Tamine Teixeira da Costa Capato

**Avaliação clínica e manejo do equilíbrio
na doença de Parkinson**

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Universidade de São Paulo para a obtenção do
título de Doutora em Ciências

Programa de Neurologia

Orientador: Prof. Dr. Egberto Reis Barbosa

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Responsável: Erinalva da Conceição Batista, CRB-8 6755

*À minha família, minha base incondicional
em todas as horas.*

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Resumo

Capato TTC. *Avaliação clínica e manejo do equilíbrio na doença de Parkinson* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2020.

Introdução: O comprometimento do equilíbrio na doença de Parkinson (DP) melhora apenas parcialmente com a medicação dopaminérgica. Portanto, intervenções não farmacológicas, como a fisioterapia, são elementos importantes no manejo clínico. Os estímulos externos são frequentemente aplicados para melhorar a marcha, mas seus efeitos no controle do equilíbrio não são claros. **Objetivos:** (1) Desenvolver um protocolo de avaliação e exercícios de equilíbrio com pistas auditivas rítmicas para melhorar e manter o equilíbrio na DP; (2) realizar um ensaio clínico prospectivo, randomizado e duplo-cego para estudar a eficácia do treinamento de equilíbrio com e sem estímulos auditivos rítmicos. **Métodos:** Nós selecionamos 201 voluntários por telefone; 154 foram distribuídos aleatoriamente em três grupos: (1) treino de equilíbrio com pistas auditivas rítmicas (treinamento de equilíbrio multimodal); (2) treino de equilíbrio padrão sem pistas auditivas rítmicas; e (3) controle de intervenção envolvendo um programa de educacional sobre DP. O treinamento foi realizado por 5 semanas, duas vezes / semana. O desfecho primário foi a pontuação do Mini-BESTest (MBEST) imediatamente após o período de treinamento. As avaliações foram realizadas por um avaliador único, cego no início do estudo, imediatamente após a intervenção, e após 1 e 6 meses de follow-up. **Resultados:** Foram incluídos 154 pacientes: treinamento multimodal (n = 56); treinamento padrão (n = 50); controles (n = 48). Grupos eram comparáveis no início do estudo. Diretamente pós intervenção, o treinamento multimodal foi mais eficaz do que o treinamento padrão ($p < 0,001$). Os pacientes alocados para ambas as intervenções ativas melhoraram em comparação aos controles no MBEST ($p < 0,001$) para treinamento multimodal e ($p < 0,001$) para treinamento padrão. As

melhorias foram mantidas no acompanhamento de um mês para ambas as intervenções ativas, mas apenas o grupo de treinamento multimodal manteve sua melhora em 6 meses. Conclusão: Tanto o treinamento multimodal quanto o treinamento padrão melhoram o equilíbrio, mas o treinamento multimodal - acrescentando pistas auditivas rítmicas à fisioterapia de rotina - tem efeitos maiores e mais sustentados.

Descritores: Doença de Parkinson; Fisioterapia; Exercícios; Estudo clínico randomizado; Equilíbrio; Marcha; Tratamento; Pistas externas.

Abstract

Capato TTC. *Clinical assessment and management of balance in Parkinson's disease* [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2020.

Background: Balance impairment in Parkinson's disease (PD) improves only partially with dopaminergic medication. Therefore, non-pharmacological interventions such as physiotherapy are important elements in clinical management. External cues are often applied to improve gait, but their effects on balance control are unclear. Objective: (1) to perform an assessment and exercises protocol with rhythmic cues to improve gait and balance in PD; (2) to performed a prospective, single-blind, randomized clinical trial to study the effectiveness of balance training with and without rhythmical auditory cues. Methods: We screened 201 volunteers by telephone; 154 were assigned randomly into three groups: (1) balance training with rhythmical auditory cues (multimodal balance training); (2) standard balance training without rhythmical auditory cues; and (3) control intervention involving a general education program. Training was performed for 5 weeks, two times/week. Primary outcome was the Mini-BESTest (MBEST) score immediately after the training period. Assessments were performed by a single, blinded assessor at baseline, immediately post intervention, and after one and 6-months follow-up. Treatment effects will be estimated with a linear mixed model, adjusted for MBEST scores and UPDRS at baseline and levodopa equivalent daily dose. Results: 154 patients were included: multimodal training (n=56); standard training (n=50); controls (n=48). Groups were comparable at baseline. Directly post intervention, multimodal training was more effective than standard training ($p<0.001$). Patients allocated to both active interventions improved compared to controls (MBEST estimated mean difference versus controls ($p<0.001$) for multimodal training and ($p<0.001$) for standard training. Improvements were retained at one-month follow-up for both

active interventions, but only the multimodal training group maintained its improvement at 6 months. Conclusion: Both multimodal training and standard training improve balance, but multimodal training – adding rhythmical auditory cues to routine physiotherapy – has greater and more sustained effects.

Descriptors: Parkinson disease; Physical therapy; Exercises; Clinical trial; Balance; Gait; Treatment; External cues.

1. Introdução

A doença de Parkinson (DP) é um distúrbio neurológico comum e complexo que envolve sintomas motores e não motores (Kalia and Lang 2015). Os sintomas motores clássicos da doença de Parkinson reconhecidos como componentes proeminentes da doença são: bradicinesia, rigidez, tremor de repouso e instabilidade postural (Gibb and Lees 1988). Foram descritos inicialmente por James Parkinson no Século XIX (1817) (Parkinson 2002) e posteriormente refinados por Jean-Martin Charcot (Goetz 2011). Pesquisas recentes estabeleceram que a instabilidade postural e alterações da marcha são comuns desde os estágios iniciais da DP (Bloem, Hausdorff et al. 2004, Tomlinson, Patel et al. 2012, Ginis, Nackaerts et al. 2018). Ambos ocasionam quedas que podem acarretar em lesões e consequentemente aumentar o medo de cair, reduzindo a mobilidade e independência funcional (van der Marck, Klok et al. 2014, Ellis, Cavanaugh et al. 2016). Fatores de risco para quedas, como instabilidade postural e congelamento da marcha, geralmente respondem apenas parcialmente à medicação antiparkinsoniana (van der Marck and Bloem 2014, Curtze, Nutt et al. 2015). Por esse motivo, as intervenções não farmacológicas, como por exemplo a fisioterapia, são atualmente recomendadas como um elemento no tratamento na DP (Fox, Katzenschlager et al. 2018, Armstrong and Okun 2020). Apesar das evidências crescentes sobre intervenções não farmacológicas para melhorar a mobilidade (Morris 2006, Keus, Munneke et al. 2014) e minimizar as quedas (Canning, Sherrington et al. 2015, Morris, Menz et al. 2015), o programa de prevenção mais eficaz a longo prazo ainda é desconhecido.

A fisioterapia vem sendo amplamente reconhecida como um importante elemento no manejo da marcha (Nieuwboer, Kwakkel et al. 2007, Rochester, Baker et al. 2010, Rochester, Baker et al. 2011, Strouwen, Molenaar et al. 2017, Ginis, Nackaerts et al. 2018). Alguns estudos também mostraram que a fisioterapia é efetiva para o equilíbrio na DP (Santos, da Silva et al. 2017, Lirani-Silva, Lord et al. 2019).

Devido à depleção dopaminérgica na via nigroestriatal, os pacientes com DP apresentam dificuldades para executar automaticamente movimentos sequenciais, como mudar os passos durante a marcha (Griffin, Greenlaw et al. 2011, Barthel, Nonnekes et al. 2018). Essa dificuldade pode ser minimizada pelo uso de pistas externas, como por exemplo, o som rítmico de um metrônomo (Rochester, Burn et al. 2009, Rochester, Baker et al. 2010). Além disso, pistas externas sensoriais (auditivas, visuais ou táteis) demonstraram eficácia na melhora dos problemas de marcha na DP (Nieuwboer, Kwakkel et al. 2007).

Atualmente, pistas externas são frequentemente aplicadas por fisioterapeutas especializados na prática clínica (Keus, Munneke et al. 2014, Barthel, Nonnekes et al. 2018, Capato, Nonnekes et al. 2019, Nonnekes, Ruzicka et al. 2019). No entanto, ainda não está claro se as pistas externas também podem ter efeito no desempenho do equilíbrio na DP. Além disso, o treinamento de equilíbrio por fisioterapeutas ainda não é padronizado. Nossa hipótese é que, em comparação com o treinamento padrão, a adição de pistas auditivas rítmicas seria mais eficaz para melhorar o desempenho não só da marcha, mas também do equilíbrio mas esses efeitos diminuiriam com o tempo (como no desempenho da marcha).

2. Objetivos

2.1. Desenvolver um protocolo de avaliação e exercícios de equilíbrio com pistas auditivas rítmicas para melhorar e manter o equilíbrio na doença de Parkinson.

2.2. Desenvolver um ensaio clínico prospectivo randomizado, com o objetivo de (1) investigar se o efeito da fisioterapia no desempenho do equilíbrio em pacientes com DP seria aumentado pela adição de sinais rítmicos auditivos ao treinamento (treinamento multimodal de equilíbrio); e (2) investigar se esses efeitos seriam mantidos a longo prazo, após a cessação do tratamento.

3. Revisão da Literatura

3.1. Doença de Parkinson

A doença de Parkinson (DP) é um distúrbio neurodegenerativo caracterizado por sintomas motores e não motores (Kalia and Lang 2015). Frequentemente é reconhecida por seus sintomas motores: tremor de repouso, bradicinesia, rigidez e instabilidade postural (Gibb and Lees 1988, Goetz 2011). À medida que a doença progride, a instabilidade postural e os distúrbios da marcha também aparecem com mais frequência (Goetz 2011). Além disso, os vários subtipos de doença de Parkinson têm hipóteses de ter etiologias e patogênese distintas (Berg, Lang et al. 2013, Marras and Lang 2013, Kalia and Lang 2015).

É importante ressaltar que os pacientes com DP também podem experimentar uma ampla gama de sintomas não motores, como uma capacidade reduzida do olfato, distúrbios do sono, déficits cognitivos e transtornos do humor (Khoo, Yarnall et al. 2013, Schapira, Chaudhuri et al. 2017). Esses sintomas motores e não motores na DP podem ser atribuídos principalmente à depleção dopaminérgica na substância negra e na via nigroestriatal ao estriado (núcleo caudado e putâmen) (Kalia and Lang 2015, Schapira, Chaudhuri et al. 2017). Entretanto, outros sistemas neurotransmissores centrais, como os sistemas noradrenérgicos, colinérgicos e serotoninérgicos, também podem ser afetados. As lesões extranigrais tornam-se mais proeminentes com a progressão da doença (Schapira, Chaudhuri et al. 2017).

3.1.3. Prevalência

Atualmente, estima-se que 6,3 milhões de pessoas no mundo têm DP (Pringsheim, Jette et al. 2014, 2017, 2018). No Brasil, há um grande número de indivíduos com DP, com taxas de prevalência de 3,3% (Barbosa, Caramelli et al. 2006). Como a incidência de DP está aumentando acentuadamente com a idade e a população mundial está envelhecendo, o número de indivíduos afetados também está posicionado para um crescimento exponencial (Dorsey and Bloem 2018, Dorsey, Sherer et al. 2018). A DP é observada principalmente acima da idade de 60 anos, mas também pode afetar pessoas mais jovens (Pringsheim, Jette et al. 2014).

3.1.3. Sinais e sintomas

As características motoras em pacientes com doença de Parkinson são heterogêneas e um consenso sobre a classificação dos subtipos ainda não foi completamente estabelecido (Marras and Lang 2013). Observações clínicas sugerem dois subtipos principais: tremor dominante (com relativa ausência de outros sintomas motores) e não tremor dominante (que inclui fenótipos descritos como síndrome rígida e distúrbio de marcha e instabilidade postural). Um subgrupo adicional de pacientes com doença de Parkinson é diferenciado por fenótipo misto ou indeterminado com vários sintomas motores (Jankovic, McDermott et al. 1990, Postuma, Berg et al. 2015).

3.1.3.4. Tremor, rigidez, bradicinesia

Tremor

Tremor de repouso é o mais comum e facilmente reconhecido sintoma de DP. Os tremores são unilaterais, ocorrem em uma frequência entre 4 e 6 Hz, e quase sempre são proeminentes na parte distal de uma extremidade. Os tremores nas mãos são descritos como supinação-pronação ("rolar pílulas" ou "contar dinheiro"). O tremor de repouso em pacientes com DP também pode envolver os lábios, queixo, mandíbula e pernas. Caracteristicamente, o tremor de repouso desaparece com a ação e durante o sono (Jankovic 2008).

Rigidez

A Rigidez refere-se à resistência independente da velocidade ao movimento passivo não refletindo apenas falha para relaxar (ou seja, distinta da espasticidade ou paratonia). O fenômeno da roda dentada está frequentemente presente (Postuma, Berg et al. 2015). Conforme a MDS-UPDRS (Goetz, Tilley et al. 2008), a rigidez é avaliada no "movimento passivo lento das grandes articulações com o paciente em uma posição relaxada e o examinador manipulando os membros e o pescoço.

Bradicinesia

A DP é, por definição, uma doença assimétrica e a bradicinesia está frequentemente presente em estádios iniciais da doença (Kalia & Lang, 2015). O conceito de acinesia pode incluir a característica do tempo de reação lenta porque o movimento não ocorre quando esperado (Berardelli, Wenning et al. 2013). Sabe-se que a Bradicinesia promove o atraso nas estratégias adequadas

de equilíbrio e reações protetoras (Horak, Mancini, Carlson-Kuhta, Nutt, & Salarian, 2016), sendo um dos aspectos que contribuem para instabilidade postural.

Embora a DP tenha sido inicialmente considerada como uma doença motora, atualmente os sintomas não motores tem sido amplamente reconhecidos (Armstrong and Okun 2020). A maioria dos sintomas não motores podem ser classificados em 3 categorias: (1) disfunção autonômica; (2) sintomas cognitivos e psiquiátricos e (3) distúrbios do sono (Khoo, Yarnall et al. 2013). Dentre as disfunções autonômicas, podemos destacar a hipotensão ortostática, constipação, disfunção urinária, disfunção sexual, salivação excessiva. Já os distúrbios cognitivos mais comuns são demência, tomada de decisão, planejamento e comportamento direcionado à metas. Os distúrbios psiquiátricos e de humor se manifestam por alucinação, depressão, ansiedade, apatia, transtornos de controle do impulso e comportamentos compulsivos. Por fim, os distúrbios do sono geralmente são problemas com início e manutenção do sono, distúrbio de comportamento do sono REM, sonolência diurna excessiva, síndrome das pernas inquietas, dificuldades para virar na cama (Khoo, Yarnall et al. 2013, Schapira, Chaudhuri et al. 2017).

Alguns desses sintomas não motores podem preceder os sintomas não motores e podem ser muito debilitantes (Seppi, Ray Chaudhuri et al. 2019). Alguns sintomas não motores tais como: hipotensão ortostática, declínio cognitivo, depressão, ansiedade, apatia e sonolência diurna excessiva, podem também prejudicar a marcha e equilíbrio e aumentar o risco de quedas (Seppi, Ray Chaudhuri et al. 2019)

3.1.4. Instabilidade postural

A instabilidade postural é comum na DP e juntamente com o *freezing da marcha* (*FOG/congelamento da marcha*), são alguns dos principais fatores de risco para quedas (van der Marck, Klok et al. 2014, Almeida, Sherrington et al. 2015). problemas alterações da marcha e equilíbrio na DP são comuns e progressivamente incapacitantes (Bloem, Hausdorff et al. 2004, Kalia and Lang 2015, Ellis, Cavanaugh et al. 2016). Essas alterações podem resultar em quedas e lesões relacionadas à quedas (van der Marck, Klok et al. 2014, Paul, Harvey et al. 2017).

Recentemente um estudo identificou os fatores de risco e as opções de manejo disponíveis para evitar quedas na DP (van der Marck, Klok et al. 2014). Este estudo enfatizou que intervenções isoladas são apenas parte da solução do problema, e que a maioria dos pacientes necessita de uma abordagem de tratamento multidisciplinar e multifacetada. De fato, a fisiopatologia das quedas em pacientes com DP é muito complexa (Bloem, Hausdorff et al. 2004), quase sempre de natureza multifatorial e difere para cada indivíduo (van der Marck, Klok et al. 2014). A identificação adequada desses distúrbios em estágios iniciais é importante porque eles podem fornecer dicas e indicar o tratamento adequado para prevenir quedas na DP (Bekkers, Dijkstra et al. 2018).

3.1.5. Marcha e Freezing of gait (FOG / congelamento da marcha)

Marcha

As alterações de marcha podem surgir nos estágios iniciais da doença. Podemos distinguir as alterações da marcha em dois tipos (1) distúrbios contínuos e (2) distúrbios episódicos (Hausdorff, Balash et al. 2003). Os distúrbios contínuos (deficiências gerais) incluem a redução assimétrica ou ausência de balanço do braço, postura inclinada, redução e variação do comprimento do passo e dificuldades para virar. Com a progressão da DP, a marcha torna-se mais lenta e com pequenos passos. O padrão de marcha geralmente piora quando uma tarefa cognitiva é adicionada (dupla tarefa) (Mak 2013). Os distúrbios episódicos incluem a festinação e o *Freezing of gait* /*congelamento da marcha* (Nutt, Bloem et al. 2011).

Freezing of gait /congelamento da marcha

O *freezing of gait* (FoG) (congelamento da marcha) é definido como ausência breve e episódica ou redução da progressão apesar da intenção de andar (Nutt, Bloem et al. 2011). A “sensação dos pés estarem colados no chão” e o deslocamento anterior da parte superior do corpo, aumenta o risco de quedas, lesões relacionadas à queda e medo de cair. De fato, o FOG acaba sendo uma das causas mais comuns de quedas em pacientes com DP (Rudzinska, Bukowczan et al. 2013). É possível provocar FOG em ambiente clínico (Snijders, Haaxma et al. 2012). O FOG comumente ocorre quando se começa a andar, virar, caminhar por portais estreitos e em dupla tarefa (Gilat, Ligia Silva de Lima et al. 2018, Nonnekes, Ruzicka et al. 2019).

Sabe-se que as redes cerebrais envolvidas no FOG, incluem as redes motora e pré-motora, a rede de atenção executiva, a rede visuoespacial do lado direito, o núcleo caudado e a região locomotora mesencefálica (Fasano, Herman et al. 2015). No entanto, ainda não é claro quais são os mecanismos subjacentes envolvidos no FOG. O *freezing*/congelamento na doença de Parkinson (DP) não se restringe à marcha (Walter Maetzler 2016). Os pacientes também podem experimentar o congelamento nos membros superiores (FOUL) (Nieuwboer, Vercruysse et al. 2009, Capato, Nonnekes et al. 2019).

3.1.6. Tratamento farmacológico e cirúrgico na Doença de Parkinson

As terapias sintomáticas para a doença de Parkinson continuam baseadas na reposição dopaminérgica (Verschuur, Suwijn et al. 2019). Nos estágios iniciais, ainda há um benefício em manter os níveis de levodopa o mais baixos possível, ou usar alternativas para o uso "reserva" ou a quantidade de levodopa (Fox, Katzenschlager et al. 2018, Kulisevsky, Oliveira et al. 2018). Um estudo clínico controlado randomizado de fase II (com uma única tabela - P2B001; combinação de inibidores de Monoamina Oxidase B de baixa dose (MAOB), rasagilina e agonista de dopamina de baixa dosagem de pramipexol) encontrou benefício muito pequeno no total na UPDRS (Olanow, Kieburtz et al. 2017). No entanto, estudos de longo prazo são necessários para determinar os possíveis efeitos no atraso das complicações motoras como as discinesias (Verschuur, Suwijn et al. 2019).

Outro estudo clínico randomizado demonstrou uma abordagem alternativa na doença de Parkinson precoce, visando receptores não-dopaminérgicos. O

antagonista da adenosina A2A, foi avaliado em fase III, como monoterapia, mas não demonstrou benefício significativo quando comparado ao placebo, ou do controle ativo da rasagilina, em mais de 1000 pacientes com doença de Parkinson precoce (Stocchi, Rascol et al. 2017).

3.1.6.1. Tratamento da marcha e equilíbrio na Doença de Parkinson

Como discutido anteriormente, a marcha e o equilíbrio são frequentemente pouco responsivos à levodopa devido ao envolvimento de vias não-dopaminérgicas (Ferraye, Ardouin et al. 2013). Estudos investigaram o uso de inibidores da colinesterase (donepezil e rivastigmina) para reduzir quedas em patologia que comprometem centros de tronco encefálico envolvidos na marcha e equilíbrio resultando em disfunção colinérgica (Chung, Lobb et al. 2010, Henderson, Lord et al. 2016). No entanto até o momento, as evidências são conflitantes em relação a esses benefícios (Fox, Katzenschlager et al. 2018).

O envolvimento adrenérgico e glutamatérgico na marcha também foi alvo de um estudo que usou metilfenidato e memantina, respectivamente (Moreau, Delval et al. 2012). Não foi encontrada evidência de benefício para o tratamento de distúrbios da marcha.

Recentemente houve um refinamento das técnicas de neuromodulação usadas para o manejo da marcha na DP (Debu, De Oliveira Godeiro et al. 2018). A estimulação bilateral do globo pálido interno (GPI) ou do núcleo subtalâmico (NST) (Odekerken, van Laar et al. 2013), tem sido utilizadas no tratamento de pacientes com DP (Fox, Katzenschlager et al. 2018). As

flutuações motoras induzidas por levodopa, como discinesias, tem boa resposta à estimulação cerebral profunda expressa pela melhora da qualidade de vida (Charles, Konrad et al. 2014). No entanto, as questões axiais podem se tornar ainda mais incapacitantes levando à um prejuízo funcional importante (Debu, De Oliveira Godeiro et al. 2018). Outros alvos tem sido estudados, como a medula espinhal (Pinto de Souza, Hamani et al. 2017, Hubsch, D'Hardemare et al. 2019).

No entanto, os estudos clínicos de estimulação da medula espinhal são muito pequenos e são necessárias mais pesquisas para verificar a efetividade desses procedimentos (Nicolelis, Fuentes et al. 2010). Além disso, esses estudos realizados até o momento, mostram variedade nos parâmetros de estimulação e heterogeneidade da população (Cury 2020). Portanto, a estimulação da medula espinhal parece ser uma terapia promissora (Prasad, Aguirre-Padilla et al. 2020). No entanto, nesse momento, ainda não é possível estabelecer um consenso robusto sobre essa intervenção (Cury 2020).

