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DAIANE BORBA DE LIMA

ANÁLISE DA RELAÇÃO ENTRE O ESTILO DE VIDA, ASPECTOS COGNITIVOS, CAPACIDADE DE COMPENSAÇÃO COGNITIVA E NÍVEIS DE BDNF EM IDOSOS

Porto Alegre
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RESUMO

O envelhecimento normal é acompanhado por mudanças em habilidades cognitivas. É importante notar que o padrão e o grau de alterações cognitivas em idosos não demenciados são heterogêneos, enquanto alguns apresentam prejuízos significativos, outros mantêm a performance constante ao longo do envelhecimento. Entre os fatores que parecem ser capazes de modular a integridade cognitiva no envelhecimento está o estilo de vida. Há várias sugestões de que as atividades sociais, intelectuais e físicas melhoram a reserva cognitiva e protegem contra o declínio cognitivo. Os mecanismos relacionados a esses benefícios ainda são desconhecidos, mas estudos de intervenção com idosos sugerem que o BDNF (fator neurotrófico derivado do cérebro) pode ser um mediador dos benefícios na função cognitiva induzidos pela atividade física. Entretanto, estudos a respeito dos efeitos das atividades sociais e intelectuais sobre esta neurotrofina são escassos. No presente estudo, foram avaliados os efeitos do estilo de vida (atividades sociais, intelectuais e físicas) sobre aspectos cognitivos e níveis de BDNF em idosos saudáveis.

A relação entre as atividades sociais, intelectuais e físicas, os níveis de BDNF e a performance neuropsicológica (atenção, memória operacional e função executiva) foi analisada em uma amostra de idosos saudáveis (≥ 60 anos de idade, n=58). Os resultados não mostraram associações significativas entre as atividades sociais e intelectuais e os níveis de BDNF, entretanto, o grupo com nível mais baixo de atividade física teve níveis mais baixos de BDNF. Adicionalmente, os achados não identificaram efeitos consistentes destes componentes do estilo de vida sobre as funções cognitivas. A possibilidade deste resultado negativo ser uma consequência da falta de sensibilidade dos testes neuropsicológicos utilizados levou à investigação de uma tarefa mais sensível: a de memória contextual incidental. Desta forma, foi avaliado o efeito da atividade física sobre a memória contextual de idosos (≥ 60 anos de idade, n=52). Observou-se que níveis mais altos de atividade física melhoraram a evocação livre e reconhecimento de memória contextual. Além disso, uma instrução codificadora associativa combinada a níveis maiores de atividade física gerou uma melhora mais pronunciada na memória contextual, principalmente na evocação livre.

Os resultados apresentados nesta tese indicam que atividade física modula os níveis de BDNF e tem potencial para beneficiar a reserva cognitiva e a performance cognitiva. Adicionalmente, os efeitos das atividades intelectuais e sociais

provavelmente não são suficientemente robustos para serem identificados em desenhos experimentais transversais especialmente quando os sujeitos se encontram em um intervalo relativamente estreito destes aspectos do estilo de vida.
Palavras - chave: Envelhecimento. Cognição. Reserva cognitiva. Estilo de vida. BDNF

ABSTRACT

It is widely accepted that normal aging is accompanied by changes in cognitive abilities. It is also important to note that the pattern and degree of cognitive alterations in non-demented older adults is heterogeneous, with some of them showing significant impairments while others maintain relatively constant performances throughout aging. Among the factors that seem capable to modulate cognitive integrity on older age is life style. There are a number of suggestions that social, intellectual and physical activities enhance cognitive reserve and protect against cognitive decline. The mechanisms related to these benefits are still unknown, but intervention studies with older adults suggest that BDNF could be a mediator of the benefits on cognitive function induced by physical activity. However, studies on the effects of social and intellectual activities on this neurotrophin are scarce. In the present study, it were evaluated the lifestyle effects (social, intellectual and physical activities) on cognitive aspects and BDNF levels of healthy older adults.

The relation between social, intellectual and physical activities, BDNF levels and neuropsychology performance (attention, working memory and executive function tests) was analyzed in a sample of healthy older adults (≥ 60 years old, n=58). The results showed no significant associations between social or intellectual activity levels with BDNF levels, but the group with the lowest level of physical activity had the lowest BDNF levels. Additionally, the findings did not identify consistent effects of these lifestyle components on cognitive functions. Since it is possible that the neuropsychological tests used had not enough sensibility to identify lifestyle effects on cognition, it was investigated a more sensible task: an incidental contextual memory test. Thus, it was evaluated the effect of physical activity on contextual memory of older adults (≥ 60 years old, n=52). It was observed that higher physical activity levels improved free recall and recognition of contextual memory. In addition, the combination of higher physical activity levels and an associative encoding instruction resulted in the better contextual memory in free recall.

The results described above indicate that physical activity modulates BDNF levels and has the potential to improve cognitive reserve and cognitive performance. Additionally, the effects of intellectual and social activities are probably not sufficiently robust to be identified in transversal experimental designs of healthy older adults,

especially when the subjects operate in a relatively narrow range of these lifestyle aspects.
Keywords: Aging. Cognition. Cognitive reserve. Lifestyle. BDNF

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1 INTRODUÇÃO

A população mundial vem passando por um processo de envelhecimento que também é observado no Brasil, sendo o Rio Grande do Sul um dos estados onde o aumento da população idosa é mais acentuado (IBGE, 2010). O processo de envelhecimento abrange um amplo espectro de implicações no organismo, dentre as mais impactantes estão as disfunções cognitivas (DRAG; BIELIAUSKAS, 2010). Entretanto, tais alterações não ocorrem de forma homogênea na população idosa, já que alguns idosos apresentam função cognitiva mais preservada do que outros (DAFFNER, 2010). Tal variabilidade tem sido atribuída a fatores ambientais, sugerindo-se que o estilo de vida dos sujeitos possa prevenir contra o declínio cognitivo (BALLESTEROS et al., 2015; DAFFNER, 2010; MILGRAM et al., 2006; VALENZUELA; BREAKSPEAR; SACHDEV, 2007).

Estudos envolvendo modelos animais tentam elucidar os mecanismos que suportam os efeitos do estilo de vida utilizando-se de protocolos de enriquecimento ambiental, e têm observado que os expondo aos ambientes que possuem mais estímulos cognitivos, sensoriais e motores eles apresentam um melhor desempenho em tarefas de aprendizado e memória. Além disso, este protocolo experimental induz alterações celulares e moleculares, tais como: a plasticidade sináptica e a neurogênese, que parecem ser induzidas, pelo menos em parte, pela elevação dos níveis de BDNF (Fator neurotrófico derivado do cérebro) (MORA; SEGOVIA; DEL ARCO, 2007; VAN PRAAG; KEMPERMANN; GAGE, 2000). Tais achados têm sido reproduzidos em humanos, indicando o BDNF como possível mediador dos efeitos benéficos da atividade física sobre o desempenho cognitivo (ERICKSON et al., 2011; VAUGHAN et al., 2014). Entretanto, existem poucos estudos a respeito das consequências dos aspectos social e intelectual do estilo de vida sobre a cognição (JAMES et al., 2011; WILSON et al., 2002) ou níveis de BDNF (SALINAS et al., 2017).

Ainda é necessário aclarar em humanos a relação entre os componentes do estilo de vida (atividades sociais, intelectuais e físicas), função cognitiva e capacidade de compensação cognitiva. Adicionalmente, é de grande relevância investigar os mecanismos moleculares envolvidos nesta relação.

1.1 ENVELHECIMENTO E ASPECTOS COGNITIVOS

O envelhecimento é um processo dinâmico e progressivo no qual ocorrem alterações morfológicas, funcionais, bioquímicas e psicológicas. Esses fatores determinam a perda da capacidade de adaptação do indivíduo ao meio ambiente, tornando-o vulnerável e mais predisposto a condições patológicas, podendo inclusive progredir para morte (FREITAS et al., 2006). Inúmeros sistemas do organismo passam por mudanças durante o envelhecimento, dentre os quais o sistema nervoso. Estruturalmente, o cérebro diminui de volume, o que não ocorre uniformemente em todas as regiões. O hipocampo, que tem sido alvo de muitos estudos, sofre mudanças estruturais mesmo em idosos saudáveis. Por outro lado, o córtex frontal é uma das áreas que se mostra mais afetada em termos de volume, apresentando declínio mais acentuado do que outras regiões que também se encontram suscetíveis aos efeitos do envelhecimento, como córtex temporal, occipital e parietal (DRAG; BIELIAUSKAS, 2010). Tais alterações frontais têm sido relacionadas a déficits cognitivos, e dentre os domínios mais afetados estão a atenção, a função executiva e a memória (DRAG; BIELIAUSKAS, 2010; GRADY; CRAIK, 2000).

Dentre os componentes atencionais que se encontram mais suscetíveis no envelhecimento estão a atenção seletiva (habilidade de manter a atenção focada em uma tarefa ao longo de determinado período de tempo), a atenção dividida (capacidade de realizar mais de uma tarefa por vez) e a atenção alternada (habilidade de mudar rapidamente o foco entre uma tarefa e outra). As alterações nesses aspectos podem provocam menor eficiência para lidar com situações da vida diária, como dirigir num local não familiar (DRAG; BIELIAUSKAS, 2010).

O idoso também apresenta dificuldades na realização de testes de função executiva. Esse aspecto cognitivo é requerido para elaboração de comportamentos adaptativos em resposta a situações ambientais desafiadoras e inclui o processamento de informações relevantes, a geração de novos conceitos e as habilidades de planejamento e resolução de problemas (DUBOIS; PILLON, 1997). Dentre os subcomponentes executivos afetados estão a memória operacional e a função inibitória (DRAG; BIELIAUSKAS, 2010). A memória operacional envolve a manutenção de uma informação na mente enquanto o indivíduo gerencia outros estímulos (IZQUIERDO, 2002). Alterações em seu funcionamento têm implicações na vida cotidiana como, dificuldades em lembrar e calcular os preços das compras no mercado. O declínio da função inibitória pode acarretar dificuldades em manter o foco numa informação central enquanto ignora outras irrelevantes (SPIELER; BALOTA; FAUST, 1996) por exemplo, participar de uma conversa, abstraindo-se de outros diálogos e estímulos do ambiente (DRAG; BIELIAUSKAS, 2010).

As dificuldades de memória representam uma das queixas mais frequentemente referidas pelos idosos. A memória é uma das mais importantes funções cognitivas do homem. Pode ser descrita como a habilidade que possuímos de armazenar as informações e os conhecimentos sobre nós mesmos e o mundo que nos cerca. Ela é a base para o desenvolvimento da linguagem, do reconhecimento das pessoas e dos objetos que encontramos todos os dias, para sabermos quem somos e para termos a consciência da continuidade de nossas vidas (YASSUDA, 2006).

Memórias autobiográficas, relacionadas a eventos aos quais assistimos ou dos quais participamos são classificadas como episódicas (IZQUIERDO, 2002). São compostas pela memória para itens, que corresponde ao conteúdo central da informação, envolvendo recordar o que aconteceu, e pela memória contextual, que se refere aos aspectos contextuais temporais, espaciais, afetivos e sociais de um acontecimento, e à fonte da qual uma informação foi adquirida (JOHNSON; HASHTROUDI; LINDSAY, 1993; TAAFFE et al., 2008). A memória contextual é adquirida de forma incidental e sem esforço, através da vinculação automática de um item ou objeto ao seu contexto (HASHER; ZACKS, 1979). No entanto, as memórias também podem ser classificadas como intencionais, aquelas cujo aprendizado acontece conscientemente.

As alterações observadas em idosos são muito mais evidentes em alguns tipos de memória do que em outras (FREIRE et al., 2008; GRADY; CRAIK, 2000). Estudos têm relatado que a memória para item encontra-se preservada, enquanto a memória contextual encontra-se prejudicada. Tais deficiências vêm sendo atribuídas à maior suscetibilidade do lobo frontal aos efeitos adversos do processo de envelhecimento (RAZ et al., 2005). Apesar de a integração do conteúdo central e contextual da memória ser atribuída ao hipocampo (EICHENBAUM; YONELINAS; RANGANATH, 2007), o córtex pré-frontal é responsável por reforçar esta vinculação (JOHNSON; HASHTROUDI; LINDSAY, 1993). O papel dos lobos frontais na memória contextual tem sido evidenciado por estudos envolvendo pacientes com lesão frontal que apresentam maior dificuldade de lembrar os aspectos contextuais do que os itens centrais (BUTTERS, MERYL A.; KASZNIAK, ALFRED W.; GLISKY, ELIZABETH L.;

ESLINGER, PAUL J.; SCHACTER, 1994). Complementarmente, estudos envolvendo neuroimagem mostram que tarefas de memória contextual geram maior atividade dos lobos frontais do que testes de memória para item (CABEZA et al., 1997). Desse modo, os déficits de memória contextual parecem estar relacionados com a maior sensibilidade do lobo frontal no envelhecimento (RAZ et al., 2005) e à uma inabilidade de vincular espontaneamente as informações contextuais às informações centrais da memória durante a codificação (NAVEH-BENJAMIN, 2000).

