UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

TESE DE DOUTORADO

TREINAMENTO COGNITIVO COMO ABORDAGEM COMPLEMENTAR À MEDICAÇÃO PARA TRATAMENTO DO TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE (TDAH) EM CRIANÇAS E ADOLESCENTES.

Virginia de Oliveira Rosa

Porto Alegre, novembro de 2018.

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Tese apresentada ao Programa de Pós-Graduação em Ciências Médicas: Psiquiatria como requisito parcial para obtenção de título de Doutor.

Virginia de Oliveira Rosa

Orientador: Prof. Dr. Luis Augusto P. Rohde

Co-orientador: Prof. Dr. Marcelo Schmitz

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em especial ao meu filho Francisco

que me acompanhou e me incentivou

na conclusão desta etapa da minha vida, e ao

meu marido, Tiago, pelo amor, lealdade e

dedicação.

“Você ganha força, coragem e confiança

através de cada experiência em que você

realmente para e encara o medo de frente”

Eleanor Roosevelt

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Lista de abreviaturas

CT	Cognitive Training – Treinamento Cognitivo
TC	Treinamento Cognitivo
TDAH	Transtorno de Déficit de Atenção e Hiperatividade
SAT	Sustained Attention Task – Teste de Atenção Sustentada
RMNf	Ressonância Magnética Nuclear Funcional
DMN	Default Mode Network

Resumo

A maioria das diretrizes atuais preconiza tratamento combinado (medicação e abordagens não-farmacológicas) para o Transtorno de Déficit de Atenção/Hiperatividade (TDAH). Intervenções não-farmacológicas, como o Treinamento Cognitivo (TC), vêm sendo amplamente estudadas para o tratamento do transtorno. Este estudo tem o objetivo de avaliar a eficácia de um programa computadorizado de TC para crianças e adolescentes com TDAH em uso de medicação psicoestimulante. Método: trata-se de um ensaio clínico randomizado que incluiu 53 crianças e adolescentes entre 6 e 13 anos com TDAH medicados com psicoestimulantes. Os participantes foram randomizados para um dos dois grupos existentes - treinamento cognitivo ou treinamento placebo - e completaram um protocolo de 48 sessões, conduzidas 4x na semana por 12 semanas. Foram selecionados 20 participantes do estudo, 10 de cada grupo, para realizarem exame de ressonância funcional sob tarefa de atenção (Sustained Attention Task – SAT: 3 condições – 2s, 5s e 8s), memória de trabalho (N-Back: 4 condições – 0-back, 1-back, 2-back, 3-back e 4-back) e controle inibitório (Go/No-Go). Os seguintes desfechos foram avaliados pré e pós intervenção: 1. sintomas de desatenção e hiperatividade; 2. desempenho neuropsicológico; 3. performance cognitiva e ativação de áreas cerebrais em imagens de ressonância magnética funcional; 4. tempo de uso de videogame e internet e 5. funcionamento clínico global. Resultados: encontrou-se uma dificuldade maior do que a esperada para a alocação dos participantes em função de problemas logísticos tais como comparecimento nas sessões presenciais. Não se encontraram diferenças significativas entre os grupos nos sintomas do TDAH (escore pais – desatenção: p=0.58; hiperatividade/impulsividade: p=0.63. Escore professores – desatenção: p=0.58; hiperatividade/impulsividade: p=0.31). No desempenho neuropsicológico, da mesma forma, não se encontrou diferença significativa entre os grupos nas três tarefas avaliadas (Flanker Test – para avaliação de controle inibitório e atenção; List Sorting Working Memory Test – para avaliação de memória de trabalho; e Go/No-Go – para avaliação de controle inibitório e flexibilidade cognitiva). Na avaliação de neuroimagem, os seguintes achados foram encontrados: a. performance neuropsicológica – na tarefa de memória de trabalho (N-back), a acurácia dos participantes no teste diminuiu com o aumento da dificuldade do mesmo, assim como houve um efeito do tempo, demonstrando uma melhora geral na acurácia pré *versus* pós intervenção; já na tarefa de atenção sustentada, encontrou-se uma interação tempo x grupo x delay em relação ao tempo de reação médio, demonstrando uma melhora com o tratamento ao longo do tempo se comparado ao grupo do treino não-ativo, apenas no delay de 5s; b. ativação cerebral – identificou-se um efeito na interação do grupo x tempo x "load" em dois clusters cerebrais (1. Ínsula e putâmen direitos; 2. Tálamo e pálido esquerdos) na tarefa de memória de trabalho, assim como um efeito na interação grupo x tempo x "delay" em quatro clusters (1. Precúneo, giro angular, giro temporal médio, córtex associativo

visual direitos; 2. Giro pós-central, giro pré-central e ínsula direitos; 3. Giro frontal superior e giro frontal médio direitos; 4. Precúneo, córtex visual associativo e giro angular esquerdos) na tarefa de atenção sustentada. Discussão: nosso estudo não encontrou evidências de benefício do TC para os sintomas nucleares do TDAH em crianças e adolescentes medicados com psicoestimulantes. Já os achados de neuroimagem apontam para uma possibilidade de que as alterações de ativação cerebral obtidas com a intervenção possam preceder a melhora na performance das tarefas neuropsicológicas. Isso evidencia uma maior necessidade de estudos de neuroimagem com delineamento semelhante e maior tempo de seguimento.

Palavras-chave: Transtorno de Déficit de Atenção/Hiperatividade (TDAH), Tratamento, Treinamento Cognitivo, Ensaio Clínico Randomizado

Abstract

Most current guidelines advocate combined treatment (medication and non-pharmacological approaches) for Attention-Deficit/Hyperactivity Disorder (ADHD). Non-pharmacological interventions, such as Cognitive Training (CT), have been widely studied for the treatment of the disorder. This study aims to evaluate the effectiveness of a computerized CT program for children and adolescents with ADHD using psychostimulant medication. Method: this is a randomized clinical trial including 53 children and adolescents between 6 and 13 years of age with ADHD medicated with psychostimulants. Participants were randomized to one of two existing groups - cognitive training or placebo training - and completed a protocol of 48 sessions, conducted 4 times a week for 12 weeks. Twenty participants were selected to perform a functional resonance imaging during 3 tasks: 1. Attention (Sustained attention task – 3 conditions: 2s, 5s and 8s delay); 2. Working memory (N-Back – 4 conditions: 0-back, 1-back, 2-back, 3-back and 4-back); 3. Control inhibition (Go/No-Go). The following outcomes were assessed pre and post intervention: 1. inattention and hyperactivity symptoms; 2. neuropsychological performance; 3. cognitive performance and activation of brain areas in functional magnetic resonance imaging; 4. time spent using videogame and internet and 5. overall clinical functioning. Results: we found a greater difficulty than expected for the allocation of participants due to logistical problems such as attendance in face-to-face sessions. We did not find significant differences between the groups in ADHD symptoms (parent score – inattention: $p = 0.58$; hyperactivity/impulsivity, $p = 0.63$. Teachers score – inattention: $p=0.58$; hyperactivity/impulsivity, $p=0.31$). In the neuropsychological performance, no significant difference was found between groups in the three tasks evaluated (Flanker Test - for inhibitory control and attention evaluation, List Sorting Working Memory Test - for working memory evaluation and Go / No-Go – for inhibitory control and cognitive flexibility evaluation). In the neuroimaging assessment, the following findings were found: a) neuropsychological performance – in working memory task (N-back), the accuracy of the participants decreased with the increase task difficulty; as well was an effect of the time, demonstrating that the participants improved their performance after the intervention; in sustained attention task, a three-way interaction was detected between time, group and delay regarding mean reaction time, meaning that there was an improvement with treatment across time if compared to non-active treatment only in the 5s delay; b) brain activation - we identified an effect on the interaction group x time x "load" in two brain clusters in the working memory task (1. right insula, right putamen; 2. left thalamus and left pallidum), as well as an effect on group x time x delay interaction in four clusters in sustained attention task (1. Right precuneus, angular gyrus, middle temporal gyrus and associative visual cortex; 2. Right postcentral gyrus, precentral gyrus and insula; 3. Right superior frontal gyrus, middle frontal gyrus; 4. Left precuneus, associative visual cortex and angular gyrus). Discussion: our study did not find evidence of

CT benefits for nuclear symptoms of ADHD in children and adolescents receiving psychostimulants. The neuroimaging findings point to a possibility that the changes in brain activation obtained with the intervention may precede the improvement in the performance of the neuropsychological tasks. This shows a greater need for neuroimaging studies with similar design and longer follow-up time.

Keywords: Attention-Deficit/Hyperactive Disorder (ADHD), treatment, cognitive training, clinical trial

Sumário

1. Apresentação

Este trabalho consiste na tese de doutorado intitulada “Treinamento cognitivo como abordagem complementar à medicação para tratamento do Transtorno de Déficit de Atenção/Hiperatividade (TDAH) em crianças e adolescentes”, apresentada ao Programa de Pós-Graduação em Ciências Médicas: Psiquiatria na Universidade Federal do Rio Grande do Sul, em 29 de novembro de 2018.

Os dados presentes na literatura, até o momento em que nos propusemos estudar o Treinamento Cognitivo como proposta terapêutica ao TDAH, indicavam resultados contraditórios em sua eficácia, além de apresentarem inconsistências metodológicas importantes como tipo da intervenção escolhida para o grupo controle; duração e intensidade dos protocolos de treino; falta de avaliadores cegados à intervenção entre outros. Além disso, o uso do treinamento concomitante à medicação psicoestimulante no tratamento do TDAH foi escassamente estudado. O objetivo principal desta tese é avaliar, em um ensaio clínico randomizado controlado, o uso do treinamento cognitivo como uma possível abordagem complementar ao uso da medicação e poder, com isso, contribuir para o campo clínico e de pesquisa nessa área.

O projeto foi desenvolvido em parceria com o grupo de pesquisa da Universidade de Yale e com a empresa C8 Sciences, os quais juntos desenvolveram o software do treinamento cognitivo utilizado em nosso estudo. O projeto deu origem a três artigos científicos: 1) descrição do protocolo e viabilidade de sua implementação; 2) avaliação do treinamento cognitivo nos sintomas clínicos do TDAH e desempenho neuropsicológico; 3) avaliação do treinamento cognitivo na neuroimagem funcional.

A tese é composta de cinco partes principais: Introdução, Revisão da literatura, Objetivos, Artigos, Considerações finais.

2. Introdução

O Transtorno de Déficit de Atenção/Hiperatividade (TDAH) é uma das desordens psiquiátricas mais prevalentes em crianças e adolescentes, com uma estimativa mundial de 5% (1). É caracterizado por sintomas persistentes de desatenção e/ou hiperatividade/impulsividade, em uma intensidade acima da esperada para a faixa etária, que acarretam interferências no funcionamento pessoal, social e acadêmico (2). Aproximadamente 65% dos indivíduos diagnosticados na infância seguem apresentando o diagnóstico ou sintomas/ prejuízos funcionais na fase adulta, caracterizando o TDAH como uma doença crônica numa proporção significativa daqueles afetados na infância (3). Diversos são os prejuízos decorrentes do transtorno, podendo-se destacar: dificuldades no desempenho escolar, com o risco de alcançarem menores graus acadêmicos (4); maior consumo de tabaco e cocaína (5); maiores taxas de acidentes automobilísticos (5) e criminalidade (6) entre outros. Tais prejuízos afetam consideravelmente a qualidade de vida dos pacientes afetados (6), acarretando um significativo custo para a sociedade (7). Evidências sugerem que esses desfechos negativos podem ser reduzidos com o tratamento adequado; entretanto, seguem sendo
mais prevalentes mesmo após tratamento, quando em comparação com controles sadios (5).

Além dos sintomas nucleares, o TDAH também é associado a anormalidades cerebrais (como hipoativação de regiões fronto-estriatais e parietais) (8), déficits no funcionamento executivo (como memória de trabalho, controle inibitório, planejamento e organização), assim como um maior risco para transtornos de aprendizagem (9).

Diretrizes clínicas, baseadas em ensaios clínicos randomizados, indicam que a intervenção medicamentosa, especialmente o uso de psicoestimulantes, representa o tratamento de primeira linha para o TDAH (10). Porém, aproximadamente 30% dos afetados pelo transtorno não respondem plenamente à medicação; apresentam respostas parciais à mesma; ou eventos adversos que impedem seu uso (11)(12). Além disso, muitos pais mostram-se resistentes ao uso de medicação pelos seus filhos (10). Outro aspecto importante a ser considerado é que a eficácia da medicação a longo-prazo, bem como a segurança do uso prolongado, ainda não foram completamente estabelecidas (13). Com isso, diversas abordagens não farmacológicas vêm recebendo destaque como alternativas complementares à medicação, dentre elas, intervenções psicoterápicas - terapia cognitivo-comportamental (TCC), terapia comportamental dialética (TCD), mindfulness – (14) e o treinamento cognitivo. Sendo assim, as abordagens multimodais – que combinam abordagens farmacológicas e não-farmacológicas – são atualmente recomendadas para o tratamento do TDAH por, possivelmente, apresentarem um maior efeito na redução dos sintomas (15)(5).

3. Revisão da literatura dos temas pertinentes a essa tese:

3.1. TDAH e Desempenho cognitivo

Embora o TDAH seja caracterizado por sintomas de desatenção, hiperatividade e impulsividade, os pacientes acometidos também podem apresentar prejuízos em diversos domínios cognitivos como déficit no funcionamento executivo - em especial memória de trabalho, mas também processamento básico, controle inibitório entre outros - podendo esses domínios representarem importantes alvos para o tratamento do transtorno (15). Além de possíveis déficits em funcionamento executivo, estudos apontam também para prejuízos em outros domínios, incluindo armazenamento de memória, tempo de reação e variabilidade no tempo de reação (16). Importante salientar que, embora esses déficits neuropsicológicos possam impactar no funcionamento de indivíduos com TDAH, nenhum deles é essencial para a causalidade do transtorno (17) assim como existe uma grande heterogeneidade na sua apresentação entre os indivíduos (18). Apesar de não fazerem parte dos critérios diagnósticos do TDAH, os déficits neuropsicológicos associados ao TDAH têm sido amplamente estudados (19).

Diferentes modelos teóricos foram propostos para explicar os déficits neuropsicológicos e seu impacto no comportamento de indivíduos com TDAH (20). O desenvolvimento desses modelos proporcionou avanços importantes no entendimento do transtorno, especialmente pelo reconhecimento de que múltiplas redes neurais estariam envolvidas (21). Estudos realizados até o momento indicam que mais de um mecanismo neuropsicológico possa estar envolvido na patofisiologia do TDAH, que nem todos os indivíduos com o transtorno apresentam o mesmo perfil de déficits neuropsicológicos, e, ainda, alguns pacientes podem não apresentar nenhum déficit (21). A limitação dos modelos iniciais somados à heterogeneidade em relação aos déficits cognitivos levaram à busca pela identificação de múltiplos caminhos desenvolvimentais, nos quais os diferentes déficits podem ser considerados complementares (22). A formulação mais recente da teoria de múltiplos caminhos para o TDAH envolve três componentes: a) um associado ao controle inibitório deficiente que estaria predominantemente associado ao córtex pré-frontal; b) outro associado à aversão à resposta tardia que estaria mais associado ao núcleo *accumbens*; c) e outro associado à percepção temporal.

A relação do funcionamento neuropsicológico com a circuitária cerebral é complexa e ainda não totalmente conhecida. Os circuitos fronto-estriatal dorsal, orbitofronto-estriatal e fronto-cerebelar parecem estar envolvidos no TDAH, interagindo através de alças em espiral no estriado e conexões do cerebelo ao córtex pré-frontal e estriado. A disfunção em qualquer um desses circuitos pode causar sintomas de TDAH: disfunção no córtex pré-frontal pode levar a uma capacidade reduzida em exercer o controle; disfunção no estriado dorsal pode levar a diferenças na habilidade de prever a

ocorrência de eventos, enquanto que disfunção no estriado ventral pode levar a déficits na motivação e processamento de recompensa; disfunção no cerebelo pode levar a problemas na capacidade de prever quando eventos irão ocorrer, assim como outros problemas relacionados ao tempo. A principal implicação disso é que, embora essa ampla gama de diferenças neurobiológicas possa levar a sintomas do TDAH, os efeitos cognitivos da disfunção nos vários níveis podem ser diferentes. Sonuga-Barke et al. demonstraram evidências preliminares de que os três componentes distintos acima descritos – tempo, controle cognitivo e recompensa - estariam associados à variação nos resultados encontrados em baterias neuropsicológicas. Das 77 crianças com TDAH incluídas neste estudo, 55 puderam ser identificadas como apresentando um déficit em um desses componentes, e a sobreposição entre os componentes não foi maior do que seria esperado ao acaso. Isso sugere que esses componentes podem de fato dependerem de sistemas neurobiologicamente separáveis. Contudo, tais dados foram baseados apenas em testes computadorizados, de modo que não houve nenhuma medida direta da neurobiologia. No entanto, as áreas cognitivas com as quais esses componentes estão relacionados sugerem que possam mapear os três circuitos anteriormente citados: o tempo é associado com alças fronto-cerebelares; o controle cognitivo com alças frontoestriatais dorsais e a recompensa com alças orbitofronto-estriatais (23).

Abaixo destacam-se as funções neuropsicológicas relacionadas ao TDAH que foram abordadas, através de testes, no presente estudo:

3.1.1. Inibição da resposta

É um aspecto do controle cognitivo. Representa a habilidade de autocontrole, envolvendo a supressão ou alteração de ações intencionais que não são apropriadas ou requisitadas num determinado momento (24). Uma inibição de resposta satisfatória permite aos indivíduos se adequarem apropriadamente às mudanças no ambiente (25). Tem-se considerado a inibição de resposta como um déficit central no TDAH já que apresentaria a capacidade de afetar múltiplas funções executivas, incluindo memória de trabalho e autorregulação, entre outras (26). Evidências de um pior controle inibitório advém de estudos que utilizaram tarefas de inibição motora, como o paradigma Go/No-Go (26). Em média, os indivíduos com TDAH inibem suas respostas mais lentamente do que os controles, como demonstrado em tempos de reação mais longos durante o estímulo de parada (sinal “No-Go”), assim como maiores taxas de erros (27). Além disso, um estudo mostrou que os sintomas do TDAH em crianças e adolescentes estão associados a uma pior inibição de resposta e menor latência de resposta (28). Os déficits de inibição da resposta também são observados a nível cerebral. Crianças e adolescentes com TDAH apresentam diminuição da ativação nas regiões frontal, medial e parietal durante testes de inibição quando comparadas a controles (29). Uma metanálise

avaliando estudos que utilizaram o mesmo paradigma encontrou diferenças com tamanhos de efeito médio entre crianças e adolescentes com e sem TDAH. A diferença mais pronunciada entre os grupos deveu-se ao desvio-padrão do tempo de reação, indicando que pacientes com TDAH são particularmente mais variáveis nos tempos de reação. Também se observou um tempo de reação total médio mais longo em indivíduos com o transtorno. A combinação de uma maior variabilidade no desempenho e maior lentidão nas respostas sugere um mecanismo subjacente, além do controle inibitório deficiente, como a falta geral de atenção (30).

3.1.2. Memória de Trabalho

Considerada a função executiva mais central, possibilita ao indivíduo manter na mente informações representadas internamente para que possam ser usadas para controlar uma resposta subsequente (31), ou seja, uso desta informação para algum propósito (32)(33). A teoria mais aceita envolvendo memória de trabalho advém do trabalho de Baddeley e Hitch (1974). O modelo descrito por eles consiste de três subsistemas: 1) a central executiva – componente mais importante do modelo: responsável pela regulação do fluxo de informação dentro da memória de trabalho, pela integração das informações mantidas na memória de trabalho com informações de outros sistemas de memória e pelo processamento e armazenamento de informações variadas na memória de trabalho, não estando atrelada a um tipo específico de informação e apresentando uma flexibilidade muito grande no seu funcionamento. A central executiva interage com os outros subsistemas na manutenção e manipulação de informações; 2) loop fonológico: responsável pela manutenção e manipulação de material verbal na memória de trabalho, exercendo papel fundamental no processamento da linguagem; 3) notebook visuo-espacial: responsável pela criação e manutenção de imagens e objetos ativos na memória por um determinado período de tempo. Em 2000, este modelo foi estendido, adicionando-se um quarto componente – o buffer episódico – que guarda representações integradas da informação fonológica, visual e espacial e, possivelmente, outras informações não cobertas pelos demais componentes do modelo (34). Evidências sugerem que o déficit de memória de trabalho representa um dos prejuízos cognitivos chave no TDAH (35)(36), sendo identificados déficits tanto na memória verbal quanto espacial, com o prejuízo mais consistentemente reportado para o domínio espacial da memória de trabalho (35). Prejuízos na memória de trabalho estão associados funcionalmente à desatenção, hiperatividade, impulsividade e problemas sociais (37), assim como à disfunção acadêmica em crianças com TDAH, tornando-se importante implementar intervenções adequadas direcionadas ao problema (33).