Em síntese, os principais tratamentos sintomáticos incluem farmacoterapia (principalmente agonistas dopaminérgicos e levodopa), estimulação cerebral profunda (para um subgrupo restrito e selecionado de pacientes) (Fox, Katzenschlager et al. 2018, Armstrong and Okun 2020), as terapias não farmacológicas (Bloem, de Vries et al. 2015, Armstrong and Okun 2020) e apoio multidisciplinar (van der Marck, Munneke et al. 2013, Ypinga, de Vries et al. 2018, Radder, de Vries et al. 2019).

3.1.6.2. Tratamento não farmacológico – Fisioterapia

Os exercícios são um subconjunto da atividade física e uma das ferramentas utilizadas pela fisioterapia para melhorar o desempenho motor dos pacientes com DP. Os exercícios aeróbicos (Schenkman, Moore et al. 2018, van der Kolk, de Vries et al. 2019) e exercícios generalizados, como por exemplo exercícios de força e resistência muscular, alongamento, dança, tai chi (Mak, Wong-Yu et al. 2017) estão sendo cada vez mais reconhecidos como elementos importantes no manejo clínico da DP (Fox, Katzenschlager et al. 2018). É reconhecido que o exercício aeróbico por si só pode não ser o único tipo de exercício que para gerenciar os sintomas da DP (Alberts and Rosenfeldt 2020). No entanto, o exercício generalizado com efeitos de longo prazo para melhorar o equilíbrio e o padrão de marcha, incluindo freezing, ainda é desconhecido.

Até o momento, as evidências mostram que as intervenções de fisioterapia são as recomendadas como elementos de escolha no manejo da marcha (Nieuwboer, Kwakkel et al. 2007, Rochester, Baker et al. 2011, Strouwen, Molenaar et al. 2017, Fox, Katzenschlager et al. 2018, Ginis, Nackaerts et al. 2018) e do equilíbrio na DP (Lofgren et al., 2019; Santos et al., 2017, (Smania, Corato et al. 2010, Santos, da Silva et al. 2017, Lirani-Silva, Lord et al. 2019, Lofgren, Conradsson et al. 2019). Os programas de exercícios multifacetados podem ter maiores benefícios para marcha, equilíbrio e sintomas axiais. O treinamento fisioterapêutico tipicamente envolve exercícios funcionais de marcha e equilíbrio (como levantar-se do sentar-se) (Tomlinson, Patel et al. 2012, Keus, Munneke et al. 2014, Mak, Wong-Yu et al. 2017), que podem ser

generalizados às atividades de vida diária (Yarnall, Rochester et al. 2011, Ferrazzoli, Ortelli et al. 2018, Paul, Dibble et al. 2018).

A fisioterapia é comumente prescrita, em conjunto com tratamentos farmacológico e cirúrgicos (Tomlinson, Patel et al. 2012, Fox, Katzenschlager et al. 2018). Devido à depleção de dopamina na via nigroestriatal, os pacientes em DP apresentam dificuldades para executar automaticamente movimentos sequenciais, como dar os passos no tamanho e velocidade adequada durante a caminhada (Griffin, Greenlaw et al. 2011, Barthel, Nonnekes et al. 2018). Essa dificuldade pode ser minimizada pelo uso de pistas externas, como o som rítmico de um metrônomo (Nieuwboer, Kwakkel et al. 2007). Pistas externas sensoriais (auditivas, visuais ou táteis) demonstraram melhorar expressivamente a marcha na DP e são frequentemente aplicadas por fisioterapeutas em pacientes com DP (Nieuwboer, Kwakkel et al. 2007, Strouwen, Molenaar et al. 2017, Barthel, Nonnekes et al. 2018). Fisioterapia associada à dupla tarefa pode beneficiar a marcha na DP (Strouwen, Molenaar et al. 2017). Usar dupla tarefa durante o treino de marcha pode aumentar o risco de quedas. Portanto, mais estudos são necessários para confirmar essas afirmações (De Freitas Tb Ms, Leite et al. 2020).

Pistas externas

Durante as sessões de fisioterapia, estratégias de compensação para deficiências de marcha e equilíbrio são aprendidas pelos pacientes com DP (Morris 2000, Morris 2006). As pistas externas são uma dessas estratégias e atuam como estímulos temporais ou espaciais que, associados ao movimento a

ser executado, facilitando o desempenho (Rochester, Baker et al. 2010). As pistas externas podem ser distinguidas em (1) pistas visuais (linhas projetadas no chão), (2) pistas auditivas (geradas por metrônomo) e (2) pistas táteis (ou proprioceptivas). Até o momento, os melhores resultados para marcha, foram obtidos com o uso de pista visual e auditiva (Nieuwboer, Kwakkel et al. 2007).

As pistas rítmicas têm um efeito imediato e expressivo no desempenho da marcha (melhora na velocidade, comprimento da passada e congelamento da marcha) (Nieuwboer, Kwakkel et al. 2007, Ginis, Nackaerts et al. 2017) e esses efeitos foram mantidos em 12 semanas de seguimento (Rochester, Baker et al. 2010). No entanto, não está claro se a fisioterapia envolvendo pistas externas também é capaz de melhorar o desempenho do equilíbrio na DP. Além disso, o treinamento de equilíbrio por fisioterapeutas atualmente não é padronizado. Nossa hipótese é que, em comparação com o treinamento padrão, a adição de pistas auditivas rítmicas seria mais eficaz para melhorar o desempenho do equilíbrio, mas esses efeitos diminuiriam com o tempo (como já foi relatado no desempenho da marcha). Por esta razão, as intervenções em estágios iniciais da doença deveriam também ser direcionadas para melhorar a disfunção da marcha e as estratégias posturais antes que os pacientes desenvolvam risco de quedas (Keus et al., 2014).

4. Métodos

4.1. Tipo de Estudo

Esse projeto envolve um estudo clínico randomizado, prospectivo, duplo-cego e paralelo. Este estudo foi registrado no Clinical trials.gov Identifier (NCT02488265). Detalhes de recrutamento, todos os procedimentos, avaliação do padronizada, diretrizes de treinamento, progressão do treinamento e o protocolo completo foram publicados anteriormente (Capato, Tornai et al. 2015) (ANEXO 1).

4.2. Casuística

Um total de 201 pacientes com DP foram recrutados para o estudo e um total de 154 pacientes foram incluídos de acordo com os critérios de elegibilidade.

4.3 Critérios de Elegibilidade

Os critérios de inclusão foram: (1) diagnóstico de DP de acordo com os critérios do UK Brain Bank (Hughes, Daniel et al. 1992); (2) Hoehn e Yahr (H & Y) estágio 1-3 (Hoehn and Yahr 1967); (3) história de quedas no ano passado; (4) capaz de caminhar 10 minutos continuamente; (5) Mini Exame do Estado Mental (MMSE) ≥ 24 (Tombaugh and McIntyre 1992); (6) capaz de andar de forma independente em ambientes fechados, sem auxílio da marcha; (7) medicação estável nos últimos 3 meses; (8) nenhuma audição ou problemas

visuais interferindo nos testes ou treinamento; e (9) configurações estáveis do estimulador cerebral profundo durante o ano que antecedeu o estudo. Nenhuma outra intervenção de fisioterapia ou exercícios complementares foram permitidos durante o estudo. Os pacientes foram categorizados como *freezer* (congelador) ou *non-freezer* (não congelador), se o congelamento estivesse presente de forma subjetiva (NFOG-Q) (Nieuwboer, Rochester et al. 2009) ou objetivamente (Rapid Turns Test) (Snijders, Haaxma et al. 2012). Se em qualquer um desses testes o paciente apresentou *freezing/congelamento*, os pacientes foram classificados como *freezers/congeladores*.

4.4. Alocação

Os sujeitos foram distribuídos aleatoriamente entre três grupos. A randomização foi obtida por meio de uma tabela de sequência aleatória gerada por computador. O primeiro grupo experimental denominado treinamento multimodal (MT) recebeu treinamento de habilidades motoras com pistas auditivas rítmicas marcadas por um metrônomo. O segundo grupo experimental recebeu o mesmo treinamento, sem pistas rítmicas (treinamento padronizado - ST). E o grupo de controle (CG) não recebeu exercícios, receberam uma intervenção controle (programa educacional - orientações sobre quedas, autocuidado e sobre a DP (Capato, Domingos et al. 2015, Capato 2016). A duração de cada um dos três programas foi de 5 semanas, com duas sessões por semana (45 minutos por sessão) para os dois braços de intervenção ativos (Capato, Tornai et al. 2015).

4.5. Procedimentos

Os pacientes recrutados foram diagnosticados por neurologistas do Ambulatório de Distúrbios do Movimento do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). Uma breve entrevista telefônica foi conduzida sobre seu histórico médico e pessoal e auto avaliação do desempenho do equilíbrio (Capato 2016).

Para as finalidades desse estudo, elaboramos uma avaliação padrozinada e específica para identificar as principais alterações de marcha e equilíbrio. Todas as escalas e testes validados para Doença de Parkinson utilizados nesse estudo para avaliar a marcha e equilíbrio podem ser encontradas na Versão em Português da Diretriz Européia de Fisioterapia para Doença de Parkinson (Capato, Domingos et al. 2015). Nessa Diretriz, as escalas foram traduzidas e adaptadas para o português. Os métodos utilizados e as etapas empregadas no processo de tradução da Diretriz foi baseado no uso de informações e experiência de uma variedade de fontes e recentemente descritos detalhadamente (Domingos, Capato et al. 2020).

Os sujeitos foram avaliados antes e imediatamente após a intervenção. O resultado primário foi o Mini BESTest obtido imediatamente após a intervenção (Franchignoni, Horak et al. 2010). Os desfechos secundários incluem uma gama de medidas para equilíbrio, marcha e quedas. O equilíbrio foi avaliado pela Escala de Equilíbrio de Berg (BBS) (Berg, Wood-Dauphinee et al. 1992), Retropulsion test (PRT) (Jacobs, Horak et al. 2006). A marcha foi

avaliada usando o teste Timed Up and Go (TUG)(Podsiadlo and Richardson 1991) e o New Freezing of Gait Questionnaire (NFOG-Q) (Nieuwboer, Rochester et al. 2009); Rapid tourn test (Snijders, Haaxma et al. 2012). As atividades de vida diária e o status motor, foram avaliados pela Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn S 1987).

O medo de cair durante uma variedade de atividades cotidianas foram medidas pela Falls Efficacy Scale (FES-I) (Yardley, Beyer et al. 2005). O número de quedas foi registrado através de entrevistas padronizadas com fisioterapeuta do hospital, utilizando um formulários de pontuação (Capato, Tornai et al. 2015). Um acompanhamento semanal de queda também foi realizado. Todos os desfechos foram avaliados por um único avaliador, que desconhecia a alocação do tratamento. O teste foi realizado em 4 visitas (antes da intervenção (*baseline*) e após o treinamento, 1 mês e 6 meses de seguimento), enquanto eles estavam em sua medicação habitual de Parkinson durante período "ON".

Cada sessão nos dois grupos de exercícios foi dividida em 5 minutos de aquecimento, 30 minutos para a parte principal e 10 minutos para o resfriamento. Os exercícios foram repetidos em sessões subsequentes para consolidar o aprendizado. Os sujeitos tinham que ser capazes de associar as correções propostas na primeira semana. Para ambos os grupos de exercícios, o fisioterapeuta usou um comando verbal antes de cada movimento, antecipando e encorajando os mais difíceis. Apenas os pacientes do grupo multimodal foram orientados para se concentrar nas pistas auditivas rítmicas fornecidas por um metrônomo. Na quarta semana, os sujeitos deveriam ser

capazes de executar 20 repetições das sequências de exercícios com velocidade crescente.

Análise Estatística

A análise primária dos dados foi realizada de acordo com o princípio da intenção de tratar, analisando todos os participantes incluídos no estudo. Usamos um modelo linear misto. Os fatores fixos foram o tratamento (MT vs ST vs. GC), visitas (1, 2, 3 e 4) e a interação entre o paciente e o grupo de tratamento. As medidas secundárias foram analisados de maneira semelhante. Dose medicação como dose equivalente de levodopa (LEDD) foi explorado como um possível efeito de interação. Os dados de frequência de queda foram analisados usando o modelo binomial.

5. Resultados preliminares

Análise primária

Nós selecionamos 201 participantes em potencial para participar do estudo, dos quais 154 foram randomizados (Figura 1). Os grupos foram semelhantes nas características demográficas na avaliação inicial (Tabela 1). Um total de 21 pacientes abandonou o estudo (14%, Figura 1). A aderência ao treinamento foi excelente; 85% no grupo de treinamento multimodal, 86% no grupo de treinamento padrão e 82% no grupo de intervenção controle. Razões para não comparecerem ao treino foram falta de tempo, problemas com transporte, injúrias, doenças secundárias e fadiga não relacionados à sessão de intervenção (Figura 1). Nenhum evento adverso ocorreu durante o treinamento.

Tabela 1. Características demográficas

	Treino Multimodal (MT)	Treino Padrão (ST)	Intervenção Controle (CG)
	N= 56	N= 50	N=48
Idade, (média (SD))	74 (8)	67 (13)	73 (10)
Sexo, homens (N (%))	27 (48%)	32 (64%)	29 (60%)
H&Y (N(%)), I	11 (20%)	11 (22%)	7 (14%)
II	17 (30%)	16 (32%)	18 (38%)
III	28 (50%)	23 (46%)	23 (48%)
Tempo desde os primeiros sintomas (média (IQR))	7 (4-13)	8 (4-14)	11 (4-20)
Tempo de Diagnóstico (média (IQR))	5 (2-9)	6 (2-10)	8 (2-15)
Deep Brain Stimulation (DBS) (N (%))	6 (10%)	7 (14%)	4 (8%)
Freezers/congeladores (N, %)	17 (30%)	15 (30%)	16 (13%)
Caidores recorrentes (N, %)	25 (45%)	21 (38%)	20 (36%)
Injúrias antes da intervenção (N, %)	26 (46%)	23 (46%)	20 (42%)
LEDD, mg/day (media (SD))	615 (424)	701 (466)	698 (389)
MMSE, score (média (SD))	27 (2)	26 (2)	25 (2)
MoCA, score (média (SD))	26 (3)	25 (3)	24 (3)
UPDRS 2, ADL score (media (SD)) (ON)	11 (7)	14 (7)	16 (8)
UPDRS 3, motor score (media (SD)) (ON)	15 (7)	17 (9)	19 (7)
Escolaridade (N, %) 2-8 (anos)	10 (18%)	11 (22%)	8 (17%)
9-14 (anos)	16 (29%)	21 (42%)	17 (35%)
>14	30 (53%)	18 (36%)	23 (48%)

N, número de participantes; SD, *Standard Deviation*; IQR, Interquartile range are presented; ON (ON-medication); LEDD, Dose diária equivalente de Levodopa; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assesment; H&Y, Hoehn & Yahr stage; UPDRS 2, ADL, Activities of daily living score; UPDRS 3, motor score.

Fluxograma

Figura 1. Fluxograma do desenho experimental do estudo, número de participantes.

Resultado primário

A Figura 2A mostra os resultados do nosso resultado primário, o MBEST. Imediatamente após o tratamento, tanto o grupo de treinamento multimodal quanto o grupo de treinamento padrão melhoraram significativamente no escore do MBEST em comparação aos controles. Além disso, o grupo de treinamento multimodal melhorou significativamente mais do que o grupo de treinamento padrão. Essas melhorias foram mantidas no seguimento de um mês para ambos os grupos, mas apenas o grupo de treinamento multimodal manteve sua melhora no seguimento de 6 meses (Tabela 2A).

Figura 2A – Mini-BESTest (MBEST) em cada visita. A linha vermelha representa o treinamento multimodal, a linha preta representa o treinamento padrão e a linha cinza o grupo controle.

Table 2A. Observed mean values and estimated differences and 95% confidence intervals for balance primary and secondary outcome measures.

	MT			Control	MT vs ST		MT vs Control		ST vs Control	
	1	2	3		1-2	1-3				
Mini BESTest	Baseline	17.1 (14.7; 19.3)	14.7 (12.1; 17.4)							
	Post Intervention	21.4 (19.7; 23.0)	19.7 (17.3; 22.9)	14.6 (12.1; 17.2)	3.6 (2.3; 4.9), P<0.001	6.7 (5.3; 8.1), P<0.001	3.1 (1.7; 4.5), P<0.001			
	1 month Follow-up	20.6 (18.8; 22.3)	18.4 (16.0; 20.6)	14.3 (11.9; 16.9)	4.1 (2.8; 5.4), P<0.001	6.1 (4.7; 7.5), P<0.001	2.1 (0.6; 3.5), P=0.005			
	6 month Follow-up	19.1 (17.2; 20.8)	17.1 (15.0; 19.2)	13.9 (11.5; 16.5)	3.8 (2.5; 5.1), P<0.001	4.9 (3.5; 6.3), P<0.001	1.1 (-0.3; 2.5), P=0.130			
Berg Balance Scale	Baseline	38.9 (35.5; 42.1)	40.6 (36.7; 44.4)	37.0 (32.7; 41.5)						
	Post Intervention	47.2 (44.5; 49.7)	43.3 (39.7; 46.9)	36.9 (32.7; 41.2)	5.3 (3.2; 7.3), P<0.001	8.7 (6.6; 10.8), P<0.001	3.4 (1.2; 5.6), P=0.002			
	1 month Follow-up	45.7 (42.8; 48.4)	41.9 (38.1; 45.5)	36.5 (32.0; 40.9)	5.3 (3.3; 7.3), P<0.001	7.8 (5.7; 10.0), P<0.001	2.6 (0.4; 4.8), P=0.023			
	6 month Follow-up	43.3 (39.9; 46.3)	40.5 (36.7; 44.2)	35.6 (31.47; 39.9)	4.2 (2.1; 6.2), P<0.001	6.0 (3.9; 8.2), P<0.001	1.8 (-0.4; 4.0), P=0.100			
Retropulsion Test	Baseline	2.3 (1.9; 2.7)	2.1 (1.7; 2.5)	2.4 (2.0; 2.8)						
	Post Intervention	1.0 (0.8; 1.4)	1.2 (0.8; 1.5)	2.4 (2.0; 2.8)	-0.2 (-0.5; 0.0), P=0.072	-1.2 (-1.6; -0.9), P<0.001	-0.9 (-1.3; -0.7), P<0.001			
	1 month Follow-up	1.2 (0.9; 1.5)	1.7 (1.4; 2.1)	2.5 (2.1; 2.9)	-0.7 (-1.0; -0.4), P<0.001	-1.2 (-1.5; -0.9), P<0.001	-0.5 (-0.8; -0.1), P=0.002			
	6 month Follow-up	1.7 (1.3; 2.1)	2.0 (1.6; 2.4)	2.5 (2.1; 2.9)	-0.4 (-1.0; -0.4), P=0.003	-0.7 (-1.0; -0.4), P=0.001	-0.3 (-0.6; 0.0), P=0.070			
Push and Release Test	Baseline	2.3 (1.9; 2.7)	2.1 (1.7; 2.4)	2.4 (2.0; 2.8)						
	Post Intervention	1.1 (0.8; 1.4)	1.2 (0.9; 1.6)	2.5 (2.1; 2.9)	-0.3 (-0.6; -1.0), P=0.005	-1.3 (-1.5; -1.0), P<0.001	-0.9 (-1.2; -0.7), P<0.001			
	1 month Follow-up	1.4 (1.1; 1.7)	1.8 (1.5; 2.1)	2.6 (2.1; 3.0)	-0.6 (-0.9; -0.4), P<0.001	-1.9 (-1.5; -0.8), P<0.001	-0.4 (-0.7; -0.2), P=0.001			
	6 month Follow-up	1.9 (1.5; 2.2)	2.1 (1.7; 2.4)	2.7 (2.2; 3.0)	-0.4 (-0.6; -0.2), P=0.001	-0.7 (-0.9; -0.4), P<0.001	-0.3 (-0.5; 0.0), P=0.038			
Falls Efficacy Scale - International	Baseline	31.5 (27.0; 35.9)	34.4 (30.0; 38.4)	36.3 (31.1; 41.3)						
	Post Intervention	25.6 (22.0; 29.3)	32.0 (27.8; 36.0)	36.2 (31.1; 41.1)	-4.0 (-6.1; -1.8), P<0.001	-6.4 (-8.7; -4.2), P<0.001	-2.5 (-4.8; -0.1), P=0.037			
	9-week Follow up	25.6 (22.1; 29.3)	33.5 (29.1; 37.6)	36.5 (31.4; 41.6)	-5.4 (-7.6; -3.3), P<0.001	-6.7 (-3.6; 1.0), P<0.001	-1.3 (-3.6; 1.0), P=0.279			
	35-week Follow up	27.8 (23.9; 31.7)	27.8 (23.9; 31.7)	38.7 (33.4; 43.9)	-4.0 (-6.2; -1.9), P<0.001	-6.8 (-9.0; -4.5), P<0.001	-2.7 (-5.0; -0.4), P=0.021			
Average Number of Falls per month (Falls Rate)	Baseline	0.66	0.50	0.80						
	Post Intervention	0.05 (0.01; 0.22)	0.25 (0.13; 0.46)	0.52 (0.25; 1.04)	-0.20 (-0.37; -0.02), P=0.026	-0.46 (-0.84; -0.09), P=0.014	-0.27 (-0.66; 0.13), P=0.202			
	1 month Follow-up	0.17 (0.07; 0.41)	0.20 (0.08; 0.52)	0.55 (0.32; 0.94)	-0.03 (-0.28; 0.21), P=0.800	-0.37 (-0.71; 0.04), P=0.029	-0.34 (-0.70; 0.01), P=0.059			
	6 month Follow-up	0.11 (0.06; 0.20)	0.13 (0.07; 0.22)	0.19 (0.12; 0.28)	-0.02 (-0.11; 0.08), P=0.751	-0.08 (-0.18; 0.02), P=0.137	-0.06 (-0.17; 0.05), P=0.260			

Group: Multimodal Training Group (MT), Standard training (ST), Control Intervention group (CG). Confidence Intervals (CI) - Adjusted Mean Difference (95% CI) Between Baseline and 35-week). Primary analysis: Adjusted for baseline MBESE score; Secondary analyses: also adjusted for baseline LEDO, baseline UPDRS 2 and 3. Average numbers off falls per month - Negative binomial analyses - Generalized Linear Models.

Table 2B. Observed mean values and estimated differences and 95% confidence intervals for secondary outcome measures.