A idade avançada também é acompanhada por dificuldades na fase de evocação da informação. A evocação livre, que é tão importante quanto o reconhecimento para a recordação de memórias episódicas, é a mais afetada, pois gera maior demanda de recursos, exigindo a utilização espontânea de operações mentais. Já o reconhecimento é menos sensível aos efeitos do envelhecimento, pois oferece suporte ambiental, facilitando a recordação da informação (CRAIK; BYRD; SWANSON, 1987; CRAIK; ROSE, 2012).

Investigações que têm como foco o envelhecimento bem-sucedido relatam que os idosos compõem um grupo heterogêneo, o que se torna evidente do ponto de vista cognitivo, pois enquanto uma parcela da população apresenta déficits, a outra apresenta a função cognitiva preservada. Muitas linhas de pesquisa vêm sendo traçadas, na tentativa de explicar essa variabilidade no padrão do funcionamento cognitivo dos idosos, e os fatores ambientais têm se mostrado capazes de explicar, pelo menos parcialmente, tais discrepâncias (BALLESTEROS et al., 2015; DAFFNER, 2010).

Nesse estudo foi averiguado o quanto os componentes intelectual, social e físico do estilo de vida podem estar envolvidos na preservação dos processos cognitivos (atenção, memória declarativa, função executiva, memória operacional). Suplementarmente, avaliamos o quanto o estilo de vida pode modular a capacidade de compensação cognitiva uma vez que, estudos têm observado que quando os idosos saudáveis recebem uma estratégia de codificação associativa (que facilita a vinculação entre objeto ao contexto) apresentam um desempenho significativamente melhor no reconhecimento de contextos, quando comparados àqueles que não recebem tais tipos de estratégias (BISOL BALARDIN et al., 2009; MORO DOS SANTOS et al., 2010).

1.2 ESTILO DE VIDA E OUTROS FATORES DETERMINANTES DO DESEMPENHO COGNITIVO NO ENVELHECIMENTO

O estilo de vida tem sido associado à prevenção de declínio cognitivo no idoso (BALLESTEROS et al., 2015; MILGRAM et al., 2006; VALENZUELA; BREAKSPEAR; SACHDEV, 2007). Sugere-se que maior envolvimento em atividades sociais, intelectuais e físicas possa trazer benefícios à função cerebral (ERICKSON et al., 2011; JAMES et al., 2011; WILSON et al., 2002).

1.2.1 Enriquecimento ambiental em animais

Estudos com animais têm fornecido evidências de que a manutenção de um estilo de vida mais ativo no que se refere ao engajamento em atividades mais cognitivamente estimulantes, com maior interação social e prática de atividade física favorece a função cerebral (MORA; SEGOVIA; DEL ARCO, 2007; NITHIANANTHARAJAH; HANNAN, 2009; VAN PRAAG; KEMPERMANN; GAGE, 2000). Essas investigações utilizam paradigmas de ambientes enriquecidos, que proporcionam uma combinação de estímulos sociais, sensoriais e motores, sendo os animais acomodados em moradias com maior espaço disponível, brinquedos, túneis e disponibilidade de aparato para prática de exercício físico (MORA; SEGOVIA; DEL ARCO, 2007; VAN PRAAG; KEMPERMANN; GAGE, 2000).

Estudos com roedores mostraram que o enriquecimento ambiental modula a sinaptogênese e a neurogênese hipocampais mesmo em animais velhos e promove um padrão mais complexo de ramificação dendrítica (BEDNAREK; CARONI, 2011; LEGGIO et al., 2005; MORA; SEGOVIA; DEL ARCO, 2007; VAN PRAAG; KEMPERMANN; GAGE, 2000). Esse tipo de protocolo experimental também é capaz de melhorar o desempenho dos animais em tarefas de aprendizado e memória (MORA; SEGOVIA; DEL ARCO, 2007; NITHIANANTHARAJAH; HANNAN, 2009; VAN PRAAG; KEMPERMANN; GAGE, 2000; WOODCOCK; RICHARDSON, 2000). Além disso, aumenta a expressão de neurotrofinas como Fator de crescimento neuronal (NGF), Fator neurotrófico derivado da glia (GDNF) e BDNF (MORA; SEGOVIA; DEL ARCO, 2007; NITHIANANTHARAJAH; HANNAN, 2009; PHAM et al., 2002; VAN PRAAG; KEMPERMANN; GAGE, 2000), que parecem ter papel importante na mediação destes efeitos.

1.2.2 Atividades físicas

A literatura a respeito dos efeitos da atividade física sobre a função cognitiva dos idosos tem relatado que tanto os exercícios aeróbicos quanto os anaeróbicos apresentam associação positiva com os aspectos cognitivos.

Estudos observam que o exercício aeróbico além de favorecer o desempenho cognitivo, também está associado a benefícios estruturais no cérebro. Um estudo intervencional mostrou que a prática de tais exercícios por 12 meses favoreceu a conectividade entre as regiões frontal, posterior e temporal, o que ocasionou um melhor desempenho em tarefas de função executiva (VOSS et al., 2010). Erickson e colaboradores (2011) relataram que após um período 12 meses de exercício aeróbico (caminhada) os idosos apresentaram um acréscimo no volume do hipocampo, o que foi associado a uma melhor performance na memória espacial. Mesmo após um período menor (3 meses) de prática de atividade física, foram observadas vantagens na velocidade de processamento dos idosos (RENAUD; BHERER; MAQUESTIAUX, 2010).

Apesar de haver um menor número de estudos que examinam os efeitos do exercício físico anaeróbico sobre a cognição, há evidências de que este tipo de atividade exerça efeitos favoráveis sobre aspectos cognitivos (KIRK-SANCHEZ; MCGOUGH, 2014). Intervenções que utilizaram o treinamento de resistência relataram melhora no desempenho dos idosos em vários testes neuropsicológicos. Outros estudos que realizaram protocolos de treinamento de resistência por 12 meses observaram resultados positivos tanto na atenção seletiva, (LIU-AMBROSE et al., 2010) quanto na função inibitória de idosas (LIU-AMBROSE et al., 2012).

Adicionalmente, atividades como o *Tai Chi* e a dança de salão, que combinam atividade física, interação social e estimulação cognitiva oferecem muitos benefícios em vários aspectos, incluindo os neuropsicológicos. A dança está associada com benefícios na postura, na memória operacional e no tempo de reação (KATTENSTROTH et al., 2010). O *Tai Chi* tem sido associado com atenuação nos sintomas de depressão e ansiedade, redução no risco de quedas (ROGERS; LARKEY; KELLER, 2009), melhora no desempenho cognitivo e aumento no volume de áreas cerebrais no idoso (MORTIMER et al., 2012).

Estudos intervencionais têm mostrado que a atividade física está relacionada a acréscimo no volume do hipocampo (ERICKSON et al., 2011) e do lobo frontal

(COLCOMBE et al., 2006), além de elevação nos níveis de neurotrofinas, em especial do BDNF, que parece estar associado positivamente com o desempenho em tarefas neuropsicológicas (ERICKSON et al., 2011; VAUGHAN et al., 2014). É importante avaliar se os efeitos da atividade física sobre a cognição e os níveis de BDNF são suficientemente robustos para serem identificados em estudos transversais.

1.2.3 Atividades intelectuais

Apesar de haver um número importante de investigações a respeito dos efeitos da atividade física sobre aspectos cognitivos, os achados que se referem à relação entre cognição e atividades intelectuais são escassos e inconclusivos, pois enquanto alguns relatam uma associação positiva (WILSON et al., 2002), outros não observam nenhuma relação (SALTHOUSE; BERISH; MILES, 2002).

O engajamento em atividades intelectuais tem sido associado a uma redução no risco de desenvolver declínio cognitivo leve (VERGHESE et al., 2006) e Doença de Alzheimer (WILSON et al., 2002). Wilson e colegas (2002) acompanharam uma amostra de idosos por cerca de 5 anos com o objetivo de investigar os efeitos das atividades intelectuais sobre a cognição. Na análise foram consideradas a frequência da realização de tarefas cognitivamente estimulantes, tais como: completar quebra-cabeças, jogar cartas, fazer palavras cruzadas, assistir televisão, ouvir rádio e visitar museus. Os resultados do estudo mostraram uma redução no declínio da cognição global e maior eficiência em tarefas de memória operacional e velocidade perceptual. Em outra investigação, Ghisletta e colaboradores (2006) verificaram a relação entre uma série de práticas mentalmente estimulantes (completar palavras cruzadas e jogar xadrez, ler livros, jornais e revistas, assistir televisão e ouvir rádio) e a função cognitiva. Todavia, apenas foi observada uma atenuação no declínio da velocidade perceptual, e nenhum efeito sobre a fluência verbal. Além disso, um estudo envolvendo neuroimagem analisou a relação entre os aspectos sociais, intelectuais e físicos sobre o volume de estruturas cerebrais. Os resultados indicaram que maior tempo dedicado às atividades mentais (usar computador, participar de atividades de artesanato ou arte, assistir a concertos, filmes, ou peças de teatro, ler, tocar instrumento musical) estava relacionado com maior volume em regiões corticais e subcorticais. No entanto, não foi encontrada relação entre volume cerebral e atividades físicas e sociais (SEIDER et al., 2016).

Salthouse e colegas (2002) investigaram o efeito de atividades intelectuais sobre o desempenho cognitivo de uma amostra composta por adultos e idosos. Foram consideradas práticas cognitivamente estimulantes: jogar xadrez, montar quebra-cabeças, assistir televisão, utilizar o computador, escrever, cuidar do jardim, encontrar amigos e realizar trabalho voluntário. Contudo, os resultados desse estudo não demonstraram relação entre o nível de atividade intelectual e a performance em tarefas de raciocínio e memória.

1.2.4 Atividades sociais

O envolvimento mais frequente em atividades sociais tem sido associado positivamente com uma maior qualidade de vida e sensação de bem-estar (RAFNSSON; SHANKAR; STEPTOE, 2015). Todavia, a literatura não apresenta consenso quanto à relação entre a interação social e a cognição. Alguns achados sugerem um papel importante do maior convívio social na prevenção do declínio cognitivo e redução do risco de desenvolver demências (FRATIGLIONI; PAILLARD-BORG; WINBLAD, 2004; JAMES et al., 2011; ZUNZUNEGUI et al., 2003), enquanto outros não mostram um efeito protetor significativo contra o desenvolvimento de quadros demenciais (AKBARALY et al., 2009; HULTSCH et al., 1999).

Seeman e colegas (2011) observaram que o contato frequente com amigos e familiares e uma rede de suporte social favorecem a memória episódica e a função executiva tanto nos adultos de meia idade quanto nos de idade avançada. James e colaboradores (2011) acompanharam uma amostra de idosos saudáveis por 12 anos e observaram que um maior engajamento social (manter contato com amigos e familiares, ir a restaurantes, museus e cinema, realizar trabalho voluntário e participar de serviços religiosos) estava associado a um menor declínio cognitivo e a uma melhor performance em tarefas que envolviam habilidades visuoespaciais, memória operacional, memória episódica e memória semântica. Outra investigação, que envolveu a realização de sessões diárias de exercícios físicos e de tarefas de interação social, observou um melhor desempenho em testes de memória, no entanto, não foi possível distinguir o quanto cada um dos tipos de atividades contribuiu para a melhora na performance neuropsicológica dos idosos (BENLOUCIF et al., 2004).

Um estudo fez o monitoramento de uma amostra de idosos por 6 anos a fim de verificar a relação entre aspectos cognitivos e atividades tais como: frequentar a igreja, participar de associações de bairro e frequentar organizações beneficentes. Contudo, os resultados não apontaram nenhuma relação entre os níveis de interação social e tarefas de aprendizado, evocação imediata e velocidade de processamento (AARTSEN et al., 2002). Da mesma forma, outra investigação longitudinal não observou associação entre domínios cognitivos e atividades sociais, como encontrar amigos e familiares e ir ao teatro e ao cinema (KÅREHOLT et al., 2011).

A investigação dos efeitos do estilo de vida sobre a cognição possui limitações importantes. Poucos estudos controlam características clínicas (depressão, níveis de cortisol, qualidade do sono e patologias) e demográficas (gênero, nível socioeconômico e nível de escolaridade) que podem influenciar os resultados dos estudos. Ademais, a maioria das pesquisas considera apenas um dos diferentes componentes (físico, intelectual e social) em suas análises. Assim sendo, o presente estudo avaliou os três aspectos do estilo de vida na mesma amostra de idosos saudáveis.

