	0.61 ± 0.16	0.049
Stroop- Word Page	69.28 ± 3.56	67.00 ± 3.87	0.668
Stroop- Color Page	50.89 ± 1.98	46.89 ± 2.83	0.255
Stroop- Color-Word Page	27.94 ± 2.1	21.83 ± 1.51	0.024

Table 2

Tasks performance	Patients	Controls	Patients X Controls (P value)	Single X Dual Task	
				Patients (P value)	Controls (P value)
text comprehension (single task)	78.33 ± 3.63	73.88 ± 3.44	0.38	0.008	0.82
text comprehension (dual task)	65.55 ± 4.21	72.77 ± 4.26	0.23	0.008	0.82
phoneme counting (single task)	47.99 ± 6.05	40.94 ± 5.57	0.39	0.011	0.49
phoneme counting (dual task)	30.94 ± 3.87	36.50 ± 4.89	0.37	0.011	0.49
arithmetic task (single task)	3.94 ± 0.72	3.50 ± 0.58	0.78	0.019	0.47
arithmetic task (dual task)	2.77 ± 0.69	3.72 ± 0.93	0.41	0.019	0.47

Comparison between patients and control were performed with independent Student's t test. Comparisons between single and dual task conditions for each cognitive task and group were performed with dependent Student's t test.

Table 3.

	Relative stance time	P	Speed	P	Average swing time	P
Baseline gait						
Control	0.61 ±0.005		4.36 ±0.175	<0.01	0.44 ±0.007	0.97
Parkinson	0.64 ±0.006	<0.01	3.22 ±0.191		0.44 ±0.015	
Gait/text comprehension						
Control	0.62 ±0.006	<0.01	3.91 ±0,20	0.01	0.46 ±0.01	0.32
Parkinson	0.65 ±0.005		3.13 ±0.21		0.44 ±0.01	
Gait/phoneme counting						
Control	0.63 ±0.005	0.01	3.81 ±0.20	0.03	0.44 ±0.01	0.26
Parkinson	0.66 ±0.010		3.10 ±0.23		0.42 ±0.02	
Gait/arithmetic task						
Control						
Parkinson	0.64 ±0.010	0,02	3.31 ±0.30	0.01	0.48 ±0.014	0.85
	0.67 ±0.011		2.25 ±0.20		0.48 ±0.025	