3.1.3. Atenção

A atenção é considerada um componente integral de todas as funções executivas, e presume-se que as limitações nos recursos atencionais reflitam déficits na memória de trabalho e em outros funcionamentos executivos. Considerando esta perspectiva, sugere-se que intervenções que foquem nos processos atencionais possam resultar em melhorias generalizadas na performance das funções executivas. Entre os diversos modelos de atenção, estudos avaliando o TDAH na infância, frequentemente concentram-se em quatro componentes de atenção: orientação/alerta – capacidade de aumentar o nível de ativação, seguindo um estímulo de alta prioridade; atenção seletiva/focada – habilidade de facilitar o processamento de uma fonte de informação ambiental enquanto atenua o processamento de outras; atenção dividida – capacidade de atender e responder simultaneamente a múltiplas tarefas ou múltiplas demandas de tarefas; vigilância/atenção sustentada – capacidade de sustentar uma resposta comportamental consistente durante uma atividade contínua (37), mantendo o foco da atenção ao longo do tempo a eventos críticos que ocorrem com pouca frequência (38). Representa uma habilidade crítica para o processamento de informações (37). Evidências sugerem déficits de moderada a grande magnitude na atenção sustentada em indivíduos com TDAH, sendo esses déficits também associados com pior performance acadêmica (37).

3.1.4. Flexibilidade cognitiva

Refere-se à capacidade de flexivelmente alterar entre tarefas ou conjuntos mentais. Estudos de metanálise revelam déficits na flexibilidade cognitiva em crianças com TDAH, sendo esses de magnitude moderada, indicando que aproximadamente 25-35% apresentariam déficits relacionados a esse domínio cognitivo (37). Descrições clínicas de crianças com TDAH sugerem que haveria maior probabilidade de que as mesmas respondessem com respostas aprendidas e automáticas ao enfrentarem situações problemáticas ou contextos que exigissem mudança flexível do pensamento (39).

3.2. Neuroplasticidade e Treinamento Cognitivo

Nas últimas décadas, novos tratamentos baseados em neuroplasticidade têm sido desenvolvidos para o tratamento dos transtornos psiquiátricos. Um dos pioneiros no assunto foi o estudo que avaliou o uso de exercícios computadorizados baseados em plasticidade para o tratamento de disfunção cognitiva em pacientes com esquizofrenia, demonstrando que os pacientes com esquizofrenia foram capazes de alcançar melhora na função cognitiva, apresentando performance dentro da média esperada (40).

Pelo fato de as crianças apresentarem uma maior plasticidade cerebral, existe um campo crescente na área da pesquisa para explorar abordagens que utilizem esse racional de tratamento. Pesquisas já demonstraram que o treino iniciado ambientalmente – como a prática sustentada com algum instrumento musical, por exemplo – pode levar a mudanças no volume cerebral e nos padrões de conectividade inter-regionais (41).

Uma abordagem em evidência na literatura atual é o uso do treinamento cognitivo. Este é baseado numa premissa na qual exercícios cognitivos são praticados com o intuito de melhorar o funcionamento dos indivíduos através da neuroplasticidade (42) – podendo resultar em um aumento na ativação cortical e fortalecimento das conexões corticais (43). Na realidade, esse tipo de tratamento já demonstrou benefício em adultos, como por exemplo, melhorando a recuperação pós acidente vascular cerebral – melhorando a performance atencional e de memória de trabalho - (44) assim como reduzindo os prejuízos cognitivos na esquizofrenia (45). Outro estudo, em pacientes bipolares, demonstrou que o grupo submetido a um treinamento cognitivo apresentou melhora na performance cognitiva, pós intervenção, nos domínios de memória de trabalho, resolução de problemas e atenção dividida (46). Da mesma forma, há evidência demonstrando possíveis benefícios da intervenção no tratamento de pacientes deprimidos, com melhora dos sintomas de humor, do funcionamento diário assim como de domínios cognitivos – atenção e memória de trabalho, por exemplo (42).

3.3. Treinamento Cognitivo no TDAH

Uma das áreas em que o uso do treinamento cognitivo vem recebendo bastante destaque é para o tratamento do TDAH já que existe uma associação do transtorno com prejuízos em diversos domínios cognitivos como memória de trabalho - e outras funções executivas - e processamento básico (16)(15). As abordagens terapêuticas baseadas no treinamento cognitivo visam tanto reduzir os sintomas nucleares do transtorno quanto melhorar o funcionamento neuropsicológico, tendo como alvo os déficits subjacentes possivelmente relacionados com o TDAH (15). Existem inúmeros estudos na literatura que avaliaram o benefício do treino, com resultados controversos, muito em função das diferentes metodologias utilizadas. O pioneiro na área a reportar evidência positiva para o TDAH foi o estudo de Klingberg et al. em que avaliaram um treino de memória de trabalho *versus* um treino não-adaptativo, de baixa demanda, encontrando uma redução dos sintomas de desatenção e hiperatividade pós treino quando os mesmos foram avaliados pelos pais; não encontrando o mesmo achado quando os escores foram avaliados por professores (47). A partir deste estudo, muitos outros surgiram buscando avaliar a eficácia desta abordagem, com diferentes protocolos de treino e diferentes desenhos de estudo, sendo que muitos apresentaram inconsistências metodológicas importantes (15). Abaixo são apresentados os principais resultados dos estudos clínicos randomizados controlados envolvendo treinamento cognitivo para o TDAH em crianças e adolescentes.

Beck et al. (2010) reportaram os efeitos de um treino de memória de trabalho (Cogmed) em comparação com lista de espera em crianças e adolescentes com TDAH (n=52). Encontraram uma melhora na memória de trabalho e uma diminuição nos sintomas de desatenção avaliados pelos pais no grupo pertencente ao treino. Quando considerado as avaliações dos professores para os desfechos, nenhum efeito significativo foi encontrado (48).

Green et al. (2012) avaliaram a eficácia de um treino de memória de trabalho para crianças com TDAH (n=26), demonstrando que as crianças alocadas para o treino de memória de trabalho, quando comparadas ao grupo controle (versão placebo do treino), tiveram benefícios significativos nas tarefas de memória de trabalho - as mesmas treinadas durante a intervenção. Entretanto, não encontraram diferença nos sintomas nucleares do TDAH avaliados pelos pais (49).

Gray et al. (2012) investigaram o benefício do Cogmed, comparado com um programa computadorizado de atividade acadêmica (matemática), em adolescentes com transtorno de aprendizagem e TDAH (n=60). Os resultados demonstraram efeitos do treino em duas tarefas de memória de trabalho (treinadas durante a intervenção), não encontrando diferença nas tarefas não-treinadas. Além disso, não encontraram melhoras nos sintomas do TDAH avaliados por pais e professores, nem nos desfechos acadêmicos (50).

Chacko et al. (2014) avaliaram a eficácia de um treino de memória de trabalho (Cogmed) em crianças com TDAH (n=85) através de um ensaio clínico randomizado controlado por um treino placebo (mesma versão do treino cognitivo, mas com baixa demanda). Os autores encontraram, no grupo do treino ativo, uma melhora significativa no armazenamento da memória de trabalho verbal e não-verbal, porém sem ganhos quando avaliado o armazenamento da memória de trabalho em combinação com o processamento/manipulação da mesma. Quando avaliados os sintomas nucleares do TDAH, não encontraram diferenças entre os grupos, assim como não encontraram diferenças em outros domínios cognitivos avaliados (como atenção) (51).

van Dongen-Boomsma et al. (2014) investigaram os efeitos do treino de memória de trabalho (Cogmed) em crianças com TDAH de 5-7 anos (n=51), não medicadas, num ensaio clínico controlado por placebo (versão não adaptativa do treino). Como desfecho primário, avaliaram a melhora dos sintomas nucleares do TDAH e como secundário a performance em tarefas neurocognitivas, funcionamento executivo diário e funcionamento clínico global. Nenhum efeito significativo do tratamento foi encontrado para os desfechos primários nem para os demais desfechos secundários (52).

Uma metanálise recente (2014) de ensaios clínicos randomizados avaliou os efeitos do treino cognitivo para o TDAH. Ao todo, avaliaram 16 artigos, totalizando 759 crianças com TDAH. O resultado

demonstrou que, ao se avaliarem todos os tipos de treinamento conjuntamente, houve um efeito significativo no escore total dos sintomas de TDAH e nos escores de sintomas de desatenção quando considerado avaliadores mais próximos ao tratamento – ou seja, tipicamente não cegados ao tipo de intervenção; quando considerado apenas estudos com grupo controle ativo, os efeitos não foram mais estatisticamente significativos para nenhum dos sintomas nucleares do TDAH. Os mesmos resultados, quando considerado avaliadores cegados, apresentaram diminuição significativa no efeito, perdendo a significância quando incluído apenas estudos com grupo controle ativo. Quando considerado apenas estudos envolvendo treino de memória de trabalho, não se encontraram efeitos na sintomatologia do TDAH. Em relação aos desfechos neuropsicológicos, encontraram efeitos do treinamento nos testes que avaliaram memória de trabalho visual e verbal, assim como no funcionamento executivo avaliados pelos pais. Não encontraram efeitos do treinamento nos testes de controle inibitório ou de atenção (53).

Dovis et el. (2015), em um estudo multicêntrico, avaliaram os efeitos de um treinamento de múltiplas funções executivas em crianças com TDAH (n=89). O estudo incluiu 3 braços para os quais os participantes foram randomizados: grupo do treinamento cognitivo completo (memória de trabalho, controle inibitório e flexibilidade cognitiva), grupo do treinamento cognitivo parcial (controle inibitório e flexibilidade cognitiva) e grupo treinamento placebo. Após a intervenção, apenas as alocadas para o treinamento completo apresentaram melhora nas medidas de memória de curto prazo visuoespacial e memória de trabalho. As medidas de controle inibitório e controle de interferência apresentaram melhora nos participantes alocados para o treinamento completo e para o parcial. Não encontraram interações entre condição do tratamento x tempo para medidas de flexibilidade cognitiva, memória de trabalho verbal, sintomas de hiperatividade/impulsividade ou desatenção, funcionamento executivo, qualidade de vida e problemas de comportamentos gerais (54).

van der Donk et al. (2015) avaliaram os efeitos do treino de memória de trabalho (Cogmed), usando um grupo controle ativo, para crianças com TDAH (n=105). Resultados demonstraram apenas um efeito do tratamento, favorecendo o grupo do treino, na tarefa de memória de trabalho visuoespacial. Nenhum outro efeito foi encontrado em relação aos demais domínios cognitivos avaliados (atenção, controle inibitório, memória de trabalho verbal), funcionamento executivo, sintomas comportamentais relacionados ao TDAH, performance acadêmica, comportamento em sala de aula e qualidade de vida (55).

Recentemente, Bikic et al. (2018) investigaram os efeitos de um programa de treino computadorizado com vários domínios cognitivos como alvo (ACTIVATE) para crianças com TDAH (n=70) comparado ao tratamento usual. Não encontraram efeitos significativos nos desfechos

primários (medida de atenção sustentada) nem nos desfechos secundários (sintomatologia do TDAH e inventário de funcionamento executivo, ambos avaliados por pais e professores) (56).

O primeiro e único estudo que se propôs a estudar os efeitos do treinamento cognitivo como complementar à medicação (ou seja, em uma amostra totalmente medicada para o TDAH) foi um estudo aberto. Os autores avaliaram o treinamento cognitivo em uma amostra de crianças e adolescentes com TDAH (n=25), usando como desfecho problemas comportamentais, qualidade de vida e estresse parental. Os autores encontraram uma redução nos escores de problemas atencionais do CBCL – Child Behavior Checklist - assim como nos escores de interação disfuncional entre pais e filhos, sem encontrar mudança nos escores que avaliaram qualidade de vida (57). Recentemente, Ackermann et al. avaliaram, em um ensaio clínico não controlado, sem avaliação cegada e sem randomização, o benefício de um treinamento em memória de trabalho concomitante à medicação em 60 adolescentes divididos em quatro grupos: 1) grupo controle de participantes sem TDAH que realizaram o treinamento; 2) grupo de participantes com TDAH medicados com psicoestimulante que realizaram treinamento; 3) grupo de adolescentes com TDAH medicados com psicoestimulante, mas que não realizaram o treinamento; 4) grupo de adolescentes com TDAH não medicados que realizaram o treinamento. Encontraram benefícios em algumas tarefas de memória de trabalho e nos sintomas de hiperatividade/impulsividade (avaliados pelos pais) nos participantes com TDAH medicados que realizaram o treinamento em comparação com os participantes apenas medicados para o TDAH. Os autores sugerem que os efeitos concomitantes da medicação + treinamento permitiram aos participantes com TDAH demonstrarem as mesmas habilidades executivas que adolescentes em desenvolvimento típico alcançaram com o treinamento (58).

Importante salientar que os estudos, até o presente momento, envolvendo o uso de treinamento cognitivo para o TDAH apresentam muitas limitações importantes a serem consideradas numa análise crítica dos resultados: 1. poucos estudos investigaram treinos tendo como alvo múltiplos domínios cognitivos; considerando que o TDAH é cognitivamente bastante heterogêneo, é importante investigar os efeitos do treinamento que apresente como alvo diversas funções cognitivas diferentes; 2. uso inadequado do grupo controle, o que pode afetar significativamente os resultados – uso de grupos não-ativos, como lista de espera ou tratamento usual, que podem dificultar o cegamento; versão não adaptativa do treino, com baixa demanda – a qual necessita consideravelmente menos tempo e esforço em relação à versão ativa, além da possibilidade de introduzir diferenças em termos de fatores externos como motivação; 3. poucos estudos avaliaram o treinamento como tratamento complementar à medicação, tendo em vista que se preconiza tratamento multimodal ao TDAH, seria um ponto da metodologia importante a ser considerado; 4. muitos estudos utilizaram avaliadores não cegados à intervenção para a análise dos desfechos do estudo.

Tendo em vista o acima disposto, estudos que avaliaram a eficácia do treinamento cognitivo para o tratamento do TDAH, com o uso de uma metodologia rigorosa - isto é, ensaio clínico randomizado, com cegamento e controlado por intervenção placebo – seguem escassos na literatura e, com isso, não há evidência consistente ainda para suportar tal intervenção como uma alternativa de tratamento para o transtorno (53).

3.4. Neuroimagem e TDAH

O avanço nas técnicas de diagnóstico por neuroimagem permite um melhor entendimento da função cerebral e, consequentemente, da fisiopatologia do TDAH. Ainda que algumas técnicas como o PET (Positron Emission Tomography) e o SPECT (Single Photon Emission Computed Tomography) tenham a vantagem de oferecer informações neuroquímicas importantes, são exames invasivos, acabando por limitar sua aplicabilidade em pesquisa (59). A revisão dos estudos com essas técnicas em TDAH fogem ao escopo dessa tese, mas o leitor interessado pode encontrar revisões sobre o assunto(60)(61)(62) .

O uso da Ressonância Magnética Nuclear Funcional (RMNf) permite estabelecer um mapeamento da conectividade cerebral em estado de repouso ou modificações na ativação de áreas cerebrais mediante alguma tarefa, sendo um exame seguro e sem uso de radiação (59).

3.4.1. Estudos de RM cerebral estrutural e TDAH

Estudos de neuroimagem demonstraram diversas anormalidades cerebrais estruturais e funcionais em crianças com TDAH (8) como, por exemplo, volumes cerebrais menores quando comparados a controles saudáveis (63), sendo que a maioria dos estudos apontam que esta redução seja decorrente de diferenças de volume nos núcleos da base (64)(65). Uma metanálise de 2012, que incluiu 11 estudos, encontrou maiores alterações estruturais no globo pálido e putâmen direito em crianças, enquanto que nos adultos, no cíngulo anterior. O mesmo estudo avaliou o efeito cerebral dos psicoestimulantes em pacientes com TDAH, sugerindo que o medicamento poderia estar relacionado a uma redução – ou até mesmo normalização – dessas alterações estruturais (66).

Shaw e col. 2007, utilizaram exames de ressonância magnética para determinar a estrutura cerebral de crianças com e sem TDAH, encontrando, naquelas diagnosticadas com o transtorno, um atraso de aproximadamente três anos até atingir o pico de maturação cortical, em especial, o córtex pré-frontal (67). Além disso, o mesmo estudo relacionou a medida inicial de espessura do córtex pré-frontal medial com o prognóstico desses pacientes – apontando que aqueles com redução sustentada da espessura apresentariam pior prognóstico (67). Estudos longitudinais envolvendo ressonância magnética demonstraram que as alterações estruturais observadas (em regiões frontais, estriatais,

parietais e cerebelares de crianças com TDAH) podem estar relacionadas a este atraso de maturação estrutural (68).

Importante salientar que o TDAH provavelmente resulte de alterações cerebrais difusas, incluindo não só o córtex frontal e núcleos da base, mas também estruturas como o córtex parietal e cerebelo (69)(70)(71).

3.4.2. Estudos de RM cerebral funcional de repouso e TDAH

A conectividade funcional de repouso analisa a atividade cerebral na ausência de qualquer tarefa específica. A rede mais frequentemente estudada com a técnica de ressonância cerebral em repouso é a *default mode network* (DMN), envolvendo áreas como o córtex pré-frontal medial, precúneo, cíngulo posterior, córtex parietal lateral inferior e lobos temporais mediais (72).

A maior parte da literatura sobre a atividade cerebral de repouso no TDAH demonstra uma menor conectividade da DMN em pacientes quando comparados aos controles – a maioria dos estudos apontam conectividade reduzida tanto em regiões anteriores (como cíngulo anterior, medial e lateral do córtex pré-frontal) quanto posteriores (córtex cíngulo posterior e precúneo)(73)(74)(75). Tais achados foram associados aos déficits funcionais (como problemas atencionais) encontrados nesses pacientes assim como a alterações estruturais (como atraso na maturação do córtex frontal)(74)(73)(76).

3.4.3. Estudos de RM cerebral funcional com testes neuropsicológicos em TDAH

Estudos envolvendo o uso de RMNf em crianças com TDAH evidenciaram disfunções de áreas cerebrais como córtex pré-frontal dorsolateral e ventral, cingulo anterior, ínsula, amigdala, hipocampo e estriado ventral (77). Existe evidência de que o tratamento com metilfenidato possa normalizar a função estriatal, e até mesmo melhorar a ativação frontal em crianças e adolescentes com TDAH (78).

A recente literatura envolvendo técnicas de RMNf em pacientes com TDAH tem revelado disfunções em regiões cerebrais de múltiplas redes neuronais envolvidas em funções sensoriomotoras e cognitivas. Cortese et. al, em uma metanálise envolvendo 55 estudos de ressonância funcional no TDAH, encontraram hipoativação de áreas cerebrais em crianças com TDAH, quando comparadas a controles, nas redes fronto-parietal – envolvida com funcionamento executivo e tomada de decisões (incluindo o cingulo anterior dorsal, córtex pré-frontal anterior dorsolateral, cerebelo lateral, ínsula anterior, lobo parietal inferior e pólo frontal lateral) e atencional ventral – envolvida com o redirecionamento da atenção - (incluindo a junção têmporo-parietal, giro supramarginal, opérculo frontal e ínsula anterior). Também encontraram hipoativação no sistema somatomotor direito e no putâmen bilateralmente. Além das áreas de hipoativação acima descritas, o estudo aponta para áreas

de hiperativação relacionadas ao TDAH, principalmente na *default mode network* – a qual é tipicamente suprimida durante o desempenho em uma tarefa específica, assim como nos sistemas somatomotor e visual (8). Já nos adultos com TDAH, Cortese et al. encontraram hipoativação principalmente no sistema frontoparietal e hiperativação nos sistemas visual e atencional dorsal (8).

Mais especificamente, as disfunções cerebrais no TDAH parecem estar relacionadas ao tipo de tarefa requisitada, demonstrando deficiências diferentes de acordo com o domínio cognitivo explorado (29).

Cortese et al. realizou metanálise focada em tarefas específicas no TDAH. Nas análises limitadas a essas tarefas, estudos que examinaram paradigmas de controle inibitório encontraram hipoativação em diversas regiões frontais bilateralmente, assim como no giro temporal superior direito, giro occipital inferior esquerdo, tálamo direito e mesencéfalo. Já a análise envolvendo tarefas de memória de trabalho revelaram hipoativação no giro frontal inferior esquerdo, ínsula anterior e giro frontal medial direito; e nas tarefas atencionais, hipoativação no giro paracingulado (8).

Os estudos envolvendo achados de RMNf sob alguma tarefa específica têm crescido substancialmente. Hoje entende-se que o TDAH reflita uma alteração na conectividade cerebral de várias redes neuronais, ao invés de anormalidades cerebrais isoladas como anteriormente pensado (79)(80).

3.4.4. Estudos de RM cerebral funcional com testes neuropsicológicos em TDAH avaliando treino de funções cerebrais

Uma das formas de se avaliar o efeito do treinamento cognitivo seria estudar as possíveis alterações a níveis cerebrais. Existem, entretanto, poucos estudos de RMNf na literatura que avaliaram os efeitos cerebrais do treinamento cognitivo em pacientes com TDAH.

Hoekzema et al. demonstraram, através de um estudo de RMNf, os efeitos cerebrais de um treinamento cognitivo, envolvendo múltiplos domínios, com 10 dias de duração, em crianças com TDAH não medicadas. Encontraram, através do paradigma de controle inibitório, aumento da ativação no córtex orbitofrontal, frontal superior, temporal medial e frontal inferior. Já sob o paradigma de atenção, encontraram aumento da ativação no cerebelo, sendo este achado associado com uma melhora nas medidas atencionais da tarefa em questão (81).