1.2.5 Outros fatores determinantes do desempenho cognitivo

Além do estilo de vida, há outros fatores que também podem modular a função cognitiva no envelhecimento e que devem ser considerados, dentre os quais estão características demográficas e clínicas, como nível de escolaridade, fatores socioeconômicos e presença de determinadas patologias, que têm sido mais frequentemente controladas em diversos estudos. Existem também outras variáveis que podem atuar de forma significativa na cognição do idoso, mas que não são rotineiramente controladas nas pesquisas, como níveis de cortisol, qualidade do sono e queixas subjetivas de memória.

O *status* socioeconômico pode influenciar diversos processos cognitivos (URSACHE; NOBLE, 2016). Idosos com maior nível socioeconômico apresentam melhor desempenho em tarefas de memória (CZERNOCHOWSKI; FABIANI; FRIEDMAN, 2008), o que parece estar relacionado com a capacidade destes sujeitos de recrutarem recursos neuronais adicionais (CZERNOCHOWSKI; FABIANI; FRIEDMAN, 2008). Outro fator capaz de modular os aspectos cognitivos é o nível de escolaridade. Um maior nível educacional vem sendo associado a um melhor desempenho cognitivo (TUCKER-DROB; JOHNSON; JONES, 2009; WILSON et al., 2009) e a uma redução no risco de desenvolver demências e Doença de Alzheimer

(BENNETT et al., 2003; SHARP; GATZ, 2011). Assim como maior nível socioeconômico, maiores níveis de escolaridade são relacionados com a manutenção da reserva cognitiva, conferindo aos indivíduos maior habilidade de lidar com os possíveis efeitos adversos inerentes ao processo de envelhecimento (SPRINGER et al., 2005).

A função cognitiva pode ser influenciada por determinadas condições patológicas muito comuns na população idosa. Doenças cardiovasculares e seus fatores de risco, como hipertensão e diabetes são associados a declínio na função cognitiva e às mudanças na estrutura cerebral (LERITZ et al., 2011). Déficits executivos e atencionais são observados tanto em pacientes hipertensivos (RAZ; RODRIGUE, 2006) como em pacientes diabéticos (CHRISTMAN et al., 2010). Outras condições médicas como depressão e câncer afetam regiões cerebrais envolvidas em processos cognitivos (ALEXOPOULOS, 2005; MCDONALD; SAYKIN, 2013), e por consequência a performance neuropsicológica (ELDERKIN-THOMPSON et al., 2003; MANDELBLATT et al., 2013).

O cortisol é um glicocorticoide cuja produção ocorre a partir do estímulo do eixo HPA (hipófise-pituitária-adrenal), pelo qual o organismo responde a eventos estressores (LUPIEN et al., 2009). Os glicocorticóides têm efeitos bastante amplos no organismo (LUCASSEN et al., 2014; LUPIEN et al., 2005), sendo o cérebro um dos principais alvos de corticosteroides, os quais são capazes de atravessar a barreira hematoencefálica e desempenhar suas ações através de receptores glicocorticoides e receptores mineralocorticoides (DATSON et al., 2008). O cortisol pode atuar em regiões cerebrais (hipocampo e lobo frontal) envolvidas com a memória e outros aspectos cognitivos (LUPIEN et al., 2005, 2007). Além dos efeitos fisiológicos que desempenha no sistema nervoso, o cortisol pode ser neurotóxico em situações de estresse crônico, por exemplo, alterando anatômica e funcionalmente estruturas envolvidas em diferentes aspectos cognitivos (BROWN; VARGHESE; MCEWEN, 2004; LUPIEN et al., 2007). A literatura mostra que uma parcela de idosos considerados saudáveis apresenta alterações nos níveis desse hormônio (LUPIEN et al., 2005) e que variações nos seus níveis são associadas a déficits executivos, de memória e de velocidade de processamento (GEERLINGS; GARCIA; HARRIS, 2015).

O sono é um processo que envolve um estado comportamental reversível de desligamento da percepção e de não-responsividade aos fatores ambientais (CIRELLI; TONONI, 2008; LU; ZEE, 2010) e possui dois estágios diferentes: o sono de ondas lentas (SWS – do inglês *slow wave sleep*), e o sono REM (do inglês – *rapid eye movement*), caracterizado pela rápida movimentação dos olhos (HIRSHKOWITZ, 2004). O SWS é associado à reparação no organismo e à manutenção metabólica e homeostática do encéfalo. Por outro lado, o sono REM possui papel de consolidar informações adquiridas no período de vigília (LU; ZEE, 2010). Estudos com neuroimagem funcional mostram que tanto o córtex pré-frontal (HARRISON, HORNE, AND ROTHWELL 2000; MUZUR, PACE-SCHOTT, and HOBSON 2002) quanto o hipocampo (FERRARA et al., 2012; SALETIN; WALKER, 2012), que suportam processos cognitivos importantes, são muito suscetíveis às alterações de sono. Existem mudanças no padrão de sono inerentes ao processo de envelhecimento, tais como: uma maior dificuldade de adormecer, diminuição na duração total do sono e de sua eficiência, menor duração das fases de sono REM e dos estágios profundos do SWS e um aumento na fragmentação do sono (YAFFE; FALVEY; HOANG, 2014; (MONK, 2005). Tais alterações podem afetar o desempenho dos idosos em tarefas de memória de trabalho, alternância atencional (NEBES et al., 2009), função executiva (WILCKENS et al., 2014), e memória (SCULLIN, 2012).

As queixas subjetivas de memória representam outro fator importante a ser controlado nas análises que envolvem aspectos cognitivos. Cerca de 25% a 79% dos idosos apresentam tais queixas (BALASH et al., 2013), o que pode depender das características da amostra estudada (idade, grau de integridade cognitiva, sintomatologia depressiva e ansiosa) e do tipo de questionário utilizado (VOGEL et al., 2016). As queixas subjetivas de memória são muito relevantes do ponto de vista clínico, uma vez têm sido consideradas preditores importantes do risco de conversão para demência (JESSEN et al., 2007; WANG et al., 2004). Um estudo longitudinal observou que os voluntários que referiam dificuldades de memória no início do estudo tiveram maior risco de desenvolver demência (WANG et al., 2004), apesar de terem apresentado performance neuropsicológica equiparada à daqueles idosos que não relatavam dificuldades de memória. Adicionalmente, as queixas subjetivas de memória vêm sendo relacionadas com o desempenho em tarefas cognitivas objetivas em idosos saudáveis (SNITZ et al., 2015).

Considerando a capacidade que as características demográficas (escolaridade e nível socioeconômico) e clínicas (qualidade do sono, níveis de cortisol, queixas subjetivas de memória e condições patológicas) possuem de influenciar os processos cognitivos, estas foram controladas em nossas análises.

1.3 RESERVA COGNITIVA

A reserva cognitiva está relacionada à maior tolerância às injúrias cerebrais, mitigando prováveis efeitos danosos e postergando o início dos sintomas cognitivos, o que se dá por mecanismos compensatórios, reorganização funcional e recrutamento de redes neurais alternativas (DAFFNER, 2010; STERN, 2002), incluindo mudanças estruturais em nível celular, como neurogênese, sinaptogênese, angiogênese e formação de dendritos (VALENZUELA; BREAKSPEAR; SACHDEV, 2007).

O processo de envelhecimento está atrelado a uma série de modificações estruturais e funcionais no cérebro, que estão associadas às alterações em vários aspectos cognitivos (DRAG; BIELIAUSKAS, 2010). A literatura relata que mesmo em idade avançada, o cérebro demonstra certa plasticidade (BERRY et al., 2010; CHENG et al., 2012; SMITH et al., 2009). No idoso o processo compensatório parece acompanhar uma mudança no padrão de ativação cerebral havendo maior ativação de áreas anteriores do que de áreas posteriores e uma ativação menos assimétrica (REUTER-LORENZ; CAPPELL, 2008).

A hipótese da reserva cognitiva vem sendo corroborada por estudos que indicam que nem sempre há uma relação direta entre o grau de patologia do cérebro e a manifestação clínica de diversas doenças neurodegenerativas (VALENZUELA; BREAKSPEAR; SACHDEV, 2007). É o caso, por exemplo, de pacientes de Alzheimer assintomáticos que apresentam alterações histológicas características da doença como emaranhados neurofibrilares, degeneração dos neurônios colinérgicos (principalmente do núcleo basal de Maynert), formação de placas senis (em especial nas áreas límbicas e córtex associado) e degeneração de fibrilas com alteração de proteínas neuronais (proteína TAU e MAP2) (MARKESBERY, 2010). O fato dos indivíduos serem assintomáticos, isto é, não apresentarem manifestações cognitivas da doença, pode ser atribuído à sua reserva cognitiva (WILSON et al., 2002).

A literatura sugere que conservar-se engajado em atividades sociais, intelectuais e físicas contribui para a manutenção da reserva cognitiva, a qual tem sido associada à preservação da função cognitiva e à diminuição no risco de desenvolver demência (BALLESTEROS et al., 2015; ERICKSON; GILDENGERS; BUTTERS, 2013; FRATIGLIONI; PAILLARD-BORG; WINBLAD, 2004). O estilo de vida fisicamente ativo vem sendo considerado como importante protetor da saúde mental. Os modelos de enriquecimento ambiental em animais mostram que atividade física é o fator preponderante na modulação da plasticidade sináptica e promoção de aprendizado e memória (KOBILO et al., 2013). Em humanos, diferentes investigações sugerem que idosos que praticam maiores níveis de atividade física além de serem menos propensos a incidência de demências, apresentam vantagem na performance de diversos domínios cognitivos (BALLESTEROS et al., 2015; ERICKSON; GILDENGERS; BUTTERS, 2013). Complementarmente, tem sido observado que idosos que praticam exercícios físicos com mais frequência apresentam maior volume de estruturas cerebrais como hipocampo e lobo frontal, as quais são envolvidas em aspectos cognitivos que se encontram mais suscetíveis no envelhecimento, como funções executivas e memória. Apesar de o mecanismo que modula esses benefícios ainda ser matéria de investigação, o BDNF vem sendo indicado como possível mediador dos efeitos positivos de um estilo de vida fisicamente ativo (ERICKSON et al., 2011; VAUGHAN et al., 2014), por isso neste estudo nos propusemos a investigar a relação entre o estilo de vida, cognição e os níveis desta neurotrofina.

1.4 BDNF

O estudo dos mecanismos celulares e moleculares que suportam os efeitos do estilo de vida e da reserva cognitiva vem sendo desenvolvido através da utilização de modelos de enriquecimento ambiental em animais, que envolvem estimulação sensório-motora, interação social e atividade física (VAN PRAAG; KEMPERMANN; GAGE, 2000). A exposição ao ambiente enriquecido favorece a plasticidade neuronal, o desempenho em diversas tarefas de memória e o aumento na expressão de neurotrofinas (MORA; SEGOVIA; DEL ARCO, 2007; PHAM et al., 2002; VAN PRAAG; KEMPERMANN; GAGE, 2000; WOODCOCK; RICHARDSON, 2000), dentre as quais, o BDNF, que parece ser o modulador destes efeitos benéficos (FARES et al., 2013). Suplementarmente, o papel do BDNF na mediação dos efeitos favoráveis do estilo de vida sobre a cognição vem sendo sugerido também por estudos de intervenção, que observam associação positiva entre atividade física, níveis de BDNF e desempeno em testes cognitivos em idosos (ERICKSON et al., 2011; VAUGHAN et al., 2014).

Não obstante o mecanismo que modula os benefícios do estilo de vida sobre a cognição ainda não ter sido elucidado, o BDNF tem sido relacionado à saúde mental.

A diminuição nos níveis dessa neurotrofina tem sido associada a prejuízo cognitivo (SIUDA et al., 2017), enquanto que o aumento tem sido associado a benefícios na performance cognitiva (KENNEDY et al., 2015).