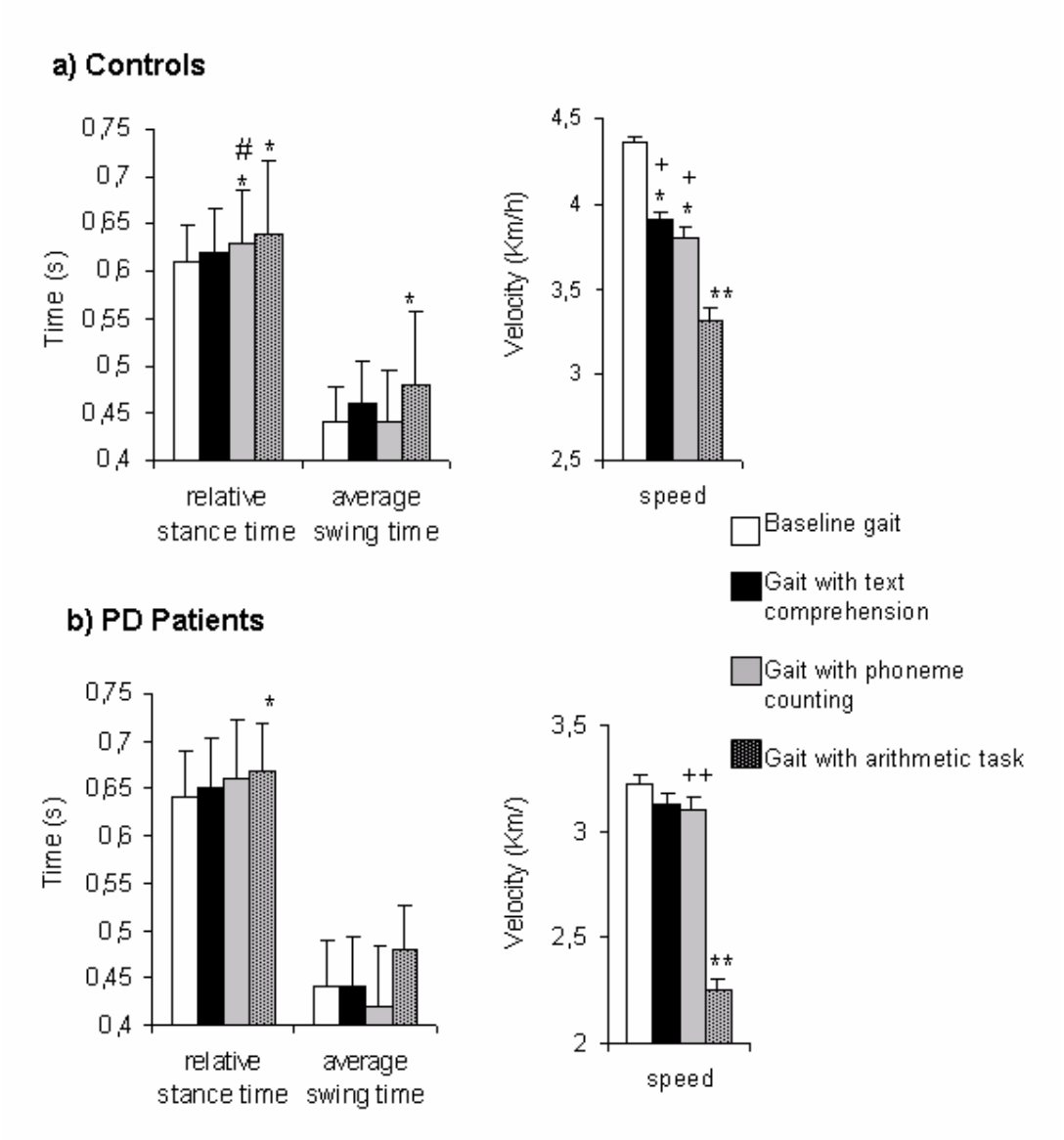
a) Controls
Time (s)
0,75
0,7
0,65
0,6
0,55
0,5
0,45
0,4
relative stance time
average swing time
Velocity (Km/h)
4,5
4
3,5
3
2,5
speed
Baseline gait
Gait with text comprehension
Gait with phoneme counting
Gait with arithmetic task
b) PD Patients
Time (s)
relative stance time
average swing time
Velocity (Km/)
3,5
3
2,5
2
speed

Figura 1

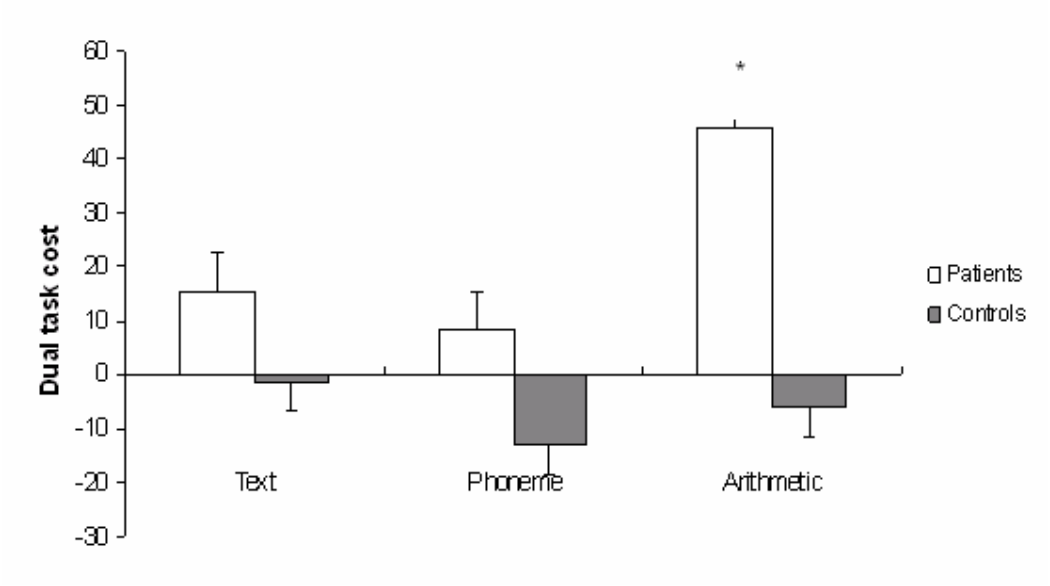
60
50
40
30
20
10
0
-10
-20
-30
Dual task cost
*
Text
Phoneme
Arithmetic
Patients
Controls

Figura 2

4 CAPÍTULO 4

4.1 CONSIDERAÇÕES FINAIS

Aspectos cognitivos dependentes do lobo frontal são modulados de forma importante pelo sistema dopaminérgico (ROBBINS, 2000) e têm se mostrado suscetíveis à interferência de fatores genéticos, como polimorfismo val158met da COMT, que modifica a atividade desta enzima (CHEN, et al., 2004), e que tem sido relacionado a alterações atencionais (WILLIAMS-GRAY, et al., 2008) e executivas (WILLIAMS- GRAY, et al., 2007) na DP.