	MT	ST	Control	MT vs ST	MT vs Control	ST vs Control
	1	2	3	1-2	1-3	2-3
Timed Up and Go	Baseline	23.6 (19.9; 28.1)	23.1 (18.0; 28.4)			
	Post Intervention	17.0 (14.3; 20.3)	14.4 (12.0; 17.5)	-0.4 (-3.3; 2.4); P=0.756	-7.05 (-10.0; -4.0); P<0.001	-6.6 (-9.7; -3.5); P<0.001
	1 month Follow-up	16.1 (13.6; 19.3)	15.8 (13.3; 18.9)	-2.7 (-5.6; 0.2); P=0.067	-8.4 (-11.4; -5.3); P<0.001	-5.7 (-8.8; -2.5); P<0.001
	6 month Follow-up	17.6 (13.6; 19.3)	16.9 (14.3; 20.2)	-2.4 (-5.3; 0.5); P=0.106	-8.3 (-11.3; -5.3); P<0.001	-5.9 (-9.0; -2.7); P<0.001
Timed up and Go Dual Task	Baseline	28.3 (23.7; 33.7)	26.0 (21.3; 31.3)			
	Post Intervention	20.6 (17.4; 24.4)	20.7 (17.0; 25.0)	-1.9 (-5.1; 1.2); P=0.219	-9.0 (-12.3; -5.7); P<0.001	-7.0 (-10.5; -3.6); P<0.001
	1 month Follow-up	19.7 (16.6; 23.4)	22.0 (18.1; 26.5)	-4.1 (-7.2; -0.9); P=0.011	-10.3 (-13.6; -7.0); P<0.001	-6.2 (-9.7; -2.4); P=0.001
	6 month Follow-up	20.7 (17.5; 24.6)	25.2 (20.6; 30.4)	-6.3 (-9.5; -3.1); P<0.001	-10.1 (-13.5; -6.8); P<0.001	-3.8 (-7.3; -0.3); P=0.030
New Freezing of Gait Questionnaire	Baseline	7.2 (4.8; 9.8)	9.2 (6.8; 11.7)			
	Post Intervention	5.6 (3.7; 7.7)	7.6 (5.1; 10.4)	-0.2 (-1.4; 0.9); P=0.676	-2.4 (-3.6; -1.2); P<0.001	-2.1 (-3.4; -0.9); P=0.001
	1 month Follow-up	5.7 (3.8; 7.8)	7.9 (5.3; 10.8)	-0.5 (-1.6; 0.6); P=0.382	-2.7 (-3.9; -1.5); P<0.001	-2.1 (-3.4; 0.9); P=0.001
	6 month Follow-up	6.6 (4.5; 9.0)	8.0 (5.5; 11.0)	0.3 (-0.8; 1.4); P=0.635	-1.7 (-2.9; -0.5); P=0.004	-2.0 (-3.2; -0.8); P=0.001
Rapid Turns test	Baseline	0.4 (0.3; 0.6)	0.4 (0.2; 0.5)			
	Post Intervention	0.1 (0.0; 0.2)	0.3 (0.2; 0.5)	-0.2 (-0.3; -0.1); P<0.001	-0.2 (-0.3; -0.1); P<0.001	0.0 (-0.1; 0.1); P=0.945
	1 month Follow-up	0.3 (0.2; 0.4)	0.3 (0.2; 0.5)	-0.0 (-0.1; 0.0); P=0.285	-0.1 (-0.2; 0.0); P=0.017	-0.1 (-0.2; 0.0); P=0.188
	6 month Follow-up	0.4 (0.3; 0.6)	0.4 (0.2; 0.5)	0.0 (-0.1; 0.1); P=0.966	-0.0 (-0.1; 0.0); P=0.537	-0.0 (-0.1; 0.1); P=0.532
LEDD	Baseline	681 (558; 812)	700 (570; 828)			
	Post Intervention	673 (552; 800)	700 (570; 829)	-8.5 (-33.1; 16.2); P=0.499	-24.1 (-50.3; 2.1); P=0.071	-15.6 (-42.4; 11.1); P=0.252
	1 month Follow-up	677 (555; 805)	706 (575; 835)	-10.4 (-35.0; 14.3); P=0.407	-66.8 (-93.0; -40.6); P<0.001	-56.4 (-83.2; -29.7); P<0.001
	6 month Follow-up	693 (573; 820)	739 (614; 869)	-27.6 (-52.3; -3.0); P=0.028	-109.0 (-135.2; -82.8); P<0.001	-81.3 (-108.1; -54.6); P<0.001
UPDRS 2	Baseline	12.6 (10.6; 14.7)	14.5 (12.5; 16.7)			
	Post Intervention	11.0 (9.1; 13.0)	13.5 (12.5; 16.7)	-0.7 (-1.3; -0.1); P=0.025	-1.9 (-2.5; -1.3); P<0.001	-1.2 (-1.9; -0.6); P<0.001
	1 month Follow-up	11.3 (9.4; 13.3)	14.6 (12.1; 16.2)	-0.9 (-1.5; -0.3); P=0.003	-1.7 (-2.3; -1.1); P<0.001	-0.8 (-1.4; -0.2); P=0.014
	6 month Follow-up	11.9 (9.9; 14.0)	14.5 (12.5; 16.6)	-0.7 (-1.2; -0.1); P=0.031	-1.3 (-1.9; -0.7); P<0.001	-0.6 (-1.3; 0.0); P=0.049
UPDRS 3	Baseline	15.1 (13.3; 17.0)	17.4 (15.0; 20.1)			
	Post Intervention	12.5 (10.8; 14.3)	16.5 (14.1; 19.2)	-1.7 (-2.5; -1.0); P<0.001	-3.0 (-3.8; -2.2); P<0.001	-1.6 (-1.9; -0.3); P=0.004
	1-month Follow up	13.1 (11.3; 14.8)	17.2 (14.8; 19.9)	-1.8 (-2.6; -1.1); P<0.001	-2.1 (-2.9; -1.3); P<0.001	-0.3 (-1.0; 0.5); P=0.498
	6-month Follow up	13.8 (11.9; 15.7)	17.5 (15.1; 20.2)	-1.4 (-2.1; -0.7); P<0.001	-1.7 (-2.4; -0.9); P<0.001	-0.2 (-1.0; 0.5); P=0.513

Group: Multimodal Training Group (MT), Standard Training group (ST), Control intervention group (CG). Confidence intervals (CI) -Adjusted Mean Difference (95% CI) Between Baseline and 35-week. Primary analysis: Adjusted for baseline MIBEST score; Secondary analyses: also adjusted for baseline LEDD, baseline UPDRS 2 and 3.

Resultados Secundários

Equilíbrio

Efeitos semelhantes foram encontrados para os desfechos secundários (Tabela 2A). Quando comparados aos controles, tanto o grupo de treinamento multimodal quanto o padrão melhoraram imediatamente após a intervenção no BBS, no teste de retropulsão, no teste de push-and-release e no FES-I. O grupo de treinamento multimodal melhorou significativamente, mais do que o grupo de treinamento padrão nos desfechos secundários (Tabela 2A). As melhorias foram mantidas no seguimento de um mês (Tabela 2A), mas apenas o grupo de treinamento multimodal manteve a melhora em 6 meses de acompanhamento. Menos quedas e ferimentos graves foram relatados após a intervenção por todos os grupos.

Marcha

Imediatamente após a intervenção, tanto o grupo de treinamento multimodal quanto o padrão apresentaram uma melhora maior do que os controles no TUG (Figura 2B), TUG DT, NFOG-Q e teste de virar rápido (Tabela 2B). Não foram encontradas diferenças entre as duas intervenções ativas. Os resultados foram mantidos em um mês e 6 meses de acompanhamento em ambos os grupos. Com exceção do teste de virar rápido, para o qual o grupo de treinamento multimodal apresentou melhores resultados que o grupo de

treinamento padrão e controle apenas na pós-intervenção (Tabela 2B). Para TUG Dupla Tarefa, o grupo de treinamento multimodal apresentou melhores resultados do que o grupo de treinamento padrão no acompanhamento de um mês e de 6 meses (Tabela 2B).

Figura 2B – TUG (Timed Up and Go Test) em cada visita. A linha vermelha representa o treinamento multimodal, a linha preta representa o treinamento padrão e a linha cinza o grupo controle.

Dose diária equivalente de Levodopa (LEDD)

Nenhuma diferença na LEDD foi observada entre o grupo de treinamento multimodal e o grupo de treinamento padrão pós-intervenção. Além disso, nenhuma diferença foi encontrada no LEDD entre os controles e o grupo de treinamento padrão. Em um e seis meses de acompanhamento, o grupo de

intervenção controle teve um maior LEDD comparado ao grupo de treinamento multimodal e grupo de treinamento padrão (Figura 2C). Não foram encontradas diferenças entre o grupo de treinamento multimodal e o grupo de treinamento padrão em um e 6 meses de acompanhamento (Tabela 2B).

Figura 2C – Dose diária equivalente de Levodopa (LEDD) em cada visita. A linha vermelha representa o treinamento multimodal, a linha preta representa o treinamento padrão e a linha cinza o grupo controle.

UPDRS

Tanto o grupo de treinamento multimodal quanto o padrão melhoraram na parte 2 da UPDRS e na parte 3 imediatamente após a intervenção (Tabela 2B). O grupo de treinamento multimodal mostrou uma melhora significativamente maior do que o grupo de treinamento padrão em ambos os resultados. Os resultados na parte 2 da UPDRS foram mantidos em 1 e 6 meses de

acompanhamento em ambos os grupos. Os resultados na parte 3 da UPDRS foram mantidos em 1 e 6 meses de acompanhamento para o grupo de treinamento multimodal (Tabela 2B). Figura 3 mostra a distribuição do tempo de diagnóstico em relação a UPDRS 3 (score motor).

Figura 3 - Os triângulos vermelhos representam pacientes que receberam Deep Brain Stimulation (DBS 1), os quadrados pretos representam os pacientes sem DBS.

Análise secundária

Nesta análise secundária, utilizamos os mesmos dados dos pacientes utilizados na primeira análise. Realizamos uma análise de subgrupos para freezers e não-freezers, nos quais incluímos as seguintes medidas de resultado: Mini-BESTest (MBEST - desfecho primário) (Franchignoni, Horak et al. 2010); Teste Timed Up and Go (TUG) (Podsiadlo and Richardson 1991); Novo

congelamento do questionário de marcha (NFOG-Q) (Nieuwboer, Rochester et al. 2009) e o Rapid tourn test (Snijders, Haaxma et al. 2012).

Figura 4 – Mini-BESTest (MBEST), New Freezing of Gait Questionnaire (NFOG) and Timed Up and Go test (TUG) em cada visita. A linha vermelha representa o treinamento multimodal, a linha preta representa o treinamento padrão e a linha cinza o grupo controle.

Table 3. Observed mean values and estimated differences and 95% confidence intervals for Balance and Gait outcomes Freezers vs Non-Freezers

Groups	multimodal training (1)		standard training (2)	control intervention (3)	multimodal training vs standard training (1-2)		multimodal training vs control intervention (1-3)		standard training vs control intervention (2-3)	
Mini BESTest										
Freezers	Baseline	31.1 (7.3; 34.3)	31.7 (8.2; 35.2)	31.2 (7.8; 34.5)						
	Post Intervention	38.4 (35.3; 41.5)	36.7 (30.8;38.4)	31.2 (7.9; 34.4)	4.0 (2.0; 6.5), P<0.001	7.3 (5.0; 9.0), P<0.001	3.4 (0.7; 5.0), P<0.011			
	1-month Follow up	37.6 (34.0; 41.2)	35.9 (30.3; 37.9)	31.2 (7.8; 34.5)	4.3 (1.9; 6.4), P<0.001	6.5 (4.2; 8.8), P<0.001	2.3 (-0.1; 4.7), P<0.051			
	6-month Follow up	35.8 (32.0; 39.5)	32.9 (30.3; 36.8)	31.0 (11.3; 20.3)	3.2 (1.0; 5.5), P<0.004	4.5 (2.2; 6.9), P<0.001	1.3 (-1.0; 3.6), P<0.278			
Non Freezers	Baseline	38.7 (34.5; 38.8)	20.7 (17.8; 23.6)	17.0 (12.4; 21.5)						
	Post Intervention	23.0 (21.0; 25.0)	23.3 (20.6; 26.0)	16.2 (12.3; 21.1)	3.3 (1.4; 4.8), P<0.001	6.5 (4.7; 8.4), P<0.001	3.4 (1.4; 6.5), P<0.001			
	1-month Follow up	22.4 (20.0; 24.4)	21.6 (18.4; 24.3)	17.2 (11.9; 20.4)	4.0 (2.3; 5.7), P<0.001	6.3 (4.4; 8.1), P<0.001	2.2 (0.2; 4.2), P<0.030			
	6-month Follow up	20.8 (18.7; 23.0)	20.0 (17.5; 22.6)	15.8 (11.3; 20.3)	4.2 (2.4; 5.9), P<0.001	5.2 (3.4; 7.1), P<0.001	1.0 (-0.9; 3.0), P<0.297			
New Freezing of Gait Questionnaire										
Freezers	Baseline	15.2 (12.2; 18.2)	20.4 (16.4; 24.5)	15.1 (12.1; 18.2)						
	Post Intervention	32.2 (30.2; 34.9)	17.7 (14.7; 20.6)	15.1 (12.0; 18.1)	0.1 (-0.5; 0.2), P=0.389	-2.1 (-2.7; -1.5), P<0.001	-2.0 (-2.4; -1.5), P<0.001			
	1-month follow up	32.9 (30.4; 35.16)	18.4 (15.8; 21.2)	16 (12.8; 19.1)	-0.6 (-1.0; -0.2), P<0.002	-1.0 (-1.5; -0.4), P<0.001	-0.4 (-0.8; 0.0), P<0.067			
	6-month follow up	34.2 (31.2; 37.3)	19.8 (16.3; 21.4)	16 (12.8; 19.1)	-1.0 (-1.4; -0.5), P<0.001	-1.0 (-1.6; -0.3), P<0.002	-4.5 (-0.4; 0.4), P=1.000			
Non Freezers	Baseline	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)						
	Post Intervention	2.3 (0.3; 4.5)	1.9 (0.3; 3.4)	3.7 (0.9; 6.4)	-0.0 (-0.3; 0.2), P=0.839	-0.4 (-0.8; -0.0), P<0.049	-0.3 (-0.6; -0.0), P<0.009			
	1-month follow up	2.3 (0.3; 4.4)	2.4 (0.3; 3.7)	3.6 (0.8; 6.3)	-0.1 (-0.4; 0.2), P=0.477	-0.1 (-0.5; 0.3), P<0.618	-0.0 (-0.4; 0.3), P<0.999			
	6-month Follow up	2.7 (0.4; 5.1)	2.1 (0.4; 3.8)	3.6 (0.8; 6.4)	0.0 (-0.3; 0.4), P=0.774	0.0 (-0.5; 0.6), P<0.838	0.1 (-0.2; 0.2), P<0.947			
Timed Up and Go Test										
Freezers	Baseline	33.5 (23.9;43.1)	27.0 (16.0; 38.0)	26.2 (17.0; 35.4)						
	Post Intervention	21.9 (14.3; 29.5)	18.0 (10.3; 25.8)	27.1 (16.9; 37.2)	0.8 (-0.7; 2.7), P=0.071	2.7 (1.4; 3.9), P<0.001	1.8 (0.9; 2.7), P<0.001			
	1-month Follow up	21.4 (13.5; 29.4)	20.4 (12.7; 28.0)	28.3 (17.3; 39.2)	0.7 (-0.2; 1.6), P=0.130	1.7 (0.4; 3.0), P<0.008	1.0 (0.0; 1.9), P<0.039			
	6-month Follow up	23.7 (15.5; 32.0)	21.7 (13.5; 29.0)	29.0 (18.3; 39.6)	4.0 (-0.9; 0.9), P=1.000	1.7 (0.4; 3.0), P<0.008	1.0 (0.0; 1.9), P<0.039			
Non Freezers	Baseline	38.9 (34.9; 42.8)	34.5 (31.6; 37.1)	20.5 (12.5; 28.5)						
	Post Intervention	34.6 (32.1; 37.3)	32.0 (30.7; 32.3)	21.1 (12.8; 29.5)	0.7 (0.3; 1.4), P<0.014	2.1 (1.5; 3.0), P<0.001	1.3 (0.7; 2.0), P<0.001			
	1-month Follow up	33.5 (31.5;35.4)	32.8 (30.6; 34.9)	20.9 (12.7; 29.1)	1.7 (0.9; 2.4), P<0.001	3.2 (2.2; 4.2), P<0.001	1.5 (0.7; 2.2), P<0.001			
	6-month Follow up	34.6 (32.1; 37.1)	34.0 (31.9; 36.7)	22.8 (12.7; 33.0)	0.5 (-0.3; 1.4), P<0.244	0.8 (-0.3; 2.0), P<0.151	0.3 (-0.5; 1.2), P<0.437			

Mini BEST- Confidence Intervals (CI) –Adjusted Mean Difference (95% CI) Between Baseline and 6 month). Adjusted for baseline MBEST. Baseline UPDRS 2 and 3. Mini BESTest – 14 items; total 28 of points, scored 0-2 (higher score better balance). New Freezing of Gait Questionnaire (NFOG) – Confidence Intervals (CI) –Adjusted MBEST Mean Difference (95% CI) Between Baseline and 6 month). Adjusted for NFOG baseline, baseline UPDRS 2 and 3. TUG – TUG – Confidence Intervals (CI) –Adjusted MBEST Mean Difference (95% CI) Between Baseline and 6 month). Adjusted for Timed Up and Go Test (TUG) baseline, baseline UPDRS 2 and 3. TUG was measured in time in seconds (time in seconds is the unit) with a range from 3-60 seconds (which is the range). A lower score means better mobility.

A Figura 4 mostra os resultados da análise secundária. Imediatamente após o tratamento, tanto os freezers quanto os não freezers no grupo de treinamento multimodal e padrão melhoraram sua pontuação no nosso resultado primário, o MBEST significativamente em comparação com os controles. Além disso, o treinamento multimodal resultou em uma melhoria significativamente maior do que o treinamento padrão para freezers e não-freezers. Em ambos os freezers e não freezers, essas melhorias foram mantidas em um mês e 6 meses de acompanhamento, apenas pelo grupo de treinamento multimodal (Tabela 3).

Os freezers em ambos os grupos de treinamento apresentaram melhora seus escores de NFOG-Q diretamente após o tratamento. No entanto, essa melhora não foi significativamente. No entanto, no acompanhamento de um mês e de 6 meses, os freezers no grupo de treinamento multimodal mostraram um resultado melhor em comparação com os freezers no grupo de treinamento regular ou no grupo de controle (Tabela 3 e Figura 4).

Em comparação com os controles, ambos os freezers e não-freezers em ambos os grupos de treinamento melhoraram sua pontuação no TUG imediatamente após o tratamento (Figura 4). Para os freezers, não foram encontradas diferenças significativas entre as duas intervenções ativas, enquanto os não-freezers no grupo de treinamento multimodal melhoraram significativamente mais do que os não-freezers no grupo de treinamento padrão. No acompanhamento de um mês, as pontuações do TUG em ambos os freezers e não freezers não diferiram em comparação com as medições pós-intervenção em ambos os grupos de intervenção e, portanto, as melhorias foram mantidas. No acompanhamento de seis meses, as pontuações do TUG não diferiram em

comparação com as medidas pós-intervenção em freezers no grupo de treinamento multimodal, mas aumentaram nos freezers no grupo de treinamento regular (embora a melhora tenha sido mantida em comparação com os valores iniciais). Os escores do TUG para os pacientes não freezers, não diferiram em comparação aos escores pós-intervenção em ambos os grupos de treinamento no acompanhamento de seis meses e, portanto, as melhorias foram sustentadas (Tabela 3).

6. Discussão

Nessa tese foi desenvolvida uma avaliação clínica padronizada e amplamente estudado o manejo do equilíbrio na doença de Parkinson. O primeiro estudo resultou no desenvolvimento de um protocolo de avaliação e exercícios de equilíbrio com pistas auditivas rítmicas para melhorar e manter o equilíbrio na doença de Parkinson (Capato, Tornai et al. 2015) (ANEXO I).

Detalhes do modo de aplicação e progressão do protocolo (ANEXO II) foi aplicado no ensaio clínico randomizado descrito nessa tese foi publicado recentemente (Capato, de Vries et al. 2020). Apresentamos aqui então, os resultados desse estudo clínico randomizado que investigou os efeitos a longo prazo de duas intervenções de treinamento de equilíbrio em um grande grupo de pacientes com DP em estágio inicial e médio. Ambos os grupos de treinamento melhoraram o desempenho do equilíbrio, medido usando o MBEST. A adição de estímulos rítmicos auditivos (treinamento multimodal) ao treinamento de equilíbrio foi mais eficaz do que o treinamento de equilíbrio sem essas dicas (treinamento padrão). Apenas o grupo de treinamento multimodal manteve o efeito no seguimento de longo prazo (6 meses).

Nosso estudo relata duas novas descobertas importantes. Primeiro, mostramos que o treinamento de equilíbrio funcional usando pistas rítmicas simultaneamente aplicadas é mais eficaz do que o treinamento de equilíbrio sem pistas (treinamento padrão). Suspeitamos que o treinamento de equilíbrio multimodal é mais eficaz do que o treinamento padrão, porque estimula as habilidades motoras cognitivas residuais na DP mais efetivamente do que o

treinamento padrão (Rochester, Baker et al. 2010). Especificamente, o treinamento de equilíbrio multimodal pode melhorar a atenção e a priorização de tarefas (controle executivo), (Rochester, Burn et al. 2009) facilitando, assim, a seleção de estratégias compensatórias de equilíbrio eficientes e aprimorando os efeitos do treinamento (Capato, de Vries et al. 2020).

Um segundo achado importante é que os efeitos do treinamento (particularmente os do treinamento multimodal) são mantidos até 6 meses de acompanhamento. Essa melhoria do MBEST após o treinamento multimodal é consistente com melhorias similares que observamos em todos os resultados do equilíbrio secundário. Estudos anteriores também descobriram que a fisioterapia melhora o equilíbrio em pacientes com DP (Duncan and Earhart 2012, Ginis, Nieuwboer et al. 2016, Ni, Signorile et al. 2016, Sparrow, DeAngelis et al. 2016). Comparado com outros estudos sobre treinamento de equilíbrio, (Conradsson, Lofgren et al. 2015, Sparrow, DeAngelis et al. 2016) os efeitos no MBEST encontrados aqui foram relativamente grandes. Possivelmente, esse grande efeito pode ser atribuído à adição de sinais auditivos rítmicos ao equilíbrio funcional e exercícios de marcha (Capato, de Vries et al. 2020). De fato, tais efeitos grandes não foram observados no grupo de treinamento padrão, onde as pistas auditivas rítmicas não foram usadas.