O BDNF é uma molécula pertencente à família das neurotrofinas que inclui por exemplo, fator de crescimento neuronal (NGF), neutrotrofina 3 (NT3) e neutrofina 4 (NT4). Esta classe de moléculas é expressa amplamente no cérebro dos mamíferos e está implicada na plasticidade,sobrevivência celular e manutenção do sistema nervoso (CHAO, 2003; PARK; POO, 2012). A ação do BDNF ocorre por meio de receptores tirosina quinase (TrkB), aos quais se liga com grande afinidade, resultando no recrutamento de proteínas que ativam duas cascatas. Uma dessas cascatas ativadas envolve o substrato-1 do receptor de insulina (IRS-1), a proteína quinase dependente de fosfatodilinoitol-3 (Pl-3K), a proteína quinase dependente de fosfoionositídeo (PDK1) e a proteína quinase B (Akt). A outra cascata está envolvida na ativação de proteínas intracelulares como a Schc/Grb2, Ras, Raf, MEKs e sinais extracelulares regulados pelas proteínas quinases extracelularmente (ERKs). Essas cascatas, por sua vez, ativam um ou mais fatores de transcrição que irão regular a expressão de genes no núcleo da célula, envolvidos na potenciação de longa duração, na modulação da secreção de neurotransmissores, na plasticidade sináptica, na resistência ao estresse e na sobrevivência celular (MATTSON; MAUDSLEY; MARTIN, 2004).

O BDNF vem sendo abordado amplamente em trabalhos envolvendo seres humanos, os quais consideram em suas análises os níveis periféricos desta neurotrofina. Entretanto ainda não foi aclarada a relação entre os níveis de BDNF no sistema nervoso e os tecidos periféricos, devido ao grande número de regiões expressoras de neurotrofinas no cérebro, assim como à grande diversidade de tecidos periféricos que expressam BDNF. Experimentos que utilizam modelo animal sugerem a relação entre os níveis de BDNF sanguíneos e plasmáticos com níveis hipocampais em roedores e suínos, respectivamente (KLEIN et al, 2011). Um estudo observou que os níveis de BDNF no cérebro e sangue eram semelhantes em ratos, tendo um aumento acentuado logo após o período pós-natal, e chegando a um platô depois do período de desenvolvimento, mantendo-se até idade avançada (KAREGE; SCHWALD; CISSE, 2002). Outra investigação relatou a manutenção dos níveis periféricos e centrais em ratos que se mostravam resistentes à depressão, por outro lado observou-se níveis periféricos mais elevados do que visto no sistema nervoso central em animais sensíveis à depressão (ELFVING et al., 2010). Apesar de estudos em modelo animal sugerirem uma relação entre os níveis periféricos e os níveis centrais de BDNF, há necessidade que pesquisas futuras investiguem esta relação em humanos.

Os níveis de BDNF são suscetíveis a fatores clínicos e demográficos diversos, dentre os quais, a qualidade do sono e os níveis de cortisol. Uma vez que esses aspectos podem se encontrar alterados no envelhecimento e que são capazes de interferir nos níveis do BDNF e na performance cognitiva (CORREA et al., 2016; GEERLINGS et al., 2015; GIACOBBO et al., 2016; SCULLIN, 2012), foram controlados na análise da associação entre estilo de vida, níveis de BDNF e cognição.

São poucos os estudos que abordam a relação entre componentes sociais e intelectuais do estilo de vida, níveis de BDNF (SALINAS et al., 2017) e cognição (JAMES et al., 2011; WILSON et al., 2002). A maioria das investigações nesse campo aborda somente os efeitos do exercício físico (ERICKSON et al., 2011; VAUGHAN et al., 2014). Desta forma, analisamos a relação dos diferentes componentes do estilo de vida (atividades sociais, intelectuais e físicas), desempenho cognitivo e níveis de BDNF.

2. JUSTIFICATIVA

Projeções demográficas apontam para um aumento substancial na parcela idosa da população brasileira nos próximos anos (IBGE, 2010).

Considerando-se que o envelhecimento é acompanhado de mudanças importantes, dentre elas, alterações cognitivas, as quais podem representar um fator incapacitante para o idoso (DEARY et al., 2009), é importante que se desenvolvam estudos sobre a função cognitiva nesta fase da vida.

Sugere-se que o estilo de vida dos idosos pode contribuir significativamente para um envelhecimento cognitivo bem-sucedido. Os níveis de atividades físicas, sociais e intelectuais vêm sendo associados à capacidade de compensação cognitiva e à proteção contra o declínio cognitivo no envelhecimento e (BALLESTEROS et al., 2015; ERICKSON; GILDENGERS; BUTTERS, 2013; FRATIGLIONI; PAILLARD-BORG; WINBLAD, 2004; MILGRAM et al., 2006), contudo, esses dados são insuficientes e pouco conclusivos. Além do que, os estudos que tratam da associação entre o estilo de vida e a cognição geralmente consideram somente um dos componentes do estilo de vida em suas análises (ERICKSON et al., 2011; LIU-AMBROSE et al., 2012; WILSON et al., 2005).

Pesquisas em modelos animais que tentam reproduzir um estilo de vida mais estimulante através de protocolos de enriquecimento ambiental (com maior oferta de estímulos sensoriais, motores e cognitivos) têm relatado benefícios como: melhora no aprendizado e memória, neurogênese, plasticidade sináptica e maior expressão de neurotrofinas, como o BDNF (MORA; SEGOVIA; DEL ARCO, 2007; VAN PRAAG; KEMPERMANN; GAGE, 2000) que tem sido sugerido como modulador desses efeitos do ambiente enriquecido (FARES et al., 2013). Da mesma forma, estudos intervencionais que observam associação positiva entre atividade física, níveis de BDNF e desempenho em testes cognitivos em idosos (ERICKSON et al., 2011; VAUGHAN et al., 2014), atribuem ao BDNF o papel de mediador dos efeitos benéficos do estilo de vida sobre a saúde mental. Todavia, os mecanismos moleculares que suportam os efeitos do estilo de vida ainda não foram completamente elucidados, sendo altamente relevante identificar marcadores biológicos do grau de integridade e declínio da função cerebral.

O presente estudo apresenta grande relevância, visto que, analisa os efeitos dos componentes social, intelectual e físico do estilo de vida sobre a capacidade de compensação cognitiva e sobre os aspectos cognitivos de uma mesma amostra de idosos, além de investigar mecanismos moleculares que podem modular os benefícios associados ao estilo de vida sobre a saúde mental. Através desta investigação pretendemos contribuir para o avanço do conhecimento a respeito de fatores importantes para a prevenção, manejo e reabilitação de distúrbios cognitivos associados ao envelhecimento.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Analisar a relação entre o estilo de vida (engajamento em atividades sociais, intelectuais e físicas), desempenho cognitivo, capacidade de compensação cognitiva e níveis de BDNF em idosos.

3.2 OBJETIVOS ESPECÍFICOS

- Caracterizar o engajamento em atividades cognitivas, sociais e intelectuais em uma amostra de idosos;
- Verificar a associação entre o desempenho cognitivo e o engajamento em atividades sociais, intelectuais e físicas;
- Averiguar a relação entre os níveis de BDNF e o engajamento em atividades sociais, intelectuais e físicas;
- Avaliar a relação entre componentes do estilo de vida e compensação cognitiva.

CAPÍTULO II

ARTIGO CIENTÍFICO I: "An investigation on the association of Social, Intellectual and Physical Activities with BDNF Levels and Cognitive performance in Healthy Older Adults: a cross-sectional exploratory study"

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CAPÍTULO II

An investigation on the association of Social, Intellectual and Physical Activities with BDNF Levels and Cognitive performance in Healthy Older Adults: a cross-sectional exploratory study

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ABSTRACT

Objectives: Explore the association of social, intellectual and physical activities with BDNF levels and cognitive performance in a sample of healthy older adults.

Methods: This cross-sectional exploratory study analyzed a sample of healthy older adults (≥ 60 years, n=58) recruited from the community. Exclusion criteria included severe depression, dementia and other neurological disorders, major unstable medical illnesses and systemic conditions or medications with known effects on serum BDNF levels and cognitive performance. Subjects were subdivided in quartiles according to the scores in social, intellectual or physical activity questionnaires. Thus, for each of these lifestyle components four subgroups with different levels of engagement were obtained. All subjects were controlled for cortisol levels (analyzed by radioimmunoassay), sleep quality and subjective memory complains and submitted to cognitive performance evaluation. Serum BDNF was measured by sandwich-ELISA.

Results: Among the lifestyle characteristics, only physical activity showed significant positive associations with BDNF levels. This result was not modified by the introduction of scores on social and intellectual activities as covariates in the statistical analysis. None of the lifestyle characteristics affected the performance on neuropsychological tests that evaluated working memory, attention, response inhibition and task switching.

Conclusion: Among the lifestyle characteristics evaluated in this study, only physical activity showed potential to modulate BDNF levels in healthy older adults. However, this effect of physical activity was not accompanied by alterations on cognitive performance.

Keywords: elderly, BDNF, exercise, lifestyle, cognition

Strengths and limitations of this study

First study to analyze the association between intellectual lifestyle activities in older adults and BDNF levels.

Social, intellectual and physical activities were simultaneously evaluated in the same sample, allowing the analysis of their effects on BDNF levels and cognition as main variables or as covariates, strengthening the outcomes.

The applicability of IPAQ-L in this study was previously examined in a small subgroup representative of our main sample, which showed an acceptable positive association between IPAQ-L scores and VO_2max.

The range and stratification of social and intellectual activities was limited by the sample size and composition, hampering the conclusions about their association with BDNF levels and cognition.

INTRODUCTION

Maintenance of an enriched lifestyle, has been associated with a decreased risk of cognitive decline and dementia, and therefore with the promotion of independence and quality of life (BALLESTEROS et al., 2015; VALENZUELA; SACHDEV, 2009). There are also evidences that engagement in social, intellectual and physical activities can improve performance on different cognitive tests (COELHO et al., 2013; JAMES et al., 2011; RAHE et al., 2015).

The mechanisms responsible for the beneficial effects of these lifestyle factors on mental health are only partially understood. Studies with animals suggest that the brain-derived neurotrophic factor (BDNF) is one of the mediators of the improving effects of environmental enrichment (increased social, sensorio-motor and physical activity opportunities) on neuronal plasticity and performance on different memory tasks (FARES et al., 2013). Among these lifestyle factors, physical activity seems to induces the most robust changes in BDNF levels and neuronal function.(KOBILO et al., 2011) Intervention studies with older adults also suggest that BDNF could be a mediator of the cognitive improvement induced by physical activity (COELHO et al., 2013; ERICKSON et al., 2011; VAUGHAN et al., 2014). However, studies on the effects of social and intellectual activities on this neurotrophin are scarce (RAHE et al., 2015; SALINAS et al., 2017). Additionally, most of the studies that evaluate the effects of social, intellectual or physical activity on mental health analyze only one of these parameters each time, without even controlling for the other lifestyle components.

The present study evaluated the social, intellectual and physical activities of a sample of community-dwelling older adults. In doing so, we aimed to explore separately the association of each of these lifestyle components with BDNF levels and cognitive performance. However, differently from former studies, we were able to control for social, intellectual, and physical activity simultaneously. Moreover, we also controlled for cortisol levels (a stress associated hormone) and sleep quality, which are known to affect BDNF levels and cognitive performance (CORREA et al., 2016; GIACOBBO et al., 2016). With this carefully designed study we intended to advance the knowledge of the association between lifestyle factors and successful aging.

METHODS

Participants

Fifty eight older adults (69.22 ± 5.94 years, 13 men) were recruited from the community. Exclusion criteria included neurological disorders, major unstable medical illnesses and systemic conditions or medications with known effects on serum BDNF levels and cognitive performance, scores on Mini Mental Status Examination (MMSE) (BERTOLUCCI et al., 1994) and Beck Depression Inventory (BDI) (CUNHA, 2011) suggestive of dementia or severe depression, respectively.

This study was approved by the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (Porto Alegre/ Brazil) under the protocol number 528/11 and performed in accordance with the ethical standards of the1964 Declaration of Helsinki. All participants gave their written informed consent.

Demographic and Clinical assessments

Socioeconomic status was assessed with the “Criterio Brasil” Questionnaire, (ABEP (ASSOCIAÇÃO BRASILEIRA DE EMPRESAS DE PESQUISA), [s.d.])

subjective memory complains were evaluated with the Memory Complaint Questionnaire (MAC-Q) (MATTOS et al., 2003) and sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) (BERTOLAZI et al., 2011).

Social and intellectual activity measurement

Intellectual and social activities within the last year were evaluated with the Intellectual and Social Activities Assessments (MENDES DE LEON; GLASS; BERKMAN, 2003; WILSON et al., 1999). The scores of these questionnaires range from 6 to 30, for social activities, and 7 to 35, for intellectual activities. The lowest scores indicate engagement in these activities only once a year or less, whereas the highest scores indicate every day or almost every day engagement.

Physical Activity measurement

Physical activity was assessed with the International Physical Activity Questionnaire – Long form (IPAQ-L) (MATSUDO et al., 2001). This questionnaire covers frequency (number of days) and average duration (minutes or hours/day) of four activity domains (work-related, transportation, domestic and recreational physical activities) within the last week. However, it is validated only for subjects up to 69 years. Thus, we first evaluated if IPAQ-L would be appropriate to be used in our study. Therefore, the association of IPAQ-L and maximal oxygen consumption (VO_2max) was investigated in a small subsample of subjects (n=23).