Stevens et al. avaliaram, pela primeira vez na literatura, os efeitos na função cerebral de um treino de memória de trabalho para adolescentes com TDAH em um ensaio clínico aberto. Através de um paradigma de memória de trabalho, os autores encontraram diversas regiões cerebrais com alteração do padrão de ativação após o treino, principalmente hiperativação, como por exemplo, no

giro frontal inferior direito e esquerdo, giro frontal medial, giro pós-central esquerdo, giro angular esquerdo, cingulado posterior direito, cingulado anterior, cúneos bilateral entre outras; enquanto encontraram um padrão de diminuição da ativação pós treino nas seguintes áreas: giro frontal medial, giro frontal superior, cerebelo esquerdo e direito (82). Os autores sugerem que uma prática intensiva e continuada de tarefas envolvendo memória de trabalho possa potencializar a ativação dentro de uma rede mais ampla de regiões cerebrais especializadas em tarefas de memória de trabalho do que anteriormente pensado, além de destacarem a importância de ensaios clínicos randomizados para melhor explorar o tema (82).

4. Justificativa

O TDAH apresenta altas taxas de prevalência na população de crianças e adolescentes em idade escolar, interferindo significativamente na vida do paciente e sua família. Embora o tratamento farmacológico configure a intervenção de primeira linha, um grupo significativo de pacientes segue apresentando sintomas residuais ou resposta parcial a essa intervenção. Com isso, tratamentos não-farmacológicos têm sido cada vez mais estudados para o tratamento do TDAH. Entre eles, o treinamento cognitivo é uma modalidade que tem mostrado alguns indicativos de melhora no funcionamento neurocognitivo de crianças e adolescentes. Seu uso, entretanto, ainda não foi estudado amplamente como uma abordagem conjunta à medicação.

5. Objetivos

5.1. Objetivos gerais

5.1.1. Avaliar a eficácia complementar do treinamento cognitivo ao tratamento medicamentoso em crianças e adolescentes com TDAH comparativamente a um treino placebo.

5.2. Objetivos específicos

5.2.1. avaliar a eficácia da intervenção na redução da intensidade dos sintomas de desatenção e hiperatividade/impulsividade. (artigo 2)

5.2.2. avaliar os efeitos da intervenção cognitiva no desempenho neuropsicológico (artigo 2)

5.2.3. avaliar os efeitos da intervenção cognitiva em áreas cerebrais através de ressonância magnética cerebral mediante teste neuropsicológico. (artigo 3)

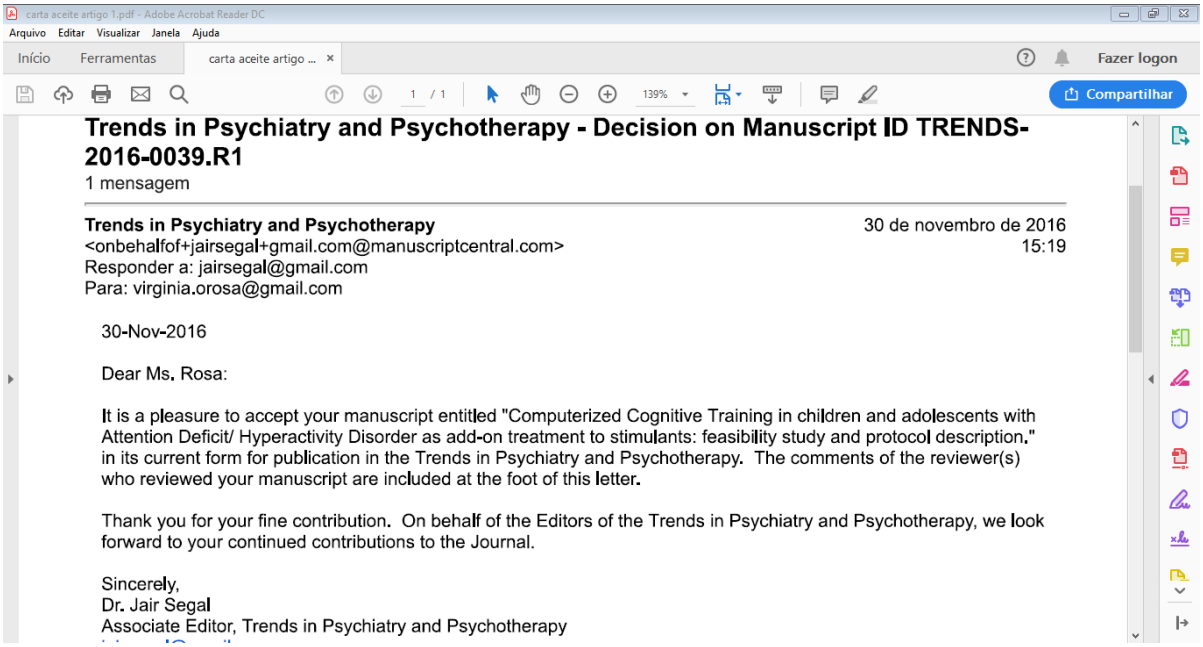
6. Aspectos Éticos

O projeto foi submetido e aprovado pelo Comitê de Ética em Pesquisa (CEP) do Hospital de Clínicas de Porto Alegre (CAAE 25048913.8.0000.5327). Todos os participantes do estudo concordaram com sua participação e assinaram o termo de consentimento livre e esclarecido (TCLE) antes de sua inclusão na coleta de dados.

7. Artigos

7.1. Artigo 1

7.1.1. Carta de aceitação



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1 mensagem

Trends in Psychiatry and Psychotherapy 30 de novembro de 2016
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Responder a: jairsegal@gmail.com
Para: virginia.orosa@gmail.com

30-Nov-2016

Dear Ms. Rosa:

It is a pleasure to accept your manuscript entitled "Computerized Cognitive Training in children and adolescents with Attention Deficit/ Hyperactivity Disorder as add-on treatment to stimulants: feasibility study and protocol description." in its current form for publication in the Trends in Psychiatry and Psychotherapy. The comments of the reviewer(s) who reviewed your manuscript are included at the foot of this letter.

Thank you for your fine contribution. On behalf of the Editors of the Trends in Psychiatry and Psychotherapy, we look forward to your continued contributions to the Journal.

Sincerely,
Dr. Jair Segal
Associate Editor, Trends in Psychiatry and Psychotherapy

7.1.2. Manuscrito

Computerized Cognitive Training in children and adolescents with Attention Deficit/ Hyperactivity Disorder as add-on treatment to stimulants: feasibility study and protocol description

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Background: Cognitive training (CT) has received increasing attention as a non-pharmacological approach for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents. Few studies have assessed cognitive training as add-on treatment to medication in randomized placebo-controlled trials. The purpose of this preliminary study was to explore the feasibility of implementing a computerized CT program for ADHD in our environment, describe its main characteristics and potential efficacy in a small pilot study. **Methods**: Six ADHD patients aged 10-12-years old receiving stimulants and presenting residual symptoms were enrolled in a randomized clinical

trial to either a standard cognitive training or a controlled placebo condition for 12 weeks. The primary outcome was core ADHD symptoms measured using the SNAP-IV scale. **Results:** We faced higher resistance than expected to patient enrollment due to logistic issues to attend face sessions in the hospital and to fill the requirement of medication status and absence of some comorbidities. Both groups showed significant decrease in parent reported ADHD symptoms without between group differences. In addition, improvements on neuropsychological tests were observed in both groups – mainly on trained tasks. **Conclusions:** The protocol cleared to the new strategies needed to assess the effectiveness of cognitive training such as the need to implement the intervention in a school environment to have an appraisement with more external validity. Given the small sample size of this pilot study, definitive conclusions on the effects of CT as add-on treatment to stimulants would be premature. The trial was registered at C*linicalTrials.gov* -NCT02184598.

Keywords: Attention-deficit/hyperactivity disorder (ADHD), treatment, cognitive training.

Introduction

Attention Deficit-Hyperactivity Disorder (ADHD) is one of the most prevalent externalizing disorders in children and adolescents [1] with estimated prevalence of 5.29% [2]. The core symptoms are inattention, hyperactivity and impulsivity that are age inappropriate, persistent and pervasive [3]. The presence of clinical symptoms and neurocognitive deficits in ADHD are consistently associated with morbidity [4] and impairments like poor academic performance and consequent school dropout [5], higher risk to nicotine and cocaine addiction, automobile accidents [6] and criminality [7]. Evidence suggests that these outcomes could be avoided with the ADHD treatment [8].

Previous literature suggests that most of the patients with ADHD show deficits on multiples executive domains. Executive functions allow individuals to regulate their behavior, thoughts and emotions and self-control [9]. Deficits in executive functions might be one of the core symptoms of ADHD and probably explain part of the daily life problems found in children with this disorder [10].

The use of medication, especially stimulants, is one of the most effective treatments for ADHD [11]. However about 30% of the patients do not respond to stimulant medication or do not tolerate the side effects [12]. In addition, ADHD cognitive symptoms usually do not fully improve and the long-term benefits of medication are still unknown [13].

Among several non-pharmacological approaches available to treat ADHD [5] Cognitive Training (CT) has received increasing attention. Researches demonstrate that CT promotes improvements in

symptoms manifested at home and at school [14]. It has been suggested that CT programs are effective as ADHD treatment or as a tool to improve cognitive ability and academic performance in all age groups [15]. The training involves a repetition of specific or multiple cognitive processes over several weeks after which period performance enhancement is expected on the trained tasks [16]. Working memory is often the target of cognitive training because of its assumed capacity to influence a range of other cognitive processes. Working memory deficits have also been associated with failure in academic performance [17]. Therefore, the training of the executive functions can be a potential strategy for ADHD treatment [18]. Assessment of the literature suggests that there are methodological limitations (i.e lack of blinded assessments; lack of an adequate control group), [19] [20] that indicate that current results must be further investigated and replicated [5].

Our objective is to assess, in a randomized clinical trial (RCT), the benefits of a cognitive training program as an add-on treatment to stimulants in children and adolescents with ADHD. In this pilot study conducted before the RCT, we mainly aimed to: a) describe our procedures to enhance reproducibility; b) test feasibility of the protocol – assess: 1. the recruitment potential and adherence rates; 2. our eligibility criteria; 3. the equipment (software) used during the training; 4. if our fMRI paradigms are ready to assess our data and carefully appraise if there are any important data forgotten about; c) describe some very preliminary findings.

Method

The study was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (HCPA) - (CAAE 25048913.8.0000.5327). At study intake, parents and children were informed about randomization to one of the two computerized programs; parent consent and child assent were obtained before the initial assessment with the signature of a Free and Informed Consent (IC) form approved by the Committee. There was no monetary compensation for participating in study procedures.

Study Design

This is a pilot study for a bigger randomized clinical trial that aims to compare a standard CT to a CT placebo offered as add-on treatments to ADHD patients medicated with stimulants and who present with residual symptoms.

Recruitment process and enrollment of participants

Participants

Participants were recruited from the Attention-Deficit/Hyperactivity Disorder Outpatient Program (ProDAH) during the period from April to September 2014. ProDAH, at the teaching hospital (HCPA) of the Federal University of Rio Grande do Sul, is an area for teaching, research and clinical work with patients suffering from ADHD disorder. Its pediatric branch is linked to the Child and Adolescent Psychiatric Division at HCPA. Since we have complete data on clinical aspects and response to treatment for patients in our unit, we assessed our data set searching subjects with our established inclusion criteria. They were invited to participate in the trial during their regular attendance at ProDAH. At this moment, the study protocol was explained to parents and participants to assess their interest and the feasibility of maintain the regular face training sessions. When accepted, they were forwarded to a psychiatrist assessment and thereafter to a neuropsychologist.

Randomization

A simple randomization was performed using random numbers (representing the two study groups – active intervention or placebo). After randomization, there were four experimental cases and two controls.

Eligibility criteria

Our inclusion criteria were: a) age range 6-13 years-old; b) clinical diagnosis of ADHD according to the DSM-5; c) patients medicated with stimulants (at least 3 months of medication with doses not inferior to 0.3mg/kg/day of methylphenidate or 30mg/d of lisdexamfetamine). Subjects were also asked about the possibility of not changing their treatments during the CT trial; d) presence of residual symptoms of ADHD despite medication (we considered at least 50% residual symptomatology according to SNAP-IV scores); and e) internet access at home. The exclusion criteria were: a) evidence of a clinically significant comorbid psychiatric disorder requiring any additional treatment; b) an estimated IQ score bellow 80 (scores were determined using block design and vocabulary subtests from WISC III or IV (Wechsler Intelligence Scale – Third or Fourth edition)), depending on the period that child was assessed [21].

Study settings

The face sessions were performed at HCPA. A dedicated area equipped with computers, earphones and access to high-speed internet was created. We carefully placed the participants in the room in order to avoid interactions between them. During each session, they received individual assistance from a learning tutor or a member of the staff. The active and placebo group sessions were scheduled at different times.

Intervention Condition

Active Cognitive Training – Cognitive Computerized Remediation Training (CCRT) - ACTIVATE™. This software was created by the C8 Sciences Company based on research from Yale University. A Brazilian Portuguese version of the software was used for this clinical trial. CCRT is computerized training software composed of six different games that target neurocognitive functions, such as working memory, speed processing, sustained and divided attention, category formation and control inhibition. During the training participants perform a wide range of cognitive tasks like memorizing sequences, completing patterns, task-switching and assigning objects into categories. Each session lasts 45 minutes and the proposed treatment length was four sessions per week over a 12-week period. The sessions were carried out after school and it was considered an adequate implementation of CT program a successful completion of 85% sessions.

This program presents four innovative procedures: a) an automatic individualization of treatment – with a graduation and plateau criteria. The games move participants quickly through exercises in areas of their strength and keep them working longer in areas of their weaknesses; the games also avoid keeping participants working in exercises for too long after their maximum gain has been reached. To address a wide range of cognitive deficits, the training has multiple exercises that focus on different aspects of cognition; b) an online error diagnostics – despite the records and evaluation of the subjects responses during the training sessions, the program recognizes different types of errors an individual makes which could provide important information to teachers and clinicians; c) online corrective strategy messaging – every time a child makes a specific type of error above a criterion frequency, the program automatically provides a corrective strategy message and an option for doing the problem correctly and 4) attention alerts – the program has an attention alert function that helps increasing child performance during the exercises. On the c8sciences website it is possible to find an example about the games and/or request a demo version: http://www.c8sciences.com/about/games/

Placebo Cognitive Training – A package composed of educational videos and questions related to school content was developed by a learning tutor and psychologists from our staff; the training package considered the academic level of the participants and was hosted on an online platform (Moodle) at the hospital. Four strata were created according to the age of participants – 6-7; 8-9; 10-11 and 12-13- years old – and to expected performance for level of schooling. The questions were selected by a team of learning tutors and the videos were chosen by two psychologists. The placebo intervention was created to avoid any kind of cognitive training; it was offered in identical conditions as the CCRT. The content of this platform can be visualized on https://www.youtube.com/watch?v=dAv6Y83BDqc - subtitles in English could be triggered at the bottom of the video as indicated.

Procedure

Study procedures were explained to all participants and at least one parent. Participants were randomly assigned to the treatment conditions (CCRT N = 4; Placebo N = 2; see figure 1 for CONSORT diagram) with a MACRO in Microsoft® Excel. All participants and their families received a schedule for implementing the intervention at home and the dates of face sessions – two face sessions and two home sessions per week were expected as well as for weekly coaching calls – a member of the staff made phone contact to detect any kind of difficulties with the platform and ensure compliance to the training.

The training sessions were followed by a control register platform to identify potential challenges to treatment compliance. Participants in both conditions received equal support. Home sessions were completed under parental supervision and weekly coaching phone calls to remember the day sessions, check adherence to the protocol and medication, troubleshoot problems and provide motivational encouragement. Performance data was checked regularly via the online platform to verify progress and identify eventual difficulties and noncompliance. Data about medication status and adherence to the treatment was collected. Post treatment assessments and rating scales were completed approximately 1-2 weeks after the final training day for each participant. The assessments were carried-out by a researcher who was blind to participant treatment group.

Please insert figure 1 about protocol flowchart here.

Outcome Measure

Clinical outcome

Parent reports of ADHD symptoms were assessed using the SNAP – IV rating scale - a well-known instrument used in ADHD clinical trials [22]. The questions were filled out by parents and the principal investigator, who was a trained child and adolescent psychiatrist blind to the treatment condition. The primary outcome measure was the difference between the SNAP-IV scores collected at baseline and endpoint (inattention, hyperactivity/impulsivity and total score).

Neurocognitive outcome

All subjects were assessed using two neuropsychological batteries pre and post intervention, conducted in two different sessions which lasted approximately 90 minutes. The post intervention assessment occurred immediately after the treatment. The first battery included six neuropsychological tests: 1) CPT II (Conner´s Continuous Performance Test II) [23] to assess response inhibition (number of commissions) and sustained attention (Hit Reaction Time Block Change – higher values indicate a slowing in reaction time as the test progresses); 2) Digit Span to assess verbal working memory (number of correct responses for backward condition) [21]; 3) Spatial Span to assess visual working memory (number of correct responses for backward condition) - spatial span task was designed based on Cambridge Neuropsychological Testing Automated Battery (CANTAB) Corsi Block Task [24]; 4) Two Choice Reaction Time Task to assess speed of processing (mean reaction time in miliseconds); 5) Trail Making Test to assess cognitive flexibility (time in seconds to complete part B) [25]; 6) Picture concepts to assess category formation and pattern recognition (number of correct responses) [21]. The second battery used was the NIH toolbox (www.nihtoolbox.org/) which includes the Flanker Test to assess control inhibition and attention; Go/NoGo task to assess control inhibition, cognitive flexibility and speed processing and the List Sorting Working Memory Test to assess working memory. These tests were selected for both their proven construct validity as well as their frequent use in ADHD clinical evaluation and research. We also chose tests that include the different cognitive functions involved in the Cognitive Training: working memory, processing speed, divided and sustained attention, category formation and control inhibition. Tasks were administered in different sessions by a trained neuropsychologist blind to treatment intervention; all subjects were instructed to take their stimulant medication 1 hour before the assessment. The outcome measure was the difference between baseline and endpoint scores.

Neuroimaging outcome

Four participants were submitted to a Functional Magnetic Resonance Imaging (fMRI) exam pre-intervention to access the effects of the cognitive training in brain areas (fronto-striatal and parietal areas). The tasks were developed based on literature experiments and with the assistance of the research team from the Brain Institute of Rio Grande do Sul. Before the fMRI, all tasks were explained to and practiced by participants on a laptop outside of the scanner. Subjects were instructed to take their medication 1h prior to the scan. During the MRI exam participants performed a neuropsychological battery of tests. The tasks were projected onto a screen and viewed by subjects through a prism mirror attached to the scanner headcoil cage. Functional images were acquired with a 3.0T MRI scanner (GE Healthcare Signa HDxt, Milwaukee, WI) with the following sequences parameters: Time repetition (TR) 2s, Time Echo (TE) 30ms, FOV 220x220mm/Matrix size 64x64/Slice thickened 3.6mm. The fMRI protocol was composed by: 1) An isotropical T1 structural image; 2) Resting state fMRI scan; 3) Working memory (WM) task – N-Back [26] [27] included 64 trials (16 trials 0-Back letters; 16 trials 0-Back figures; 16 trials 1-Back letters; 16 trials 1-Back figures), a stimulus of 2ms and an interstimulus interval of 1s. This WM task consisted of 2 conditions. During the "0"-back condition subjects must respond any time the target (letter) presented in the beginning of the test appears on the screen. During the "1"-back condition subjects were presented with series of letters and figures and responded whenever the stimuli presented is identical to the stimulus before it; 4) Conflict Control Task [28] – 200 trials (150 congruent trials and 50 incongruent trials), a stimulus of 1.5s and an interstimulus interval of 1.5ms. In congruent trials, green arrows appeared on the screen pointing left or right and the subject was instructed to press the button in the same direction of the arrow (buttons in right and left hands); in the incongruent trials, red arrows appeared on the screen pointing left or right and the subject was instructed to press the button in the opposite direction of the arrow; 5) Go/NoGo [28] – 200 trials (150 Go and 50 NoGo), a stimulus of 1.5ms and interstimulus interval of 1.5ms. Arrows were presented pointing either left or right (representing Go signals); at each of these arrows' presentation, participants had to press a button. Arrows pointing up represented No-Go signals. A button response had to be selectively executed with the right thumb to Go stimuli or inhibited to No-Go signals. The order of presentation of the three different tasks was randomly assigned for each participant. All images were analyzed on the Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/), using the automated preprocessing pipeline (afni_proc.py).

Feasibility

We assessed each step as feasible using the following criteria: the compliance to the intervention (adherence) was defined as completing ≥ 41 of the 48 training sessions (85%) within a 12-week period; another important issue was to assess if our inclusion criteria was too restrictive – we

evaluated it considering how many subjects were excluded due to comorbidities or not meeting the criteria for medication status; the training software was assessed during the sessions – we were concern if the platform was running normally; if the internet was sufficient to support its use; if there are any kind of bugs –; to test our fMRI paradigms we assess the images observing the activations maps and running a statistical analysis; in addition, we carefully evaluated the movement during exam.