Todos os três grupos relataram igualmente um número menor de quedas e lesões após o estudo. É surpreendente que o número de quedas tenha diminuído nos controles, apesar da falta de melhora na marcha e no equilíbrio. Possivelmente, o programa educacional foi eficaz na mudança de comportamento e, portanto, previne quedas. Tal efeito do programa educacional

sobre a redução de quedas na DP não foi relatado antes. Esse achado exige replicação em estudos futuros.

Na análise secundária, investigamos se o treinamento multimodal para o equilíbrio e a marcha são eficazes em freezers e não-freezers. Imediatamente após o tratamento, tanto os freezers quanto os não freezers no grupo de treinamento multimodal e padrão melhoraram significativamente seu escore de MBEST em comparação aos controles, mas a melhora foi maior no grupo de treinamento multimodal comparado ao grupo de treinamento padrão (Capato, de Vries et al. 2020) (ANEXO III). Além disso, apenas os freezers e os não freezers do grupo de treinamento multimodal mantiveram as melhorias em um mês e 6 meses de follow-up. Esses resultados estão de acordo com nossa análise primária, tanto para freezers quanto para não freezers. Quando se pretende melhorar o desempenho do equilíbrio na DP, a inclusão de sinais auditivos externos aos exercícios deve ser considerada, independentemente de os pacientes congelarem ou não.

Com relação à marcha, na análise secundária, observamos duas novas descobertas. Primeira, o treinamento de equilíbrio multimodal com dicas auditivas não foi eficaz para reduzir o FOG, conforme medido pelo NFOG-Q (Capato, de Vries et al. 2020). À primeira vista, isso é surpreendente, pois há um extenso corpo de evidências mostrando os efeitos benéficos do estímulo auditivo externo no desempenho da marcha na DP (Nieuwboer, Kwakkel et al. 2007, Rochester, Burn et al. 2009, Rochester, Baker et al. 2010, Kadivar, Corcos et al. 2011, Ghai, Ghai et al. 2018, Lirani-Silva, Lord et al. 2019). Por exemplo, o estudo RESCUE relatou uma redução do congelamento da gravidade da marcha

(medida com o FOG-Q), após um programa de exercícios de 3 semanas realizados em ambiente doméstico (Nieuwboer, Kwakkel et al. 2007). É importante ressaltar, no entanto, que estudos anteriores se concentraram especificamente no FOG (Nieuwboer, Kwakkel et al. 2007), ao passo que os nossos programas de treinamento se concentraram principalmente no equilíbrio. Esses achados reforçam a possibilidade de que o FOG possa surgir (em parte) de um problema de equilíbrio (Bekkers, Dijkstra et al. 2018).

Além disso, torna-se cada vez mais claro que medir o efeito de uma intervenção de treinamento em FOG usando o NFOG-Q tem limitações (Mancini, Bloem et al. 2019, Hulzinga, Nieuwboer et al. 2020). Um estudo recente relatou que o NFOG-Q tem uma mudança mínima detectável de 9,9 pontos (mudança mínima detectável relativa de 35,5%)(Hulzinga, Nieuwboer et al. 2020). Importante salientar, que pacientes com DP com FOG geralmente apresentam grave comprometimento do equilíbrio, o que amplifica muito seu risco de quedas (Bekkers, Dijkstra et al. 2017). Estudos futuros são, portanto, necessários para quantificar os efeitos usando medidas adicionais que poderiam capturar relevância clínica, incluindo, por exemplo, medidas objetivas (por exemplo, usando sensores vestíveis), idealmente no ambiente doméstico e em períodos de tempo mais longos (Mancini, Bloem et al. 2019). Estudos futuros também podem avaliar se o treinamento multimodal com pistas auditivas rítmicas pode ajudar a prevenir a ocorrência de congelamento em não congeladores, facilitando assim a aplicação de uma ampla gama de intervenções fisioterapia com foco na melhoria da marcha ou equilíbrio, ou no modo de aplicação de treinamento físico.

Um segundo achado importante na análise secundária é que a mobilidade funcional (TUG) melhorou tanto para intervenções ativas em freezers quanto em não freezers (Capato, de Vries et al. 2020). O grau de melhoria excedeu a diferença mínima clinicamente relevante de 3,5 segundos (Huang, Hsieh et al. 2011). Consistente com nossa análise primária, os resultados não mostram diferenças entre as duas intervenções ativas nos resultados do TUG nos freezers (Capato, de Vries et al. 2020). No entanto, imediatamente após a intervenção, os não freezers no grupo de treinamento multimodal melhoraram significativamente mais do que os não freezers no grupo de treinamento padrão. Isso é surpreendente, como seria de se esperar que os freezers em particular se beneficiariam de dicas adicionais. É importante ressaltar que a falta de significância nos freezers é provavelmente devida a um problema de poder da análise, já que o grau de melhora foi maior nos grupos multimodais em comparação com o grupo de treinamento padrão.

Nosso estudo não se abstém de limitações. Primeiro, estudamos pacientes com DP leve a moderada (H&Y 1-3) e sem comprometimento cognitivo. Portanto, ainda não está claro se os resultados do treinamento multimodal do equilíbrio são generalizáveis para pacientes com doença em estágio tardio (H&Y4) ou aqueles com comprometimento cognitivo (Domingos, Godinho et al. 2015). Recentemente, mostramos em um estudo piloto que o treinamento de equilíbrio multimodal é viável em estágios avançados da doença de Parkinson. Além disso, os efeitos parecem durar mais tempo no grupo de treinamento multimodal do que no grupo de treinamento padrão (Capato T.T.C 2020). No entanto, é necessária investigação em larga escala. Em segundo lugar, houve mais desistências entre os controles, e isso poderia ser uma fonte

de viés (viés de atrito), especialmente porque os participantes conheciam a tarefa do grupo. Terceiro, não podemos fazer nenhuma afirmação sobre possíveis efeitos quando os pacientes estão com medicação OFF. Nós propositalmente testamos todos os pacientes em fase ON, pois isso refletiria melhor o efeito da intervenção acima e acima do tratamento médico padrão na prática clínica diária. Além disso, geralmente o equilíbrio melhora pouco com a medicação dopaminérgica (Bloem, Marinus et al. 2016) por isso, esperamos que os pacientes testados em fase OFF não mostrem uma grande diferença. No entanto, estudos futuros devem examinar os efeitos do treinamento multimodal sobre o equilíbrio em pacientes testados na fase OFF da medicação.

Conclusão

Tomados em conjunto, os resultados dessa tese mostram que os problemas multifatoriais de marcha e equilíbrio na DP requerem um programa de tratamento para o equilíbrio multidisciplinar e sob medida. Devido à efetividade da avaliação e do protocolo de intervenção proposto nesse estudo, pode, portanto, ser utilizado para esse fim. Avaliações multidisciplinares periódicas são necessárias para monitorar o desempenho motor e ajuste do tratamento.

Os resultados da análise primária do estudo clínico controlado randomizado apresentado nessa tese, indicam que o treinamento de equilíbrio multimodal (combinado com estímulos auditivos rítmicos) é mais efetivo e duradouro do que o treinamento de padrão para DP. A análise secundária sugere que a adição de pistas auditivas rítmicas para o treinamento do equilíbrio é benéfica para freezers e não-freezers em estágios leves e moderados da doença. Além disso, os resultados desse estudo contribuem para uma crescente base de evidências para fisioterapia, resultando em cuidados especializados e otimizados para pacientes com PD.

Nossos achados apoiam ainda mais a importância da intervenção não farmacológica no manejo do equilíbrio e nos problemas de marcha em pacientes com DP. As diretrizes clínicas e de fisioterapia para doença de Parkinson não fornecem, até o momento, recomendações sobre como aplicar o treinamento de equilíbrio. Portanto, o estudo clínico randomizado de Classe II apresentado nessa tese, pode contribuir como uma forte recomendação no manejo clínico da Doença de Parkinson.

ANEXO I

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STUDY PROTOCOL

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Randomized controlled trial protocol: balance training with rhythmical cues to improve and maintain balance control in Parkinson's disease

Tamine Teixeira da Costa Capato^{1,2*}, Juliana Tornai², Patrícia Ávila², Egberto Reis Barbosa³ and Maria Elisa Pimentel Piemonte¹

Abstract

Background: Postural instability is a particularly incapacitating disorder, whose loss of motor independence by Parkinson's Disease (PD) patients marks a significant stage of disease onset. Evidence suggests that deficits in automatic motor control, sensory integration and attention are associated with the lack of balance in PD. Physiotherapy together with medication play an important role in the treatment of this state, although no consensus has been reached on the best treatment modality. The aim of this randomized controlled trial protocol is to evaluate the effects of balance training with rhythmical (BRT), which is a motor program to improve balance associated with rhythmical auditory cues (RACs). This study is ongoing in the stage 1.

Methods and design: A total of 150 PD patients at H&Y stages II–III and asymptomatic for depression and dementia are enrolled in a single-blind randomized study. Randomization is achieved via a computer-generated random-sequence table. All patients should also present a fall history. They will be assigned into one of three groups, and their balance and gait will be assessed before and after 10 training sessions, and after 4 and 30 weeks subsequent to the end of the training. The BRT group will receive a motor program to improve balance associated with RACs, the MT group will perform motor training with the same aims as those in the BRT group but without RACs, and the control group (CG) will be trained only in orientations. The exercise program specific to balance is of 5 weeks' duration with two sessions per week, 45 min each, and consists of general physiotherapy exercises. Each session will be divided into five warm-up minutes—30 min for the main part and 10 min for the cool down. The training progresses and intensifies each week depending on the individual's performance. The subjects should be able to execute 10 repetitions of the exercise sequences correctly to progress to the next movement.

Discussion: This randomized study protocol will evaluate the effects of a motor program designed to improve balance associated with RACs, and will also assess whether balance training leads to activation of balance reactions at the appropriate time. We hypothesize that if this motor program is maintained long-term, it will prevent falls.

Trial registration: Clinicaltrials.gov NCT02488265; Ethics Committee of the University of São Paulo Faculty of Medicine Clinics Hospital 1,102,464.

Keywords: Randomized clinical trial, Parkinson's disease, Physical therapy, Balance training, Postural control, Cues

* Correspondence: taminec@yahoo.com.br

¹Department of Physiotherapy, University of São Paulo, Av Dr Enéas de Aguiar, 255 – 05403-000 São Paulo, São Paulo, Brazil

²PHYSICAL, Rua Cubatão 929 conj. 142 - 04013-043 São Paulo, São Paulo, Brazil

Full list of author information is available at the end of the article

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Background

The balance disturbances of Parkinson's disease (PD) are progressive and limit the functional independence of the patients, thus affecting their quality of life [1]. The balance disturbance and freezing correlate with the evolution and severity of the PD and can be presented in other parkinsonian syndromes. These symptoms are more apparent and debilitating when patients show midline signs and cognitive declines (especially those of executive function) [2].

The neural control of posture is compromised in patients with PD [3, 4]. Automatic postural responses can be influenced by cortical processing related to learning, previous experiences, and initial postural conditions [5]. The basal nucleus plays an important role in the control of axial tone [6, 7] and postural responses [8] and in the interpretation of somatosensory information [9]. Nevertheless, the dopaminergic loss in the basal ganglia not only affects automaticity, but also causes cognitive decline in executive functions, especially mental flexibility and set-shifting related to alterations in fronto-striatal connectivity [10]. The execution of challenging voluntary tasks leads to reduced postural stability in individuals with PD, whereas no influence on the voluntary task performance is observed [11, 12]. Currently available techniques have not been adopted yet by practitioners in the treatment of routine clinical assessment gait and balance disturbances [13].

Physiotherapy is commonly prescribed in association with medical and surgical treatments [14], aiming to reduce functional losses due to motor alterations in PD [15]. Recently, there have been strong evidences that exercise can improve motor [16–18] and cognitive performance [19] in PD. External sensory cues (auditory, visual and somatosensory) have been shown to improve motor function in subjects with PD, including improvement of gait [20–23].

Studies have demonstrated that physiotherapy may improve balance in individuals with PD [24–26]. Researchers suggest that balance training should start before the patient develops a high risk of falls, aiming at prevention of falls through the optimization of compensatory mechanisms [27, 28]. Recently, different exercise modalities have been used in PD patients to promote cognitive engagement, enhanced by feedback (verbal or proprioceptive), attentional demand through cueing, or dual tasking (as in the performing one of two motor activities such as tai chi [29] and tango dancing [30], or the simultaneous performing of motor and cognitive tasks, as in the use of the Nintendo Wii [31]).

Current studies describe how the action mechanisms of external cues are able to promote balance. Evidence shows that an internal model integrates the afferences received by the cortex before the movement execution to the motor-sensory afferences received during or after

the execution of the movements. Studies have indicated that cues may minimize a deficit in the generation of the basal ganglia signal, and even more it could function as a guide to a movement previously learned. Therefore, owing to dopamine depletion, PD patients can have difficulties in executing the automatic form of sequential movements. This difficulty could be minimized by the use of external cues [32]. Another possible mechanism would be to increase the attentional engagement on movement [19]. Considering that a deficiency in internal cues affects the automatic execution of movement, attentional strategies will allow a greater attentional control on the task, minimizing deficits in performance [33]. Patients with PD can present difficulty in the activation of balance reactions at the correct time as a main dysfunction; however, the mechanisms of action are unclear [34, 35].

Our hypothesis is that rhythmical cues associated with exercises and motor training may facilitate an anticipatory and compensatory reaction [27, 28], thus improving gait and preventing falls. In fact, there are cognitive components in the generalization and maintenance of balance training that may be applied to the daily activities. The aim of this proposed randomized controlled trial protocol is to evaluate the effects of a motor program based on improving balance associated with rhythmical auditory cues.

Methods

Trial design

This was a parallel, prospective, single-blind, randomized clinical trial.

Design and procedures

First, we defined the training guidelines and its progression. Subsequently, we developed an exercise program specifically to promote balance (active global exercises and rhythmical auditory cues, generated by a metronome). Subjects were randomly distributed among three groups. The first experimental group will be led by a physiotherapist, it will receive motor skill training with rhythmical auditory cues marked by a metronome (GBRT); the second experimental group will receive the same training without rhythmical cues (MT); and the control group (CT) will receive exercises in general orientation only with a general orientation. To verify retention after the training, subjects will be assessed and reassessed as a follow up 4 and 30 weeks after the end of their training (Fig. 1). The patients will be diagnosed by neurologists in the Movement Disorders Ambulatory Clinic of the University of São Paulo Faculty of Medicine Clinics Hospital (MD HC FMUSP). Physiotherapists will recruit patients on the database of the MD HC FMUSP and Motor-Sensory Learning Laboratory. They will conduct a brief telephone interview based on questions about their personal and medical history and self-perceived balance performance.

Then, on a first visit, the subjects will be informed about the procedure and they will sign a consensual form.

This study is ongoing in the stage 1. This study was approved by the Ethics Committee of the University of São Paulo Faculty of Medicine - 1.102.464 and the Clinical trials.gov Identifier is NCT02488265.

Participants

We will examine 150 PD patients before and after training.

Inclusion criteria

All of the subjects will be diagnosed by neurologists from the Movement Disorders Ambulatory Clinic of the University of São Paulo Faculty of Medicine Clinics Hospital, according to the UK Brain Bank criteria [36] and they should be at H&Y classification stage II or III, with a Mini Mental Status Examination (MMSE) [37] and they should have a score of above 24. All patients should also present fall history in the past months. They should have the capacity to ambulate independently indoors without aid.

Exclusion criteria

These are the presence of neurological, orthopedic or cardiopulmonary problems, an unstable medication regime, and an inability to understand or adhere to the protocol because of, for example, cognitive, auditory or

visual problems. Patients receiving physical therapy training will also be excluded from the training.

Sample size calculation

The sample size calculation was based on the Mini-Balance Evaluation Systems Test (Mini-BESTest) score. The mean adopted—based on a pilot study of PD patients with similar characteristics to those of the patients in this trial—was 27, and indicated a 3-point difference between motor training and rhythmical auditory cues training. Based on this difference, the sample size calculation revealed that 150 patients (50 per group) would be sufficient for a power greater than 90 % ($\alpha = 0.05$).

Randomization and blinding

Randomization is achieved through a computer-generated random-sequence table. The subject's randomization will be carried out by a researcher who is not involved in enrolling the participants, in assigning them to their groups, or in performing follow-up measurements. This researcher will keep the allocation concealed, and will prepare sealed envelopes, which shall be opened individually only when each participant starts their training. Subjects will be distributed among three groups. Only the researcher responsible for conducting the training will know how the participants are distributed. The researcher responsible for follow-up reviews will be aware of the allocations at any time during the data collection. He/she will

understand the data analysis process because the evaluator will also be the same researcher that analyzes the full set of data.

Outcome measures and test procedure

The primary outcome is balance, which will be assessed by the Berg Balance Scale (BBS) [38], postural stress test (PST) [39], push and release test (PRT) [40] and Mini BESTest (MBESTest) [41]. The secondary outcome is gait, which will be evaluated by the timed up and go test (TUG) [42] and by the freezing of gait, using the Freezing of Gait Questionnaire [43]. Independence in activities of daily living (ADLs), and motor performance will be assessed by the unified Parkinson's disease rating scale (UPDRS) [44]. Falls and fear of falling will be evaluated during a variety of everyday activities and measured by the Falls Efficacy Scale-International (FES-I) [45].

The number of falls will be registered by the physiotherapist at the hospital and by the patient at home. A weekly follow-up of falling will be conducted.

Guidelines

The balance rhythmical training (BRT) guidelines are: 1) self-perception (verbal and visual guidance); 2) motor performance (speed, range of motion, trunk mobility, turning, balance exercises); 3) attention strategies (attention sharing between guidance, environment and your own movement; maintenance of attention during all set strategies); and 4) cues (rhythmical auditory cues).

The program

The exercise program aimed at improving balance is of 5 weeks' duration with two sessions a week, 45 min per session, and consists of general physiotherapy exercises. Each session will be divided into five warm-up minutes—30 min for the main part and 10 min for the cool down. General exercises will be taught in each part of the therapy [46, 47], as well as balance improvement exercises, which will be defined according to the program guidelines. The training sessions will be in groups comprising 10 participants and 2 physiotherapists. The physical therapists will place themselves behind the patients so that they can catch or hold the patients if they fall.

Interventions

Training progression

The training progresses and intensifies each week. In the first week, before training, each exercise will be explained and demonstrated by the physiotherapist; patients will be encouraged to pay particular attention to the most difficult aspects of movement execution. The subjects will perform five repeated movements (5 RM) of each exercise.

The session will be divided into three parts:

1. Warm-up: Of 5 min' duration, starting with muscle stretches, and followed by joint movements, global movement of the upper and lower limbs, and a wide range of joint movements, being performed in all axes of movement as well as free active movement of the scapulohumeral joint, wrist and elbows, hip, knees and ankles. The movements will involve flexion and extension, lateral inclination and rotation of the trunk; and flexion and extension, lateral inclination and rotation of the cervical spine. The exercises will be performed with the feet in neutral position, together and apart, with decreasing and increasing of the base of support, with and without support (support bar or chair).
2. Motor training: Balance exercises will take 30 min' duration. They consist of three sections:
 - A. Balance—axial and proximal movement displacements in different planes and axes; coordinated movements with upper and lower range and speed; functional reach, weight shifts in different directions (anterior, posterior and lateral), using foam, using stable and unstable ground, mats and disks with textures. Postural reactions, trunk rotation. Head movement: bending, rotation, and leaning sideways (eyes opened and closed).
 - B. Gait training: stationary and gait training on a stable and instable surface. In this part, foam of different sizes and densities is used.
 - C. Functional movements (stand up from the chair, turn around, and bend over to pick up different objects on the floor—of differing weight, size, texture and color).
3. Cool down: Of 10 min' duration. The execution rhythm becomes progressively slower. Slow walking, breathing exercises associated with free active movement of the upper limbs, global muscular relaxation and stretching. Posture training in the orthostatic position. The exercises will be initially performed in neutral position and the eyes will be opened and closed. The patients will be encouraged to pay attention to the position of the body and limbs in all parts; range of motion; posture; basis of support.

In the first phase the patients may make some mistakes and may need specific instructions on how to correct the movement that they will be attempting to execute (attentional strategies). The exercises will be repeated in subsequent sessions to consolidate learning. The subjects must be capable of associating the corrections to the exercises that were proposed in the first week. In each group

repetition, for both groups, the physiotherapist will use a verbal command before each movement change, anticipating it and encouraging the patients to pay particular attention to the most difficult ones. Only the GBRT will be oriented to focus on the rhythmical auditory cues provided by a metronome; in warm-up, the metronome will be set at 100 BPM; in motor training, the metronome will be set at 110–150 BPM, and on cool down the metronome will be set at 80–90 BPM.

In the second week, the subjects will perform a series of 10 repetitions (10 RM) and in the third week, two series of 10 repetitions (20 RM). In the fourth week, the subjects must be able to execute 20 RM of the exercise sequences with increasing speed (Additional file 1: Table S1).

Weekly screening of progression and falls

Scheduled screening of progression in training will be used to indicate the capacity to continue to progress. The patients, who complete all the settings with good and high quality performance in 10 RM, will be able to progress to the next week. Those patients who will not show a good quality of performance will receive additional guidance on the exercises and will receive special attention from the orientation physiotherapist in terms of how to perform the exercises correctly. Thereby, if these patients complete all the parts with good and high quality of performance in 10 RM, they will be able to progress to the next week (Additional file 2: Table S2 and Additional file 3: Table S3).

Screening of progression and falls

The number of falls will be noted by the physiotherapist at the hospital and by the patient at home. Weekly questionnaires will be used to follow up on any falls.

Statistical analysis

Baseline values of the demographic characteristics and primary and secondary outcome measures of the participants in the MT, CG and the BRT will be compared using an unpaired *t*-test.

The Lilliefors and Levene tests will be used to examine the normality and homogeneity of variance for the primary and secondary outcome measures.

The participants' performance in the training will be analyzed by three repeated-measures analyses of variance (RM-ANOVA), one for each part of the training (i.e., part 1, part 2 and part 3, with the training session as the within-group factor).

The training effects for each primary and secondary outcome measure will be analyzed for the three training conditions (i.e., control, motor and experimental) at the four assessment time points (i.e., Before the Training (BT), After the Training (AT), Follow up 1 and Follow

up 2) using a mixed-design ANOVA with training as the between-group factor and the assessment time point as the within-group factor.