The VO_2max test was conducted by an experienced cardiologist and followed a validated maximal graded treadmill test (MEEUSEN et al., 2010). The electrocardiogram was monitored during the exercise (POLAR Accurex, Kempele, Finland) and respiratory gases were measured using an ergoespirometer (VO2000 Medical Graphics, St. Paul, Minnesota, USA).

In the IPAQ-L questionnaire only those activities with a minimum length of 10 consecutive minutes were scored and data are expressed as energy requirements, defined in multiples of the resting metabolic rate (MET- minute), for the set of physical activities reported by the subjects.(“International Physical Activity Questionnaire”)

Serum BDNF measurement

Serum BDNF was analyzed as previously described (CORREA et al., 2016). In short, blood was collected by venipuncture into a free-anticoagulant vacuum tube, centrifuged at 4000 g for 10 min and serum was then frozen at −80°C until further analysis. BDNF levels were measured using and ELISA kit and following the manufacturer’s instructions (catalogue no. CYT306, Millipore, USA).

Salivary Cortisol measurement

Saliva was collected at home at wake- up time (between 7 and 8 AM), 4 PM and 10 PM. The samples were stored between 0º C and 4ºC by the subjects and delivered to the laboratory, where they were frozen at -80º C until further analysis. After thawing, samples were centrifuged (1500 rpm/3 minutes) and cortisol levels analyzed by radioimmunoassay (Beckman Coulter, California – USA). The sensitivity of these assays was estimated at 0.06 nmol/L. The intra- and inter-assay coefficients of variation were less than 10%. Results for salivary cortisol are expressed as the area under the curve (AUC_G) (PRUESSNER et al., 2003).

Neuropsychological measures

Participants completed neuropsychological tests to evaluate effect of life style on cognitive functions including working memory, attention, response inhibition and task switching. Therefore, Trail Making A and B (SPREEN O, 2006), Digit Span (NASCIMENTO, 2004) and the Stroop Color and Word (SPREEN O, 2006) tests were administered to the volunteers. All procedures related to the neuropsychological assessments followed the recommended guidelines for each specific task and have been briefly described elsewhere (CORREA et al., 2016; GIACOBBO et al., 2016).

Data analysis

Differences between groups on demographic and clinical characteristics were analyzed with one-way analysis of variance (ANOVAs) and chi-squared statistics. The association between VO_2max and IPAQ-L was assessed by curve estimation analysis. The effects of lifestyle on BDNF and neuropsychological aspects were investigated after the subdivision of the main sample into quartiles according to the scores obtained in the lifestyle questionnaires (see results section). The resulting subgroups were analyzed with ANOVAs followed by Bonferroni’s post hoc test, whenever necessary. These statistical evaluations were repeated entering significant between group differences on demographic and clinical parameters as covariates (to evaluate their potential effects as confounding variables). All variables met parametric assumptions.

Results are expressed as mean ± standard deviation (M±SD) and $p<0.05$ was accepted as statistically significant.

RESULTS

Association of IPAQ-L scores and VO_2max results

Demographic and physical activity data of the sample can be seen in Table 1. The regression analysis, in which IPAQ-L was the independent and VO_2max the dependent variable, showed a significant S curve (R^2=0.44; p= 0.001), suggesting that IPAQ-L has a better association to VO_2max for subjects in the lowest and highest limits of the physical activity range of the sample.

Insert table 1

Demographic, clinical and lifestyle characteristics

Table 2 summarizes the demographic, clinical and lifestyle characteristics of the main sample subjects. The sample is relatively homogeneous in relation to social and intellectual activity. Moreover, the scores for these lifestyle characteristics suggest that subjects are more frequently engaged in intellectual than social activity. Analysis of the mean IPAQ-L scores suggest that the study sample could be classified in the moderate level category of physical activity. Notwithstanding, the standard deviation of the IPAQ-L mean indicates a rather heterogeneous sample, including subjects from sedentary to intense physical activity lifestyles. The IPAQ-L questionnaire also revealed that most of the study volunteers performed mainly aerobic activities (walking, running, oriented aerobic exercises and activities related to housework and gardening) and could be classified in different levels of the moderate exercising category.(“International Physical Activity Questionnaire”)

Insert table 2

Social activity and its relation with BDNF and cognition

In order to explore the associations among these variables we first ranked the main sample according to the scores on the social activity questionnaire, subdividing it in quartiles and originating four subgroups (levels of social activity in brackets): 1st quartile [10.35±0.92], 2nd quartile [12.35±0.92], 3rd quartile [13.6±0.50] and 4th quartile [17.46±2.06]. The comparison of these subgroups showed no significant differences for demographic, clinical and lifestyle (intellectual and physical activities) characteristics (all $p>0.05$). Moreover, no consistent differences were seen for BDNF levels and neuropsychological parameters between the subgroups (all $p>0.05$).

Intellectual activity and its relation with BDNF and cognition

A new ranking and subdivision of the main sample was done based on the scores of the intellectual activity questionnaire, originating four new subgroups (levels of intellectual activity in brackets): 1st quartile [18.50±2.62], 2nd quartile [22.64±1.00], 3rd quartile [25.26±0.79] and 4th quartile [28.53±1.30]. The comparison of these subgroups indicated that they were homogenous for demographic, clinical and lifestyle (intellectual and physical activities) characteristics (all $p>0.05$). Besides, no consistent differences were identified for BDNF levels and scores on neuropsychological tests between these subgroups (all $p>0.05$).

Physical activity and its relation with BDNF and cognition

After a third ranking and subdivision of the main sample according to the scores on the IPAQ-L, four subgroups with different levels of physical activity emerged (Table 3). The comparison of demographic, clinical, physiological and neuropsychological parameters of these four subgroups indicated significant differences between them only for MMSE [$F(3,54)= 3.532$, $p= 0.021$], intellectual [$F(3,54)=3.561$, $p=0.020$] and social [$F(3,54)=5.909$,$p=0.01$] activity scores, BDNF levels [$F(3,54)=4.685$, $p= 0.006$] and performance on Backward Digit Span [$F(3,54)=4.987$, $p= 0.004$]. Social activity scores were higher and BDNF levels were lower in the 1st quartile subgroup in relation to all other subgroups (all $p<0.05$). Scores on MMSE and intellectual activity questionnaire were slightly higher for the 3rd quartile subgroup in the relation to the 4th quartile subgroup ($p = 0.031$ for MMSE and $p=0.024$ for intellectual activity), whereas performance on Backward digit span was better in 2nd quartile subgroup in relation to the 3rd ($p=0.011$) and 4th quartile ($p=0.008$) subgroups. The statistical analysis to evaluate the effects of physical activity on BDNF levels was repeated entering scores on MMSE, Backward digit span and social and intellectual activities as possible confounding factors. However, covariance analysis showed no significant effects of these variables as covariates [all $p>0.05$]. Thus, the results described earlier for BDNF remained unchanged.

DISCUSSION

The main objective of this study was to verify if the beneficial effects of social, intellectual and physical activity on mental health (previously shown by longitudinal and interventional investigations) could be identified in a transversal analysis of healthy older adults. The results did not identify consistent effects of these lifestyle factors on cognitive functions, but showed a beneficial effect of physical activity on BDNF levels.

In this study lifestyle characteristics were evaluated with subjective validated questionnaires. This is a well-accepted method to evaluate social and intellectual activities. However, physical conditioning is normally analyzed using physiological (e.g. VO_2max) or motor activity (e.g. accelerometer measures) parameters (DE ARAÚJO et al., 2015; TUDOR-LOCKE et al., 2010; VAUGHAN et al., 2014). We choose to evaluate subjects' physical activity levels with the IPAQ-L questionnaire to maintain the maximum possible uniformity across the methods used to analyze social, intellectual and physical activity. The IPAQ-L is a widely used questionnaire (VAN POPPEL et al., 2010), with excellent test-retest reliability (CRAIG et al., 2003) and capable to capture a reliable picture of the physical activity routine. However, we were also aware that its applicability to elderly populations remains scarce and controversial (DE ARAÚJO et al., 2015; DE FÁTIMA CABRAL et al., 2017; MILANOVIĆ et al., 2014; VAN POPPEL et al., 2010). Thus, we first analyzed the relation of IPAQ-L with VO_2max in a small subgroup representative of our main sample. The results indicated that IPAQ-L and VO_2max had an acceptable positive association (showing the strongest correlations at the 1^{th} and 4^{th} quartiles of the IPAQ-L range), providing the necessary confidence for the use of IPAQ-L questionnaire in the present study.

There is no consensus in the literature about the beneficial effect of social or intellectual engagement on cognition (LAM et al., 2015; SALTHOUSE; BERISH; MILES, 2002). In the present study, no significant associations between social or intellectual activity levels with the mental health parameters (BDNF, objective neuropsychological performance and subjective memory complains) were identified. It must be emphasized here that our sample showed a relatively narrow distribution in the social and intellectual activities range. This is not surprising. The subjects of this study were healthy, independent community-dwelling older adults with similar demographic and clinical parameters, making them more likely to participate in similar types and levels of intellectual and social activities. Thus, future studies should investigate a sample with a broader range of social and intellectual activity.

Physical activity was also not significantly associated with objective tests of attention, executive function and working memory, or with subjective memory complains. However, the results showed that subjects with the lowest levels of physical activity in the sample (1st quartile subgroup according to IPAQ-L) also had the lowest BDNF levels. There are different intervention studies that support the idea that physical activity can improve BDNF levels in older adults and promote mental health (ERICKSON et al., 2011; VAUGHAN et al., 2014). Even so, the most appropriate type of physical intervention to increase BDNF levels and improve cognition remains a matter of debate (BARHA et al., 2017). Based on the formal IPAQ-L classification of low, moderate and intense physical activity, (“International Physical Activity Questionnaire”) we realized that most of the subjects of the present study performed mainly aerobic activities of moderate intensity, which seem to be among the most effective physical activities for BDNF modulation in older adults (COELHO et al., 2013).The subgroups of the 2nd, 3rd and 4th quartiles of IPAQ-L represent different levels among the range of moderate intensity exercises, and showed no significant differences in BDNF levels between them. This result could reflect that moderate activity has always the same effect on BDNF, irrespective of the level in which it is performed. However, it cannot the ruled out that this lack of between group differences reflects a lack of sensitivity of the IPAQ-L in this range of physical activities, especially at the 2nd and 3rd quartile subgroups, as suggested by our regression analysis. On the other hand, the only subgroup that included subjects with physical activity levels below the cut-off for moderate intensity was precisely the subgroup that showed the lowest BDNF levels, i.e., 1st quartile subgroup. Thus, our results clearly show that the increase in exercise levels from low to moderate intensity is accompanied by BDNF increases.

The conclusion that moderate physical activity levels have positive effects on BDNF levels is reinforced by the homogeneity of the subgroups on their demographic and clinical characteristics and the lack of effects, as covariates, of the variables that were significantly different between groups (scores on social and intellectual activities, MEEM and Backward Digit Span). Of special importance is the fact that precisely the IPAQ-L subgroup that had the lowest physical activity and BDNF levels had the highest social activity scores. However, the covariance analysis indicated that the negative effect of low physical activity on BDNF levels could not be compensated by the greater social activity of the 1st quartile subgroup.

BDNF has been repeatedly suggested as a possible mediator of the positive effects of physical activity on mental health (LECKIE et al., 2014). Moreover, have been suggested that its decrease is associated with cognitive impairments (SIUDA et al., 2017) and that its increase is associated with cognitive improvement (KENNEDY et al., 2015). However, the results of this study indicated that, despite subjects in the 1st quartile of physical activity had lower BDNF levels, their cognitive performance was not significantly different from the subgroups with higher BDNF levels. This lack of an association of BDNF levels and cognitive performance could have many explanations, including the characteristics of our sample (healthy subjects), the poor sensitivity of the neuropsychological tasks to minor cognitive differences and the fact that BDNF is not the only substance capable to modulate cognitive function. Future studies should include especially sensible neuropsychological measures, e.g. incidental memory and free-recall tasks, besides combining the analysis of more substances influenced by physical activity and capable to modulate cognition, such as other trophic factors and neurotransmitters (FABEL et al., 2003; WINTER et al., 2007).