Data analyses

The analysis was performed with the SPSS Statistics (22.0) and is presented as mean ± SD. We also performed a t-test to compare the means, considering a p value ≤ .05.

Results

Sample characteristics

Table 1 presents the demographic and clinical characteristics of the study sample. A total of six subjects fulfilled the inclusion criteria and consented participation in the study. The study sample included children aged between ten to twelve years. The mean age was 10.83 years (SD 0.75) and 66.7% were male participants.

Please insert table 1 about sociodemografic characteristics here.

Clinical outcomes

We analyzed data for the completers. In general, participants in both groups showed a decrease in their scores for different domains of the parental SNAP-IV scale during the protocol (Table 1). The mean inattention and total SNAP-IV scores were, respectively, 2.19 (.36) / 1.74 (.68) for cases and 2.21 (.47) / 1.93 (.47) for controls at the beginning of the study and 1.36 (.06) / 1.18 (.14) for cases and 1.27 (.07) / 1.27 (.23) for controls after intervention. As expected, due to the small sample size, there were no statistically significant differences in the clinical measures pre and post intervention assessment.

Neurocognitive functioning outcomes

Tables 2, 3 and 4 show results from our neuropsychological assessment and from the NIH toolbox, respectively. Before and after intervention scores for each individual were presented. Again, the population sample was too small to establish statistical significance. In addition, due to the wide

age range, the scores should have been corrected for age. The pre and post-intervention results are presented individually for each subject. Higher values indicate better performance for Picture Concepts, Digit Span Backwards, Spatial Span Backwards, No-Go Accuracy and Working Memory Total Score.

Please insert tables 2, 3 and 4 about our neurocognitive outcomes here.

Neuroimaging

After the pre-intervention scans, it was possible to identify some limitations involving ours fMRI paradigms; one of the limitations was the need to improve the Go/No-Go task (with a *jitter* inclusion); the Conflict Control task did not generate a good activation map, among others. Due to the limitations in the results obtained with fMRI scans, we did not perform the post-intervention scans. It was decided that pre and post intervention scans would be carried out in a larger, subsequent study.

Compliance to the training

Among the four participants assigned to CCRT and two assigned to placebo, 50% of each group met compliance criteria.

Feasibility analyses

We faced some problems with the adherence of one participant on maintaining the face sessions at the hospital due to difficulties involving distance and logistic issues: Case 1, male, 10 years, member of active group: dropped-out during the first weeks of the protocol due to logistic issues – difficulty attending the face sessions at the hospital due to schedule problems.

In two another cases the participants did not reach the minimum sessions to an adequate CT trial due to problems with the internet at home. Based on these findings, in order to optimize CT protocol, we decided to modify our protocol for the RCT running the training three times a week at the schools like an after-school program and one time at home. We learned that careful assessment of the quality of high-speed internet availability at home would be crucial for developing any session at home.

Regarding the enrollment of participants, there were difficulties to find patients that fit the inclusion criteria. In this pilot phase, it was requested that participants should be in their stimulant's regime at a minimum of three months and with a stable dose. Taking into account that most of the participants interrupt their treatment during school holidays and considering that stimulants present rapid onset of action, it was decided that the criterion would change to one month of stable dose to

facilitate the allocation of participants. Similarly, it was decided that subjects with some comorbidities would be accepted, like oppositional defiant disorder, anxiety disorders, tic disorders, enuresis and using other psychotropic medications; however, the request that patients were clinically stabilized and without changes in drug regimen in the previous month before the protocol were maintained. This change in prerequisites attends to issue of external validity since it is known that comorbidities are found in the majority of ADHD cases [4] [29] [30] [1]. The criterion regarding the clinical outcome was also adapted: instead of considering a threshold of at least 50% of residual symptoms, that made recruitment of patients a difficult task, an average score in SNAP-IV inattention dimension by parents and teachers ≥ 1 was adopted. A teacher-rated snap-IV score was also included to assess outcome. Considering that the training targets focuses mainly on cognitive domains like working memory, attention and speed processing, it was decided that the inattention scores would be a better parameter to assess the main outcome

The present findings contributed to the understanding of which adjustment was necessary to improve the protocol in order to test cognitive training as add-on treatment approach to ADHD. An ongoing randomized controlled trial will generate further evidence concerning this CT program. The new protocol for the current study may be found at *clinicaltrials.gov.*

Discussion

The purpose of this preliminary study was to describe the procedures employed in a protocol for investigating the benefits of CCRT compared to a placebo intervention in an ADHD sample and to assess the feasibility of the strategy proposed. In addition, some very preliminary findings are discussed. As far as we know, there is a scarcity of published studies exploring the CCRT as an add-on intervention for ADHD stimulant treated subjects.

Regarding the design of the study, we believe that the add-on design of this protocol could be very interesting since different profiles of treatment – in this case stimulants plus CT – can be used together with the intent to cover a greater magnitude of symptoms and therefore reaching the goal of improving the psychiatric illness. Reflecting the real-world situations, use of concomitant psychotropic medications or adjuvant therapy approaches have substantially increased. Evidence-based guidelines to ADHD mostly recommended treatments that include pharmacological and psychological interventions [31]. Working memory elements can be modified by both therapeutic interventions for ADHD: working memory training and psychostimulants. Moreover, it has been suggested that cognitive training could lead to greater enhancements in working memory elements than medication alone [32]. We believe, in this study, that use of medication during training could enlarge the benefits of cognitive training program.

Across the literature CT appears to have effects on certain aspects of working memory domains like already showed by randomized clinical trials [20 19 33]. Nevertheless the effectiveness of CT on some cognitive and clinical symptoms of ADHD has been questioned in several meta-analyses [34 15] and reviews [35 36] and these results should be carefully interpreted since many studies bring methodological limitations (i.e lack of an adequate control group [36]. Moreover, in terms of potential variable influence, it has been suggested that working memory training could be superiorly effective on visual working memory [37]; in children with learning disabilities [36] and in individuals with low-performing cognitive ability, as there is more room for improvement [38]. However, a recent study that evaluated computerized adaptive working memory intervention program in improving long-term academic outcomes in children with low working memory did not found any benefits except to visuospatial short-term memory [39].

Similarly, to other feasibility study, according to unpublished observations, we faced difficulties for enrolling participants because the frequency of the sessions and the long-time follow-up intervention (12 weeks). Furthermore, the fact that the subjects must be in psychostimulants treatment at least 3 months before the entrance, reduced our possibility to reach an optimal sample size. Nevertheless, the difficulties in allocating subjects helped us to rethink our inclusion/exclusion criteria and some logistic arrangements were done for the ongoing study - as follows below. Similarly, we had one drop-out and two participants that did not reached a minimum of training sessions to be considered an adequate protocol due to logistical barriers for families. A study that assess a protocol of computer-based attention training in schools showed that it is feasible to implement this kind of treatment approach in a school setting as well as support an inclusion of a large and more diverse sample [40]. We believe that implementing our protocol at school could be a good strategy to ensure adherence to intervention.

Proposed strategies to deal with problems found:

1. Intervention: a) we started a partnership with private and public schools in Porto Alegre in order to implement a substantial part of the cognitive program in this environment, enhancing the acceptability of this approach by parents and participants; b) modification in the protocol: each session of the cognitive training or placebo training was shortened. They have now 30 minutes of duration occurring three times at school / hospital and one time at home (and in some particular cases four times at school for participants that face difficulties with their internet or computer access). In addition, C8 Sciences Company developed a more inviting and interactive lay-out platform to optimize adherence to games.

2. Outcomes: a) We added an internet scale[41] and questions about the time spent with videogames and internet to assess potential adverse events of the CT, as increasing internet/games addiction; b) We included the CGI / CGAS to increase our coverage of clinical improvement; c) We added an assessment by teachers throughout the use of the SNAP-IV scale; d) We decided to change the inclusion criteria regarding the domain and intensity of residual symptoms (a mean parent + teacher inattention SNAP-IV score ≥ 1. Previous literature suggest that the training could be mainly effective in inattention symptoms [42]; similarly we decided to include children on medication when type and dosage were unchanged at least 4 weeks prior to the start and during the intervention period [43]; e) Regarding the neuropsychological battery, a divided attention task - TEA-ch[44] - was included in this protocol to better assess the magnitude of the CT on this domain .
3. Randomization – in order to produce more comparable groups and reduce the source of bias in treatment assignments we decided to include a minimization method to allocate the participants. To ensure this we used the QMinim service (freeware minimization program available at http://qminim.sourceforge.net/demo/index.php). The aim of this method is to minimize the imbalance between the number of the patients in each treatment group over a number of factors (we chose age, gender and socio-economic status). The randomization process will be carried out by an external member of our research team, according to Cochrane guidelines [45].
4. Neuroimaging – to minimize problems involving subject movement inside the machine, we now carry out an initial rehearsal in a mock-scan. Similarly our tasks suffered some modifications in order to improve the acquisition of activation maps including a more complex and demanding working memory test (N-Back)[46], a different Go-No/Go task[47] and a Sustained attention task (SAT) [48]. N-Back – it is a 6-min working memory task consisting of four conditions. During '1-back', '2-back' and '3-back' conditions, subjects are presented with series of letters (1s duration, inter-trial interval = 2 s) and must respond with their right thumb using a button box whenever the letter presented is the same as one, two or three before it, respectively. This requires both storage and continuous updating of stimuli being held in WM. In the baseline vigilance '0-back' condition, subjects must respond to each X that appears on the screen. The task consists of 12 randomized blocks. Go-No/Go - Frequent arrows (160 trials: 76%, 500ms duration) pointing to either the left or right (Go signals) appeared in the middle of the screen with a mean inter-trial interval of 1.8s (jittered 1.6–2s). Infrequently, arrows point up (24 trials, 12%, No-Go signals) or slightly slanted (by 22.5%) arrows (24 trials, 12%, oddball signals) appeared. A button response had to be selectively executed with the right thumb to Go or oddball stimuli or inhibited to No-Go signals. The oddball trials control for the low frequency of the No-Go trials and thus the oddball attentional capture effect. SAT - during this 12-min sustained attention task the subjects need to respond as quickly as possible to the appearance of a visual timer counting up in milli-seconds. The visual timer

appears either after short predictable consecutive delays of 0.5s (in series of 3-5 stimuli) or after unpredictable time delays of 2, 5 or 8s pseudo-randomly interspersed into the blocks of 3-5 delays of 0.5s. The long infrequent unpredictable delays place a higher load on sustained attention/vigilance whereas the short, predictable 0.5s delays are typically anticipated placing a higher demand on sensorimotor synchronization.

Our very preliminary results suggesting that CT did not improve parent-rated ADHD symptoms compared to the placebo group concur with previous meta-analyses [42]. In our study, both our placebo and active training group improved. This suggests that when a more rigorous control group is employed, no benefits regarding cognitive training approach emerge.

One of the strengths of this pilot intervention is the neuropsychological evaluations that added objective data for the assessment process. Relative to placebo condition, participants in CT improved performance mainly on the working memory NIH toolbox which has similarities between subtests and the tasks involved on the CT games. Unlike this trained tasks, CT had no differential effect on non-trained outcome measures as described previously, regardless to some tendency to improve visual working memory - this finding has already been shown in prior clinical trials [37].

Our main limitation is the small sample size. Thus, any findings regarding efficacy must be considered preliminary. However, it is important to highlight that our main goals describing this protocol were to offer opportunities for replicability of the strategies and procedures and to allow investigators to have an overview of challenges and how to solve them in implementing a computerized CT for ADHD in a clinical trial.

Conclusions

Interventions that have the magnitude to improve ADHD symptoms and related executive functions like working memory are extremely important nowadays because of their potentially relevant role in enhancing academic performance. Given the small sample size of this pilot study, conclusions on the effects of CT as add-on treatment to stimulants would be premature.

This study sets the stage for our future steps on this research area to more consistently determine whether CT could significantly improve ADHD clinical and neurocognitive symptoms, as well as to establish the impact of the intervention on brain interconnectivity through fMRI assessment.

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Conflict of interest – Luis A. Rohde has received Honoraria, has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Janssen-Cilag, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He also received travel awards for taking part of 2014 APA and 2015 WFADHD meetings from Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. Carlos Roberto Maia received financial research support from the government agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). CRMM received fees in February 2016 for the development of educational materials on excessive daytime sleepiness, for Libbs. CRMM received travel and accomodation support for a speaker training from Shire. CRMM received travel awards from the Health Technology Assessment Institute (IATS), Universidade Federal do Rio Grande do Sul (UFRGS); and travel, accommodation and registration support to the fourth and fifth World Congress on ADHD from the World Federation of ADHD.

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Flow Diagram – figure 1

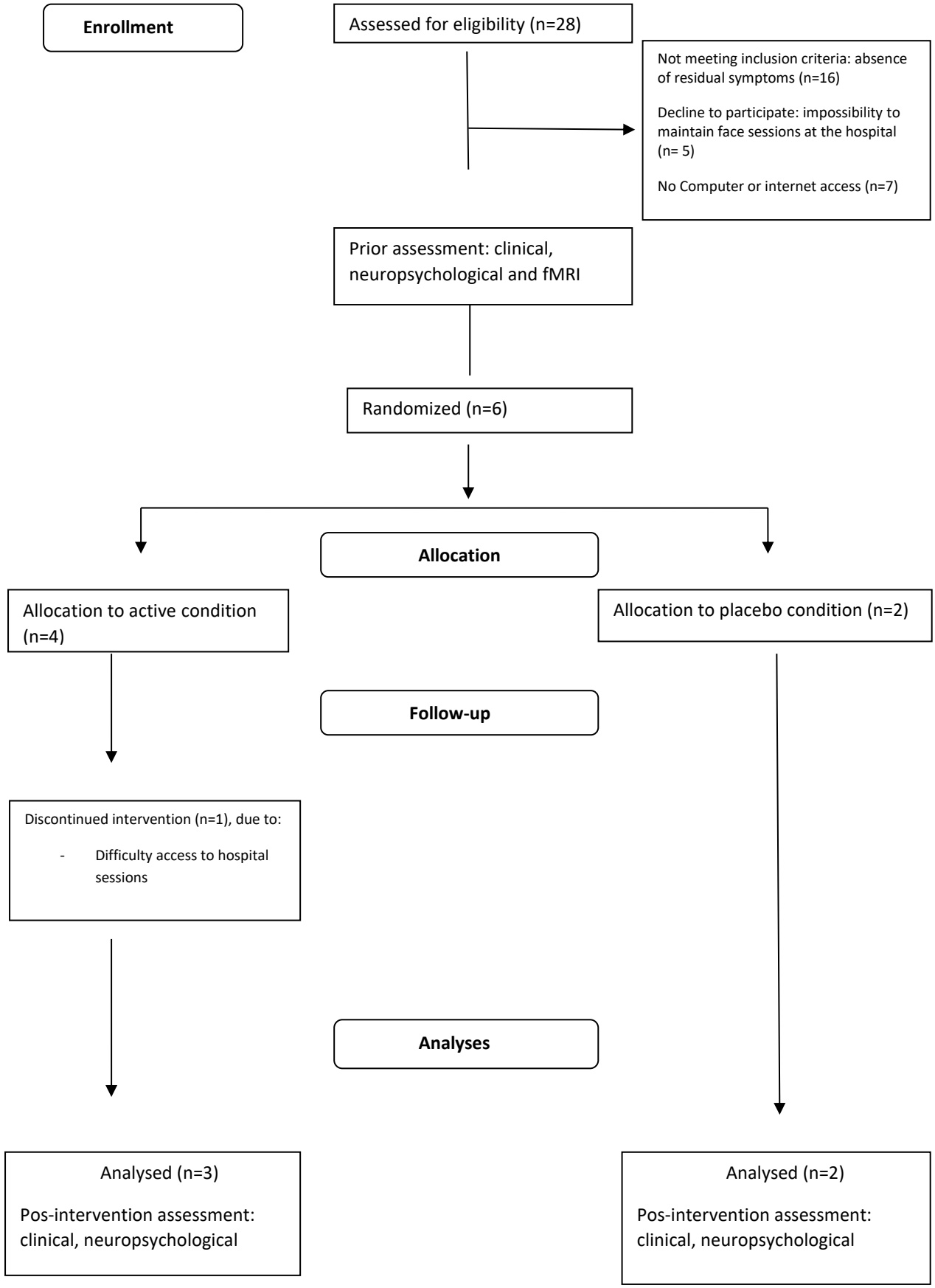


Table 1: Sociodemographic characteristics

Subject	Age (y)	Gender	IQ	SES	ADHD diagnoses	Group	Comorbidity	Completed sessions (%)	SNAP IV						Medication Status (mg/kg/day)
									Baseline			Endpoint			
									Inatt	H/I	T	Inatt	H/I	T	
1	10	M	90	C	C-ADHD	Case	ODD	-	2.44	2.11	2.27	-	-	-	0.59
2	11	F	95	B	C-ADHD	Control	-	93,75	2.55	2	2.27	1.33	1.55	1.44	0.98
3	11	M	80	C	C-ADHD	Case	-	95,8	2.55	2.22	2.38	1.33	1.33	1.33	0.71
4	12	M	87,5	B	C-ADHD	Case	ODD;LD	66	1.77	0.33	1.05	1.44	0.66	1.05	0.7 (LDX)
5	10	F	102,5	C	C-ADHD	Control	-	77	1.88	1.33	1.6	1.22	1	1.11	0.48
6	11	M	87,5	-	I-ADHD	Case	-	91,66	2	0.66	1.33	1.33	1	1.17	0.32

SES: socioeconomic status (ABEP). IQ: intelligence quotient. SNAP – Inatt: inattention; H/I: hyperactive/impulsive score; T: total score. ODD: oppositional-defiant disorder. LD: learning disability. LDX (lisdexamfetamine)

Table 2: Neuropsychological assessments

Subject	Group	Picture Concepts*		Digit Span Backward*		Spatial Span Backward*		CPT II Comissions		CPT II RT Block Change (time in miliseconds)		Trail Making Test B (time in seconds)		Two Choice RT (time in miliseconds)	
		Pre	Pos	Pre	Pos	Pre	Pos	Pre	Pos	Pre	Pos	Pre	Pos	Pre	Pos
1	case	11	-	6	-	0	-	28	-	0,00	-	38	-	289.38	-
2	control	13	16	8	6	3	3	20	22	0.03	0.00	39	32	300.05	301.56
3	case	15	19	6	5	0	3	27	-	0.01	-	42	92	433.46	127.29
4	case	19	21	9	7	5	1	21	31	-0.03	0.02	35	83	363.55	-
5	control	17	18	7	8	3	5	32	25	0.03	-0.01	43	44	283.98	356.22
6	case	14	17	7	5	2	4	18	15	-.0.01	0.02	58	60	394.26	444.13

All measures are presented in raw scores. CPT II: Continuous Performance Test II; RT: Reaction Time; *higher values indicate better performance

Table 3 – Neuropsychological Assessments: NIH toolbox

Subject	**Group**	**Flanker Correct Incongruent RT**		**No-Go Accuracy**		**WM – total score**	
		Pre	Post	Pre	Post	Pre	Post
2	Control	501.85ms	571.46	0.733	0.366	20	10
3	Case	869.9ms	677.82	0.266	0.266	2	16
4	Case	660.35ms	583.43	0.6	0.6	3	14
5	Control	684.82ms	498.66	0.46	0.36	9	2
6	Case	554.11ms	608.82	0.266	0.833	6	12

RT: reaction time; WM: working memory

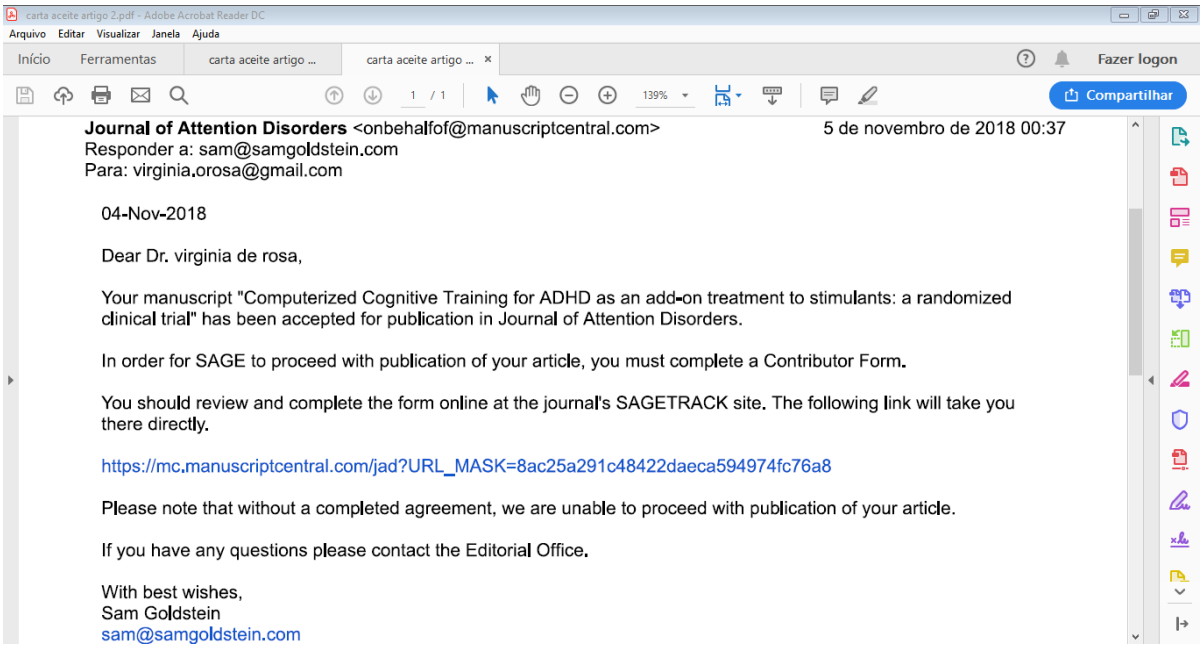
Table 4 – Neuropsychological Assessments: NIH toolbox

RT: reaction time

	Flanker Inconguent Accuracy Pre	**Flanker Incongruent Accuracy Post**	**Flanker Correct Incongruent RT pre**	**Flanker Correct Incongruent RT post**	**No-Go Accuracy Pre**	**No-Go Accuracy Post**	**WM Pre**	**WM Post**
Placebo	.91	.88	593ms	535ms	.47	.37	14.5	6
Active	.86	.98	695ms	623ms	.38	.57	4	14

7.2. Artigo 2

7.2.1. Carta aceitação



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04-Nov-2018

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7.2.2. Manuscrito

Computerized Cognitive Training for ADHD as an add-on treatment to stimulants: a randomized clinical trial

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Supporting information

Conflict of interest - Luis A. Rohde has received honoraria, has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Medice, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He also received travel awards for taking part of the 2015 WFADHD and 2016 AACAP meetings from Shire. The ADHD and Juvenile Bipolar

Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Janssen-Cilag, Novartis, and Shire. Dr. Carlos Renato Moreira-Maia has received financial research support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); development of educational materials for Libbs, Novartis and Pfizer; has received travel and accommodation support for a speaker training and participated in the development of a cell phone applicative for Shire; has received travel, accommodation and registration support to the fourth and fifth World Congress on ADHD from the World Federation of ADHD. Other authors do not have conflicts to declare.