The effect sizes (ES) will be calculated for all comparisons at $\alpha = 0.05$. A Tukey HSD post-hoc test will be used for multiple comparisons. The statistical software Statistica 11 from StatSoft (United States of America (USA)) will be used for all analyses, and *p*-values below 5 % will be considered to be statistically significant.

Discussion

Even with the ideal medical treatment, PD patients still present problems with functional activities, gait and balance [2]. To minimize these deficits, physiotherapy is prescribed as a coadjuvant to drug treatment, being more effective when integrated with specific training linked to sensorial cues and cognitive strategies [16–18, 20, 21].

Physiotherapy exercises lead to improved performance in PD patients, as shown in the literature [22, 28].

As physiotherapy has a highly beneficial effect on balance [24], there is some distinction among compensatory mechanisms that could be useful in gait and balance therapeutic intervention. Therefore, our hypothesis is that rhythmical cues associated with exercises and motor training can facilitate an anticipatory and compensatory reaction [27, 28], improving gait and preventing falls, in the following ways: 1) by increasing attentional engagement, thus promoting an improvement in performance [19]; 2) by increasing sensory-motor integration through thalamic activation of subcortical structures from the internal globus pallidus and cerebellum [32]; and 3) by stimulating internal signals from the basal nucleus, facilitating previously learned movements [34].

The exercises and motor training proposed in this study may improve the performance of balance-related activities in PD. The long-term effects of the exercises and motor training in this population are not clear [25]; however, the precocious and regular physiotherapeutic intervention in PD preserves and improves motor function [15], which suggests a neuroprotective effect [19]. The disease is progressive and the motor training and exercises should be adapted to the patient's needs and PD progression [16].

It is likely that PD patients diagnosed by neurologists in the Movement Disorders Ambulatory Clinic of the University of São Paulo Faculty of Medicine Clinics Hospital, H&Y stage II–III, will be able to learn how to use the compensatory mechanisms necessary to improve postural instability. The inclusion of rhythmical auditory cues in the motor program may help to improve balance in this group of PD patients [26]. We intend to promote strong evidences that this training program may be more

effective than others and will be save compensatory and anticipatory reactions at the exact moment that a response is necessary to prevent a fall. Application and progression of the motor program may promote improvement in automatic postural responses. Such responses are influenced by cortical processing related to learning, previous experiences and initial postural conditions [5].

The cues mostly influenced temporal aspects, facilitating sensory-motor integration, as suggested by previous studies [19]. Therefore, auditory cues may facilitate anticipatory responses sufficiently early to avoid loss of balance in the same way that they may promote compensatory responses. The compensatory adjustments depend on detection of the imbalance through different sensorial modalities [6–9]. A possible explanation for this mechanism of action is that, under challenging conditions, PD individuals prioritize voluntary tasks over postural control [11]. In addition, rhythmical cues may increase attentional control, serving as dual-task training.

We suggest that BRT may facilitate attentional engagement with the tasks. External cue stimulation of the sensorial systems may be a good strategy for improving sensorial integration and compensating for basal nucleus deficits. One explanation for the transfer of the benefits of exercise may pertain to the repair or consolidation of overlapping motor circuitry involved in cognitive and automatic components of movements [19]. In fact, there are many cognitive aspects that may assist with the generalization and maintenance of BRT, which can then be applied to activities of daily living.

We suggest that balance training should be started early, as falls occur clinically when the patient has already exhausted all compensatory resources used by the nervous system, which is compromised by basal ganglia deficits, and when postural and cognitive responses are no longer effective [27, 28]. The long-term follow up in the proposed study will be very important to verify important questions concerning the potential effects of, and limitations of, balance training. Our belief is that this trial will provide evidences about the effectiveness of rhythmical cues on balance in PD patients, providing a therapeutic strategy that can be used to treat such dysfunctions.

The physiotherapy proposed to improve balance in individuals with PD is effective, low-cost, and easy to apply. This study contributes to the subject knowledge, with specific knowledge about balance in PD patients and the mechanisms involved in motor control. It also provides data about functional diagnosis, prognosis, clinical programs, and the management of balance treatment programs. This program may also be allied to different sorts of parkinsonisms and other motor disorders that influence balance.

Additional files

Additional file 1: Table S1. Interventions. (PDF 246 kb)

Additional file 2: Table S2. Weekly Schedule Screening of Progression. (PDF 344 kb)

Additional file 3: Table S3. Weekly Screening of falls. N: Number of Falls (PDF 376 kb)

Abbreviations

PD: Parkinson's disease; BRT: Balance training with rhythmical cues; MT: Motor training; CG: Control group; RAC: Rhythmic auditory cues; RM: Repeated movements; BBS: Berg Balance Scale; PST: Postural stress test; PRT: Push and release test; MBEST: Mini-Balance Evaluation Systems test; TUG: Timed up and go test; ADLs: Activities of daily living; UPDRS: Unified Parkinson's disease rating scale; GRT: Motor training with rhythmical cues group.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TC conceived the idea for the study and was principally responsible for the drafting of the manuscript. MP contributed to the research design and statistical analysis. JT, PA and EB were involved in patient recruitment. All authors contributed to intervention and outcome measures. All authors assisted in editing the final submitted manuscript. All authors have read and approved the manuscript.

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Author details

¹Department of Physiotherapy, University of São Paulo, Av Dr Enéas de Aguiar, 255 - 05403-000 São Paulo, São Paulo, Brazil. ²PHYSICAL, Rua Cubatão 929 conj. 142 - 04033-043 São Paulo, São Paulo, Brazil. ³Department of Neurology, University of São Paulo, Av Dr Enéas de Aguiar, 255 - 05403-000 São Paulo, São Paulo, Brazil.

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Parts of the Training	Interventions	Orientations
Warm-up 5 minutes	Starting by muscle stretching, joint movements, global movement of upper and lower limbs, and joint movements of wide range, being performed in all axes of movement as well as free active movement of the scapulohumeral joint, wrist and elbows, hip, knees and ankles. Flexion and extension, lateral inclination and rotation of the trunk; flexion and extension, lateral inclination and rotation of the cervical. Only GBRT – cues with metronome- 100 BPM.	The exercises were performed with the feet on neutral position, together and apart, with decreasing and increasing of the base of support and with and without support (support bar or chair).
Motor Training 30 minutes	Consisted on 3 sets : A. Balance - Axial and proximal movements displacements in different planes and axis; coordinated movements with Upper and Lower range and speed; Functional reach, weight shifts in different directions (anterior, posterior and lateral), using foam, using stable and unstable ground, mats and disks with textures. Postural reactions, trunk rotation. Head movement: bending, rotation, and leaning sideways (eyes open and close). B. Gait training: stationary and gait training on stable and instable surface. In this part we used foam in different sizes and densities. C. Functional movements (stand up from the chair, turn around, and bend over to pick up different objects on the floor- weight, size, texture and color). Only GBRT – cues with metronome- 110 to 150 BPM.	The exercises were performed with the basis in neutral position and eyes opened and closed. Pay attention in all sets in body and limbs position; range of motion; posture; basis of support.
Cool down 10 minutes	The execution rhythm becomes progressively slower. Slow walking, breathing exercises associated to the active movement of upper limbs, global muscular relaxation and stretching. Posture training in up orthostatic position. Only GBRT – cues with metronome 80 to 90 BPM.	

Additional file 1: Table S1- Interventions

Week 1, 2, 3, 4 e 5	Complete / RM	Performance Quality of movements	Able to continue progression
Activities Part 1	☐ YES ☐ NO RM	☐ Poor ☐ Good ☐ High Quality	☐ YES ☐ NO
Activities Part 2 Set 1	☐ YES ☐ NO RM	☐ Poor ☐ Good ☐ High Quality	☐ YES ☐ NO
Activities Part 2 Set 2	☐ YES ☐ NO RM	☐ Poor ☐ Good ☐ High Quality	☐ YES ☐ NO
Activities Part 2 Set 3	☐ YES ☐ NO RM	☐ Poor ☐ Good ☐ High Quality	☐ YES ☐ NO
Activities Part 3	☐ YES ☐ NO RM	☐ Poor ☐ Good ☐ High Quality	☐ YES ☐ NO

Additional file 2: Table S2 - Weekly Schedule Screening of Progression

Week	Number of Falls	Time	Place / Environment/Circumstance	Medication	FREEZING
1	☐ YES ☐ NO N	☐ Morning () ☐ Afternoon () ☐ Night ()	Dual task: () YES () NO _____ _____ _____	☐ On ☐ Off	☐ YES ☐ NO
2	☐ YES ☐ NO N	☐ Morning () ☐ Afternoon () ☐ Night ()	Dual task: () YES () NO _____ _____ _____	☐ On ☐ Off	☐ YES ☐ NO
3	☐ YES ☐ NO N	☐ Morning () ☐ Afternoon () ☐ Night ()	Dual task: () YES () NO _____ _____ _____	☐ On ☐ Off	☐ YES ☐ NO
4	☐ YES ☐ NO N	☐ Morning () ☐ Afternoon () ☐ Night ()	Dual task: () YES () NO _____ _____ _____	☐ On ☐ Off	☐ YES ☐ NO
5	☐ YES ☐ NO N	☐ Morning () ☐ Afternoon () ☐ Night ()	Dual task: () YES () NO _____ _____ _____	☐ On ☐ Off	☐ YES ☐ NO

Additional file 3: Table S3 – Weekly Screening of falls. N: Number of Falls.

Research Report

Multimodal Balance Training Supported by Rhythmical Auditory Stimuli in Parkinson's Disease: A Randomized Clinical Trial

Tamine T.C. Capato^{a,b,c,*}, Nienke M. de Vries^a, Joanna Int'Hout^c, Egberto R. Barbosa^b, Jorik Nonnekens^d and Bastiaan R. Bloem^a

^aDepartment of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Centre of Expertise for Parkinson & Movement Disorders, Nijmegen, The Netherlands

^bDepartment of Neurology, University of São Paulo, Movement Disorder Center, São Paulo, Brazil

^cDepartment for Health Evidence, Radboud University Medical Centre, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

^dDepartment of Rehabilitation, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

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Abstract

Background: Balance impairment in Parkinson's disease (PD) improves only partially with dopaminergic medication. Therefore, non-pharmacological interventions such as physiotherapy are important elements in clinical management. External cues are often applied to improve gait, but their effects on balance control are unclear.

Objective/Methods: We performed a prospective, single-blind, randomized clinical trial to study the effectiveness of balance training with and without rhythmical auditory cues. We screened 201 volunteers by telephone; 154 were assigned randomly into three groups: (1) multimodal balance training supported by rhythmical auditory stimuli ($n = 56$) (RAS-supported multimodal balance training); (2) regular multimodal balance training without rhythmical auditory stimuli ($n = 50$); and (3) control intervention involving a general education program ($n = 48$). Training was performed for 5 weeks, two times/week. Linear mixed models were used for all outcomes. Primary outcome was the Mini-BESTest (MBEST) score immediately after the training period. Assessments were performed by a single, blinded assessor at baseline, immediately post intervention, and after one and 6-months follow-up.

Results: Immediately post intervention, RAS-supported multimodal balance training was more effective than regular multimodal balance training on MBEST (difference 3.5 (95% Confidence Interval (CI) 2.2; 4.8), $p < 0.001$). Patients allocated to both active interventions improved compared to controls (MBEST estimated mean difference versus controls 6.6 (CI 5.2; 8.0), $p < 0.001$ for RAS-supported multimodal balance training; and 3.0 (CI 2.7; 5.3), $p < 0.001$ for regular multimodal balance training). Improvements were retained at one-month follow-up for both active interventions, but only the RAS-supported multimodal balance training group maintained its improvement at 6 months.

Conclusion: Both RAS-supported multimodal balance training and regular multimodal balance training improve balance, but RAS-supported multimodal balance training—adding rhythmical auditory cues to regular multimodal balance training—has greater and more sustained effects.

Keywords: Parkinson's disease, clinical trial, physical therapy, balance, postural control, cueing

*Correspondence to: Tamine Capato, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, The

Netherlands. E-mail: tamine.capato@radboudumc.nl

INTRODUCTION

Balance and gait impairments in Parkinson's disease (PD) are both common and disabling [1–3], resulting in falls and fall-related injuries [4]. Because these axial symptoms only improve partially with dopaminergic medication [2, 5–8], non-pharmacological interventions such as physiotherapy are important to manage these problems [9–12]. There is growing evidence that physiotherapy interventions improve gait [13–19] and balance performance in PD [20–28]. Physiotherapy typically involves functional gait and balance exercises [9, 10, 24] that translate directly to daily life activities [29–31]. Moreover, compensation strategies such as rhythmic auditory cueing [32] have an immediate effect on walking speed, stride length and cadence [16, 17, 33]. However, their effects decline over time [16, 33]. In addition to their positive effect, rhythmic cues may also have a positive effect on balance performance. In contrast to gait performance, balance control is not rhythmic in nature. However, adding rhythmic auditory cueing might enhance the balance training effects by improving attention and task prioritization [34]. In this prospective randomized clinical trial, we aimed to: (1) investigate whether the effect of physiotherapy on balance performance in patients with PD would be maximized by adding rhythmical auditory stimuli to the training (RAS-supported multimodal balance training); and (2) investigate whether these effects would be retained in the long-term, after cessation of treatment. We hypothesized that, compared to control intervention (educational program) and regular multimodal balance training, adding rhythmical auditory stimuli would be more effective in improving balance performance, but that these effects would decline over time (as has been reported for gait performance).

METHOD

Study design and participants

We performed a prospective, single-blind, parallel group randomized clinical trial. The University of São Paulo Faculty Medicine Clinics Hospital received ethical approval for the study (Comissão de Ética para Análise de Projetos de Pesquisa – CAPPesq). The protocol was registered at clinicaltrials.gov (NCT02488265). Participants signed an informed consent form before participation and a photo and videos release as part of the informed

consent procedure. Patients were recruited from the Movement Disorders Center of the University of São Paulo Faculty Medicine Clinics Hospital. Inclusion criteria were: (1) diagnosis of PD according to the UK Brain Bank criteria [35]; (2) Hoehn and Yahr (H&Y) stage 1–3 [36]; (3) history of falls in the past year; (4) able to walk 10 minutes continuously; (5) Mini-Mental Status Examination (MMSE) ≥ 24 ; [37] (6) able to walk independently indoors without walking aid; (7) stable medication over the past 3 months; (8) no hearing or visual problems interfering with the tests or training; and (9) stable deep brain stimulator settings during the past year. After the inclusion, no other physiotherapy interventions or complementary exercises were allowed during the study. We categorized patients as freezer or non-freezer based, if freezing was present subjectively (NFOGQ; [38]) or objectively (Rapid Turns Test [39]) assessment of freezing. If either one of these tests showed freezing, patients were classified as freezers.

Study procedure

After screening for eligibility, subjects were randomly assigned (1:1:1) into either one of the two experimental groups, or one control intervention group (RAS-supported multimodal balance training, regular multimodal balance training and the educational program). A computerized block randomization procedure (block size 6) was performed by an independent study collaborator before the baseline assessment, with stratification for disease severity (H&Y stage). Group allocation was performed by the same study collaborator, who was not involved in interventions or assessments. This collaborator delivered a sealed envelope to the physiotherapist to ensure concealment. The trial was conducted between July 2015 and May 2017. Measurements were performed by five blinded assessors at four time points: baseline, i.e., 14 days prior to training; one day after the last 5th week training; at one-month follow-up; and 6-months follow-up. Both assessors and patients were instructed not to talk about the allocation. We did not formally test for the success of blinding. All participants were tested while they were on their usual Parkinson medication (ON-medication state), which was defined as maximally 1 hour after ingestion of their regular dose of dopaminergic medication (as self-reported by the patients) and when patients experienced a subjectively good On state. We chose exercises that are common in routine clinical treatment of gait and bal-

ance problems. These exercises involve 5 elements of posture, gait and balance: (a) sensory integration (e.g., walking tasks on varying surfaces); (b) anticipatory postural adjustments (e.g., voluntary arm, leg and trunk movements, postural transitions, and multidirectional stepping); (c) compensatory postural adjustments and motor agility (e.g., interlimb coordination under varying gait conditions and quick shifts of movement during predictable and unpredictable conditions); (d) performance at stability limits (e.g., controlled leaning tasks performed while standing with varying bases of support, stimulating weight shifts in multiple directions and turning); and (5) use of attentional strategies (maintenance of attention to the gait and balance task). No modification of the intervention protocol occurred.

Intervention

Interventions were delivered in at the University of São Paulo Clinics Hospital, Movement Disorders Clinic, Department of Neurology. The three interventions occurred on the same day and at the same location, but during different timeslots during the afternoon. This minimizes the risk of contamination. In addition, the physiotherapists were well trained to follow the different training protocols for the different training groups. Both experimental groups received multimodal balance training; one intervention group received all exercises combined with rhythmical auditory stimuli, provided by a metronome (RAS-supported multimodal balance training; Supplementary Video), whereas the other intervention group received balance training without rhythmical auditory stimuli (regular multimodal balance training). Both intervention groups also received gait training with visual cues (as this is part of routine physiotherapy care), but rhythmical auditory stimuli to maximize the balance exercises were only added in the RAS-supported multimodal balance training group on top of the training (Supplementary Video). The physiotherapists gave instructions to the patients to perform the movements on the beat of the metronome. The training program was performed in group's intervention of 10 participants supervised by 2 physiotherapists.

Training in both intervention groups involved 40 balance and gait exercises, provided during 10 sessions of 45 minutes (2 sessions/week over a 5-week period). The exercises, training progression and intensity are described in Supplementary Tables 1 and 2. The rhythmical auditory stimuli were delivered in

an open-loop by a metronome (MA-1 KORG, which was amplified using a JBL GO Portable Wireless Speaker). Progression over time was facilitated by dividing the training period into two 5-week sessions. Each exercise component was introduced separately to the participants in week 1, with emphasis on the quality of performance rather than on difficulty level. In week 2, the level of difficulty for each exercise component was increased, whereas movement complexity was further increased in week 3, 4 and 5 by combining the exercise components and increasing the demands. To further promote training progression, the aim was to increase or decrease the speed throughout the parts of the training. The control intervention group received no functional balance and gait training, but received a general education program about PD, falls prevention and self-care, which also involved 10 sessions of 45 minutes (2 sessions/week over a 5-week period) (Supplementary Tables 1 and 2).

Outcome measures

Although the UPDRS was initially selected as the primary endpoint, the research team later changed the primary outcome to Mini-BESTest (MBEST) [40] because this better suits the aim of the intervention (namely to improve balance), as was also published in the study protocol [41]. Importantly, this adjustment was made before the end of patient recruitment, and hence also well before any analyses were performed. We acknowledge that this procedure is imperfect, but we certify that the decision to change the primary outcome was driven solely by scientific arguments and taken before any data analyses had been performed. The MBEST test has a maximum score of 28 points based on 14 items that are each scored from 0–2. “0” indicates the lowest level of functioning and “2” the highest level of functioning [42]. Secondary outcomes included measures of balance and gait: Berg Balance Scale (BBS) [43], retropulsion test of the UPDRS [44], push-and-release test [45], Timed Up and Go Test (TUG) [46]. Before the actual start of the trial, the following secondary outcomes were added to the original protocol: TUG-dual task test (14 domain in MBEST) [40] and Rapid Turns Test [39]. Also, the FOG-Questionnaire was replaced with the New Freezing of Gait Questionnaire (N-FOGQ) [38]. Activities of daily living and motor performance were assessed using the UPDRS [44]. Fear of falling were evaluated using the Falls Efficacy Scale-International (FES-I) [47]. We monitored adverse events only during the training, and did not address serious events

because this was a low risk study. In addition, falls and serious adverse events were assessed through standardized weekly interviews.

Statistical analysis

Statistical analysis was performed according an intention-to-treat (ITT) which was better regarded as a complete trial strategy for our design. The intention-to-treat population was defined as all patients who received the intervention, provided baseline efficacy data, and from whom at least one measurement after baseline was obtained. All participants were analyzed as they were randomized, as there were no inconsistencies between the randomization and the actual treatment. Following discussions with an independent statistician (J.I.H., PhD) who was not involved in the study design or data collection, the statistical plan was optimized, specifically, by replacing the originally planned repeated measures ANOVA with a mixed effects model to analyze the repeated measurements, which can handle data that are missing at random and is more flexible than a repeated measures ANOVA [48, 49]. The sample size calculation was based on the MBEST as outcome. Based on the results of a pilot study (unpublished data) with exactly the same methodology and intervention, we performed a power calculation. The pilot study included 10 participants in each group. We found a 3-point difference between standard training and multimodal training. Assuming a 3-point difference and an SD of 4 (~an effect size of 0.75), 37 patients per group would be enough for 90% power, using a two-sided significance level α of 0.05. Assuming a dropout rate of 25%, this resulted in 50 patients per group. We included 154 patients instead of 150 because we reasoned that several extra participants would correct for a potential higher drop-out rate. Linear mixed models were used for all outcomes. The primary endpoint was the MBEST immediately post-intervention. We used treatment (RAS-supported multimodal balance training vs regular multimodal balance training vs controls), visit (immediately post-intervention, one-month follow-up, and 6 months follow-up) and the interaction between visit and treatment group as fixed factors. The model was adjusted for baseline MBEST, UPDRS part 2 and 3 and levodopa equivalent daily dose (LEDD), and, if not yet included, for the baseline value of the dependent variable. We adjusted for these variables, despite the randomized design of the study, to correct for possible imbalances due to a somewhat higher dropout rate in the control group than

in the training groups. Patient was included as a random factor. Berg Balance Scale, Retropulsion Test, Push and Release Test, Falls Efficacy Scale- International, Timed Up and Go, Timed up and Go Dual Task, New Freezing of Gait Questionnaire, Rapid Turns test were also analyzed with a linear mixed model, similar to the MBEST. A Bonferroni adjustment for multiple testing (three pairwise comparisons at 5 weeks follow-up) was applied, resulting in a significance threshold of 0.017 that was used for all tests. No interim analyses were performed before the recruitment target was reached.

RESULTS

We screened 201 potential participants of whom 154 were randomized (Fig. 1). The groups were similar on baseline characteristics (Table 1). A total of 21 patients dropped out of the study (14%, Fig. 1). The training compliance was determined by the number of sessions that the patients attended. Training compliance was 85% in the RAS-supported multimodal balance training group, 86% in the regular multimodal balance training group and 82% in the control intervention group. Reasons for not being compliant were lack of time, problems with transport, injuries, illness and fatigue not related to the intervention session. No adverse events occurred during the training.