Among the limitations regarding the current study is sample size, which was not large enough to allow a greater range and stratification of lifestyle activities, especially of intellectual and social activities. Moreover, the limitations of the questionnaires used for the evaluation of the life style components must also be taken into account (VAN POPPEL et al., 2010; WILSON et al., 1999). On the other hand, it must be highlighted that the control of a great number of variables, including sociodemographic, clinical and lifestyle parameters, is a strength of this study. Although some of these variables are routinely controlled (age, gender, education, scores on MMSE and BDI), others are normally ignored, despite the evidences of the literature that show their potential to affect BDNF levels and cognitive performance of older adults (sleep quality, cortisol levels, lifestyle variables and subjective memory complains) (CORREA et al., 2016; GIACOBBO et al., 2016; HOHMAN et al., 2011; JAMES et al., 2011; KENNEDY et al., 2015; RAHE et al., 2015; SALINAS et al., 2017).

In conclusion, among the lifestyle constituents that were evaluated only physical activity showed potential to benefit mental health, as indicated by the positive association between exercise and BDNF levels. However, far from simply meaning that social and intellectual activities are not important for mental health, our results suggest that the effects of these lifestyle parameters are probably not sufficiently robust to be identified in transversal experimental designs of healthy, independent, community-dwelling older adults. This is especially true when the subjects operate in a relatively narrow range of these lifestyle conditions, as it was the case for social and intellectual activities in our sample. Future studies with greater samples and ranges of social and intellectual activity should be designed to permit a deeper analysis of the effects of these lifestyle parameters on mental health as well as their interaction with physical activity.

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Disclosure statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

Project designed: E. Bromberg, I. I. Argimon and D. B. Lima. Data collection: D. B. Lima, A. Trapp and M. Corrêa. Data analysis and interpretation: E. Bromberg and D. B. Lima. Manuscript draft: E. Bromberg and D. B. Lima. All authors read and approved the final manuscript. E. Bromberg has full access to the data in the study and takes responsibility for the integrity and the accuracy of the data analyses.

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Table 1. Demographic, clinical and physical activity characteristics of subjects included in the evaluation of the association of IPAQ-L and VO_2max. [a]

	M+SD (N= 23)
Age (years)	64.65 + 4.06
Education (years)	14.91 + 2.93
Gender (female/male)	13/10
MMSE	28.21+ 1.85
BDI	1.95 + 2.61
IPAQ-L (MET-min/week)	2349.71 + 2078.37
VO_2max (mL · kg^{-1} · min^{-1})	11.56 + 7.71

[a] Results are expressed as the mean ± standard deviation (M ± SD). Abbreviations: MMSE, Mini Mental Status Examination; BDI, Beck Depression Inventory; IPAQ-L, International physical activities questionnaire- long form; MAC-Q, Memory Complaint Questionnaire; VO_2max, Maximal oxygen consumption.

Table 2. Demographic, clinical, lifestyle and neuropsychological characteristics of subjects of the main sample[a].

	M±SD (N= 58)
Demographic Characteristics	
Age (years)	69.22±5.94
Education (years)	12.86±4.57
Gender (female/male)	45/13
Socioeconomic status	27.56±5.68
Clinical Characteristics	
MMSE	28.14±1.33
BDI	1.55±2.27
MAC-Q	25.21±2.83
PSQI	5.19±2.92
BMI	43.06±6.86
Most frequent comorbidities (% of sample)	
Arterial hypertension	58%
Hypercholesterolaemia	37%
Diabetes Mellitus	15%
Thyreoid dysfunction	31%
Lifestyle Characteristics	
Social activities questionnaire	13.51±2.83
Intellectual activities questionnaire	23.84±4
IPAQ-L (MET-min/week)	1842.75±1574.07
Neuropsychological characteristics	
Trail A	39.31±8.35
Trail B	108.33±35.86
Stroop color-word	30.30±6.74
SPAN D	6.77±1.61
SPAN I	4.52±1.22

[a] Results are expressed as mean ± standard deviation (M±SD). Abbreviations: MMSE, Mini Mental Status Examination; BDI, Beck Depression Inventory; MAC-Q, Memory Complaint Questionnaire; PSQI, Pittsburgh Sleep Quality Assessment; BMI, body mass index; IPAQ-L, International physical activities questionnaire- long form.

Table 3. Demographic, clinical, lifestyle and neuropsychological characteristics of subjects in the experimental subgroups representing the subdivision of the main sample in quartiles according to the IPAQ-L scores[a].

	IPAQ-L Subgroups			
	1 st quartile N=14	2nd quartile N=14	3rd quartile N=15	4th quartile N=15
Demographic characteristics				
Age (years)	71.71±6.01	69.42±7.15	67.26±5.52	68.66±4.62
Education (years)	14.00±4.81	11.14±4.84	14.00±4.62	12.26±3.78
Gender (female/male)	13/1	13/1	10/5	9/6
Socioeconomic status	27.92±5.53	25.21±5.82	28.46±5.75	28.53±5.55
Clinical Characteristics				
MMSE	27.81±1.41	28.50±0.85	28.80±0.33**	27.46±1.84
BDI	2.14±2.17	1.50±2.62	1.00±2.00	1.60±2.35
MAC-Q	25.35±2.70	24.99±3.05	25.85±2.68	24.63±3.03
PSQI	5.53±3.36	5.28±2.39	5.20±3.38	4.80±2.67
BMI	43.23±5.22	40.08±4.48	45.17±8.17	43.59±8.19
Lifestyle Characteristics				
Social activity questionnaire	15.64±3.31***	11.85 ± 1.95	13.20±2.39	13.46±2.89
Intellectual activity questionnaire	24.85±4.53	23.07±3.58	25.80±3.58**	21.66±3.26
IPAQ-L (MET-min/week)	685.46±258.24*	1255.46±184.11	1852.83±180.12	3460.96±2339.23
Biological measures				
BDNF (ng/l)	331.62±122.82#	442.21±93.93	432.06±53.61	449.70±103.13
Cortisol AUC	144.98±37.95	142.07±40.99	140.77±42.35	126.52±18.92
Neuropsychological characteristics				
Trail A	41.00±10.26	39.15±8.11	35,79±8.36	41.42±5.85
Trail B	114.50±38.86	102.54±35.19	97.62±37.37	117.75±31.26
Stroop color-word	29.79±3.74	30.98±4.07	33.26±6.65	27.20±9.58
SPAN D	7.17±1.51	7.00±1.88	6.33±1.87	6.61±1.12
SPAN I	4.63±0.70	5.42±1.39##	4.06±1.09	4.02±1.13

[a] Results are expressed as mean ± standard deviation (M±SD). [b] Mean ± SD of IPAQ-L , expressed as MET- min, of each subgroup. Abbreviations: MMSE, Mini Mental Status Examination; BDI, Beck Depression Inventory; MAC- Q, Memory Complaint Questionnaire; PSQI, Pittsburgh Sleep Quality Assessment; BMI, body mass index; IPAQ-L, International physical activities questionnaire- long form; BDNF, Brain-derived neurotrophic factor; Cortisol AUC, cortisol area under the curve.
*p<0.0001 compared to other groups
**p<0.05 compared to 4th quartile group
***p<0.05 compared to other groups
# p<0.05 compared to other groups
##p< 0.05 compared to 3rd and 4th quartile groups

CAPÍTULO III

ARTIGO CIENTÍFICO II: “ Exploring the association of encoding strategies and physical activity on contextual memory improvement of older adults.”

Artigo aceito pelo periódico aging and Mental Health

CAPÍTULO III

Episodic memory boosting in older adults:

Exploring the association of encoding strategies and physical activity

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Abstract

Background: Contextual memory is susceptible to the effects of aging and its impairment compromises episodic memories and quality of life in older adults.

Objective: Compare the effect of cognitive support on incidental contextual memory free recall and recognition with a naturalistic experimental paradigm and explore the association of encoding strategies and physical activity on memory improvement.

Methods: Subjects (≥ 60 years, n=52) were assigned to one of two encoding conditions for the contextual memory task: with or without an incidental associative instruction to encourage association of an item to its spatial context. Immediate free recall and recognition tests were run to assess the encoding instruction efficiency. The analysis of the association of memory performance and physical activity was done using the scores on the International Physical Activity Questionnaire (IPAQ-L) to subdivide each experimental group into Low IPAQ-L (bellow median) and High IPAQ-L (above median) subgroups.

Results: The associative encoding instruction increased contextual memory free recall and recognition, with greater effects on free recall. The most robust associations between physical activity and contextual memory were also seen for free recall, in which higher levels of physical activity corresponded to increased baseline performance (no associative encoding condition) and greater improvement of memory by the encoding support (associative encoding condition).

Conclusion: As recognition, free recall of contextual memory is sensible to encoding strategies and prone to rehabilitation. Moreover, higher physical activity levels were positively associated with encoding strategies on contextual memory improvement, increasing the availability of latent process-based components of the cognitive reserve.

Keywords: cognition, elderly, episodic memory, physical activity

Introduction

Among the most common subjective memory complains of older adults are those related to episodic, or autobiographical, content (Craik & Rose, 2012). Although they can remember that a particular event occurred or have knowledge of a fact, older adults are less able to remember where or when the event happened, how they acquired knowledge about some fact and what where the particular features or attributes of the learning situation (Grady & Craik, 2000). These spatiotemporal and perceptual attributes of episodic memories are known as contextual memory (Johnson, Hashtroudi, & Lindsay, 1993).

It is assumed that the hippocampus is responsible for the integration of central and contextual features of episodic memories (Eichenbaum, Yonelinas, & Ranganath, 2007; Johnson et al., 1993). However, the efficiency of this integration depends largely on the prefrontal cortex, which organizes incoming information during encoding, thereby enhancing binding by the hippocampus (Dennis et al., 2008; Johnson et al., 1993). Thus, contextual memory impairments in older adults seem to be especially related to the high vulnerability of prefrontal cortex to the adverse effects of aging (Raz et al., 2005) and, consequently, to an inability to spontaneously bind contextual details to memory for the item itself (Naveh-Benjamin, 2000; Smith, Park, Earles, Shaw, & Whiting, 1998).

Different studies indicate that contextual memory impairments can be reduced, or even abolished, when environmental support is present (Bisol Balardin et al., 2009; Glisky, Rubin, & Davidson, 2001; Naveh-Benjamin & Craik, 1995). However, most of these studies were based on intentional learning and/ or recognition tests (Cohn, Moscovitch, & Davidson, 2010; Gutchess et al., 2007; Kirchhoff, Anderson, Barch, & Jacoby, 2012). Notwithstanding, in daily life contextual features of episodic memories are mainly acquired without conscious effort (i.e., incidentally acquired) and free recall is more common than recognition or cued recall. Unfortunately, older people's performance is worse on free recall, probably because it requires more self-initiated activity or more processing resources than recognition and cued recall tasks do (Craik & McDowd, 1987), making the process of memory retrieval less automatic and more difficult (Hasher & Zacks, 1979). Thus, the improvement of daily life activities that depend upon episodic memories requires a better understanding of factors than can help to effectively enhance the incidental aspects of contextual memory and its free recall.

At this point, it is worth mentioning that the pattern and degree of cognitive alterations in non-demented older adults is heterogeneous, with some of them showing significant impairments while others maintain relatively constant performances throughout the aging process (Daffner, 2010). The reason for this heterogeneity is only partially understood, but among the factors that seem capable to modulate cognitive integrity on older age is life style. Active lifestyles, including social, cognitive and physical activities, seem to enhance cognitive reserve and protect against cognitive decline (Wang, MacDonald, Dekhtyar, & Fratiglioni, 2017). Physical activity seems to be one of the most robust modulators of mental health (Gorelick et al., 2017), showing consistent positive associations with cognitive performance (Tarazona-Santabalbina et al., 2016; Vedovelli et al., 2017) as well as with prefrontal and hippocampal volumes in older adults (K. Erickson, Leckie, & Weinstein, 2014).

Given the importance of contextual memory in daily functioning and the impact that its impairment may have on quality of life (Rajah, Languay, & Valiquette, 2010) we aimed to evaluate if free recall of incidental contextual memory can be improved (as already shown for contextual memory recognition) and if late life physical activity is able to contribute to contextual memory amelioration. Thus, using a cross-sectional approach and a sample of community dwelling older adults, we first evaluated the effect of cognitive support at encoding on free recall and recognition of contextual memory. The performance on the encoding condition without cognitive support is believed to reflect the use of cognitive resources that still can be automatically (i.e., spontaneously) engaged by the subject to link the central item to its context. Cognitive support at encoding, on the other hand, is expected to improve performance if latent process-based components (such as neural reserve and neural compensation) are available, thus indicating the existence of a cognitive reserve that, although not automatically engaged, is prone to rehabilitation. Secondly, we investigated the association between different levels of physical activity and different encoding conditions (with or without cognitive support) on free recall and recognition tests for contextual memory. In order to strengthen the study, we controlled for different lifelong (educational level, socioeconomic status), late life (current intellectual and social activities), health (subjective memory complains depression symptoms, sleep quality, cortisol levels) and neuropsychological parameters that could interfere with the interpretation of our results (Czernochowski, Fabiani, & Friedman, 2008; Geerlings et al., 2015; James, Boyle, Buchman, & Bennett, 2011; Scullin, 2012; Snitz et al., 2015; Tucker-Drob, Johnson, & Jones, 2009; R. S. Wilson et al., 2002). Our hypothesis were that (I) cognitive support at encoding would improve free recall besides recognition, and that (II) subjects with higher physical activity levels would show an advantage on contextual memory performance on both encoding conditions (with and without cognitive support).