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Abstract

Background: Computerized Cognitive Training (CCT) as add-on treatment to stimulants for ADHD core symptoms is scarcely investigated. The purpose of this study is to assess the effect of CCT in a randomized controlled clinical trial for ADHD in children and adolescents treated with stimulants. **Methods**: Fifty-three subjects aged 6 to 13 years receiving stimulant treatment and presenting ADHD residual symptoms were randomized either to a CCT (n = 29) or to a controlled non-active condition (n = 24) for 4 sessions/week during 12 weeks. The main outcome measure was inattentive symptoms assessed using the SNAP-IV scale. Secondary outcomes include, among others, hyperactive/impulsive symptoms and cognitive tests. **Results:** There were neither significant group differences on ADHD-inattentive symptoms after the intervention nor on both ADHD-hyperactivity/impulsivity symptoms and cognitive measures. **Conclusions:** Our study does not provide evidence for the benefits of cognitive

training over non-active training on core ADHD symptoms in medicated ADHD children and adolescents.

Keywords: Attention-deficit/hyperactivity disorder (ADHD), treatment, cognitive training, randomized trial.

Introduction

Attention Deficit-Hyperactivity Disorder (ADHD) is one of the most prevalent externalizing disorders in children and adolescents (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). It is characterized by persistent and pervasive symptoms of inattention and or impulsivity/hyperactivity, impairing the individual and their family (American Psychiatric Association, 2013). ADHD can cause several negative outcomes including poorer academic performance and interpersonal problems (Faraone et al., 2015; E. Sonuga-Barke et al., 2013). Evidences suggest that some of these negative outcomes could be avoided by pharmacological treatment (Faraone et al., 2015). However, additional treatment can be necessary for the residual symptoms – i.e., symptoms of inattention and hyperactivity/impulsivity even in the presence of an appropriate dose of psychostimulant treatment. Thus, the majority of clinical guidelines preconize combined pharmacological and non-pharmacological interventions as first line treatment for ADHD (Caye et al., in press).

There is a growing body of evidence demonstrating an association between ADHD and several impairments in cognitive domains including deficits in executive functions (e.g., working memory, inhibitory control, vigilance and planning) and basic processing efficiency (Coghill et al., 2014; E. Sonuga-Barke, Brandeis, Holtmann, & Cortese, 2014) and these cognitive domains represent important targets to the ADHD neurotherapeutics (E. Sonuga-Barke et al., 2014). It is well established that working memory deficits, for instance, are associated to high risk of cognitive dysfunction and academic deficits (Fried et al., 2016), thus representing an important aspect to be considered in the therapeutic approach. ADHD medications, particularly the stimulants, are somehow efficacious for the neuropsychological deficits – e.g., deficits on working memory, response inhibition, attention, planning (Coghill et al., 2014; Ni et al., 2013); however, with smaller effects compared to those for clinical symptoms – inattention, hyperactivity and impulsivity (E. Sonuga-Barke et al., 2014). Taking also into account that cognitive deficits may be associated with the etiology of ADHD, improving the neuropsychological performance in individuals with the disorder can also determine an improvement in the clinical symptomatology (Cortese et al., 2015).

Despite of pharmacological treatment, a significant group of patients with ADHD have residual symptoms and, accordingly, several impairments that can affect their life and self-esteem (Modesto-Lowe, Charbonneau, & Farahmand, 2017). Add-on strategies can represent a good approach to deal with residual symptoms and several approaches are available as psychotherapeutic interventions - e.g., cognitive behavioral therapy (CBT), dialectical behavioral therapy, mindfulness - (Modesto-Lowe et al., 2017) and cognitive training. Data suggest that cognitive training, for instance, can be beneficial as add-on treatment to some psychiatric disorders like schizophrenia (Kurtz, Seltzer, Shagan, Thime, &

Wexler, 2007). Studies demonstrated that cognitive remediation can improve cognitive function (as working memory) in these patients (Bell, Fiszdon, Greig, Wexler, & Bryson, 2007) with the possibility of gains generalizing to untrained neurocognitive tasks (Kurtz et al., 2007).

Cognitive Training (CT) for ADHD has become a focus of research in the last years (van Dongen-Boomsma, Vollebregt, Buitelaar, & Slaats-Willemse, 2014). Its action is grounded in the notion of neuroplasticity based on the fact that brain networks involved in ADHD could be strengthened, improving cognitive process through exposure to some kinds of tasks (Cortese et al., 2015) which drives learning and promote new cognitive skills (Willis & Schaie, 2009). The CT approach consists of the repetition of one or more cognitive processes over few weeks, varying accordingly to the specific protocol employed (E. Sonuga-Barke et al., 2014). Working memory deficits, among the most commonly reported executive dysfunctions in ADHD (van der Donk et al., 2017), is often the target of CT as it is known to influence a wide range of other cognitive domains (Chacko et al., 2014). However, since there is a wide heterogeneity among ADHD individuals with regard to associated neurocognitive deficits, it would be important to better evaluate the effectiveness of training that targets other important cognitive domains. In this regards, a meta-analysis evaluated the clinical and neuropsychological outcomes of randomized clinical trials with cognitive training and found that training targeting multiple domains presented substantially more effects compared to those that used only working memory training (Cortese et al., 2015). The same meta-analysis points to the importance of more studies with blinded assessments to better evaluate these results.

Klingberg et al. reported the earliest positive evidence of CCT for ADHD treatment. The authors studied a working memory training program against a comparison program (low-demand, non-adaptive training). They found a significant reduction in ADHD symptoms according to parent ratings but not for teacher ratings (Klingberg et al., 2005). Subsequent randomized clinical trials (RCTs) with several different training programs, and different study designs, have emerged to assess the effects of CCT, but most of them presented methodological inconsistencies (e.g., type of control arms, length and intensity of training programs, lack of blinded assessments) (E. Sonuga-Barke et al., 2014). Most of these studies had heterogeneous samples with regard to medication trials and did not find any robust evidence (Bikic, Christensen, Leckman, Bilenberg, & Dalsgaard, 2017; Chacko et al., 2014; van Dongen-Boomsma et al., 2014). Similarly, it is important to highlighted that these studies have a considerable heterogeneity in the outcomes of interest, presenting a lack of uniformity in how they evaluated the efficacy of the proposed treatment. A recent open-label study with ADHD medicated children (Lee, Kim, & Yoo, 2017) evaluated the augmentative effects of a working memory program on behavioral problems, quality of life and parental stress. The authors found a decrease in both the Child Behavior Checklist (CBCL) attention problems scores and parent-child dysfunctional interaction, but no

change on quality of life measures. Well-designed (i.e. randomized, with blind assessments and placebo-controlled) CCT studies are scarce, but paramount to support this intervention as an add-on treatment for ADHD patients (Cortese et al., 2015).

Our main objective is to assess the benefits of a CCT intervention as an add-on to the stimulant medication treatment in children and adolescents with ADHD in a randomized clinical trial. Our main hypothesis was that the addition of CCT to stimulants would provide a significantly greater reduction in ADHD-inattentive residual symptoms compared to the addition of a non-active comparator. Secondarily, we expected positive findings in hyperactivity/impulsivity symptoms and in cognitive domains.

Methods

Ethics approval

This research was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (HCPA) - (CAAE 25048913.8.0000.5327). A parent written informed consent and child assent were obtained before the initial assessment. No monetary compensation was offered to the patients for participating in the study.

Participants

The sample included children and adolescent aged 6 to 13 years, recruited from: 1) the Attention-Deficit/Hyperactivity Disorder Outpatient Program dataset – ProDAH (located at the teaching hospital [HCPA] of the Federal University of Rio Grande do Sul, in Porto Alegre, Brazil) and; 2) public and private schools from the same city. We visited each school and organized a meeting with the parents to present our protocol and invite them to participate in our study. This age range was selected based on the nature of the tasks trained by the program. Younger children might be too immature and older adolescents might not feel enough challenged by these tasks.

Eligibility criteria

The inclusion criteria for participating in this study were: a) ADHD clinical diagnosis – diagnostic process relied on the use of a semi-structured interview (the Kiddie Schedule for Affective Disorders

and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL)] (Kaufman et al., 1997) administered to the parents by trained child and adolescents psychiatrists (A.S and C.R.M.M) and a clinical evaluation of ADHD and comorbid conditions using DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, 2000) criteria by the same child and adolescent psychiatry with the child and the family. Information about the symptoms in the school environment is obtained through the use of the Attention Problems scale of the Child Behavior Checklist – Teacher´s Report Form as well as a Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) (J. Swanson et al., 2001) rated by the classroom teacher; b) at least 4 weeks of the same type and dosage of stimulant treatment, i.e. long-acting or immediate release methylphenidate (MPH) ≥ 0.3mg/kg/day (Brown, Samuel, & Patel, 2018) or lisdexamfetamine (LDX) ≥ 30mg/d (*Canadian attention deficit hyperactivity disorder resource alliance (CADDRA): Canadian ADHD practice guidelines 4th Edition.*, 2018) (it is important to note that MPH and LDX are the only stimulants commercialized in Brazil); c) a mean parent + teacher inattention SNAP-IV score ≥ 1 – we focused in inattentive scores since previous literature suggest that CCT could be mainly effective in inattention (Cortese et al., 2015); d) fluency in Portuguese; and e) a computer and internet access at home or school. The exclusion criteria were: a) evidence of a comorbid psychiatric disorder not stabilized requiring any additional pharmacological treatment; b) estimated IQ score lower than 80 [scores were determined using block design and vocabulary subtests from WISC III or IV (Wechsler Intelligence Scale – Third or Fourth edition)], depending on the period that child was assessed (Wechsler, 2004); c) any change in the dose of stimulant treatment during the protocol; d) the inclusion of any other medication and/or psychosocial treatment in order to control ADHD symptoms during the protocol (if the patient was already in pharmacological or psychosocial treatments – in these case, supportive psychotherapy, psychodynamic psychotherapy and psychopedagogical attendance - we obtained permission from the family to contact the professionals and ask them to maintain all interventions to avoid any confounders influencing the outcomes).

Randomization

A minimization method of randomization was performed to allocate the subjects through the QMinim service (http://qminim.sourceforge.net/demo/). The software minimizes the imbalance between patients in each treatment arm over a number of factors – in this study we choose age, gender and socio-economic status. According to the Cochrane Risk of Bias Tool for Randomized Controlled Trials the randomization process was also carried-out by a technician not involved with the clinical trial, and blinded to any information from the participants (Higgins et al., 2011).

Interventions

The Computerized Cognitive Training - Cognitive Computerized Remediation Training (CCRT) - ACTIVATE™ is a software created by the C8 Sciences Company based on research from the Yale University. A Brazilian Portuguese version of the software was used for this study. Briefly, ACTIVATE™ is a computerized training composed of six different games, with different levels of difficulty, designed to address different neurocognitive domains, such as working memory, speed processing, sustained and divided attention, category formation and control inhibition. The program matches difficulty level according to child´s performance during the sessions which means that the game has a hierarchical nature, starting with a basic level and then graduating to considerably more complex tasks. Participants perform a wide range of cognitive tasks like memorizing sequences, completing patterns, task-switching and assigning objects into categories. More details about the ACTIVATE™ program, can be found in our published protocol (Rosa et al., 2017) or at the c8sciences website (http://www.c8sciences.com/about /games/).

The protocol was composed by 48 sessions, each one lasting 30 minutes. The proposed treatment length was four sessions per week (3 face-to-face sessions – school or lab - and one session at home; or all times face-to-face sessions) during 12 weeks, always under supervision of parents or a tutor. We considered the completion of at least 85% of the sessions as an adequate implementation of the CCT program.

The non-active intervention - To assure that the non-active condition had no neurocognitive effect, we developed educational packages composed by videos and questions related to school content. Psychologists and learning tutors from our staff previously evaluated each package and stratified them according to age groups (6-7; 8-9; 10-11 and 12-13y) and school grade. The training package considered the academic level of the participants and was hosted on an online platform as the same way as the intervention. The videos and questions were related to general knowledge, Brazilian Portuguese grammar, history, and geography. A detailed description can be found in our published protocol (Rosa et al., 2017), and the content of this platform is available in a video at www.youtube.com/watch?v=dAv6Y83BDqc, where subtitles in English could be triggered at the bottom of the video as indicated. This non-active protocol was identically implemented in the same way of the CCT program, with the same duration and number of sessions.

Study settings

The face-to-face sessions were performed at our lab at the University Hospital or at public and/or private schools. An appropriate room equipped with computers, earphones and access to high-speed internet was created in each local. To assure the blinding of the process, we carefully organized

the rooms where participants were prevented to see each other computer screen, or to have interactions among them. During each session, they received individual assistance from a trained tutor or a member of the staff, both not involved into the outcome assessments, and they were never left alone in the room. Similarly, the development of partnerships with participant´s private and public schools enhanced the acceptability of the offered approach by parents and participants. Importantly, in order to maintain blindness in the evaluation of clinical outcomes, teachers were not aware of the group that the children belonged to in the study as well as training activities occurring outside the classroom in the laboratory set up for the study (for those children trained in the school lab).

Primary Outcome Measure

The Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) - this is a well-known instrument used in ADHD clinical trials (J. Swanson et al., 2001). It was filled out by parents during a clinical interview with investigators and by teachers at the baseline and at the end of the protocol. Both investigators and teachers were blinded to the treatment condition during the study protocol. The primary outcome measures were group-differences in SNAP-IV endpoint scores (inattention scores). We chose inattentive scores based on previous studies assessing CT in ADHD in which this kind of intervention seems to be more effective in the symptoms of inattention.

Secondary Outcome Measures

Hyperactivity/impulsivity (HI) symptoms: assessed trough SNAP-IV rated by parents and teachers at the baseline and the end of the protocol.

Safety: Excessive internet, videogame or computer use is a very common concern among parents and mental health professionals. To understand if the participation in the CCT or the non-active condition increased the use of electronical devices, we also included the Internet Addiction Test – IAT – (Conti et al., 2012) and questions about the time spent per day with videogames and internet.

Neurocognitive outcomes

All participants underwent neuropsychological testing before and after the intervention. Their performance on the tasks was recorded on the same online training platform. Upon logging in, they were directed to the tasks and before each one of them, subjects received instructions on the task. They were accompanied during the performance by a team member familiar with the battery. The last assessment occurred within a week after the end of the protocol.

The neuropsychological battery was included in the CCT platform and was composed by two tests from the National Institutes of Health (NIH) toolbox (www.nihtoolbox.org/) – 1. Flanker Test to

assess inhibitory control and attention; 2. the List Sorting Working Memory Test to assess working memory - and a standard Go/No-Go test, programmed by the Yale team, to assess information processing, inhibitory control and cognitive flexibility. The NIH battery is validated for subjects aged 3 to 85 and its use guarantees that assessment methods and outcomes can be used for comparisons across current and future studies. All scores for a given domain are on a common scale and can be used for a longitudinal measurement. Validation studies were conducted for all NIH toolbox measures to assure that this important tools for research follow rigorous scientific standards. The neuropsychological tests are embedded in the platform of the cognitive training program. Each task tested cognitive domains that have already been associated with the disorder: inhibitory control, attention, working memory, information processing and cognitive flexibility. More details can be found in https://www.c8sciences.com/about/nih-toolbox-assessments/.

Global clinical functioning outcomes

We used the Clinical Global Impression (CGI) (Guy, 1976) and the Clinical Global Assessment Scale (CGAS) (Shaffer et al., 1983) to assess global improvement. The outcome measure was also the between-group difference in endpoint scores. The scales were filled in by one of the investigators (A.S. and C.R.M.M.), blind to the treatment condition.

Procedures

Participants and their parents were submitted to an initial assessment that consisted of a clinical interview, previous medical and psychiatric history, as well as the application of the SNAP-IV and IAT scales. If participants fulfilled the inclusion criteria, their IQ was determined. If no exclusion criteria were applied, subjects were randomly assigned to one of the treatment conditions (CCT N= 29; Non-active control N= 24; see figure 1 for CONSORT diagram).

Study procedures were explained in detail to participants and parents. All participants and their families received a schedule for implementing the intervention as well as weekly coaching calls – a member of the staff made phone contact to discuss possible problems with the platform and to ensure compliance to the training. The patients maintained their usual drug regimen during the training sessions.

Statistical methods

For each parameter, mean and standard deviation (*SD*) were computed. Demographic and clinical characteristics were compared between groups by means of t-tests for continuous variables and chi-squared tests for categorical variables. The same procedure was used to compare participants who dropped-out and those who finished the protocol to investigate any differences between the

groups. The potential confounders tested were age, IQ, gender, socio-economic status and comorbidities. Regarding outcomes, Shapiro-Wilk test was used to assess variables distribution. The means of the variables between groups, times and interaction (group*time) were compared using the Generalized Estimates Equation Model (GEE). This model was constructed with an unstructured working correlation matrix and a robust estimation of covariance matrix. For the variables with normal distribution an identity binding function was used, for those with gamma distribution a logarithmic function. The Bonferroni post-hoc test was used when there was statistical significance in GEE. We also assessed effect-size for clinical and neuropsychological outcomes through Hedges effect size (g). The level of significance was set at p-value ≤ 0.05 (two-tailed) for all analysis. The Statistical Package for Social Sciences version 21 (IBM SPSS 21) was used for analyzing the sample characteristics and overall treatment effects.

The trial protocol has been published (Rosa et al., 2017) and the protocol was registered at Clinicaltrials.gov ("Randomized Controlled Trial With Use of Cognitive Training in Children and Adolescents With ADHD"-NCT02184598).

Results

We visited 17 schools and 11 accepted to participate in our study. From these schools, 79 students were potential candidates for enrollment in the study. Similarly, we contacted 72 patients from our ProDAH dataset. From this total, 98 children and adolescents were both assessed for eligibility and clinically examined. Fifty-three subjects met the inclusion criteria, consented to participate in the study and were randomized: 29 were allocated to CCT and 24 to the non-active control group (Figure 1 - flowchart).

In the non-active control arm, three participants declined to participate before start the protocol due to logistical problems (difficulty of the families to maintain four sessions per week). In the CCT group, five participants declined to participate after starting the protocol due to same logistical problems, each one completing respectively 43.7% - 35.5% - 20.8% - 4% - 2% of the sessions. There were no statistical differences between the dropout participants (n=8) and the participants who finished the protocol (n=45) in all baseline characteristics except mean age (9.12 [1.35] and 10.66 [1.79] respectively; *p*=0.025).

Demographic and clinical characteristics

The analysis was conducted with 45 subjects (24 cases and 21 controls). The mean age for the total sample was 10.66 years (SD=1.79) and 60% were male. Table 1 presents the demographic and

clinical characteristics of the study sample. No between-group differences were found on baseline characteristics.

Primary outcomes

There were no treatment effects on the primary outcome measures, i.e., inattentive ADHD SNAP-IV scores (parent-rated inattention: $\chi^2(1)=0.3$, p=0.58, g=0.03; teacher-rated inattention: $\chi^2(1)=0.3$, p=0.58, g=0.21). In general, participants showed a decrease in their parental and teacher SNAP-IV scores during the protocol in both groups (Figure 2). We did not find any predictors (baseline variables as gender, IQ, age, ADHD subtype and comorbidities) for response to the intervention either defined continuously or dichotomized at a response rate of 25%.