Primary outcome

Figure 2A shows the results of our primary outcome, the MBEST. Immediately post treatment, both the RAS-supported multimodal training group and regular multimodal training group had improved significantly on the MBEST score compared to controls (RAS-supported multimodal balance training 6.6 (95% Confidence Interval (CI) 5.2; 8.0)), $p < 0.001$; regular multimodal balance training 3.0 (CI 2.7; 5.3), $p < 0.001$). Moreover, the RAS-supported multimodal balance training group improved significantly more than the regular training group (RAS-supported multimodal balance training difference 3.5 (95% CI 2.2; 4.8)), $p < 0.001$. These improvements were retained at one-month follow-up for both groups, but only the RAS-supported multimodal balance training group maintained its improvement at 6-month follow-up (Table 2A).

Fig. 1. Flow diagram of participants through the trial, number of participants.

Table 1
Participants' characteristics at the baseline visit

	RAS-supported N = 56	Regular N = 50	Control N = 48
Age, years (mean (SD))	74 (8)	67 (13)	73 (10)
Gender, men(N (%))	27 (48%)	32 (64%)	29 (60%)
H&Y (N(%)), I	11 (20%)	11 (22%)	7 (14%)
II	17 (30%)	16 (32%)	18 (38%)
III	28 (50%)	23 (46%)	23 (48%)
Time since first symptoms (median (IQR))	7 (4–13)	8 (4–14)	11 (4–20)
Disease duration (median (IQR))	5 (2–9)	6 (2–10)	8 (2–15)
Deep Brain Stimulation (N (%))	6 (10%)	7 (14%)	4 (8%)
Freezers of gait (N, %)	17 (30%)	15 (30%)	16 (33%)
Recurrent Fallers (N, %)	25 (45%)	21 (38%)	20 (36%)
Injuries before protocol (N, %)	26 (46%)	23 (46%)	20 (42%)
LEDD, mg/day (mean (SD))	615 (424)	701 (466)	608 (389)
MMSE, score (mean (SD))	27 (2)	26 (2)	25 (2)
MoCA, score (mean (SD))	26 (3)	25 (3)	24 (3)
UPDRS 2, ADL score (mean (SD)) (ON)	11 (7)	14 (7)	16 (8)
UPDRS 3, motor score (mean (SD)) (ON)	15 (7)	17 (9)	19 (7)
Years of education (N, %) 2–8 (primary school)	10 (18%)	11 (22%)	8 (17%)
9–14 (secondary school)	16 (29%)	21 (42%)	17 (35%)
>14	30 (53%)	18 (36%)	23 (48%)

Group: Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), Multimodal balance training without rhythmical auditory stimuli (Regular), Control Intervention group (Control). N, number of participants; SD, Standard Deviation; IQR, Interquartile range are presented; ON (ON-medication); LEDD, levodopa equivalent daily dose; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; H&Y, Hoehn & Yahr stage; UPDRS 2, ADL, Activities of daily living score; UPDRS 3, motor score.

Secondary outcomes

Balance

Similar effects were found for the secondary outcomes (Table 2A). When compared to controls, both the RAS-supported group and regular group improved immediately post-intervention on the BBS (RAS-supported vs control $p < 0.001$; regular vs control $p = 0.002$), retropulsion test (RAS-supported vs control $p < 0.001$; regular vs control $p < 0.001$), push-and-release test (multimodal vs control $p < 0.001$; standard vs control $p < 0.001$). Only RAS-supported group improved immediately post-intervention on FES-I when compared with the controls (RAS-supported vs control $p < 0.001$; regular vs control $p = 0.062$). The RAS-supported group improved significantly more than the regular group these secondary outcomes (BBS $p < 0.001$; push and release test $p = 0.002$; FES-I $p = 0.001$) except on retropulsion test (RAS-supported vs regular $p = 0.164$) (Table 2A). Improvements were retained at one-month follow-up (Table 2A), but only the RAS-supported multimodal training group maintained their improvement at 6-month follow-up. Fewer severe injuries outside the training were reported after the intervention by all groups.

Gait

Immediately post-intervention, both the RAS-supported multimodal balance training and regular multimodal balance training group showed a larger improvement on the TUG (Fig. 2B), TUG Dual Task, N-FOGQ, and rapid turns test than controls (Table 2B). No differences were found between both active interventions. The results were maintained at one month and 6 months follow-up in both groups. Except for the rapid turn test, for which the RAS-supported multimodal balance training showed better results than the regular multimodal training group and control intervention only in post-intervention (Table 2B). For the TUG Dual Task the RAS-supported multimodal balance training showed better results than the regular multimodal training group at one-month and 6-month follow-up (Table 2B).

UPDRS

Both the RAS-supported multimodal balance training group and regular multimodal training group improved on the UPDRS part 2 and part 3 immediately post-intervention (Table 2B). The RAS-supported multimodal balance training group showed a significantly larger improvement than the regular multimodal training group on both outcomes. The results on the UPDRS part 2 were retained at one

Fig. 2. (A) Mini-BESTest (MBEST) at each test visit. The red line represents RAS-supported multimodal balance training, the black line represents regular multimodal balance training and the gray line represents the control intervention group. Error bars represent the 95% confidence intervals. **all groups are significantly different, *except regular multimodal balance training vs control. (B) TUG (Timed Up and Go Test) at each test visit. The red line represents RAS-supported multimodal balance training, the black line represents regular multimodal balance training and the gray line represents the control intervention group. Error bars represent the 95% confidence intervals.

and 6-month follow-up in both groups. The results on the UPDRS part 3 were retained at one and 6-month follow-up for the RAS-supported multimodal balance training group (Table 2B).

Levodopa equivalent daily dose (LEDD)

The LEDD was not significantly different between groups for either of the follow-up moments post-intervention (Table 2B).

Table 2A
Observed mean values and estimated differences and 95% confidence intervals for balance primary and secondary outcome measures

		RAS-supported 1	Regular 2	Control 3	RAS-supported vs Regular 1-2	RAS-supported vs Control 1-3	Regular vs Control 2-3
Mini BESTest	Baseline	14.8 (12.9; 16.6)	17.3 (14.9; 19.7)	15.1 (12.4; 17.7)			
	Post Intervention	21.9 (21.0; 22.7)	18.3 (17.3; 19.2)	15.2 (14.2; 16.3)	3.5 (2.2; 4.8), $P < 0.001$	6.6 (5.2; 8.0), $P < 0.001$	3.0 (2.7; 5.3), $P < 0.001$
	1 month Follow-up	21.1 (20.2; 22.0)	17.0 (16.1; 18.0)	15.0 (13.9; 16.0)	4.0 (2.7; 5.3), $P < 0.001$	6.0 (4.7; 7.4), $P < 0.001$	2.0 (0.6; 3.4), $P = 0.005$
	6 month Follow-up	19.6 (18.7; 20.4)	15.8 (14.8; 16.7)	14.7 (13.2; 15.7)	3.7 (2.4; 5.1), $P < 0.001$	4.8 (3.4; 6.2), $P < 0.001$	1.0 (-0.3; 2.4), $P = 0.136$
Berg Balance Scale	Baseline	38.9 (35.6; 42.3)	40.9 (37.0; 44.9)	37.5 (33.0; 41.9)			
	Post Intervention	47.0 (44.7; 48.4)	41.7 (40.3; 43.2)	38.3 (36.7; 39.92)	5.2 (3.2; 7.3), $P < 0.001$	8.6 (6.; 10.8), $P < 0.001$	3.4 (1.2; 5.6), $P = 0.002$
	1 month Follow-up	45.6 (44.2; 46.9)	40.3 (38.8; 41.8)	37.8 (36.1; 39.4)	5.2 (3.2; 7.3), $P < 0.001$	7.8 (5.6; 9.4), $P < 0.001$	2.5 (0.3; 4.7), $P = 0.024$
	6 month Follow-up	43.1 (41.7; 44.5)	38.9 (37.5; 40.4)	37.1 (35.5; 38.7)	4.1 (2.1; 6.2), $P < 0.001$	6.0 (3.8; 8.1), $P < 0.001$	1.8 (-0.3; 4.0), $P = 0.098$
Retropulsion Test	Baseline	2.3 (1.9; 2.7)	2.1 (1.7; 2.4)	2.4 (2.3; 2.8)			
	Post Intervention	1.0 (0.9; 1.2)	1.3 (1.0; 1.5)	2.2 (2.0; 2.4)	-0.2 (-0.5; 0.0), $P = 0.164$	-1.1 (-1.4; -0.8), $P < 0.001$	-0.9 (-1.3; -0.6), $P < 0.001$
	1 month Follow-up	1.2 (1.0; 1.4)	1.8 (1.6; 2.1)	2.3 (2.1; 2.6)	-0.6 (-0.9; -0.3), $P < 0.001$	-1.1 (-1.4; -0.8), $P < 0.001$	-0.5 (-0.8; -0.1), $P = 0.002$
	6 month Follow-up	1.7 (1.5; 1.9)	2.1 (1.9; 2.3)	2.4 (2.1; 2.6)	-0.3 (-0.6; -0.0), $P = 0.011$	-0.6 (-0.9; -0.3), $P < 0.001$	-0.3 (-0.6; 0.0), $P = 0.070$
Push and Release Test	Baseline	2.4 (2.0; 2.7)	2.1 (1.8; 2.5)	2.4 (2.0; 2.8)			
	Post Intervention	1.1 (0.9; 1.2)	1.4 (1.2; 1.5)	2.3 (2.1; 2.5)	-0.3 (-0.5; -0.4), $P = 0.029$	-1.2 (-1.4; -0.9), $P < 0.001$	-0.9 (-1.1; -0.6), $P < 0.001$
	1 month Follow-up	1.4 (1.2; 1.5)	2.0 (1.8; 2.1)	2.4 (2.2; 2.6)	-0.6 (-0.8; -0.3), $P < 0.001$	-1.0 (-1.2; -0.7), $P < 0.001$	-0.4 (-0.7; -0.1), $P = 0.001$
	6 month Follow-up	1.9 (1.7; 2.0)	2.1 (2.0; 2.4)	2.5 (2.3; 2.7)	-0.3 (-0.6; -0.1), $P = 0.003$	-0.6 (-0.9; -0.3), $P < 0.001$	-0.2 (-0.5; 0.0), $P = 0.049$
Falls Efficacy Scale - International	Baseline	31.5 (26.8; 36.2)	34.3 (30.0; 38.4)	36.2 (31.0; 41.4)			
	Post Intervention	27.8 (22.0; 29.3)	31.4 (29.9; 32.9)	36.2 (31.9; 35.3)	-3.6 (-5.7; -1.5), $P = 0.001$	-5.7 (-8.0; -3.5), $P < 0.001$	-2.1 (-4.4; -0.1), $P = 0.062$
	1 month Follow-up	27.8 (22.1; 29.3)	32.9 (31.4; 34.4)	36.5 (32.4; 35.6)	-5.0 (-7.1; -2.9), $P < 0.001$	-6.0 (-8.3; -3.8), $P < 0.001$	-0.9 (-3.2; 1.3), $P = 0.394$
	6 month Follow-up	30.0 (23.9; 31.7)	33.6 (32.1; 35.2)	38.7 (33.8; 37.2)	-3.6 (-5.7; -1.5), $P < 0.001$	-5.5 (-7.7; -3.2), $P < 0.001$	-1.8 (-4.1; -0.4), $P = 0.113$

Group: Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), Multimodal balance training without rhythmical auditory stimuli (Regular), Control Intervention group (Control). Confidence Intervals (CI) - Adjusted Mean Difference (95% CI) Between Baseline and 35-week. Primary analysis: Adjusted for baseline MHEST score; Secondary analyses: also adjusted for baseline LEDD, baseline UPDRS 2 and 3. Mini BESTest - 14 items, total 28 of points, scored 0-2 (higher score better balance). Berg Balance Scale - 14 items total 56 of points, scored 0-4 points (higher score better balance). Retropulsion test and Push-and-release test scored between 1-4 points, lower score means better balance. Falls Efficacy Scale International - 16 items, total 64 of points scored, higher scores greater fear of fallen.

Table 2B
Observed mean values and estimated differences and 95% confidence intervals for secondary outcome measures

		RAS-supported 1	Regular 2	Control 3	RAS-supported vs Regular 1-2	RAS-supported vs Control 1-3	Regular vs Control 2-3
Timed Up and Go	Baseline	23.6 (19.2; 27.9)	19.4 (14.8; 23.2)	22.5 (17.3; 27.7)			
	Post Intervention	16.7 (14.6; 18.5)	16.2 (14.1; 18.3)	23.0 (20.7; 25.3)	-0.3 (-2.5; 3.2); $P=0.820$	-6.4 (-9.5; -3.3); $P<0.001$	-6.7 (-9.9; -3.6); $P<0.001$
	1 month Follow-up	15.7 (13.3; 17.6)	17.7 (15.5; 19.7)	23.5 (21.2; 25.8)	-1.9 (-4.8; 0.9); $P=0.189$	-7.8 (-10.9; -4.7); $P<0.001$	-5.8 (-9.0; -2.7); $P<0.001$
	6 month Follow-up	17.2 (15.2; 19.1)	18.8 (16.7; 20.9)	24.8 (22.4; 27.1)	-1.6 (-4.5; 1.2); $P=0.273$	-7.6 (-10.9; -4.5); $P<0.001$	-6.0 (-9.1; -4.5); $P<0.001$
Timed up and Go Dual Task	Baseline	28.3 (23.1; 33.4)	25.0 (20.6; 30.6)	31.6 (24.0; 39.1)			
	Post Intervention	21.4 (19.3; 23.6)	22.9 (20.6; 25.2)	30.2 (27.6; 32.8)	-1.4 (-4.6; 1.7); $P=0.360$	-8.8 (-12.2; -5.3); $P<0.001$	-7.3 (-10.8; -3.6); $P<0.001$
	1 month Follow-up	20.6 (18.4; 22.7)	24.2 (21.1; 26.5)	30.8 (28.2; 33.4)	-3.6 (-6.8; -0.4); $P=0.027$	-10.1 (-13.6; -6.7); $P<0.001$	-6.5 (-10.0; -3.0); $P<0.001$
	6 month Follow-up	21.5 (19.4; 23.7)	27.4 (25.0; 29.7)	31.3 (28.7; 33.9)	-5.8 (-9.0; -2.6); $P<0.001$	-9.7 (-13.1; -6.3); $P<0.001$	-3.9 (-7.4; -0.4); $P=0.028$
New Freezing of Gait Questionnaire	Baseline	5.7 (3.6; 7.8)	8.3 (4.8; 11.8)	8.3 (5.5; 11.1)			
	Post Intervention	7.1 (6.0; 8.2)	6.6 (5.5; 7.8)	8.7 (7.3; 10.0)	-0.4 (-1.1; 2.0); $P=0.594$	-1.5 (-3.3; -0.1); $P<0.038$	-2.0 (-3.8; -0.2); $P=0.026$
	1 month Follow-up	7.2 (6.0; 8.3)	7.0 (5.8; 8.2)	9.0 (7.7; 10.4)	-0.1 (-1.4; 1.7); $P=0.831$	-1.8 (-3.6; -0.1); $P<0.036$	-2.0 (-3.8; -0.7); $P=0.024$
	6 month Follow-up	8.0 (6.9; 9.1)	7.1 (5.9; 8.3)	9.1 (7.7; 10.4)	0.8 (-0.7; 2.4); $P=0.299$	-1.0 (-2.8; -0.6); $P=0.223$	-1.9 (-3.7; -0.1); $P=0.033$
Rapid Turns test	Baseline	0.4 (0.3; 0.5)	0.3 (0.2; 0.5)	0.5 (0.3; 0.7)			
	Post Intervention	0.1 (0.0; 0.2)	0.3 (0.2; 0.4)	0.3 (0.2; 0.4)	-0.2 (-0.3; -0.1); $P<0.001$	-0.2 (-0.3; -0.0); $P<0.001$	0.0 (-0.1; 0.1); $P=0.883$
	1 month Follow-up	0.3 (0.2; 0.4)	0.3 (0.3; 0.4)	0.4 (0.3; 0.5)	-0.0 (-0.1; 0.0); $P=0.433$	-0.0 (-0.2; 0.0); $P=0.135$	-0.0 (-0.1; 0.0); $P=0.458$
	6 month Follow-up	0.4 (0.3; 0.4)	0.4 (0.2; 0.5)	0.4 (0.3; 0.5)	0.0 (-0.0; 0.1); $P=0.756$	-0.0 (-0.1; 0.1); $P=0.750$	-0.0 (-0.1; 0.0); $P=0.089$
LEDD	Baseline	680 (545; 815)	700 (556; 833)	761 (633; 909)			
	Post Intervention	695 (678; 712)	704 (686; 722)	739 (699; 739)	-9.0 (-33.7; 15.7); $P=0.474$	-24.0 (-50.1; 2.1); $P=0.072$	-15.0 (-50.1; 2.1); $P=0.072$
	1 month Follow-up	699 (683; 716)	710 (692; 728)	765 (745; 785)	-10.9 (-35.6; 13.8); $P=0.385$	-65.4 (-91.6; -39.2); $P<0.001$	-54.5 (-81.1; -27.8); $P<0.001$
	6 month Follow-up	715 (699; 732)	743 (726; 761)	821 (801; 841)	-28.1 (-52.9; -3.4); $P=0.026$	-106.0 (-132.1; -79.8); $P<0.001$	-77.8 (-104.4; -51.2); $P<0.001$
UPDRS 2	Baseline	12.6 (10.4; 14.8)	14.5 (12.3; 16.8)	17.0 (14.2; 19.7)			
	Post Intervention	12.7 (12.3; 13.1)	13.4 (13.0; 13.8)	14.6 (14.2; 15.1)	-0.6 (-1.2; -0.0); $P=0.024$	-1.9 (-2.5; -1.2); $P<0.001$	-1.2 (-1.8; -0.6); $P<0.001$
	1 month Follow-up	13.1 (12.7; 13.5)	14.0 (13.6; 13.8)	14.8 (14.3; 15.3)	-0.9 (-1.5; -0.3); $P=0.003$	-1.7 (-2.3; -1.0); $P<0.001$	-0.8 (-1.4; -0.1); $P=0.013$
	6 month Follow-up	13.7 (13.5; 14.1)	14.4 (13.9; 14.8)	15.0 (14.5; 15.5)	-0.6 (-1.2; -0.0); $P=0.030$	-1.3 (-1.9; -0.6); $P<0.001$	-0.6 (-1.2; 0.0); $P=0.045$
UPDRS 3	Baseline	15.2 (13.1; 17.0)	17.4 (14.8; 20.1)	18.9 (16.6; 21.2)			
	Post Intervention	14.2 (13.7; 14.7)	16.1 (15.5; 16.6)	17.0 (16.4; 17.6)	-1.9 (-2.6; -1.1); $P<0.001$	-2.8 (-3.6; -2.0); $P<0.001$	-0.9 (-1.7; -0.1); $P=0.018$
	1 month Follow up	14.7 (14.2; 15.2)	16.7 (16.2; 17.3)	16.8 (16.2; 17.3)	-2.0 (-2.7; -1.2); $P<0.001$	-2.0 (-2.9; -1.3); $P<0.001$	-0.0 (-0.8; 0.7); $P=0.846$
	6 month Follow up	15.5 (14.9; 15.9)	17.0 (16.5; 17.6)	17.1 (16.6; 17.7)	-1.6 (-2.3; -0.8); $P<0.001$	-1.7 (-2.4; -0.9); $P<0.001$	-0.1 (-0.9; 0.6); $P=0.773$

Group: Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), Multimodal balance training without rhythmical auditory stimuli (Regular), Control Intervention group (Control). Confidence Intervals (CI) - Adjusted Mean Difference (95% CI) Between Baseline and 35-week. Primary analysis: Adjusted for baseline MBIEST score; Secondary analyses: also adjusted for baseline LEDD, baseline UPDRS 2 and 3. TUG and TUGDT were measured in time in seconds (time in seconds is the unit) with a range from 5-60 seconds (which is the range). A lower score means better mobility. N-FOGQ - 10 items, total 29 of points, scored 0-3 or 4. A lower score, less freezing problems. Rapid turns test was scoring 0 - no freezing and 1 - freezing. UPDRS 2-13 items, 52 of points, scored 0-4. A lower scores means better capacity in activities of daily living. UPDRS 3-18 items a total 108 points, scored 0-4. Lower scores means better motor performance.

DISCUSSION

Here, we present the results of an RCT investigating the long-term effects of two balance training interventions in a large group of early to mid-stage PD patients. Both training groups improved balance performance, as measured using the MBEST. Compliance in both training groups was good. Adding auditory rhythmical cues (RAS-supported multimodal balance training) to the balance training was more effective than balance training without these cues (regular multimodal balance training). Only the RAS-supported multimodal balance training group retained the effect at long-term follow-up (6 month).

Our study reports two important new findings. First, we show that multimodal balance training using simultaneously applied rhythmical cues is more effective than multimodal balance training without cueing. We suspect that RAS-supported multimodal balance training is more effective than regular multimodal balance training because this stimulates residual motor-cognitive abilities in PD more effectively than regular multimodal balance training [14]. Specifically, RAS-supported multimodal balance training may improve attention and task prioritization (executive control) [34], thereby facilitating the selection of efficient balance compensatory strategies and enhancing the training effects.

A second important finding is that the training effects (particularly those of RAS-supported multimodal balance training) are maintained up to 6-months follow-up.

The improvements on the MBEST-scores were not only significant, but also exceeded the previously found standard error for a test-retest measurement (3 points) [50]. Moreover, two studies have examined the responsiveness of the Mini-BESTest. Tsang et al. [51] concluded that the minimal detectable change score is 3.0 for individuals with stroke. In a mixed population of people with balance impairments involving 25 PD patients, Godi et al. [52] concluded that the minimally important change score is 4.0 points, and we therefore expect our results to be clinically relevant. Although both studies were performed in non-PD populations, the effect size observed by us was in the range of what was considered minimally important there, and we therefore expect our results to also be clinically relevant for PD patients. However, comparable trials using the Mini-BESTest are sparse and data on the minimal clinically important difference (MCID) in PD is lacking. The only study that can be compared with ours was that

by Conradson et al., 2015 [53], who found a clinical change of 3 points on the MBEST.

This MBEST improvement following RAS-supported multimodal balance training is consistent with similar improvements that we observed for all secondary balance outcomes. Earlier studies also found that physiotherapy improves balance in PD patients [18, 25, 54, 55]. Our results showed larger effect sizes on MBEST than other high challenging physiotherapy interventions [25, 53]. Possibly, this large effect might be ascribed to the addition of rhythmical auditory cues to the functional balance and gait exercises. Indeed, such large effects were not observed in the regular multimodal balance training group, where rhythmical auditory cues were not used. One possible explanation for this might be that we included patients who had never received specialized physiotherapy before. It is likely that the earlier studies [25, 53]—which had been performed in the western world—included patients who had received physiotherapy before. We suspect that previously untreated patients might show greater improvements, perhaps because expectations and placebo effects contributed, but also because of the younger age of these patients, and perhaps also their milder disease stage (we included some patients with HY stage 1) in whom the physiologic reserve is greater and learning processes are better preserved, rendering patients more amenable to interventions.