Methods

Participants

Fifty two older adults (68.84 ± 6.25 years, 10 men) were recruited through advertising in different older adults groups from the community (Porto Alegre, Brazil). Sample size was calculated considering previous results of our research group on contextual memory of healthy older adults (Corrêa et al., 2014). Exclusion criteria included neurological disorders and injuries, major unstable illnesses, current use of medications with known effects on cognitive performance or hypothalamus-pituitary-adrenal axis, Mini Mental Status Examination (MMSE) suggestive of dementia (cut-off adjusted for the Brazilian population) (Bertolucci, Brucki, Campacci, & Juliano, 1994), Beck Depression Inventory (BDI) (Cunha, 2011) indicating severe symptoms, visual and hearing impairments that could compromise the neuropsychological assessment. This study was approved by the Research Ethics Committee of the Pontifical Catholic University (Porto Alegre, Brazil) under the protocol number 528/11. All participants gave written informed consent before beginning the experimental procedures.

Demographic and Clinical assessments

Socioeconomic status was assessed with the “Criterio Brasil” Questionnaire (ABEP (Associação Brasileira de Empresas de Pesquisa), subjective memory complains were evaluated with the Memory Complaint Questionnaire (MAC-Q) (Mattos et al., 2003) and sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) (Bertolazi et al., 2011).

Social and intellectual activity measurement

Intellectual and social activities within the last year were evaluated with the Intellectual and Social Activities Assessments (Mendes de Leon, Glass, & Berkman, 2003; R. Wilson et al., 1999). The scores of these questionnaires range from 6 to 30, for social activities, and 7 to 35, for intellectual activities. The lowest scores indicate engagement in these activities only once a year or less, whereas the highest scores indicate an every day or almost every day engagement.

Physical activity Evaluation

Physical activity was examined with the widely used International Physical Activity Questionnaire – Long form (IPAQ-L) (Matsudo et al., 2001). This 19-item questionnaire has excellent test-retest reliability (pooled r= 0.81) and acceptable validity (mean ρ= 0.30) for subjects aged 15-69 years (Craig et al., 2003). It covers frequency (in number of days) and average duration per day (in hours and minutes) of four activity domains (work-related, transportation, domestic and recreational physical activities) within a time frame of the last week. Only those activities with a minimum length of 10 consecutive minutes are scored. Data are expressed as energy requirements, defined in multiples of the resting metabolic rate (MET- minute/week), for the set of physical activities reported by the subjects.

Neuropsychological measures

Participants completed objective neuropsychological tests to control for significant between group differences in attention, working memory, visuospatial perception and executive function, since limitations of older adults on such resources could hinder contextual memory establishment (Dennis et al., 2008; Gagnon, Soulard, Brasgold, & Kreller, 2007; Spreen & Strauss, 2006). Therefore, Digit Span

(Nascimento, 2004), Trial Making A and B (Spreen & Strauss, 2006) and the Stroop Color and Word Test (Spreen & Strauss, 2006), were administered to the volunteers.

Contextual memory task

The methods for evaluation of encoding strategies on incidental context recognition have already been described (Bisol Balardin et al., 2009; Corrêa et al., 2012, 2014; Moro dos Santos et al., 2010). Briefly, subjects were randomly assigned to one of two different incidental encoding conditions (with or without cognitive support at encoding) and completed a training session being unaware that a test session (composed by free recall and recognition tasks) would follow. During training 18 target objects were depicted in different spatial contexts (a living room, a kitchen and an office) and participants judged how often each portraited object is used in their daily activities (no associative condition, corresponding to the condition without cognitive support at encoding) or how well it fitted into the room displayed (associative condition, corresponding to the condition with cognitive support at encoding). The associative condition is expected to encourage the participants to integrate item and context at encoding, increasing performance in the test session.

For the contextual free recall test, participants were encouraged to enumerate all the objects they remembered from the training session and specify the location (living room, kitchen or office) in which the object was shown. This free recall test was run 5 min after the training session and immediately before the recognition test.

At the contextual recognition test 36 objects were shown (18 targets plus 18 distractors). For each object correctly identified (forced old/new judgment), three photographs were presented (object in the living room, kitchen or office) and participants were requested to make a context recognition (indicate in which of the three locations the object appeared in the training session).

Incidental contextual memory scores were calculated as follows: (1) free recall: proportion of correct contexts recalled from objects accurately remembered; (2) recognition: proportion of objects attributed to the correct context considering the objects accurately identified as old. Performance increases from the no associative to the associative encoding condition will be considered as indicative of cognitive reserve.

In order to evaluate the relation of physical activity on memory for contexts we subdivided each of the experimental groups (with or without an associative encoding condition) according to their IPAQ-L median into two subgroups: Low IPAQ-L (IPAQ-L values bellow the median) and High IPAQ-L (IPAQ-L values above median) (Table 2).

The results obtained in the contextual memory will be interpreted as follows: (1) scores on the no associative encoding condition indicates the use of cognitive resources that still can be automatically engaged by the subject to link the central item to its context; (2) performance improvement on the associative encoding condition indicates the existence of cognitive reserve components that, although not automatically engaged by the subject (as shown by the performance in the low support condition), are prone to rehabilitation (as shown by the performance in the low support condition).

Salivary Cortisol measurement

Saliva was collected at home at wake- up time (between 7 and 8 AM), 4 PM and 10 PM. The samples were stored between 0º C and 4ºC by the subjects and delivered to the laboratory, where they were frozen at -80º C until further analysis. After thawing, samples were centrifuged (1500 rpm/3 minutes) and cortisol levels analyzed by radioimmunoassay (Beckman Coulter, California – USA). The sensitivity of these assays was estimated at 0.06 nmol/L. The intra- and inter-assay coefficients of variation were less than 10%. Results for salivary cortisol are expressed as the area under the curve (AUCG) (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Data analysis

Demographic, clinical, physical activity and neuropsychological characteristics were analyzed with independent samples t tests, one-way analysis of variance (ANOVA) and chi-squared statistics.

Effects of the encoding condition on contextual memory were evaluated with two-way ANOVA, with type of memory test (free recall X recognition) as the within variable and type of encoding instruction (associative or no associative encoding condition) as the between group variable. These results were further explored with one-way ANOVAs for dependent (free recall X recognition) and independent (associative or no associative encoding condition) samples, followed by Bonferroni's post hoc test, whenever necessary.

The relations of physical activity and memory performance were also evaluated with a two-way ANOVA, with type of memory test (free recall X recognition) as the within variable and the physical activity level in the different encoding conditions (Low IPAQ-L no associative encoding X High IPAQ-L no associative encoding X Low IPAQ-L associative encoding X High IPAQ-L associative encoding) as the between group variable. These analysis were also followed by separate one-way ANOVAs and Bonferroni's post hoc test, whenever necessary.

Finally, all these statistical evaluations were repeated entering significant between group differences on demographic, clinical and neuropsychological parameters as covariates, to evaluate their potential effects as confounding variables. All data met parametric assumptions. Results are expressed as mean ± standard deviation (SD) and $p<0.05$ was accepted as statistically significant.

Results

Demographic, clinical and lifestyle characteristics

Table 1 summarizes the demographic, clinical, lifestyle and neuropsychological characteristics of the experimental groups that performed the contextual memory task in the no associative and associative encoding conditions. As can be seen, no significant between group differences were found for any of these variables (all $p>0.005$)

Insert table 1 about here.

Contextual free recall and recognition – Evidences for the existence of Cognitive Reserve

Overall free recall and recognition performance on contextual memory can be found in Figure 1. The two-way ANOVA indicated a significant effect of type of memory test [$F(1,50)=7.931$, $p=0.007$], encoding instruction [$F(1,50)= 21.26$, $p < 0.001$] and an interaction between encoding instruction and type of memory test [$F(1, 50)=12.933$, $p<0.001$]. Further data analysis showed that contextual recognition scores were significantly greater than free recall scores in the no associative encoding condition [$F(1,21)=12.352$, $p=0.002$]. Introduction of the associative encoding instruction increased the performance on contextual memory recognition [$F(1,50)=6.062$, $p=0.017$] and free recall [$F(1,50)=27.173$, $p<0.001$], suggesting the existence of a cognitive reserve. Moreover, the introduction of the associative encoding condition was able to match the scores of contextual memory free recall and recognition [$F(1,29)=0.529$, $p=0.473$], abolishing the disadvantage initially seen for free recall in comparison to recognition in the no associative encoding condition [$F(1,29)= 12.352$, $p=0.002$].

Insert figure 1 about here.

Relation between physical activity and contextual memory performance

As explained before, in order to evaluate the relation of physical activity and cognitive reserve we subdivided each of the experimental groups (with or without an associative encoding condition) according to their IPAQ-L median into two subgroups: Low IPAQ-L (IPAQ-L values bellow the median) and High IPAQ-L (IPAQ-L values above median). The composition of the four experimental subgroups is shown in table 2. As expected, we found significant differences for exercise energy requirements (MET-min/week) between Low IPAQ-L and High IPAQ-L subgroups [all $p<0.05$]. However, no significant differences of physical activity scores between the two Low IPAQ-L subgroups [$p =0.588$], or between the two High IPAQ-L subgroups [$p=0.820$], were found. Moreover, as can be seen in Table 2, some between group differences emerged for gender [$p=0.031$], MMSE [$p=0.007$].

Insert Table 2 about here

Statistical analysis of contextual free recall and recognition performances also indicated significant effects of the type of memory test [$F(3, 48)=8.950$, $p=0.004$], of the physical activity level in the different encoding conditions [$F(3, 48)=16.015$, $p<0.001$] and revealed an interaction between physical activity and type of memory test [$F(3,48)= 7.676$, $p< 0.001$]. One-way ANOVAs indicated significant between group differences for contextual recognition [$F(3,48)=4.452$, $p=0.008$] and free recall [$F(3,48)=20.065$, $p< 0.0001$]. The only significant difference indicated by Bonferroni's post hoc test for context recognition was between subjects of the no associative encoding condition with Low IPAQ-L and subjects of the associative encoding condition with High IPAQ-L, which showed the best performance [$p=0.011$] (Figure 2). Regarding contextual free recall, Bonferroni's post hoc tests indicated a significant stepwise increase in performance from the no associative encoding condition of the low IPAQ-L subgroup, which had the lowest performance among all subgroups [all $p<0.001$], to the associative encoding condition of the High IPAQ-L subgroup, which had the best performance among all subgroups [all $p<0.001$]. Thus, the high IPAQ-L subjects showed a better free recall than the low IPAQ-L subjects on the no associative [$p=0.011$] and associative [$p=0.009$] encoding conditions, suggesting that physical activity is able to improve, respectively, processes that were automatically engaged as well as latent components of the cognitive reserve (as shown in the associative encoding condition).

Insert Figures 2 and 3 about here

The statistical analysis to evaluate the relation of physical activity and free recall and recognition memory for objects and contexts was repeated entering gender and scores on MMSE as possible confounding factors since, as explained before, significant between groups differences were found for these variables. None of these variables showed significant effects as covariates [all $p>0.05$]. Thus, all results described earlier for free recall and recognition memory of objects and contexts remained unchanged.

Discussion

This study evaluated the association of cognitive support and physical activity on an incidental memory task. Our results clearly indicate that an associative encoding instruction can improve contextual memory free recall and match its performance to contextual memory recognition, eliminating the disadvantage that older adults normally show when more self-initiated activity or more processing resources are required (Craik & McDowd, 1987). Moreover, the degree of the improving effect of cognitive support was positively associated with the actual physical activity level of the volunteers. Thus, the fact that High IPAQ-L subjects outperformed the Low IPAQ-L subgroups on contextual memory free recall suggests that, besides increasing the capacity to engage automatic processes to bind the central item to its context, physical activity is also able to expand the cognitive reserve resources, improving episodic memory.