Secondary outcomes

There were no treatment effects on HI scores (parent: $\chi^2(1)=0.23$, p=0.63, g=0.21; teacher: $\chi^2(1)=0.99$, p=0.31, g=0.07).

In our neuropsychological battery (NIH), there were no significant between-group differences in the three tasks (see table 2).

Participants in both groups showed an improvement in their CGAS scores (CCT group: 72±15.44 / 80.46±11.61; and non-active group: 77.95±14.55 / 81.66±11.95, *p*= 0.1) and CGI scores (CCT group: 4.33±1.16 / 2.91±1.58; and non-active group: 3.71±1.35 / 3.19±1.29, *p*= 0.13) with no significant differences between them.

There was significant between-group difference on IAT total score (χ^2 (1) =4.33, p=0.037) with CCT group showing reduction on their scores and the non-active group showing increased scores after intervention (CCT group = 27.3±19.78 / 22.75±17.41; and non-active group = 21.9±19.15 / 26.57±19.29). Importantly, we did not find increase of the time spent on internet or videogames after CCT nor after non-active interventions.

Compliance to the treatment

Among participants who finished the protocol (n=45), all of them met compliance criteria of 85% of attendance to the sessions.

Discussion

To our knowledge, this is one of the first studies to use a RCT design to compare the effects of a cognitive training as an add-on to pharmacological treatment in children and adolescents with ADHD. In addition, our training program included a variety of cognitive domains and our non-active

intervention included the same duration of exposure to a computer without elements of cognitive training. First of all, it is important to note that the CCT approach used showed that the intervention was feasible to be implemented at schools and home and participants compliance was high.

In our study, both groups showed reduction in ADHD symptoms scores comparing baseline to post intervention scores, as well as improvement on global clinical functioning outcomes. However, we found no significant between-group differences on SNAP-IV scores neither rated by parents nor by teachers. In addition, no differences were found in global clinical functioning rated by blinded clinicians. The majority of controlled trials to date have used cognitive training in non-medicated individuals with ADHD as the only treatment and found mixed results. Our findings were consistent with the majority of those that found no significant impact of CT *versus* placebo for ADHD symptoms rated by teachers and/or parents (Chacko et al., 2014, 2017; Roberts et al., 2016; van Dongen-Boomsma et al., 2014). Similarly, our results were consistent with a recent RCT that assessed the same program (ACTIVATE), albeit with an earlier version compared to that used in our study, which found neither significant effect of the training on ADHD symptomatology nor on cognitive measures (Bikic, Leckman, Christensen, Bilenberg, & Dalsgaard, 2018). A meta-analysis by Cortese et al. assessed only RCT´s with interventions intended to train a cognitive function found that CCT had statistically significant effects on ADHD core symptoms when rated by individuals unblinded to treatment but, when assessments were based on probably blinded raters, the effects were reduced substantially. Similarly, the positive effects of the intervention were reduced when analyses included only trials with an active control group in the same meta-analysis, concluding that there are little evidence to support the efficacy of cognitive training (Cortese et al., 2015). Together these findings point to the need of studies with a more rigorous methodology to assess the clinical effects of CCT for ADHD. Nevertheless, the absence of significant between-group differences may be due to the small sample size of our trial. It is important to highlight some aspects: 1) the effect sizes for primary outcome were all in the range considered clinically insignificant; 2) for some outcomes like parent inattentive scores, the baseline to post-intervention difference was greater in the non-active control group. Thus, increasing sample size would just maximize the difference in the opposite direction than hypothesized; 3) even for primary outcomes like teacher inattentive scores, increasing 8 times the sample size while keeping the same original data (n = 360) would still not produce significant findings. For this reason, and due to logistical difficulties, we stopped enrolling subjects with n=53.

On cognitive outcomes, there was no significant difference between the intervention and the non-active condition. There are many trials that assessed training effects on neuropsychological deficits (Bikic et al., 2017; Gray et al., 2012; Tamm, Epstein, Peugh, Nakonezny, & Hughes, 2013) with mixed results. The majority of studies found in the literature demonstrated near-transfer effects

showing improvements on tasks tapping the same deficit as targeted by the intervention (Chacko et al., 2014; Hovik, Saunes, Aarlien, & Egeland, 2013). Evidence for transfer to more distal processes is still needed in the literature to better evaluate the potential of CCT (Rapport, Orban, Kofler, & Friedman, 2013).

Our study has some strengths. It has a RCT design that was never used in any add-on study for CCT in ADHD. Our CT program targeted multiples neurocognitive domains, as recently recommended in a meta-analysis on effects of CT in ADHD. Our non-active comparator was carefully conceived during more than one year to have non-challenging cognitive characteristics while exposing patients to the same dose of intervention in the computer. Some of the outcomes assessed were blinded (teachers and clinicians' ratings) and some as the neuropsychological tasks are objective measures. Participants were recruited from different places allowing generalizability, and the retention rate was high. However, some limitations should be also highlighted. First, the sample size was smaller than planned due to recruitment difficulties, and we cannot exclude that this fact may explain why some differences did not reach significance. Future studies with multiple centers are highly recommended. Second, we did not measure motivation rates of the participants neither in CCT nor in non-active group. Motivation is key in maintaining sustained attention during activities, and low levels of motivation may result in negative influences on treatment effects (Bikic et al., 2017) . Third, participants had probably little room for improvement, since our sample was composed of children and adolescents medicated with stimulants for ADHD. However, we took extra care in our inclusion criteria to guarantee some level of residual symptomatology in the outcome described with higher chance to be affected by CCT (inattentive symptoms). Forth, similarly, we did not allocate only individuals with specific neuropsychological deficits to be trained. Thus, we probably deal with little room for improvement where no deficits exist with this approach. Fifth, 48 sessions may not be enough dose to detect the beneficial effects of the CCT as an add-on intervention to the medication treatment. However, much longer treatment periods decrease acceptability of the intervention. Sixth, our analyses were based on completers and not intent to treat to avoid penalizing CCT results with subjects with low adherence. However, if this approach produces any bias it would be in the direction of increasing possibility of detecting effects of treatment.

Conclusion

We found neither significant effects on ADHD symptoms nor on cognitive performance, indicating no impact of this cognitive training protocol on the disorder. More multisite studies are recommended to assess ways to improve CCT treatment effects both on ADHD symptoms and neuropsychological tasks.

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Table 1 – Demographic and clinical characteristics (n=45)

		Group		p-value
		Cases (n=24)	Non-active group (n=21)	
Gender, n (%)				
	Male	13 (54.2)	14 (66.7)	0.39
Age, m (SD)		10.41 (1.74)	10.95 (1.85)	0.32
IQ, m (SD)		99.18 (11.52)	97.92 (11.3)	0.71
Socio-economic level, n (%)				0.34
	A	6 (25)	5 (23.8)	
	B	9 (37.5)	12 (57.1)	
	C	9 (37.5)	4 (19.1)	
ADHD subtype, n (%)				0.47
	Inattentive	10 (41.7)	11 (52.4)	
	Combined	14 (58.3)	10 (47.6)	
Comorbidities (KSADS), n (%)				
	Anxiety	8 (33.4)	2 (9.5)	0.19
	Conduct disorder	1 (4.2)	0	0.34
	Oppositional Defiant Disorder	10 (41.7)	5 (23.8)	0.20
	Mood disorder	0	0	
	Others (enuresis/Tic disorder /Tourrete)	8 (33.4)	3 (14.3)	0.13
Baseline SNAP scores, m (SD)				
Parents	Inattentive	1.59 (0.36)	1.70 (0.51)	0.40
	Total	1.3 (0.34)	1.4 (0.56)	0.43
Teachers	Inattentive	1.33 (0.61)	1.39 (0.56)	0.75
	Total	1.04 (0.54)	1.04 (0.47)	0.99

Abbreviations: n, number of participants; m, mean; SD, standard deviation. Socio-economic level - the economic strata would correspond approximately to: A – upper class; B – high middle and middle classes; C – low middle class and vulnerable.

Table 2. NIH battery

		CCT group (n=23)	Non-active group (n=21)	Total	Group x Time-effect	g[CI95%]	*p*
		mean [CI95%]	mean [CI95%]	mean [CI95%]			
GNG[1]	Baseline	63.51 [56.24; 70.78]	57.84** [49.60; 66.08]	60.68 [55.18; 66.17]	χ^2 (1)= 0.78	0.46[-0.14;1.07]	0.38
	Endpoint	67.96 [59.86; 76.06]	58.79** [50.70; 66.88]	63.37 [57.65; 69.10]			
	Total	65.74 [58.70; 72.77]	58.31 [50.49; 66.14]				
WM[2]	Baseline	19.86*** [16.45; 23.98]	15.60****[13.08; 18.61]	17.60 [15.47; 20.02]	χ^2 (1)= 3.41	0.13[-0.48;0.74]	0.065
	Endpoint	21.43*** [16.58; 27.69]	22.95**** [19.34; 27.23]	22.18 [19.01; 25.87]			
	Total	20.63 [16.86; 25.24]	18.92 [16.89; 21.20]				
FK RT[2]	Baseline	763.63 [658.26; 885.87]	699.47 [622.06; 786.52]	730.85 [664.87; 803.37]	χ^2 (1)= 0.003	0.3[-0.3;0.9]	0.96
	Endpoint	728.32 [645.58; 821.68]	669.53 [600.99; 745.89]	698.31 [644.01; 757.18]			
	Total	745.77 [656.53; 847.14]	684.34 [619.49; 755.98]				
FK RT SD[2]	Baseline	214.49* [141.06; 326.13]	172.53 [117.67; 252.96]	192.37 [144.84; 255.48]	χ^2 (1)= 0.54	0.01[-0.58;0.61]	0.46
	Endpoint	166.15* [116.80; 236.35]	168.02 [120.47; 234.32]	167.08 [131.13; 212.89]			
	Total	188.78 [136.22; 261.61]	170.26 [128.60; 225.40]				

For all measures, it was presented the mean and confidence interval.
Abbreviations: CCT group, cognitive training group; n, number of participants with valid scores according a cut-off values for each NIH tests; GNG, Go/No-Go test; WM, working memory test; FK RT, Flanker test reaction time; FK RT SD, flanker test reaction time standard deviation; χ^2 , Wald chi-square; g, Hedges effect-size. $p \leq 0.05$. 1 – Normal distribution; 2 – Gamma distribution.
* n=22;** n=19; ***n=21; ****n=20

Fig. 1. Flow-chart of enrollment

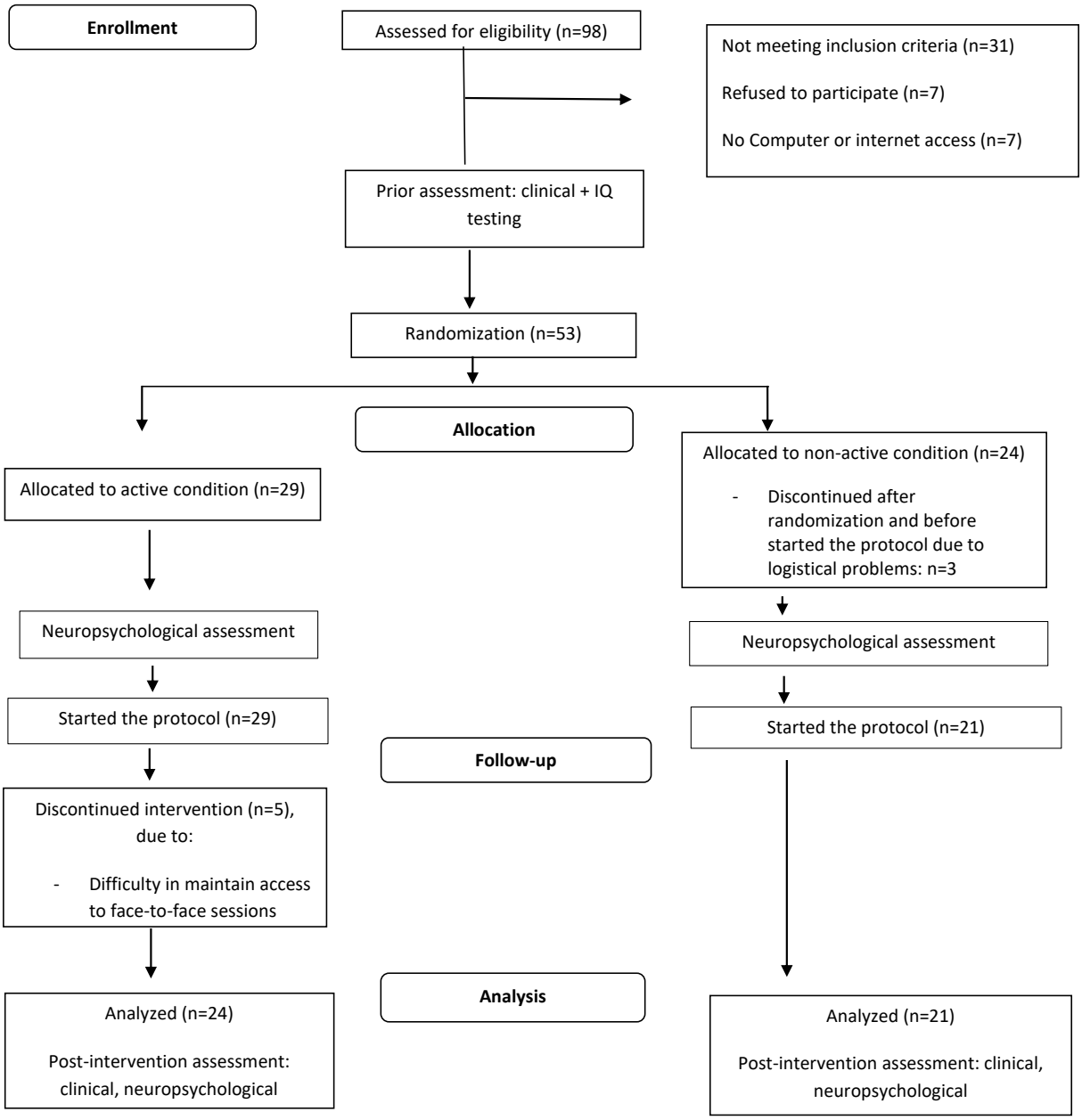
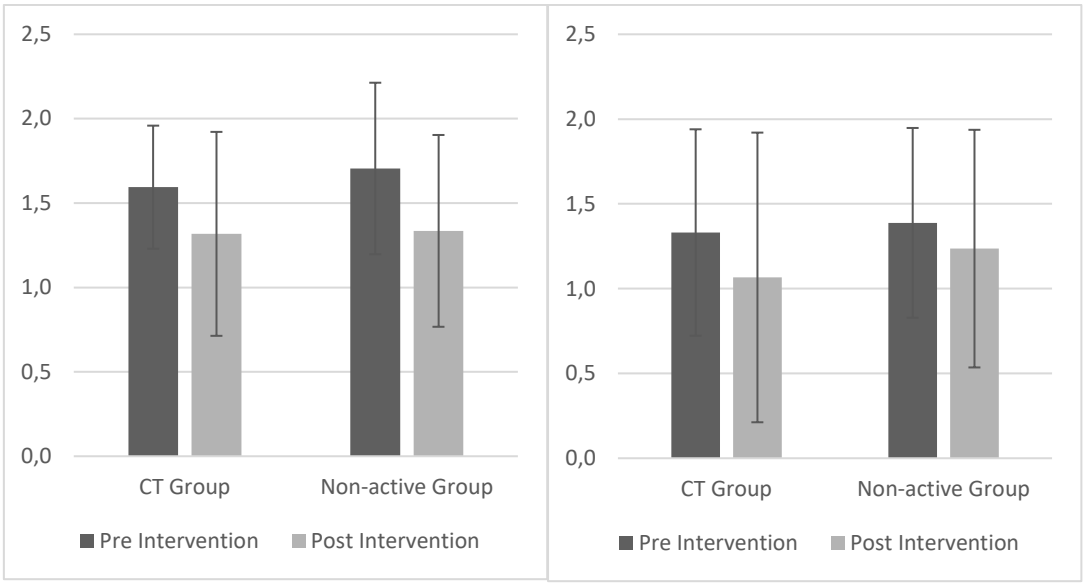


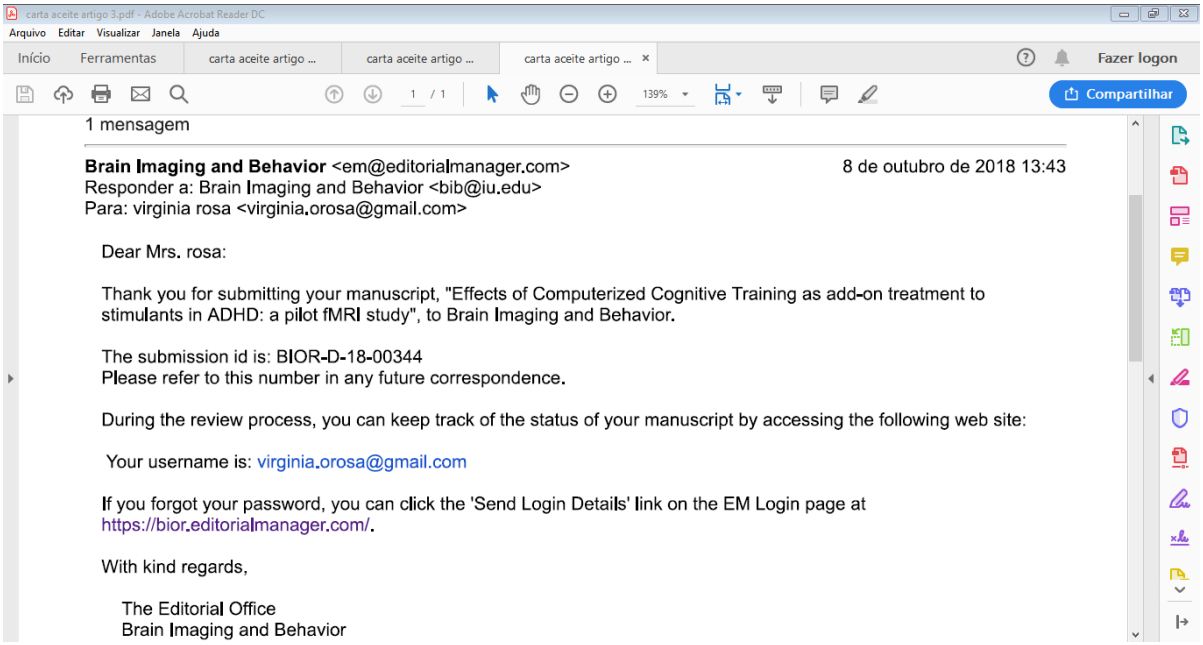
Fig. 2. a. Baseline and Post-intervention SNAP-IV Inattention Parent Score in CT and Non-active groups (p=0.58; g=0.03); b. Baseline and Post-intervention SNAP-IV Inattention Teacher score in CT and Non-active groups (p=0.58; g=0.21)

a. b.



7.3. Artigo 3

7.3.1. Carta de submissão



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7.3.2. Manuscrito

Effects of Computerized Cognitive Training as add-on treatment to stimulants in ADHD: a pilot fMRI study.

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Abstract

Introduction: The neurofunctional effects of Cognitive training (CT) are poorly understood. Our main objective was to assess fMRI brain activation patterns in children with ADHD who received CT as an add-on treatment to stimulant medication.

Methods: We included twenty children with ADHD from a clinical trial of stimulant medication and CT (10 in medication + CT and 10 in medication + non-active training). Between-group differences were assessed in performance and in brain activation during 3 fMRI paradigms of working memory (N-back: 0-back, 1-back, 2-back, 3-back), sustained attention (Sustained Attention Task - SAT: 2s, 5s and 8s delays) and inhibitory control (Go/No-Go).

Results: We found significant group x time x condition interactions in working memory (WM) and sustained attention on brain activation. In N-back, decreases were observed in the BOLD signal change from baseline to endpoint with increasing WM load in the right insula, right putamen, left thalamus and left pallidum in the CT compared to the non-active group; in SAT - increases in the BOLD signal change from baseline to endpoint with increasing delays were observed in bilateral precuneus, right insula, bilateral associative visual cortex and angular gyrus, right middle temporal, precentral, postcentral, superior frontal and middle frontal gyri in the CT compared to the non-active group.

Conclusion: CT in ADHD was associated with changes in activation in task-relevant parietal and striato-limbic regions of sustained attention and working memory. Changes in brain activity may precede behavioral performance modifications in working memory and sustained attention, but not in inhibitory control.

Key-words: ADHD, methylphenidate, cognitive training, fMRI, neuroimage

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood and adolescence (Buitelaar & Medori, 2010) with an estimated prevalence of around 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). It is characterized by age-inappropriate symptoms of inattention, impulsivity and hyperactivity, resulting in several impairments to the individuals and their families (American Psychiatric Association, 2013), as well as substantial economic impact to society (Maia et al., 2016).

There is evidence suggesting an association between ADHD and several neurocognitive deficits mainly on executive functions such as working memory, attention and inhibitory control (Coghill et al., 2014). fMRI studies have furthermore shown that ADHD patients have underactivation in task-relevant frontal, striatal and parietal regions during performance of these tasks (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Norman et al., 2016; Rubia, 2018). These deficits may lead, as the nuclear symptoms of ADHD, to important impairments to the patient´s functioning, especially in academic performance (Bikic, Christensen, Leckman, Bilenberg, & Dalsgaard, 2017).