The observed results cannot be explained by a differential increase in dopaminergic medication across the intervention groups. In fact, the control intervention group reported a significantly higher dose of dopaminergic medication during follow-up, yet their performance on functional tests was statistically worse than the groups receiving an active intervention. These findings suggest that the beneficial effects following the interventions resulted from the training itself.

In addition to balance, gait also improved with both trainings immediately after the intervention. This effect was retained at follow-up. However, the clinically relevant findings reported for the TUG only apply to the change between baseline and post-intervention, not for the follow-up periods. We found no differences between RAS-supported multimodal balance training and regular multimodal balance training. This can likely be explained by the fact that visual cueing was applied during gait training in both groups. We chose to apply visual cues during gait training in both groups, as this is usual care for gait training [9]. Our results indicate that addi-

tion of rhythmical auditory cueing does not have an additional effect over and above that afforded by the visual cues. The effects are clinically relevant, as the observed improvements for, e.g., the TUG-test exceeded the minimally clinically important difference of 3.5 seconds [56]. The long-term effects are promising, in contrast to the earlier, in contrast to the earlier Rehabilitation in Parkinson's Disease: Strategies for Cueing (RESCUE) trial, where rhythmical auditory stimuli provided no long-term benefits on gait and gait-related activity [15]. We are not sure why our results are so different of RESCUE trial. Perhaps dosing (dose-response) contributed to these discrepant findings, as the treatment 'dose' was considerably higher in the present study (450 minutes) compared to the RESCUE trial (270 minutes). Recent work emphasized that dose can certainly affect the treatment response in Parkinson patients, at least when it comes to aerobic exercise [57]. Another strength of our trial was the structured training as delivered by skilled trained physiotherapists delivered in a clinical setting, whereas the RECUE intervention was performed at home. While training at home is convenient and reduces travel burden, dosing can be less well monitored during a home-based training [58]. The long-term effect of physiotherapy training with auditory cueing on the TUG has been reported before in a small group of 8 patients with a shorter follow-up (8-weeks) [59]; our study extends these findings. The auditory stimulus may even have guided attention away from, instead of towards, the movement (forcing implicit motor learning). However, it is plausible that the internal and external cueing strategies used in this study, likely had enabled patients to switch from automatic motor control to goal-directed motor control [60]. We hypothesize that the distinctions between fully automatic motor control and more goal-directed motor control are not strict [61], but that there is in fact a continuum of relatively more automatic motor control on the one hand (e.g., when the patient is performing gait or maintaining posture), and relatively more goal-directed motor control on the other hand (e.g., when subjects must perform the exercises focusing attention on the auditory cues). This might explain the long-term retention effects on RAS-supported group. Originally, we planned see only patients in H&Y stage 2 and 3. However, patients with H&Y1 stage were also included (it is not well-known which disease stages respond best to treatment), and the intervention appeared to be effective even for this now overall relatively mildly affected patient group. Future work

could consider examining the effects of cued balanced training for separate subgroups.

Our study has several limitations. First, we studied patients with mild to moderate PD and without cognitive impairments. It therefore remains unclear whether the results are generalizable to those with later stage disease or those with cognitive impairment [62]. Second, there were more drop-outs among controls, and this could be a source of bias (attrition bias), especially because participants knew their group assignment. Third, activity monitors were not employed to determine the overall level of activity both during and after the intervention, which could have contributed to the differences between groups. Finally, we cannot make any statements about possible effects when patients are OFF medication. We purposely tested all patients while ON-medication, as this would best reflect the effect of the intervention over and above standard medical management in daily clinical practice. Also, dopaminergic medication usually does little to improve balance, [63] so we expect that testing patients in an OFF phase would not make a big difference. However, future studies should examine the effects of RAS-supported multimodal balance training on balance in patients tested while OFF-medication.

Taken together, our findings further support the importance of non-pharmacological intervention in the clinical management of balance and gait problems in patients with PD. Current physiotherapy guidelines [9, 64] provide no recommendations on how to apply balance training. The present results, indicating that RAS-supported multimodal balance training is more effective and longer lasting than routine training, help to fill this gap and contribute to an increasing evidence base for specialized physiotherapy, eventually leading to optimized care for patients with PD.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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ANEXO III

TITLE: Multimodal Balance Training Supported by Rhythmic Auditory Stimuli in Parkinson Disease: Effects in Freezers and Nonfreezers

RUNNING HEAD: RAS-Supported Multimodal Balance Training in PD

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AUTHOR BYLINE: Tamine T.C. Capato, Nienke M. de Vries, Joanna Int'Hout, Jordache Ramjith, Egberto R. Barbosa, Jorik Nonnekkes, Bastiaan R. Bloem

AUTHOR INFORMATION:

T.T.C. Capato, PT, MsC, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, and Center of Expertise for Parkinson & Movement Disorders, Radboud University Medical Center, Nijmegen, the Netherlands; and Movement Disorders Clinic, Department of Neurology, University of São Paulo, São Paulo, Brazil. Address all correspondence to Dr Capato at:

tamine.capato@radboudumc.nl, @tamine_capato, <https://orcid.org/0000-0003-4235-4141>

N.M. de Vries, PT, PhD, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, and Center of Expertise for Parkinson & Movement Disorders, Radboud University Medical Center.

J. Int'Hout, PhD, Department for Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands.

J. Ramjith, PhD, Department for Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center.

E.R. Barbosa, MD, PhD Movement Disorders Clinic, Department of Neurology, University of São Paulo.

J. Nonnekès, MD, PhD, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, and Center of Expertise for Parkinson & Movement Disorders, Radboud University Medical Center; Nijmegen, the Netherlands; and Department of Rehabilitation, Sint Maartenskliniek, Nijmegen, the Netherlands.

B.R. Bloem, MD, PhD, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, and Center of Expertise for Parkinson & Movement Disorders, Radboud University Medical Center, Nijmegen, the Netherlands

Objective. To fulfill the potential of nonpharmacological interventions in Parkinson disease (PD), individually tailored treatment is needed. Multimodal balance training supported by rhythmic auditory stimuli can improve balance and gait in PD. The purpose of this study is to determine whether both freezers and nonfreezers benefit.

Methods. A secondary analysis was conducted on a large randomized controlled trial that included 154 patients with PD (Hoehn & Yahr Stages 1-3 while ON-medication) who were assigned randomly to 3 groups: (1) multimodal balance training with rhythmic auditory stimuli delivered by a metronome (RAS-supported multimodal balance training), (2) regular multimodal balance training without rhythmic auditory cues, and (3) a control intervention (involving an educational program). Training was performed for 5 weeks, twice per week. The primary outcome was the Mini-BESTest score directly after the training period. Assessments were performed by a single, masked assessor at baseline, directly postintervention, and after 1-month and 6-month follow-up. Outcomes were analyzed in 1 analysis, and the results were presented separately for freezers and nonfreezers with a linear mixed model, adjusted for baseline Mini-BESTest scores, Unified Parkinson's Disease Rating Scale scores, and levodopa equivalent dose.

Results. In both freezers and nonfreezers, both RAS-supported multimodal training and regular training significantly improved the Mini-BESTest scores compared with baseline scores and with the control group scores. The improvement was larger for RAS-supported training compared with regular training, for both freezers and nonfreezers. Only the RAS-supported training group retained the improvements compared with baseline measurements at 8-month follow-up, and this was true for both freezers and nonfreezers.

Conclusion. RAS-supported multimodal training is effective in improving balance performance in both freezers and nonfreezers.

Impact. Until this study, it was unknown whether both freezers and nonfreezers could benefit from multimodal balance training. With this information, clinicians who work with people with PD will be better able to apply personalized gait rehabilitation.

Lay Summary. Adding rhythmic auditory stimuli to balance training is beneficial for both freezers and nonfreezers, at least in persons with mild to moderate disease stages. This RAS-supported multimodal training has good potential for a wider clinical implementation with good long-term effects.

Non-pharmacological interventions are an important element of the management of gait and balance impairments in people with Parkinson disease (PD).^{1,2} Particularly physical therapy can improve gait and balance.³⁻⁷ A recent prospective randomized clinical trial studied the efficacy of adding rhythmic auditory stimuli to standard physiotherapy to improve gait and balance (RAS-supported multimodal balance training).⁸ In this study, the effects were compared to both regular multimodal balance training (but without rhythmic auditory stimuli) and a control group who received an educational program. Both RAS-supported multimodal training and regular training improved balance and gait performance after 5 weeks of training, compared to controls. The effects were larger for RAS-supported training group than regular training. Only the RAS-supported training group retained the effects at long-term follow-up (6 months).

These results are promising, but to reach the full potential of non-pharmacological interventions, individually tailored treatment is needed.⁹ To this end, clinicians must know which subgroup of PD patients benefits most from an intervention. Previous subgroup analyses showed that PD patients with freezing of gait (FOG) may respond differently to non-pharmacological interventions compared to nonfreezers.¹⁰ For example, freezers perform better with closed-loop cueing strategies compared to open-loop strategies,¹⁰ but this difference was not found for nonfreezers. Moreover, the optimal cueing frequency for freezers is somewhat lower than the baseline step frequency, whereas nonfreezers perform optimally with a cueing frequency of 10% above their baseline stepping frequency.^{11,12} Additionally, freezers have less retention of dual-task training compared to nonfreezers.¹³ However, a recent secondary analysis on the V-TIME study involving a treadmill intervention did not find a difference between freezers and nonfreezers.¹³ A possible explanation for this lack of difference may be the fact that both freezers and nonfreezers did not differ with respect to cognitive impairments.

Here, we present a secondary analysis of the Multimodal Balance Training trial,⁸ evaluating whether RAS-supported multimodal balance training is effective in both freezers and nonfreezers. As our intervention specifically focused on balance, we expected that both freezers and nonfreezers would improve on the primary outcome measures (Mini-BESTest), as balance impairments occur in both subgroups. Second, we aimed to evaluate whether possible treatment effects would retain over time, in both freezers and nonfreezers.

[H1] Methods

[H2] Study Design and Participants

The design and outcomes of the RAS-supported multimodal balance trial have been published elsewhere.^{8,14} In summary, we performed a single-blind, randomized, controlled trial (RCT) between July 2015 and May 2017 at the Movement Disorders Clinic of the University of São Paulo Faculty Medicine Clinics Hospital. The study was approved by the local ethical committee and participants signed an informed consent form before participation. The protocol was registered at clinicaltrials.gov (NCT02488265). After screening for eligibility, subjects were randomly assigned (1:1:1) into either two experimental groups (RAS-supported multimodal balance training, regular multimodal balance training) or one control intervention group (educational program). Randomization was performed by an

independent study collaborator before baseline assessments by a computerized block randomization procedure (block size 6) using stratification for disease stage (Hoehn & Yahr stage, H&Y). Inclusion criteria were: (1) diagnosis of PD according to the UK Brain Bank criteria;¹⁵ (2) H&Y stage 1-3;¹⁶ (3) history of falls in the past year; (4) Mini Mental Status Examination (MMSE) ≥ 24 .¹⁷ No other physiotherapy interventions or complementary exercises were allowed during the study. Exclusion criteria were H&Y > 3 , dementia or other severe cognitive impairment (MMSE < 24), history of others neurological disorders, orthopedic or cardiopulmonary disease; no stable DBS-setting; excessive low back pain; unable to attend or adhere to the training schedule; problems with transportation. We included all freezers and nonfreezers who fulfilled the inclusion criteria. More freezers were excluded ($n = 9$) because of cognitive impairments compared to nonfreezers ($n = 4$).

We categorized patients as freezer or nonfreezer based on either self-report (if freezing was present subjectively, as indicated in the New Freezing of Gait Questionnaire (NFOG-Q)¹⁸) or when patients manifested freezing of gait during the Rapid Turns Test.¹⁹ Measurements were performed by a blinded assessor at four time points: baseline, ie, 14 days prior to training; directly after the last training (5 weeks); at one-month follow-up; and 6-months follow-up. Both assessors and patients were instructed not to talk about the allocation. All participants were tested while taking their usual Parkinson medication (ON-medication state), at least 1 h after ingestion of their regular dose of levodopa.

[H2] Interventions

The intervention was delivered by trained physiotherapists. Both training groups received multimodal balance training; one training group received all exercises combined with rhythmic auditory stimuli provided by a metronome (RAS-supported), whereas the other training group received regular multimodal balance training without rhythmic auditory stimuli. Both intervention groups also received gait training with visual cues (as this is part of routine physiotherapy care), but rhythmic auditory stimuli to maximize the balance exercises were only added in the RAS-supported training group. Training in both intervention groups involved 40 balance and gait exercises, provided during 10 sessions of 45 minutes (2 sessions/week

over a 5-week period). We chose exercises that are common in routine clinical treatment of gait and balance. No modification of the intervention protocol occurred in order to benefit freezers.

The control group received no functional balance or gait training, but was offered a general education program about PD, falls prevention and self-care, which also involved 10 sessions of 45 minutes.⁸ Details of the exercises, training progression and intensity are described elsewhere⁸ and also can be found in Table 1. Table 1 shows an overview of the training program contents and prescription of the RAS-supported multimodal balance training (supported by rhythmical auditory) stimuli and regular multimodal training (without rhythmical auditory stimuli)⁸ and control intervention (educational program).^{4,8,20,21} Please note that these interventions were exactly the same for freezers and nonfreezers.

[H2] Outcomes

This secondary subgroup analysis for freezers and nonfreezers included the Mini-BESTest (MBEST) as primary outcome;²² this test has a maximum score of 28 points for 14 items that are each scored from 0-2.²³ Secondary outcomes were Timed Up and Go Test (TUG);²⁴ New Freezing of Gait Questionnaire (NFOG-Q).²⁵

[H2] Statistical Analysis

Statistical analysis was performed according to the intention-to-treat principle (IBM SPSS version 22; IBM Corp., Armonk, NY, USA). Linear mixed models were used for all outcomes. The primary endpoint was the MBEST directly post-intervention. We used treatment (RAS-supported training vs. regular training vs. controls), visit (immediately post-intervention, one-month follow-up, and 6 months follow-up), subgroup (freezer vs. nonfreezers) and the 2- and 3- fold interactions between visit, treatment group and subgroups (freezers/nonfreezers) as fixed factors. To adjust for baseline imbalances, the model was adjusted for baseline MBEST, UPDRS part 2 and 3 and levodopa equivalent daily dose (LEDD). Patient was included as a random factor. In separate linear mixed models, we modelled the outcomes of the Timed Up and Go, and New Freezing of Gait Questionnaire tests. These models were built in the same way as we modelled the MBEST test but for each of these models we additionally adjusted for the baseline measure of the outcome variable. The descriptive statistics included means, standard deviations, and 95% confidence intervals.

[H2] Role of the Funding Source

The funder played no role in the design, conduct, or reporting of this study.

[H1] Results

Baseline characteristics of the 154 participants (freezers ($n = 59$), nonfreezers ($n = 95$)) are presented in Table 2. Post-hoc tests revealed that freezers in the control group had a higher UPDRS part II score compared to freezers in both intervention groups ($p < 0.050$). All other baseline parameters did not differ between the groups, both for freezers and nonfreezers (Tab. 2).

[H2] Balance

The Figure shows the results for our primary outcome, the MBEST. Immediately post-treatment, both freezers and nonfreezers in the RAS-supported and regular training group improved their MBEST score compared to baseline (Tab. 4) and compared with participants in the control group (Tab. 3). Moreover, RAS-supported training afforded significantly larger improvement than regular training, both for freezers and nonfreezers (Tab. 3). Compared to the post-intervention measurement, both freezers in the RAS-supported group and regular training group did not significantly change in their MBEST scores at one-month follow-up and improvements were therefore retained. Compared to the post-intervention measurements, scores did deteriorate at 6-months in both intervention groups (Tab. 4). However, compared to the baseline measurement, freezers in the RAS-supported group still had MBEST improvements at 6-month follow, and improvements in freezers in the RAS-supported group were therefore retained compared to baseline measurements. Compared to the post-intervention measurement, both nonfreezers in the RAS-supported and regular training group did not change MBEST scores at one-month follow up, and improvements were therefore retained. When looking at the post-intervention measurements, improvements were not retained at 6-month follow-up in both intervention groups, but compared to the baseline measurement, nonfreezers in the RAS-supported group still had MBEST improvements at 6-month follow.

[H2] Freezing of gait

Freezers in both training groups did not significantly improve their NFOG-Q scores directly post-treatment or at follow-up (Tab. 4). However, at one-month and 6-month follow-up

freezers in the RAS-supported group showed a better result compared to freezers in the regular training group or control group (Tab. 3 and Figure), because the latter two deteriorated their NFOG-Q scores (Tab. 4).

[H2] Functional mobility freezers vs nonfreezers

Freezers and nonfreezers in both training groups improved their TUG score immediately post-treatment compared to baseline measurement (Tab. 4) and compared to participants in the control group (Figure). For freezers, no significant differences were found between RAS-supported and regular training, whereas nonfreezers improved more with RAS-supported training compared to regular training. At one-month follow-up, TUG-scores in both freezers and nonfreezers did not differ compared to the post-intervention measurements in both intervention groups, and improvements were therefore maintained. At six-month follow-up, TUG scores did not differ compared to post-intervention measurements in freezers in the RAS-supported training group, but did increase in freezers in the regular training group (although improvement retained compared to the baseline measurement (Tab. 4)). In nonfreezers, TUG scores did not differ compared to post-intervention measurements in both training groups at six-month follow-up, and improvements were therefore sustained (Tab. 3 and Tab. 4).

[H1] Discussion

In this secondary analysis we evaluated whether multimodal balance training supported by rhythmic auditory stimuli is effective in both freezers and nonfreezers. In line with our hypothesis, both freezers and nonfreezers in the RAS-supported and regular training groups significantly improved their MBEST score immediately post-treatment compared to baseline scores and compared to controls. This improvement was larger for RAS-supported training compared to regular training. Moreover, only participants receiving RAS-supported training retained the improvements at 6-month follow-up (compared to baseline measurements), and this was true for both freezers and nonfreezers. These findings indicate that both freezers and nonfreezers respond largely similarly compared to the overall group reported earlier (8). When aiming to improve balance performance in PD, adding external auditory cues to exercises should therefore be considered, irrespective of whether patients freeze or not.

With respect to gait, we report two new findings. First, RAS-supported multimodal balance training was not effective in reducing FOG, as measured with the N-FOGQ. This is surprising, as there is a large body of evidence showing beneficial effects of external auditory cueing on gait

performance in PD.^{7,10,25,26} However, our training program focused primarily on balance, and external cues were not used after the training in daily life situations, which may explain these findings. Additionally, it becomes increasingly clear that measuring the effect of a training intervention on FOG using the NFOG-Q has limitations.^{27,28} A recent study reported that the NFOGQ has a minimal detectable change of 9.9 points (relative minimal detectable change of 35.5%).²⁸ Future studies are therefore needed to quantify the effects using additional measures that could capture clinical relevance, including for example objective measures (eg, using wearable sensors), ideally in the home-setting and over longer time frames.²⁷ Future studies may also evaluate whether RAS-supported multimodal training may help to prevent to occurrence of freezing in nonfreezers, thereby facilitating delivery of a wide range of physiotherapy interventions focusing on improving gait or balance, or delivery of exercise training.

A second important finding is that functional mobility (TUG) improved in both freezers and nonfreezers. The degree of improvement exceeded the minimal clinically relevant difference of 3.5 seconds.²⁹ Among freezers, we found no differences between both active interventions on the TUG outcomes, which is consistent with our primary analysis.⁸ However, among nonfreezers, the RAS-supported training group improved significantly more compared to the regular training group when measured directly after the intervention. This is surprising, as one would expect that particularly freezers would benefit from additional cueing. This lack of greater improvement among freezers may be due to a power problem, as the degree of improvement was larger following RAS-supported training compared to regular training.

In contrast to several other intervention studies,¹⁰⁻¹² multimodal training (with and without auditory cues) was effective in both freezers and nonfreezers. Differential effects between freezers and nonfreezers may arise because of differences in disease severity (freezers are often more severely affected than nonfreezers) or the presence of cognitive impairments (cognitive impairments are more frequently seen in freezers compared to nonfreezers). In our study, disease severity was longer in freezers, but scores of cognitive tests (Tab. 2) were comparable between freezers and nonfreezers (as cognitive impairments was an exclusion criterium). The lack of differences in cognitive status may explain why we did not find differences between both subgroups. This is in line with a recent study from Bekkers and colleagues,¹³ which also found no difference between freezers and nonfreezers when evaluating a treadmill intervention. In this study, freezers and nonfreezers neither differed with respect to cognitive impairments. Apparently, cognitive status could be an important

determinant of the efficacy of physical therapy and possibly other comparable nonpharmacological interventions. This aspect deserves further study in future work.

Our study is not without limitations. First, we only included patients without cognitive impairments and who were in mild to moderate disease stages. Future studies should also investigate the effects of our intervention in PD patients with more pronounced cognitive impairments, as this could be an important determinant of the efficacy of nonpharmacological interventions such as the RAS-supported intervention tested here. Second, we did not perform a formal power analysis for this subgroup analysis, although we do not expect that the magnitude or direction of the findings would have been different with a larger sample. Third, we cannot make any statements about the possible effects when patients are OFF medication because we purposely tested and trained all patients in an ON-medication state, as this would best reflect the effect of the intervention over and above standard medical management in daily clinical practice, where patients are typically seen and be treated during a regular ON state. This, however, means that the primary and secondary outcomes scores are a reflection of the patients' optimal functioning, leading to overall lower scores(8). Future studies should examine the effects of RAS-supported multimodal balance training on balance in patients with more advanced stages, cognitive impairments and also while they are being tested in an OFF-medication state.

Taken together, this secondary analysis suggests that adding rhythmic auditory stimuli to balance training is beneficial for both freezers and nonfreezers, at least in persons with mild to moderate disease stages that were included in the present study. Future studies are needed to evaluate the effect of training interventions such as RAS-supported balance training in patients with later disease stages (eg, Hoehn and Yahr stage 4).