Nossos resultados indicaram que não houve associação entre o desempenho dos pacientes nas tarefas que mensuram função executiva (Teste de stroop, e de Classificação de Cartas de Wisconsin), os quais dependem do funcionamento do CPF, e o polimorfismo val158met da COMT. Outros estudos já investigaram a relação entre o genótipo da COMT e o desempenho de pacientes com DP na função executiva, entretanto, os resultados obtidos são controversos, pois enquanto uns trabalhos observam alteração no desempenho executivo em função do genótipo (FOLTYNIE et al., 2004; WILLIAMS-GRAY et al., 2007), outros não relatam tais achados (HOOGLAND et al., 2010).

Outro aspecto cognitivo dependente do CPF avaliado nos pacientes com DP foi a memória contextual, a qual não demonstrou estar associada com o genótipo da COMT. O que está de acordo com um estudo prévio, que investigou a influência do polimorfismo sobre outro tipo de memória (FOLTYNIE et al., 2004) e não encontrou nenhuma relação.

Apesar de não ter sido observada associação entre o polimorfismo val158met da COMT e memória contextual, estudos futuros são necessários para identificar marcadores biológicos capazes de predizer o desempenho cognitivo dos pacientes com DP, os quais representariam importante ferramenta para o estabelecimento de diretrizes do tratamento destes pacientes.

Considerando-se que os pacientes com DP com alta (val/val) e baixa atividade da COMT (met/met) não diferiram quanto ao desempenho nas tarefas dependentes da função frontal (Teste de Stroop, de Classificação de Cartas de Wisconsin e memória contextual), foram reunidos num único grupo e então verificou-se a interferência da realização de atividades concomitantes sobre o desempenho cognitivo destes pacientes em comparação a um grupo de voluntários saudáveis.

As alterações cognitivas observadas na DP referem-se a déficits na função frontal. Deste modo, torna-se importante investigar tais alterações, considerando o impacto negativo que podem acarretar na qualidade de vida dos pacientes.

Os pacientes com DP tiveram prejuízos na performance cognitiva durante a realização das tarefas simultâneas, em comparação à performance nas tarefas cognitivas não associadas à caminhada, diferentemente dos voluntários saudáveis que não apresentaram tal alteração.

Através da mensuração do custo associado à realização das tarefas simultâneas, em inglês denominado “dual-task cost” (DTC), observamos que a realização das tarefas concomitantes acarretou mais dificuldade para os pacientes, já que quando comparados aos voluntários saudáveis, os valores de DTC dos pacientes foram superiores para todas as tarefas cognitivas (interpretação de texto, contagem de fonemas e tarefa aritmética), apesar de somente o valor de DTC associado à tarefa aritmética ter alcançado significância estatística.

O fato de o aumento nos valores de DTC não ter sido homogêneo para todas as tarefas desempenhadas pelos pacientes pode ter sido influenciado pela natureza e dificuldade das tarefas. Trabalhos que tem investigado alterações cognitivas em idosos sugerem que tarefas que envolvem subtrações matemáticas, exigindo maior demanda de memória de trabalho, geram maior carga cognitiva do que aquelas tarefas de fluência verbal, que estão mais relacionadas à memória semântica (BEAUCHET et al., 2005).

Considerando que a maior alteração no desempenho cognitivo ocorreu na tarefa que demandou mais atenção e função executiva, treinamentos envolvendo habilidades de realização de tarefas simultâneas com ênfase em estratégias atencionais e executivas poderiam ser promissores, com implicações bastante amplas na qualidade de vida dos pacientes.

Em resumo, não foi observada associação entre a função frontal dos pacientes em estágios iniciais da DP, e o polimorfismo val158met da COMT. A realização de tarefas simultâneas gerou maiores alterações cognitivas para os pacientes com DP, em relação aos controles, e o grau em que o desempenho cognitivo foi afetado pode estar associado à carga atencional e executiva exigida por cada tarefa.

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