Cognitive training (CT) is a non-pharmacological approach that could cover both clinical symptoms and the co-existent neurocognitive deficits, becoming an alternative tool to treat the disorder. It usually consists of a computer-delivered intervention of several game-like activities that is aimed to improve cognitive functions (Bikic et al., 2017) through strengthening of brain networks underlying these functions (Cortese et al., 2015). There is evidence that CT improves cognitive function, including enhancements on WM performance (Chacko et al., 2013; Gray et al., 2012; Green et al., 2012). The effects of CT on reducing ADHD symptoms are more controversial and a recent meta-analysis concluded that the effects of cognitive training on ADHD symptoms is only significant for unblinded raters; the effects were substantially reduced when considering probably blinded raters or when an active control arm was used, showing the need for more studies on this topic using more rigorous designs (Cortese et al., 2015). However, CT approaches targeting several cognitive functions relevant to ADHD have been shown to be more promising (Cortese et al., 2015).

Another way to assess if cognitive training could be an effective approach for ADHD would be demonstrating that this training leads to changes in brain activity. It has been demonstrated that WM training, for instance, can alter brain function, including increase in WM-related brain activity in several frontal, parietal and temporal lobe regions in ADHD patients (Stevens, Gaynor, Bessette, & Pearlson, 2016). Moreover, a fMRI study using a motor inhibition task to assess the benefits of a CT program targeting several cognitive domains observed increased brain activation after the training in the left orbitofrontal, right middle temporal, left superior frontal and right inferior frontal cortices. During

another paradigm – an attention task - the same study found increased activity in the right superior posterior cerebellum post treatment (Hoekzema et al., 2010). Despite these promising few studies, the functional correlates of changes in brain activity following CT compared to a non-active control condition remains largely understudied. Those studies could provide clues on the mechanisms by which cognitive training changes brain function in ADHD patients.

In this fMRI study, we tested the effects of a CT program that targets several brain cognitive functions at the same time (i.e. sustained and selective attention, working memory, inhibitory control, cognitive flexibility and category formation) in ADHD children and adolescents. For this purpose, we selected three fMRI tasks – a Sustained Attention Task (SAT), a working memory task (N-back) and a motor inhibition task (Go/No-Go) - that encompass important cognitive domains related to ADHD and trained with the CT program. These tasks are consistently associated with reduced activation in ADHD patients relative to healthy controls in inferior and dorsolateral prefrontal, striato-thalamic and parietal regions (Chantiluke et al., 2015; Christakou et al., 2013; Norman et al., 2017; Smith, Taylor, Brammer, Toone, & Rubia, 2006). We hypothesized that CT would modulate activity in neural structures targeted by the fMRI-paradigms, in particular the dorsolateral prefrontal cortex (DLPFC) for WM and SAT, the inferior frontal cortex (IFC) for inhibition and parietal regions for all 3 tasks, and that CT would lead to better performance during the neuropsychological tasks.

MATERIALS AND METHODS

Study design and participants

The study was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (HCPA) – (CAAE 25048913.8.0000.5327) and was registered in the Clinical Trials database (NCT02184598). A parent written informed consent and child assent were obtained before the initial assessment. No monetary compensation was offered to the patients for participating in the study.

The current fMRI study is part of a randomized controlled clinical trial comparing the effects of an add-on cognitive training program *versus* a non-active training on ADHD core symptoms and neuropsychological performance. Participants were recruited from the Attention-Deficit/Hyperactivity Disorder Outpatient Program – ProDAH (located at the University hospital [HCPA] of the Federal University of Rio Grande do Sul, Porto Alegre, Brazil) and from public and private schools in the same city. A total of 53 participants were randomized to one of the two groups using a minimization method and following the guidelines of the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Higgins et al., 2011), resulting in 29 subjects in the CT group and 24 individuals in the non-active group. There

was a loss of n=8 participants – five belonging to CT group – due to logistical problems (difficulty in maintain access to face-to-face sessions). From the full sample of completers, we selected 20 subjects balanced by demographic and clinical characteristics – 10 from each group - to participate in the fMRI acquisition before and after the trial. A total of 20 ADHD subjects, of both genders, all medicated with stimulants (at least 4 weeks of the same type and dosage of stimulant treatment before start of the intervention), aged 9 to 13 years old, with an IQ≥80 were included.

The inclusion criteria for the current study were as follows: age 6-13 years; diagnosis of ADHD according to the DSM-IV criteria; current use of a stable dose of stimulants; residual symptoms of inattention despite the maximum dose of stimulants; fluency in Portuguese; and a computer and internet access at home or school. Participants were excluded if they had a non-stabilized comorbid psychiatric condition requiring any additional treatment; an estimated IQ score lower than 80; any change in the dose of stimulant treatment, or the inclusion of any other medication and/or psychosocial treatment in order to control ADHD symptoms during the protocol. Additional exclusion criteria were MRI-specific contraindications (e.g. metal implants, phobia).

Treatment

The Computerized cognitive training program (ACTIVATE™) is composed of six different games, designed to address different neuropsychological domains such as speed processing, sustained, selective and divided attention, visual-spatial working memory, category formation, cognitive flexibility and inhibitory control. The program starts at a basic level, going through gradual and more complex levels of the tasks and adapting the degree of difficulty according to the participant's performance during the task. Throughout the sessions, participants perform several different cognitive tasks like completing patterns, assigning objects into categories, holding sequences in working memory, responding to some stimuli but not others (motor and interference inhibition), and task-switching. More information about ACTIVATE™ can be found in our published protocol (Rosa et al., 2017) or at the c8sciences website (http://www.c8sciences.com/about /games/).

For the non-active intervention, we created an online platform with educational issues composed by videos and questions related to school content. Each package was stratified according to age groups (6-7, 8-9, 10-11, 12-13y) and school grade. The material was related to general knowledge, Brazilian-Portuguese grammar, history and geography. More information can be found in our published protocol (Rosa et al., 2017), and the content of this platform is available in a video at www.youtube.com/watch?v=dAv6Y83BDqc, where subtitles in English can be triggered at the bottom of the video as indicated. By implementing this approach, we aimed to include a potential benefit for

the subjects assigned to the control group (such as school reinforcement) without directly stimulating cognitive functions.

Both interventions had online access and were composed by 48 sessions of 30 minutes duration each. The proposed protocol length was four sessions per week, always under supervision of the parents (at home) or a tutor (at school). We considered the completion of at least 85% of the sessions as an adequate implementation of the Computerized Cognitive Training (CCT) program.

fMRI Tasks

All subjects were submitted to a practice task prior to the fMRI scan in a mock scanner, in order to get accustomed to the scanning environment and to be trained in the fMRI tasks, avoiding unsuccessful scans.

fMRI task - sustained attention task: this is an event-related parametric vigilance task with 3 different difficulty loads of sustained attention (Christakou et al., 2013; Murphy et al., 2014; Norman et al., 2017). In the 10 min 48 s sustained attention task, participants were asked to respond as quickly as possible to the appearance of a visual timer via a right-hand button response within 1 s. The visual stimuli appear either after a short, predictable consecutive delays of 0.5 s, in series of 3-5 stimuli (240 in total: 20 blocks of 5, 20 blocks of 4 and 20 blocks of 3 consecutive stimuli) or after an unpredictable time delays of 2, 5 or 8 s (20 delays of 2s; 19 delays of 5s and 20 delays of 8s), pseudo-randomly interspersed into the blocks of 3-5 delays of 0.5 s. The long, infrequent, unpredictable delays place a higher load on sustained attention/vigilance, whereas the short, predictable 0.5 s delays are typically anticipated placing a higher demand on sensorimotor synchronization. Please, see figure 1 for additional information.

fMRI task - WM task (n-back): the block design 9 min 58 s WM task consists of four load factors ("0-back" to "3-back") (Chantiluke et al., 2015; Cubillo et al., 2014). It requires participants to respond on every trial by indicating the letter shown "n" trials earlier. During 1-back, 2-back and 3-back conditions, subjects are presented with series of letters (A-Z) (1 s duration, inter-trial interval = 2 s) and must respond with their right thumb using a button box whenever the letter presented is the same as one, two or three before it, respectively (e.g. 3-back: N/M/L/H/M). This task requires simultaneous storage and processing of the material presented. The 0-back condition served as control condition, when subjects must respond to each "X" that appears on the screen. The task consists of 12 randomized blocks (3 blocks of each N-back condition). Before each block, written instructions are shown to inform which condition is next. In each of the WM blocks of 45 s duration (1 s stimuli + 2 s interstimulus interval -ISI) only one WM condition is presented and contains 15 stimuli: 3 targets and

12 non-targets. Each condition is presented 3 times. Performance data were recorded during scanning. Please, see figure 1 for additional information.

fMRI task - Go/No-Go (GNG) task: the event-related 8 min 32 s Go/No-Go task consists of frequent arrows (160 stimuli, 76.9%, with 500 ms duration) pointing to either the left or right direction (Go signals) that appear in the screen with a mean interstimulus interval of 1.8 s (jittered 1.6 s / 1.8 s / 2 s). Infrequently, arrows pointing up (24 stimuli, 11.5%, with 500ms duration) (No-Go signals) or arrows slanted to the right or left with a 45° angle (24 stimuli, 11.5%, with 500ms duration) (oddballs signals) appear. A button response had to be selectively executed to Go or oddball stimuli or inhibited to No-Go signals. The oddball trials control for the low frequency of the No-Go trials and thus the oddball attentional capture effect (Rubia et al., 2006; Smith et al., 2006). Please, see figure 1 for additional information.

fMRI data acquisition

Neuroimaging data was collected on a GE HDxt 3T scanner using an eight-channel radio-frequency (RF) head coil. At the beginning of each scanning session, a single, high resolution T1-weighted [TE (echo time) = 2.18ms, TR (repetition time) = 6.1ms, flip angle = 11°, number of excitations (NEX) = 1, slice thickness = 1mm, FOV (field of view) = 256mm, resolution = 256 x 256, 196 slices] anatomic image was collected. A total of three fMRI runs were conducted. All runs were collected using a single-shot, gradient-echo planar pulse BOLD sequence [TE = 30ms, TR = 2000ms, flip angle = 90°, FOV = 220mm, matrix size = 64 x 64]. Twenty-nine interleaved, sagittal 3.6mm thick slices with a 0.3mm gap were selected to provide whole-brain coverage (in plane resolution: 3.44 x 3.44 mm^2). For each paradigm, there were a total of 256, 299, 324 volumes collected for the Go/No-Go, N-Back and Sustained Attention Task, respectively. The first three volumes were subsequently eliminated to account for T1 equilibrium effects.

fMRI preprocessing

All preprocessing and statistical analyses were carried out in the Analysis of Functional NeuroImages (AFNI) toolbox (R W Cox, 1996). Preprocessing was performed using the afni_proc.py function which included slice-time and motion correction. The motion corrected fMRI images were co-registered to the individual´s anatomical images (T1). The T1 images were segmented into the gray matter, white matter and cerebrospinal fluid, as well as spatially normalized using a nonlinear registration to a standard space – Haskins Pediatric Template (Molfese, Peter J., Daniel Glen, Laura Mesite, Kenneth R. Pugh, 2015). Using the same registration parameters for the T1 image, fMRI images were registered to the template space and then smoothed using a 6mm FWHM Gaussian filter.

Censoring was performed on time-points that had functional imaging outliers above 0.15 (Robert W. Cox, 2002).

Statistical Imaging Data Analysis

All neuroimaging statistical results were corrected for multiple comparisons using AFNI's 3dClustSim function (Robert W. Cox, Chen, Glen, Reynolds, & Taylor, 2017). Residuals from multiple regression analysis were used to calculate the correction for multiple comparisons. Neuroimaging results were considered statistically significant for the adjusted p-value (α<0.05), using a threshold of p<0.005 and minimum cluster size of 2430 µL for Go/No-Go task and 2376 µL for N-Back and SAT.

Go/No-Go Task: Using multiple regression, the hemodynamic response function was fitted for each of the five conditions; go-left, go-left-up, go-right, go-right-up, and up. The go-left and go-right conditions were labeled as Go conditions, the go-right-up and go-left-up were labeled as Oddball conditions, and the Up was labeled as the No-Go condition. With an Analysis of Variance (ANOVA), the within subject interaction of time (baseline and endpoint) and condition (No-Go and Oddball) was calculated. A between subject interaction was also calculated comparing groups (active x non-active group).

N-Back Task: In the N-back task each of the Working Memory Loads (WML) was fitted to a hemodynamic response function, including the N-0 back, N-1 back, N-2 back and N-3 back conditions. The N-0 back condition was modeled as a baseline condition and hence not used in the ANOVA. The contrast 0-back vs. each condition was then used as the main dependent variable of the analysis to test for time, group, condition and time x group x condition interactions in the model.

Sustained Attention Task: For the sustained attention task, the hemodynamic response function was fitted for each of the Inter Stimulus Intervals (ISI) (0.5, 2.0, 5.0 and 8.0 seconds). The 0.5 ISI was modeled as the baseline condition. The interaction between Group x Time x ISI was calculated in a 2x2x3 (Group x Time X 3 long delays) ANOVA.

Performance data analysis

Performance data were analyzed using mixed design ANOVA. In all analyses, we tested the effects of group (between-subject variable; 2 levels), time (within-subject variable; 2 levels) and time by group interactions as independent variables for all the models tested in the study. In SAT another within subject variable was added, delay (3 levels), as well interactions between delay, time and group; dependent variables were mean reaction time, intrasubject deviation of reaction time, omission and premature errors. In Go/No-Go the dependent variables were proportion of commission errors. In N-

back another within subject variable was added, working memory load (3 levels), as well interactions between working memory load, time and group; dependent variables were percentage of correct responses.

Effect sizes were quantified using omega squared (ω^2). Interpretations for ω^2 have been suggested that values of 0.01, 0.06 and 0.14 represent small, medium and large effect sizes respectively (Kirk, 1996).

RESULTS

Demographic and clinical characteristics

The mean age for the total sample was 11.4 years (SD = 1.5) and 55% were male. Table 1 presents the demographic and clinical characteristics of the study sample. There were no significant group differences for age, gender, IQ, socio-economic status (SES), ADHD subtype and comorbidities. The analysis was conducted with 19 subjects (10 cases and 9 controls) on the SAT paradigm; 18 subjects (10 cases and 8 controls) on the WM paradigm and 18 subjects on the GNG (9 cases and 9 controls). The images from one subject on SAT and two subjects on WM, all belonging to the non-active group, were lost due to excess of head-movement during the exam as well as two subjects on GNG each belonging to one of the groups.

Behavioral performance data

Working memory performance

Across all participants, there was a WM load effect in mean accuracy ($F_{3,51}$=51.5, p<0.001), showing that accuracy decreased with increasing WM load (0-back=.94, 1-back=.79, 2-back=.60, 3-back=.47) and a main effect of time ($F_{1,17}$=4.81, p=0.043) showing an overall improvement in accuracy over time (baseline=.66, endpoint=.75), but neither a main effect of group, nor of two and three-way interactions with group and time were significant (all p-values>0.05). See table 2.

Inhibitory-based Executive Function Performance

No significant time or time by group interactions emerged for commission errors (all p-values > 0.05). See table 2.

Sustained Attention

There was a significant delay-effect in accuracy, meaning that performance decreased with larger delays, except for 8s delay, for which performance increased. We also detected a three-way

interaction between time, group and delay, regarding mean reaction time. This meant that there was an improvement with treatment across time if compared to non-active treatment only in the 5s delay. No other main effects or interactions were found to be significant (p-values >0.05). See table 2.

Neuroimaging results

WM

There was a group x time x WM-load interaction effect in two clusters in the N-back task, 1) in the right insula and putamen (Brodmann Area – BA – 13), and 2) in left thalamus and pallidum ($p<0.001$). (see table 3). The interaction reflected decreases in the BOLD signal change from baseline to endpoint with increasing working memory load in the cognitive training group, which contrasted with patterns from the non-active group. See figure 2 and 3.

SAT

We found four clusters of activation in SAT task presenting a time x group x ISI interaction, which include: 1) right precuneus, angular gyrus, middle temporal lobe and associative visual cortex (BA 19, 39); 2) right postcentral and precentral gyrus and right insula (BA 3, 6, 13); 3) right superior frontal and middle frontal gyrus (BA 8, 9) and 4) left precuneus, associative visual cortex and angular gyrus (BA 19, 39) ($p<0.001$)(see table 3). The interaction reflected increases in the BOLD signal change from baseline to endpoint with increasing delays in the cognitive training group, which contrasted with patterns from the non-active group. See figures 2 and 3.

GNG

No cluster emerged from the analyses involving the task of inhibitory control.

DISCUSSION

The purpose of this study was to assess differences in brain activity from pre to post-intervention between cognitive training and a non-active intervention in children with ADHD on stimulant treatment. To the best of our knowledge, this is the first fMRI study with a rigorous design comparing the effects of cognitive training as an add-on treatment to stimulants on brain activation in ADHD.

Regarding the brain activation patterns, during the sustained attention task, our cognitive training program resulted in greater activation relative to the control group with increasing levels of delay, reflecting sustained attention load, in several right hemispheric brain regions that are crucial for

sustained attention such as dorsolateral prefrontal cortex, and inferior and superior parietal regions. These findings possibly indicate that the CT group activated more intensively right fronto-parietal brain areas that mediate sustained attention after the intervention.

Previous research with the same task showed that with increasing delays there is increased activation in healthy controls of a typical sustained attention network including dorsolateral prefrontal cortex (DLPFC) and right inferior prefrontal cortices, cingulate, supplementary motor area, parieto-temporal regions, cerebellum, basal ganglia, thalamus and hippocampus (Christakou et al., 2013; Murphy et al., 2014). Furthermore, dorsolateral prefrontal, striato-thalamic and parietal regions were underactivated in ADHD patients relative to healthy controls (Christakou et al., 2013). The findings of increased activation after the CT intervention in right fronto-parietal regions during sustained attention may hence potentially reflect a shift towards the norm, given that they have been found to be underactivated during the same task relative to healthy controls. The findings of upregulation of dorsolateral fronto-parietal regions after CT are also in line with and extend previous findings of increased activation in ADHD children after CT in task-relevant regions during other tasks. Thus, a fMRI study found that cognitive training that exercises working memory, cognitive flexibility, attention, planning and problem solving – in unmedicated ADHD children elicited increases in activity after cognitive training in the right superior posterior cerebellum during an attention paradigm and increased activity in orbitofrontal, superior and inferior frontal, and middle temporal cortices during an inhibition paradigm (Hoekzema et al., 2010). Interestingly, a fMRI study that investigated the effects of methylphenidate on brain activation in ADHD children during a sustained attention task found that medication, compared to placebo, enhanced activation in inferior frontal, premotor, inferior parietal and cingulate cortices as well as cerebellum and precuneus (Rubia et al., 2009). These findings suggest that cognitive training and psychostimulant medication might act on similar neural circuitry of sustained attention. No other fMRI study has assessed the effects of pharmacological or non-pharmacological interventions on brain activation during a sustained attention task in ADHD individuals. The findings of enhanced activation in task-relevant fronto-parietal regions after the intervention in the CT compared to the control group hence suggests that complex training of a range of executive functions appear to improve the underlying fronto-parietal neurofunctional substrates of sustained attention in ADHD.

On the other hand, during the working memory paradigm, the CT group showed decreased activation during the 3-back condition in subcortical regions, including the insula and striato-thalamic regions. It is possible that participants, after the intervention, no longer needed to activate these brain areas to maintain cognitive performance even with the increase of WM load – demonstrating, perhaps, greater efficiency. On the other hand, insula and striato-thalamic regions are not key part of the WM

network (Andre, Picchioni, Zhang, & Toulopoulou, 2015; Braunlich, Gomez-Lavin, & Seger, 2015). The anterior insula in particular has been associated with increased saliency processing in ADHD and there is evidence for abnormal resting state connectivity of the salience network with the cognitive control and attention networks in ADHD (Cai, Chen, Szegletes, Supekar, & Menon, 2018). Although not considered classical default mode network (DMN) regions, posterior thalamus and striatum form part of the DMN in the automatic fMRI meta-analyses generated in the neurosynth database under the search term: "default network" (www.neurosynth.org) (Yarkoni, Poldrack, & Nichols, 2011). Furthermore, children and adolescents have an immature DMN, and a recent meta-analysis of the DMN in children includes the thalamus, striatum and posterior insula (Mak et al., 2017). The DMN is thought to reflect mind-wandering and has been shown to be less deactivated in ADHD children during cognitive tasks (Rubia, 2018), in particular during the most difficult conditions of tasks of working memory or the same sustained attention task (Christakou et al., 2013; Cubillo et al., 2014). It is hence possible that the CT downregulated areas of saliency processing (insula) and/or insula-thalamic areas of the default mode network. A study that tested fMRI effects after a working memory intervention in ADHD adolescents, showed increased less recruitment of anterior insula, medial frontal gyrus, and inferior frontal gyrus with increasing WM load, but increased recruitment in several other regions including inferior/middle frontal gyri, superior/middle temporal gyri, anterior cingulate and inferior parietal cortex (Stevens et al., 2016). The upregulation findings in fronto-parietal regions are more in line with the upregulation findings we observed in the sustained attention task. It is possible that findings of upregulation or downregulation effects after CT may be task- or region-dependent. Unfortunately, we did not include a control group in the study design which would have been helpful to establish whether the respective up and downregulation effects in the two tasks represented a shift towards the norm.