Author Contributions and Acknowledgments

Concept/idea/research design: T.T.C. Capato, E.R. Barbosa, B.R. Bloem

Writing: T.T.C. Capato, N.M. de Vries, J. Int'Hout, E.R. Barbosa, J. Nonnekes, B.R. Bloem

Data collection: T.T.C. Capato, E.R. Barbosa,

Data analysis: T.T.C. Capato, J. Int'Hout, J. Ramjith, E.R. Barbosa, J. Nonnekes,

Project management: T.T.C. Capato, B.R. Bloem

Fund procurement: B.R. Bloem

Consultation (including review of manuscript before submitting): N.M. de Vries, J. Int'Hout, J. Ramjith,

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Ethics Approval

The primary study, conducted at the Movement Disorders Clinic of the University of São Paulo Faculty Medicine Clinics Hospital, São Paulo, Brazil, was approved by the local ethical committee, and participants signed an informed consent form before participation.

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Clinical Trial Registration

The protocol was registered at clinicaltrials.gov (NCT02488265).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Tables

Table 1. Training Program Contents and Prescription of the RAS-Supported Multimodal Balance Training (Supported by Rhythmical Auditory) Stimuli and Regular Multimodal Training (Without Rhythmical Auditory Stimuli) and Control Intervention (Educational Program)

<i>Intervention</i>	<i>Frequency / Intensity</i>	<i>Duration/ Dose</i>	<i>Progression / Dose</i>
	2x/Week (During 5 Weeks)	45 min: Warm-up: 5 min; Main Part: 30 min; Cool down: 10 min	Personalized
<i>General content</i>	<p>Both interventions (RAS-supported multimodal balance training and regular multimodal training) consisted of 3 parts: balance, gait and functional movements [8].</p> <p>The auditory rhythmical cues in the RAS-group were delivered in an open-loop fashion (throughout the whole duration of the exercises) by a metronome at 50, 80, 100, 120 or 140 bpm beats per minute (bpm), according the exercises.</p> <p>When the patient was unable to perform the movement safely or with enough quality, the rhythm was personalized, and the patient was instructed to use double the time to execute the movements (eg. 100 bpm instead of 50 bpm).</p>	<p>Week 1 - each exercise was explained and demonstrated by the physiotherapist; patients were encouraged to pay attention on the most difficult aspects of movement execution. They performed five repetitions of each movement/ exercise (5 RM).</p>	<p>Week 2 and 3, the subjects performed a series up to 10 repetitions per movement/exercise (RM) and in the third week, two series up to 10 RM (20 RM in total).</p> <p>Week 4 and Week 5, if the subjects were able to execute 20 RM, they were instructed to progressively increase or decrease the movement speed depending on the exercise (and thereby making the exercise more difficult).</p>
<i>Exercises involve 5 elements of posture, gait and balance:</i>	<p>(a) sensory integration (eg. walking tasks on varying surfaces);</p> <p>(b) anticipatory postural adjustments (eg. voluntary arm, leg, and trunk movements, postural transitions, and multidirectional stepping);</p> <p>(c) compensatory postural adjustments and motor agility (eg. interlimb coordination under varying gait conditions and quick shifts of movement during predictable and unpredictable conditions);</p> <p>(d) performance at stability limits (eg. controlled leaning tasks performed while standing with varying bases of support, stimulating weight shifts in multiple directions and turning); and (5) use of attentional strategies (maintenance of attention to the gait and balance task).</p>		

Balance	<p>Anticipatory postural adjustments (postural transitions, and multidirectional stepping, emphasizing movement velocity and amplitude);</p> <p>Compensatory postural adjustments (quick shifts of postures during predictable and unpredictable conditions);</p> <p>Performance at stability limits (controlled leaning tasks performed while standing with varying bases of support, stimulating weight shifts in multiple directions and turning);</p> <p>Attentional strategies (maintenance of attention during all exercises).</p>	<p>Patients who did not show a good performance in Week 1, received additional instructions from a physiotherapist in terms of how to perform the exercises correctly.</p> <p>In the RAS-supported group, patients were instructed to perform the movements slowly (twice the beat of the metronome) (see example in supplementary video⁴).</p>	<p>Decreasing and increasing of the base of support.</p> <p>Increasing and decreasing movement velocity and amplitude.</p> <p>Progress - not holding on wall, bar or chair</p>
Gait	<p>Motor agility (eg, interlimb coordination under varying gait conditions and quick shifts of movement characteristic during predictable and unpredictable conditions);</p> <p>Performance at stability limits (controlled leaning tasks performed while walking with varying bases of support, in multiple directions and turning);</p> <p>Attentional strategies (maintenance of attention during all exercises).</p>	<p>Focusing on big steps, and visual cues</p> <p>In the RAS-supported group, patients were instructed to perform the movements on the beat of the metronome (see example in supplementary video³).</p>	<p>Increase environmental demands: uneven and narrow surfaces, spaces, doorways, varying bases of support, in multiple directions and turning</p>
Functional movements	<p>Performance at stability limits (controlled leaning tasks performed while standing with varying bases of support, stimulating weight shifts in multiple directions and turning);</p> <p>Posture core stabilization;</p> <p>Attentional strategies (maintenance of attention during all exercises).</p>	<p>Focusing attention on the most difficult part of the movement</p> <p>In the RAS-supported group, patients were instructed to perform the movements slowly (twice the beat of the metronome)</p>	<p>Increase coordination demands; sit-to-stand, start-stop; increase or decrease the speed</p>
<p>Materials: Chairs, Ball (65 cm, 55 cm, 30 cm); Rubbers band (120cm - medium density); Sticks (100cm), Foams: 160 x 23 x 6 cm; 50 x 41 x 6 cm; 100 x 41 x 6 cm; 185 x 100 x 1,5 cm); Bar, Colored adhesive tapes; MA-1 KORG Metronome.</p>			
Educational program	<p>Contents of components were distributed in lectures, video sessions, general orientations about Parkinson's Disease and Discussions^{4,20}</p>	<p>45 min</p> <p>The educational program was delivered in Portuguese (as the study was conducted in Brazil and all participants spoke Portuguese)²¹</p>	
Lectures	<p>Week 1. Parkinson Disease – Epidemiology, Path physiology and diagnosis</p> <p>Week 2. Treatment Pharmacological, Neurosurgery and Rehabilitation (general information).</p>	<p>5 min – Welcome; 30 min – Lecture; 10 min-Discussion</p>	

	<p>Week 3. Quality of life and self-management</p> <p>Week 4. Patient centered care. How to be involved?</p> <p>Week 5. Falls prevention</p>	
<i>Video session</i>	<p>Week 6. Advocating for Parkinson's disease. Videos of famous people with Parkinson's Disease</p> <p>Week 7. Discussion about lectures and videos sessions (hot topics chosen by the group)</p>	5 min – Welcome; 30 min –Video; 10 min- Discussion
<i>Orientations and discussions</i>	<p>Week 8. Make a list of your PD problems and try guiding us to help you.</p> <p>Week 9. What people with Parkinson's disease should do and are able to do? Making your plans to the future.</p> <p>Week 10. Doubts (question and answers about all educational program topics)</p>	5 min – Welcome; 30 min Orientations; 10 min- Discussion

UNCORRECTED MANUSCRIPT

Table 2. Subgroups Participants' Characteristics at Baseline Visit^a

		FREEZERS (59)			NONFREEZERS (95)		
	RAS-supported (n = 19)	Regular (n = 18)	Control (n = 22)	RAS-supported (n = 36)	Regular (n = 34)	Control (n = 25)	
Age, y (mean (SD))	74 (8)	63 (13)	76 (7)	72 (9)	68 (12)	70 (10)	
Sex, men (N (%))	10 (55.6%)	9 (50%)	18 (81.8%)	16 (42.9%)	22 (78.6%)	11 (44%)	
H&Y (N (%)), I	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (34.6%)	14 (39.4%)	7 (26%)	
II	2 (11%)	3 (17.6%)	4 (18.2%)	11 (32.9%)	10 (30.3%)	6 (24%)	
III	16 (88.9%)	14 (82.4%)	18 (72.7%)	10 (32.3%)	10 (30.3%)	12 (50%)	
Disease duration, years (median (IQT))	8 (3-12)	10 (4-16)	10 (3-15)	3 (2-8)	5 (2-7)	7 (1-10)	
LEDD, mg/day (mean (SD))	902 (514)	889 (493)	913 (457)	563 (430)	557 (359)	611 (324)	
MMSE, score (mean (SD))	26 (2)	25 (2)	24 (2)	27 (2)	25 (2)	26 (2)	
MoCA, score (mean (SD))	25 (3)	24 (2)	23 (2)	26 (3)	24 (3)	25 (3)	
UPDRS 2, ADL score (mean (SD))	19 (7)	20 (8)	23 (6)	10 (6)	12 (6)	12 (6)	
UPDRS 3, motor score (mean (SD))	20 (7)	23 (10)	24 (7)	13 (6)	15 (6)	17 (7)	
Mini BESTest (mean (SE))	11.0 (1.5)	9.9 (1.6)	11.8 (1.4)	16.8 (1.1)	21.4 (1.1)	18.1 (1.4)	
New Freezing of Gait Questionnaire (mean (SE))	14.2 (1.3)	21.0 (1.4)	15.3 (1.2)	0 (0)	0 (0)	0 (0)	
Timed Up and Go Test (mean (SE))	33.4 (3.5)	28.5 (3.6)	25.8 (3.2)	18.4 (2.5)	15.9 (2.7)	18.9 (3.1)	

^aADL = ; IQT = ; LEDD = levodopa equivalent daily dose; MMSE = Mini Mental Status Examination ; MoCA = ; UPDRS = Unified Parkinson's Disease Rating Scale; SD = standard deviation ; SE = standard error.

Table 3. Observed Mean Values and Estimated Between Groups Differences in Improvement From Baseline and 95% CIs for Balance and Gait Outcomes for Freezers and Nonfreezers^a

Mini BESTest^c							
Freezers	Baseline	11.1 (7.8; 14.3)	11.7 (8.2; 15.2)	11.2 (7.8; 14.5)			
	Post intervention	18.4 (15.3; 21.5)	14.7 (10.8; 18.4)	11.2 (7.9; 14.4)	4.0 (2.0; 6.5), P<0.001	7.3 (5.0; 9.0), P<0.001	3.4 (0.7; 5.0), P=0.011
	1-month Follow up	17.6 (14.0; 21.2)	13.9 (9.9; 17.9)	11.2 (7.8; 14.5)	4.1 (1.9; 6.4), P<0.001	6.5 (4.2; 8.8), P<0.001	2.3 (-0.1; 4.7), P=0.051
	6-month Follow up	15.8 (12.0; 19.5)	12.9 (8.9; 16.8)	11.0 (11.3; 20.3)	3.2 (1.0; 5.5), P=0.004	4.5 (2.2; 6.9), P<0.001	1.3 (-1.0; 3.6), P=0.278
	Nonfreezers						
	Baseline	16.7 (14.5; 18.8)	20.7 (17.8; 23.6)	17.0 (12.4; 21.5)			
	Post intervention	23.0 (21.0; 25.0)	23.3 (20.6; 26.0)	16.2 (12.3; 21.1)	3.1 (1.4; 4.8), P<0.001	6.5 (4.7; 8.4), P<0.001	3.4 (1.4; 6.5), P=0.001
	1-month Follow up	22.4 (20.0; 24.4)	21.6 (18.4; 24.3)	17.2 (11.9; 20.4)	4.0 (2.3; 5.7), P<0.001	6.3 (4.4; 8.1), P<0.001	2.2 (0.2; 4.2), P=0.030
	6-month Follow up	20.8 (18.7; 23.0)	20.0 (17.5; 22.6)	15.8 (11.3; 20.3)	4.2 (2.4; 5.9), P<0.001	5.2 (3.4; 7.1), P<0.001	1.0 (-0.9; 3.0), P=0.297
	New Freezing of Gait Questionnaire^d						
Freezers	Baseline	15.2 (12.2; 18.2)	20.4 (16.4; 24.5)	15.1 (12.1; 18.2)			
	Post intervention	12.2 (9.2; 14.9)	17.7 (14.7; 20.6)	15.1 (12.0; 18.1)	0.1 (-0.5; 0.2), P=0.389	-2.1 (-2.7; -1.6), P<0.001	-2.0 (-2.4; -1.5), P<0.001
	1-month Follow up	12.9 (9.4; 15.16)	18.4 (15.6; 21.2)	16 (12.8; 19.1)	-0.6 (-1.0; -0.2), P=0.002	-1.0 (-1.6; -0.4), P=0.001	-0.4 (-0.8; 0.0), P=0.067
	6-month Follow up	14.2 (11.2; 17.3)	18.8 (16.3; 21.4)	16 (12.8; 19.1)	-1.0 (-1.4; -0.5), P<0.001	-1.0 (-1.6; -0.3), P=0.002	-4.5 (-0.4; 0.4), P=1.000
	Nonfreezers						

Nonfreezers	Baseline	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)			
	Post intervention	2.3 (0.3; 4.5)	1.9 (0.3; 3.4)	3.7 (0.9; 6.4)	-0.0 (-0.3; 0.2), P=0.839	-0.4 (-0.8; -0.0), P=0.049	-0.3 (-0.6; -0.0), P=0.009
	1-month Follow up	2.3 (0.3; 4.4)	2.4 (0.3; 3.7)	3.6 (0.8; 6.5)	-0.1 (-0.4; 0.2), P=0.477	-0.1 (-0.5; 0.3), P=0.618	-0.0 (-0.4; 0.3), P=0.999
	6-month Follow up	2.7 (0.4; 5.1)	2.1 (0.4; 3.8)	3.6 (0.8; 6.4)	0.0 (-0.3; 0.4), P=0.774	0.0 (-0.5; 0.6), P=0.838	0.1 (-0.4; 0.2), P=0.947
Timed Up and Go Test*							
Freezers	Baseline	33.5 (23.9;43.1)	27.0 (16.0; 38.0)	26.2 (17.0; 35.4)			
	Post intervention	21.9 (14.3; 29.5)	18.0 (10.3; 25.8)	27.1 (16.9; 37.2)	0.8 (-0.7; 1.7), P=0.071	2.7 (1.4; 3.9), P<0.001	1.8 (0.9; 2.7), P<0.001
	1-month Follow up	21.4 (13.5; 29.4)	20.4 (12.7; 28.0)	28.3 (17.3; 39.2)	0.7 (-0.2; 1.6), P=0.130	1.7 (0.4; 3.0), P=0.008	1.0 (0.0; 1.9), P=0.039
	6-month Follow up	23.7 (15.5; 32.0)	21.7 (13.5; 29.0)	29.0 (18.3; 39.6)	4.0 (-0.9; 9.9), P=1.000	1.7 (0.4; 3.0), P=0.008	1.0 (0.0; 1.9), P=0.039
Nonfreezers	Baseline	18.9 (14.9; 22.8)	14.6 (11.6; 17.1)	20.5 (12.5; 28.5)			
	Post intervention	14.6 (12.1; 17.3)	12.0 (9.7; 12.3)	21.1 (12.8; 29.5)	0.7 (0.1; 1.4), P=0.014	2.1 (1.3; 3.0), P<0.001	1.3 (0.7; 2.0), P<0.001
	1-month Follow up	13.5 (11.5;15.4)	12.8 (10.6; 14.9)	20.9 (12.7; 29.1)	1.7 (0.9; 2.4), P<0.001	3.2 (2.2; 4.2), P<0.001	1.5 (0.7; 2.2), P<0.001
	6-month Follow up	14.6 (12.1; 17.1)	14.0 (11.9; 16.7)	22.8 (12.7; 33.0)	0.5 (-0.3; 1.4), P=0.244	0.8 (-0.3; 2.0), P=0.151	0.3 (-0.5; 1.2), P=0.437

*LEDD = levodopa equivalent daily dose; MMSE = Mini Mental Status Examination; NFOG = New Freezing of Gait Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale; SD = standard deviation; SE = standard error; TUG = timed up and go.

^aGroup: Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), Multimodal balance training without rhythmical auditory stimuli (Regular), Control Intervention group (Control).

^aMini BEST— between groups differences (95% CI) in improvement from baseline— Adjusted for baseline MBEST, baseline LEDD, and baseline UPDRS 2 and 3. Mini BEST— 14 items, total 28 of points, scored 0-2 (higher score better balance).

^bNew Freezing of Gait Questionnaire (NFOG) Adjusted NFOG Mean Difference (95% CI) from baseline). Adjusted for NFOG baseline, baseline LEDD, baseline UPDRS 2 and 3.

^cTimed Up and Go Test (TUG): TUG - Adjusted TUG Mean Difference (95% CI) from baseline). Adjusted for baseline TUG, baseline LEDD, baseline UPDRS 2 and 3. TUG was measured in time in seconds with a range from 5-60 seconds. A lower score means better mobility.

Table 4. Estimated Differences From Baseline and Post-Intervention Measures With 95% Confidence Intervals for Primary And Secondary Outcomes, for Freezers and Nonfreezers^a

Groups ^b		RAS-supported (1)	Regular (2)	Control (3)	RAS-supported (1)	Regular (2)	Control (3)
Mini BEST ^c							
Freezers	Baseline						
	Post Intervention	6.8 (5.2; 8.3)	2.5 (0.9; 4.2)	-0.5 (-2.3; 1.2)			
	1-month Follow up	5.9 (4.4; 7.5)	1.8 (0.1; 3.4)	-0.5 (-2.3; 1.2)	-0.6 (-0.7; 0.0)	-0.7 (-1.6; 0.2)	0.0 (-0.9; 0.9)
	6-month Follow up	4.1 (2.5; 5.6)	0.8 (-0.8; 2.4)	-0.4 (-2.3; 1.3)	-2.7 (-3.9; -1.5)	-1.7 (-3.0; -0.4)	0.0 (-1.2; 1.4)

Nonfreezers		Baseline					
	Post Intervention	6.4 (5.2; 7.5)	3.2 (1.9; 4.6)	-0.1 (-1.6; 1.3)			
	1-month Follow up	5.6 (4.4; 6.7)	1.5 (0.2; 2.8)	-0.6 (-2.2; 0.8)	-0.7 (-1.4; -0.1)	-1.7 (-2.4; -0.9)	-0.5 (-1.4; 0.3)
	6-month Follow up	4.2 (3.1; 5.3)	0.0 (-1.2; 1.3)	-1.0 (-2.5; 0.5)	-2.1 (-3.0; -1.3)	-3.2 (-4.2; -2.2)	-0.8 (-2.0; 0.3)
New Freezing of Gait Questionnaire^d							
Freezers		Baseline					
	Post Intervention	-1.5 (-3.3; 0.2)	0.0 (-2.4; 2.5)	0.5 (-1.8; 2.8)			
	1-month Follow up	-1.4 (-3.1; 0.3)	0.7 (-1.8; 3.2)	1.5 (-0.8; 3.8)	7.7 (4.1; 11.2)	8.2 (4.7; 11.7)	7.0 (3.4; 10.5)
	6-month Follow up	0.0 (-1.7; 1.7)	1.1 (-1.4; 3.6)	1.5 (-0.8; 3.8)	3.6 (-0.0; 7.3)	4.4 (0.7; 8.2)	2.8 (-0.8; 6.5)
Nonfreezers		Baseline					
	Post Intervention	0.9 (-0.6; 2.4)	-0.2 (-1.9; 1.4)	2.1 (0.1; 4.1)			
	1-month Follow up	0.9 (-0.6; 2.4)	0.0 (-1.7; 1.6)	2.1 (0.1; 4.1)	-1.7 (-4.6; 1.2)	-1.6 (-4.6; 1.3)	-2.0 (-5.0; 0.9)
	6-month Follow up	1.3 (-0.1; 2.9)	0.0 (-1.7; 1.6)	2.1 (0.1; 4.1)	0.3 (-2.8; 3.6)	0.3 (-2.9; 3.5)	-0.1 (-3.3; 3.1)
Timed Up and Go Test^e							
Freezers		Baseline					
	Post Intervention	-8.2 (-11.4; -5.1)	-9.2 (-12.9; -5.5)	0.7 (-3.1; 4.6)			
	1-month Follow up	-9.3 (-12.4; -6.2)	-6.9 (-10.6; -3.2)	1.8 (-2.0; 5.7)	1.6 (-1.1; 4.3)	2.1 (-0.5; 4.8)	1.1 (-1.5; 3.8)

	6-month Follow up	-7.3 (-10.5; -4.2)	-6.0 (-9.7; -2.3)	2.2 (-1.6; 6.1)	2.0 (-0.5; 4.7)	2.9 (0.2; 5.5)	1.5 (-1.1; 4.1)
Nonfreezers	Baseline						
	Post Intervention	-4.3 (-7.2; -1.6)	-3.9 (-6.8; -1.0)	0.8 (-2.6; 4.3)			
	1-month Follow up	-5.1 (-7.8; -2.4)	-3.2 (-6.1; -0.2)	0.7 (-2.7; 4.2)	-1.1 (-3.2; 0.9)	-1.0 (-3.1; 1.0)	-1.4 (-3.5; 0.6)
	6-month Follow up	-3.9 (-6.6; -1.2)	-2.0 (-4.9; 0.9)	2.8 (-0.6; 6.3)	1.2 (-1.0; 3.5)	1.1 (-1.0; 3.4)	0.7 (-1.5; 3.0)

^aLEDD = levodopa equivalent daily dose; MMSE = Mini Mental Status Examination; NFOG = New Freezing of Gait Questionnaire; SE = standard error; TUG = timed up and go; UPDRS = Unified Parkinson's Disease Rating Scale.

^bGroup: Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), Multimodal balance training without rhythmical auditory stimuli (Regular), Control Intervention group (Control).

^cMini BEST – between groups differences (95% CI) in improvement from baseline. Adjusted for baseline MBEST, baseline LEDD, and baseline UPDRS 2 and 3. Mini BEST – 14 items, total 28 of points, scored 0-2 (higher score better balance).

^dNew Freezing of Gait Questionnaire (NFOG) Adjusted NFOG Mean Difference (95% CI) from baseline. Adjusted for NFOG baseline, baseline LEDD, baseline UPDRS 2 and 3.

^eTimed Up and Go Test (TUG); TUG - Adjusted TUG Mean Difference (95% CI) from baseline. Adjusted for baseline TUG, baseline LEDD, baseline UPDRS 2 and 3. TUG was measured in time in seconds with a range from 5-60 seconds. A lower score means better mobility.

Figure Caption

Figure. – Mini-BESTest (MBEST), New Freezing of Gait Questionnaire (NFOG) and Timed Up and Go test (TUG) at each test visit. The blue line represents Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), the dark blue line represents Multimodal balance training without rhythmical auditory stimuli (Regular) and the gray line represents the control intervention group. Error bars represent the 95% confidence intervals.

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