Regarding the cognitive training effects on cognitive performance, in our study, we found improvement on SAT in the CT group only on the middle load difficulty condition, the 5s delay. Between-group gains did not occur for both WM and GNG tasks. There are several studies demonstrating the effects of pharmacological and non-pharmacological approaches on cognitive functions during similar tasks with mixed results depending to the specific domain and measures used (Sonuga-Barke, Brandeis, Holtmann, & Cortese, 2014). A fMRI study that assessed the effects of a cognitive training targeting multiple neuropsychological domains in ADHD children, using an inhibition and attentional paradigm, indicated reductions in omission errors on an inhibition paradigm and reduction in incorrect targets and target omissions on a selective attention paradigm for participants in the CT group, albeit not Bonferroni-corrected (Hoekzema et al., 2010). Another fMRI study, using the same CT program in ADHD, found no significant differences in task-performance post-intervention

during a task that assessed attention performance (Hoekzema et al., 2011). Our results are in agreement with another study that assessed the neuropsychological changes of a cognitive training program in ADHD using a GNG paradigm which found no significantly reaction times change after the intervention (Siniatchkin et al., 2012). Regarding non-pharmacological approaches, studies have shown some benefits on sustained attention performance (Bigorra, Garolera, Guijarro, & Hervás, 2016; Johnstone et al., 2012; O'Connell, Bellgrove, Dockree, & Robertson, 2006) which is in line with our results. On tasks that assessed working memory, regarding cognitive training, there are studies that have shown some benefits of interventions targeting working memory plus inhibitory control (Johnstone et al., 2012) and working memory alone (Bigorra et al., 2016) on working memory measures. A recent study that assessed the effects of working memory training on brain function in ADHD adolescents found significant improvement on WM tests after the intervention (Stevens et al., 2016). To our knowledge there is no study that used exactly the same paradigms that we used to test the neuropsychological effect of CT.

Our study has some strengths. The sample was derived from a larger study with a randomized controlled trial design that was never used in any add-on study for CT in ADHD. Our CT protocol was not restricted to one or two cognitive abilities, but targeted several cognitive domains. However, the results reported here should also be considered in the light of some limitations. The sample size was small and particularly underpowered to assess task performance changes and this could explain why we did not find substantial differences in task performance and limited findings on brain activation only in two of the fMRI tasks. Similarly, the difference found between groups only at 5s delay in the SAT is more likely to reflect a spurious finding than a real effect due to the lack of a clear pattern of differentiated response between groups with the increase in demand.

Conclusion

To our knowledge, this is the first fMRI study to test neural effects of a cognitive training program acting as an add-on approach to stimulant treatment in ADHD. Our results extend previous findings that training cognitive functions in ADHD can alter brain function underlying the performance on related tasks than the trained ones. These brain modifications after CT may occur earlier and before neuropsychological changes take place. Studies with larger sample sizes are needed to replicate the findings, and to further elucidate the effects of cognitive training as an add-on strategy to improve brain function in ADHD children.

Conflict of interests:

Luis A. Rohde has received honoraria, has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Medice, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He also received travel awards for taking part of the 2015 WFADHD and 2016 AACAP meetings from Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Janssen-Cilag, Novartis, and Shire. Dr. Carlos Renato Moreira-Maia has received financial research support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); development of educational materials for Libbs, Novartis and Pfizer; has received travel and accommodation support for a speaker training and participated in the development of a cell phone applicative for Shire; has received travel, accommodation and registration support to the fourth and fifth World Congress on ADHD from the World Federation of ADHD. Other authors do not have conflicts to declare. Dr. Schmitz has received financial support from Shire Laboratories to participate in international meetings. Katya Rubia has received grants for other projects from Shire and Lilly and speaker's honoraria from Shire, Lilly, Medice and Novartis.

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Table 1 – Demographic and clinical characteristics (n=20)

		Group		p-value
		CT (n=10)	Non-active group (n=10)	
Gender, n (%)				
	Male	5 (50)	6 (60)	0.65
Age, m (SD)		10.9 (1.6)	11.9 (1.3)	0.14
IQ, m (SD)		99.15 (13.09)	100.55 (12.62)	0.81
Socio-economic level, n (%)				0.45
	A	3 (30)	3 (30)	
	B	4 (40)	6 (60)	
	C	3 (30)	1 (10)	
ADHD subtype, n (%)				0.65
	Inattentive	4 (40)	6 (60)	
	Combined	5 (50)	5 (50)	
Comorbidities (KSADS), n (%)				
	Anxiety	3 (30)	1 (10)	0.52
	Conduct disorder	1 (10)	0	0.3
	Oppositional Defiant Disorder	5 (50)	3 (30)	0.36
	Others (enuresis/Tic disorder /Tourrete)	4 (40)	2 (20)	0.32
Baseline SNAP scores, m (SD)				
Parents	Inattentive	1.65 (0.34)	1.82 (0.38)	0.31
	Total	1.36 (0.28)	1.51 (0.41)	0.33
Teachers	Inattentive	1.31 (0.41)	1.42 (0.62)	0.65
	Total	1.06 (0.45)	1.1 (0.56)	0.85

Abbreviations: n, number of participants; m, mean; SD, standard deviation; CT, cognitive training

Table 2. Mixed-effects analysis of variance investigating the effects of time, group and their interactions for cognitive performance indicators

	ANOVA	*p*	ω^2
Working Memory (N-back)			
Time	F(1,17)=4.81	0.043	0.16
WM load (accuracy)	F(3,51)=51.5	<.001	0.72
Time x group	F(1,17)=0.91	0.35	0.05
WM load x group	F(3,51)=1.19	0.32	0.003
Time x WM load x group	F(3,51)=1.8	0.16	0.04
Inhibitory Control (GNG)			
Mean RT			
Time	F(1,17)=3.77	0.07	0.12
Time x group	F(1,17)=0.14	0.71	0
SD RT			
Time	F(1,17)=1.57	0.22	0.03
Time x group	F(1,17)=0.4	0.53	0
Accuracy			
Time	F(1,17)=0.63	0.43	0
Time x group	F(1,17)=0.13	0.72	0
Sustained Attention (SAT)			
Mean RT			
Time x group	F(1,18)=0.32	0.57	0
Delay x group	F(3,54)=1.24	0.3	0.006
Time x delay x group	F(3,54)=3.04	0.037	0.09
SD RT			
Time x group	F(1,17)=0.13	0.72	0
Time x delay x group	F(3,51)=0.8	0.49	0
Accuracy			
Time x group	F(1,18)=0.83	0.37	0
Delay	F(3,54)=65.87	<.001	0.75
Delay x group	F(3,54)=2.04	0.12	0.01
Time x delay x group	F(3,54)=1.11	0.35	0.006

Notes: Mixed-effects analysis of variance investigating the effects of time, group (and task load) and their interactions with cognitive performance indicators (accuracy and reaction time). Effect sizes were quantified using omega squared (ω^2). Abbreviations: RT, reaction time; SD, standard deviation.

Table 3. Clusters exhibiting the main interaction effect for Sustained Attention Task (SAT) and the Working Memory (WM) task

	Region	BA	Peak MNI coordinates			Cluster Size (Voxels)	Cluster Size (µL)	ANOVA (3-way)	p
			x	y	z				
SAT									
1	R Precuneus; R Angular and Middle Temporal Gyrus; R associative visual cortex	19; 39	34.5	-74.5	36.5	224	6048	F (1;17)= 16.9	<.001
2	R Postcentral Gyrus; R Precentral Gyrus; R Insula	3; 6; 13	37.5	-17.5	30.5	192	5184	F (1;17)= 12.27	<.001
3	R Superior Frontal Gyrus; R Middle Frontal Gyrus;	8; 9	28.5	27.5	51.5	190	5130	F (1;17)= 22.46	<.001
4	L Precuneus; L associative visual cortex; L Angular Gyrus	19; 39	-37.5	-74.5	36.5	109	2943	F (1;17)= 14.72	<.001
WM									
1	R insula; R Putamen	13	34.5	3.5	15.5	162	4374	F (1;16)= 8.82	<.001
2	L Thalamus; L Pallidum	-	-1.5	-14.5	3.5	112	3024	F (1;16)= 9.24	<.001

Note: BA: Brodmann Area; R, right; L, left; Cluster numbers correspond to numbering in Figures 2 and 3.

Fig. 1 Schematic representations of fMRI tasks. 1A - Go/No-Go (GNG). Participants had to press the left or right button according to the direction of the arrows displayed on the screen (Go signals). When the arrows pointed up (No-Go signals) the participants were not supposed to respond. During the oddball arrows, slightly slanted arrows pointing either to the left or to the right appeared and the subjects were told to respond as they would to a "go" prompt. 1B - Sustained attention task (SAT). Participants are required to press the button as soon as possible when it appears a timer on the screen. The timer appears after either predictable short delays of 0.5 s in blocks of 3-5 stimuli or after unpredictable long delays of 2,5,8 s, pseudo-randomly interspersed into the blocks of 0.5 s. 1C - N-back. Each trial had 15 stimuli - 3 of them are targets and the other 12 are random letters. The figure shows 8 stimuli. The "n-back" letters where participants should respond are indicated by dotted paths

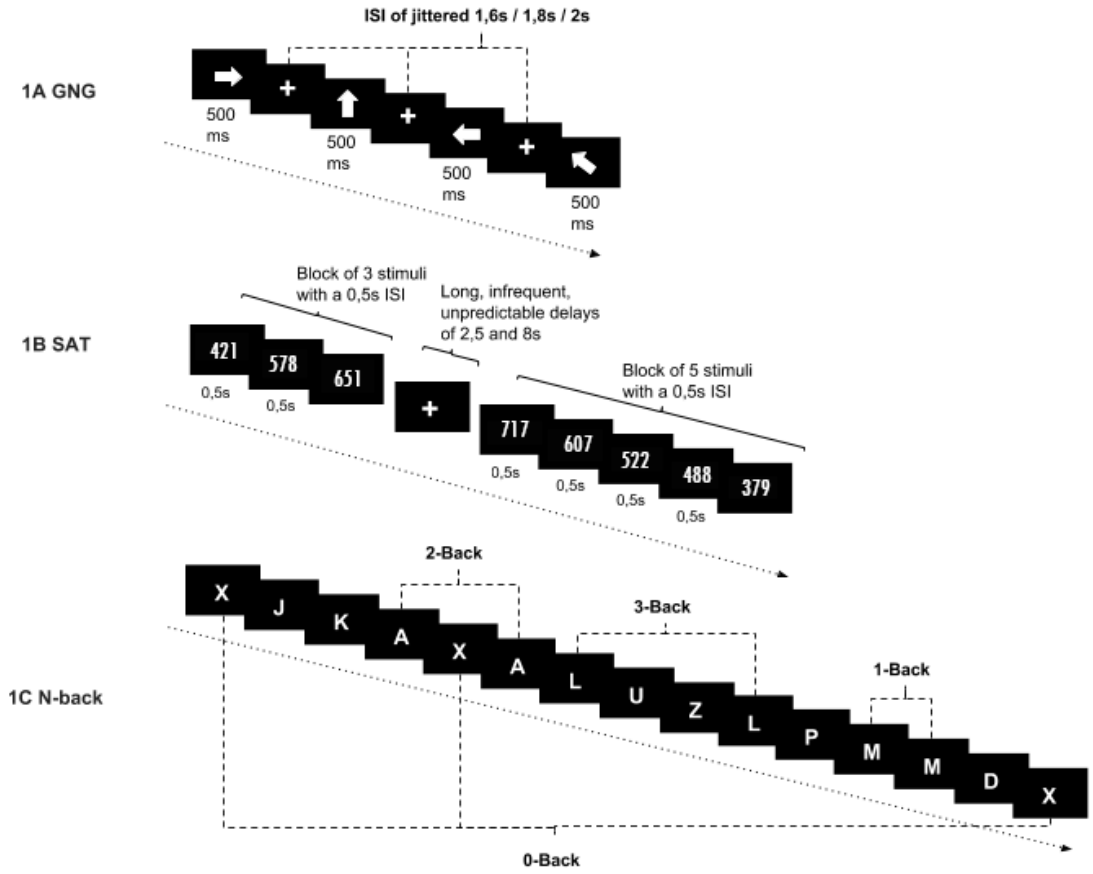
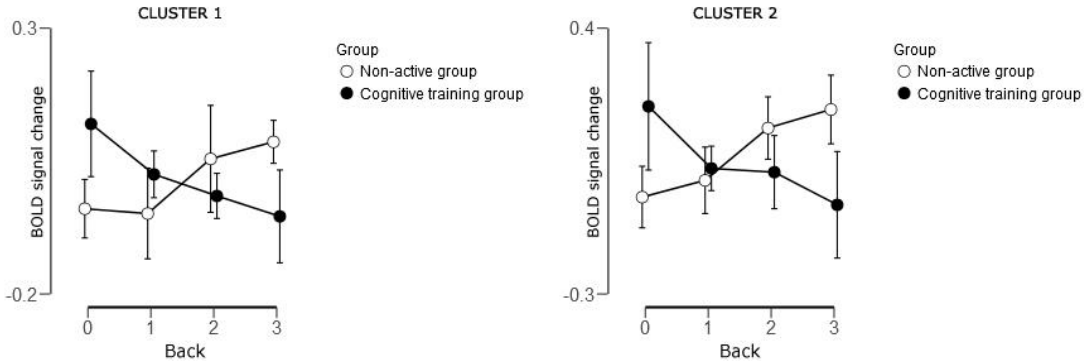


Fig. 2 Descriptive plots – 2A. Clusters of working memory activation (pre *versus* post intervention) showing that with increase in working memory load, during 3-back condition, the non-active group shows increased brain activation whereas the cognitive training CT group shows decrease in activation. 2B. Clusters of SAT activation (pre *versus* post intervention) showed that with increasing delay, the cognitive training group showed an increase in brain activation whereas the non-active group showed decreased activation. The following clusters are described detailly in table 3

2A)



2B)

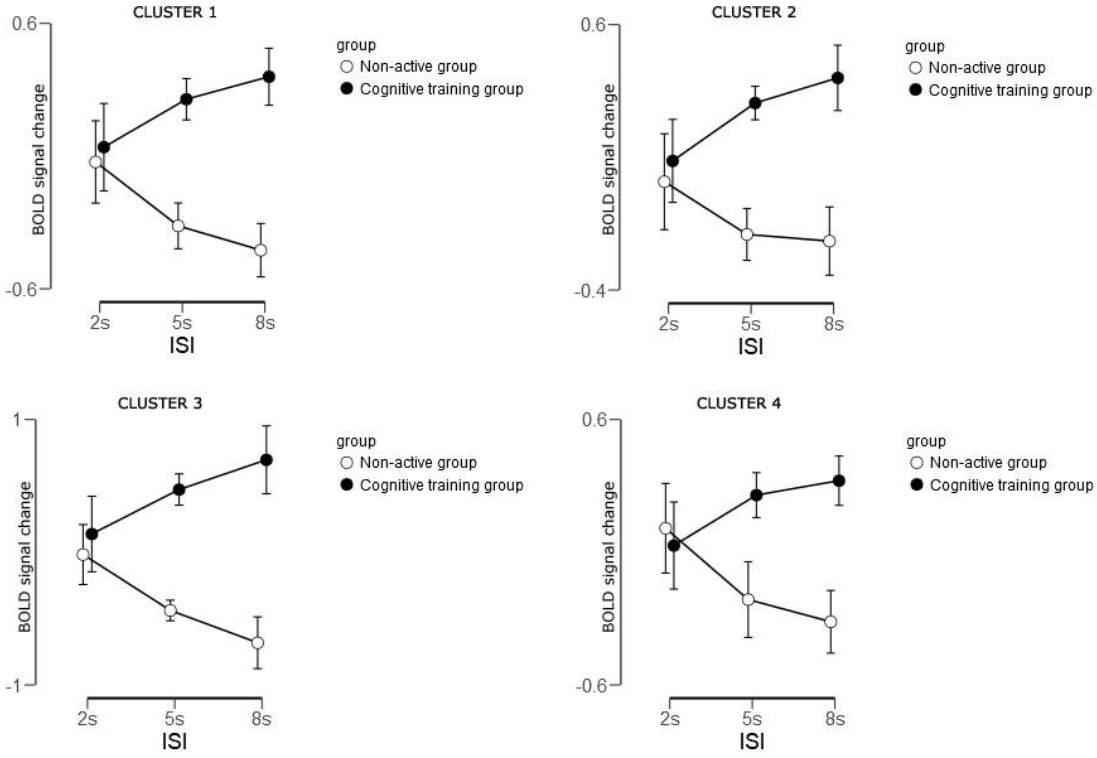
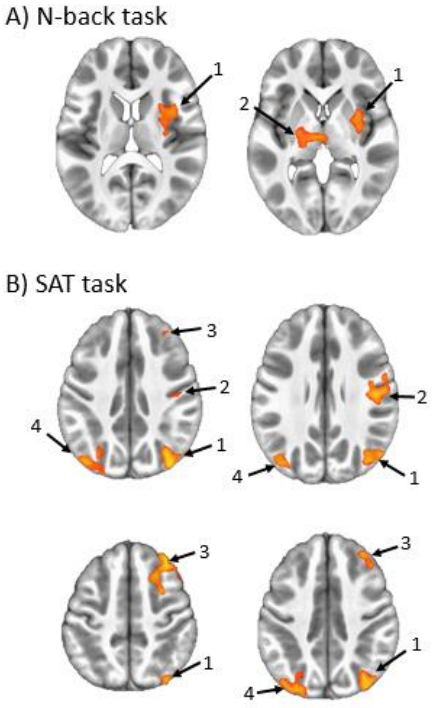


Fig. 3 Results from the main group comparisons. Axial sections showing the ANOVA between-group differences in brain activation between CT and non-active group A) During N-back task. Clusters denote areas with a significant group x time x WM-load interaction effect. B) During SAT task. Clusters denote areas with a time x group x ISI interaction. The figure shows brain regions in which the regions of interest consist of are listed in table 3. The right side of the image corresponds to the right side of the brain



CT, cognitive training; SAT, sustained attention task; ISI, inter-stimulus interval.

8. Considerações Finais

Nesta tese foram apresentados três artigos que têm em comum o estudo do treinamento cognitivo (TC) para crianças e adolescentes com TDAH. O primeiro artigo apresenta o protocolo de pesquisa e demonstra a viabilidade de sua implementação. O segundo artigo apresenta os resultados de um ensaio clínico randomizado controlado de treinamento cognitivo como tratamento adjuvante ao manejo medicamentoso com psicoestimulantes de crianças e adolescentes com TDAH. Segundo nossos resultados, não houve benefício na adição do TC ao tratamento medicamentoso, tanto em relação à melhora dos sintomas nucleares do TDAH quanto em relação à performance neuropsicológica. No geral, ambos os grupos demonstraram uma diminuição nos escores dos sintomas clínicos avaliados tanto por pais quanto por professores, mas sem diferença estatisticamente significativa. O estudo adotou um delineamento rigoroso, com um grupo controle ausente de características de treinamento cognitivo e com avaliações cegadas; além disso, avaliou a eficácia do treinamento em pacientes medicados para o TDAH, algo pouco encontrado na literatura. O método estatístico usado para avaliar os desfechos desse estudo foi o de Equações de Estimações Generalizadas (GEE) que, para análise de dados longitudinais, em muitas ocasiões, é considerado melhor que a análise de variâncias para medidas repetidas.

Esse foi um dos primeiros estudos a avaliar o TC em pacientes com TDAH medicados com psicoestimulantes, através de um ensaio clínico randomizado controlado com avaliadores cegados à intervenção. Nosso estudo vai ao encontro da maioria de achados da literatura que têm encontrado resultados desanimadores no emprego do TC para os sintomas nucleares do TDAH, entretanto, muitos deles apresentaram inconsistências metodológicas importantes como já citado. Em função disso, é essencial que esta estratégia terapêutica seja testada usando metodologia científica rigorosa e com maior tamanho amostral e seguimento.

O terceiro estudo apresenta os resultados da intervenção utilizando neuroimagem funcional, em que buscamos resultados da abordagem na performance de testes cognitivos e na ativação cerebral dos pacientes que realizaram o protocolo do treinamento cognitivo. Alguns dos achados da performance neuropsicológica, nas tarefas escolhidas, vão ao encontro de estudos na literatura que investigaram tarefas que mediram os mesmos domínios cognitivos após intervenções não-medicamentosas. Da mesma forma, encontramos diferenças na ativação cerebral em regiões relacionadas com a tarefa testada, porém diversas da maioria encontrada na literatura envolvendo TDAH, muito provavelmente em função de utilizarmos tarefas diferentes. Um ponto importante que levantamos, é que, provavelmente, as diferenças na ativação cerebral pós intervenção possam ocorrer antes da mudança na performance cognitiva, havendo necessidade de mais estudos avaliando

neuroimagem em intervenções para tratamento do TDAH e com maiores tempos de seguimento e tamanho amostral.

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