The improving effect of the associative encoding instruction on contextual memory recognition seen in this study is in agreement with former results for healthy older adults and patients with psychiatric conditions, such as depression and bipolar disorder (Bisol Balardin et al., 2009; Corrêa et al., 2012, 2014). However, in this study we expand these findings to contextual memory free recall. The fact that the introduction of the associative encoding instruction was able to match the scores of contextual memory free recall and recognition suggests that the contextual memory impairments of older adults are more dependent on encoding than retrieval dysfunctions. This conclusion can be drawn when we realize that the presence (in the recognition test) or absence (in the free recall test) of cognitive support at memory retrieval had no significant effect when cognitive support at encoding was present. Thus, our results support the notion that more than an irreversible dysfunction, age-related contextual memory impairments seem to reflect an under recruitment of executive and monitoring functions (Logan, Sanders, Snyder, Morris, & Buckner, 2002). It seems that the failure of these cognitive functions could be compensated by the introduction of the associative encoding strategy (Gutchess et al., 2007). Thus, healthy older adults have cognitive reserve components that, although not spontaneously engaged by the subject (as shown by the performance on the no associative encoding condition), are prone to rehabilitation (as shown by the performance in the associative encoding condition). These conclusions are reinforced by the fact that the experimental groups of this study where homogeneous for aspects that could interfere on the cognitive reserve (educational level, socioeconomic status, current intellectual, social and physical activities) mental health (subjective memory complains, depression symptoms, sleep quality, cortisol levels) and contextual memory performance (attention, working memory, visuospatial capacity and executive function).

The findings of this study also indicate that physical activity is positively associated to contextual memory performance. The most robust evidences for this association were seen on free recall, in which higher exercise levels corresponded to: (a) increased performance on the no associative encoding condition, i.e., increased baseline levels of contextual memory and (b) better memory in the associative encoding condition, i.e., increased ability to take advantage of the associative encoding strategy (suggesting an increased cognitive reserve). These results remained even with the introduction of the significant between group differences in demographic (gender), clinical (MMSE scores) and) data as covariates in the statistical analysis. Thus, performance on the task increased significantly and steadily from subjects with lower physical activity levels that performed the more difficult memory task (without support at encoding and retrieval) to subjects with higher physical activity levels that performed the easiest memory task (with support at encoding but without support at retrieval). The same pattern of results was found for contextual recognition, although its association with physical activity was not as evident as for free recall. However, this result was not surprising, since recognition tests always provide cognitive support at retrieval, improving performance and eventually masking the effects of factors that facilitate other memory components, such as free recall (Bisol Balardin et al., 2009).

Most of the volunteers of our study were engaged in aerobic exercises and those that performed these activities in the highest quartiles of moderate intensity showed better contextual memory. These characteristics of our sample are in accordance with the notion that moderate aerobic physical activities are capable to reduce the risk for cognitive decline and dementia in later life (Abbott et al., 2004; Hamer & Chida, 2009;

Taaffe et al., 2008; Wang et al., 2017), as well as improve cognitive functions in older adults (Desjardins-Crépeau et al., 2016; Eggenberger, Schumacher, Angst, Theill, & de Bruin, 2015; K. Erickson et al., 2014). These positive effects of the exercise seem to be mediated by its ability to enhance cerebral blood flow (Burdette et al., 2010), hinder prefrontal and hippocampal age-related volume loss (Colcombe et al., 2006; Erickson et al., 2010) increase the efficiency of key networks for executive function (Colcombe et al., 2004; Rosano et al., 2010) and enhance the fronto-temporal connectivity (Voss et al., 2010). Although the experimental design of our study does not allow the establishment of a cause-effect relationship between higher physical activity levels and contextual memory performance, it clearly indicates a potential association between physical activity and incidental contextual memory under different encoding conditions. Thus, future studies should investigate this issue with experimental designs aimed to compare the effects of encoding conditions alone, physical activity alone and a combination of these two variables on contextual memory.

One of the limitations regarding the current study is that the classification of subjects in different physical activity levels was based only on the IPAQ-L scores. Research investigating the applicability of this questionnaire to the older population remains scarce. Although some studies indicate that IPAQ-L is valid for older adults ranking and useful for generating internationally comparable data (Cerin et al., 2012; Helmerhorst HJ, Brage S, Warren J, Besson H et al., 2012; Milanović et al., 2014), caution is recommended in the interpretation of the IPAQ-L results. Thus, although we are confident on the positive effects of exercise on contextual memory, conclusions about recommended levels of physical activity for contextual memory improvement cannot be drawn. Only more objective measures of aerobic conditioning (such as VO2max) should be used for this purpose.

In conclusion, incidental contextual memory impairments of healthy older adults are prone to rehabilitation, as indicated by the effects of the cognitive support and its association with physical activity. The importance of the findings of this study can be better appreciated when the naturalistic experimental paradigm used in this study is considered. It was designed to reflect a very common everyday situation, in which contextual memory is incidentally acquired and used to help the intentional free recall of episodic memory details. For example, if we cannot remember where we put something, we start to think where we have been or what we have done (contextual details), to guide us in recollecting that information. Thus, the association of an item to a context (e.g., of an object to a location) has a key role in establishing perceptual continuity within the dynamic environments of everyday experiences (Hollingworth & Rasmussen, 2010) and is essential for the formation of coherent episodic memory representations. Moreover, our experimental paradigm also suggests an association between later life physical activity and cognitive reserve modulation, an issue that has a broader impact on healthy cognitive aging than contextual memory alone. Thus, the exciting results of this study should be further investigated with greater sample sizes, objective measures of physical activity and experimental groups designed to evaluate if associative encoding conditions and exercise can have additive effects, in order to contribute with the establishment of adequate cognitive rehabilitation and/or managing interventions.

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Disclosure statement

The authors declare no conflict of interest.

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Table 1. Demographic, clinical, lifestyle and neuropsychological characteristics (mean ± SD) of subjects in the experimental groups

	No associative condition (N=22)	Associative condition (N=30)	P value
Demographic characteristics			
Age	69.13 ± 6.74	68.63 ± 5.98	0.778
Education (years)	12.18 ± 4.58	13.90 ± 4.05	0.159
Gender (female/male)	19/3	23/7	0.381
SES	27.59 ± 6.94	28.86 ± 5.76	0.473
Clinical Characteristics			
MMSE	27.90 ± 1.60	28.16 ± 1.74	0.588
BDI	2.27 ± 3.64	1.83 ± 2.21	0.592
MAC-Q	26.54 ± 3.82	25.43 ± 3.57	0.287
PSQI	4.63 ± 2.12	5.36 ± 3.59	0.4
BMI	26.64±4.86	25.86±2.98	0.478
Cortisol AUC	160.87±70.41	145.19±47.61	0.343
Current Lifestyle Characteristics			
Social activity	14 ± 3.32	12.93 ± 2.21	0.171
Intellectual activity	23.22 ± 4.12	24.03 ± 3.42	0.446
Physical Activity[a]	1944.02 ±1530.27	1896.90 ± 1740.19	0.920
Neuropsychological Characteristics			
Trail making A	45.21 ± 17.36	39.92 ± 11.79	0.196

Trail making B	118.83 + 60.27	115.56 + 51.63	0.835
Stroop (color-word)	32.00 + 8.09	29.73 + 6.41	0.265
Digit span (forward)	7.18 + 2.03	6.80 + 1.64	0.746
Digit span (backward)	5.18 + 1.59	4.36 + 1.86	0.105

Abbreviations: SES, socioeconomic status; MMSE, Mini Mental Status Examination; BDI, Beck Depression Inventory; MAC-Q, Memory Complaint Questionnaire; PSQI, Pittsburgh Sleep Quality Assessment; BMI, body mass index; cortisol AUC, cortisol area under the curve

[a]Physical activities of participants (Met-min/week) consisted mainly of aerobic activities, such as walking, running, oriented aerobic exercises and activities related to housework and gardening.

Table 2. Demographic, clinical, lifestyle and neuropsychological characteristics (means ± SD) of subjects in the experimental groups.

	Low IPAQ-L without associative encoding (N=11)	High IPAQ-L without associative encoding (N=11)	Low IPAQ-L with associative encoding (N=15)	High IPAQ-L with associative encoding (N=15)	P value
Demographic characteristics					
Age	68.50 + 7.52	69.41 + 5.58	71.06 + 4.84	66.20 + 6.16	0.198
Education (years)	13.91 + 3.77	10.83 + 4.76	13.13 + 5.11	14.66 + 2.58	0.141
Gender (female/male)	11/0	8/3	14/1	9/6*	0.033
SES	26.90+5.71	28.27+8.22	27.86+6.10	29.86+5.43	0.682
Clinical Characteristics					
MMSE	28.16 + 1.40	27.58 + 1.67	27.20 + 1.89	29.13 + 0.83**	0.07
BDI	2.41 + 2.74	2.50 + 4.56	2.06 + 2.25	1.60 + 2.22	0.883
MAC-Q	26.18+3.48	26.90+4.27	25.73+3.82	25.13+3.41	0.680
PSQI	4.36+1.50	4.90+2.66	5.86+3.40	4.86+3.81	0.649
BMI	25.55+4.78	27.73+4.91	25.07+2.69	26.65+3.14	0.326
Cortisol AUC	171.61+63.46	150.13+78.29	158.22+42.65	132.16+50.12	
Lifestyle Characteristics					
Social activity questionnaire	15.27+3.28	12.72+2.96	12.93+2.31	12.93+2.18	0.082
Intellectual activity questionnaire	23.81+4.40	22.63+3.95	24.80+3.21	23.26+3.57	0.501
IPAQ-L (Met-minute)[a]	999.04 + 403.10***	2889 + 1670.51	1085.26 + 390.78***	2708.53 + 2169.91	0.001
Neuropsychological Characteristics					
Trail making A	41.65 + 16.75	46.74 + 17.61	42.73 + 15.26	37.10 + 6.16	0.343

Trail making B	114.85 ± 60.39	124.91 ± 57.64	134.20 ± 63.70	96.93 ± 26.81	0.280
Stroop (color-word)	34.25 ± 6.25	30.25 ± 9.12	28.06 ± 4.83	31.40 ± 7.47	0.117
Digit span (forward)	8 ± 2.13	6.5 ± 1.56	6.53 ± 1.3	7.06 ± 1.94	0.192
Digit span (backward)	5.82± 1.08	4.27 ± 1.19	4.2 ± 1.61	4.53 ± 2.13	0.067

Abbreviations: SES, socioeconomic status; MMSE, Mini Mental Status Examination; BDI, Beck Depression Inventory; MAC-Q, Memory Complaint Questionnaire; PSQI, Pittsburgh Sleep Quality Assessment; BMI, body mass index; cortisol AUC, cortisol area under the curve

[a]Physical activities of participants (Met-min/week) consisted mainly of aerobic activities, such as walking, running, oriented aerobic exercises and activities related to housework and gardening.

* p<0.05 compared to Low IPAQ-L subgroups with and without associative encoding

**p<0.05 compared to Low IPAQ-L subgroup with associative encoding

***p<0.05 compared to High IPAQ-L subgroups

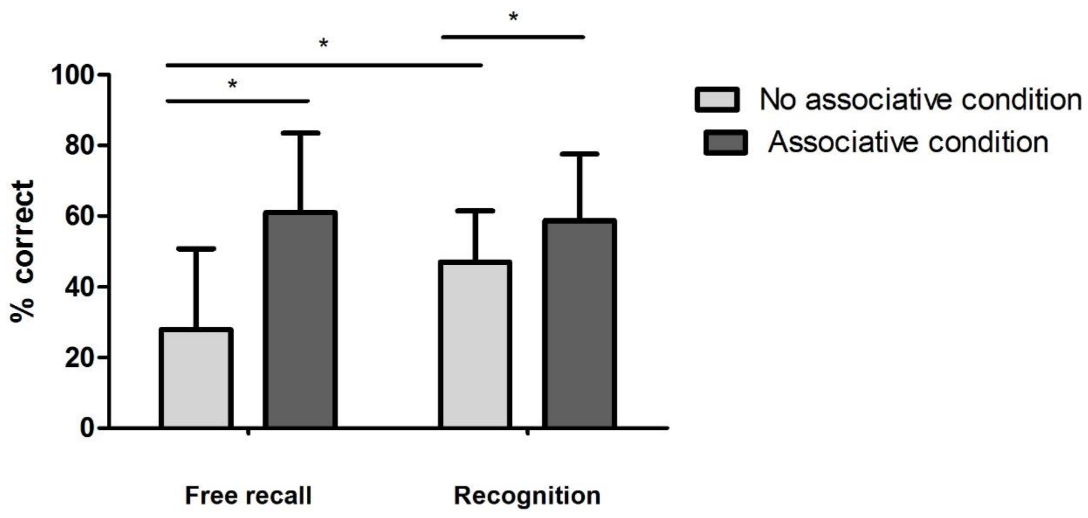

Fig 1. Effects of different encoding conditions on free recall and recognition of contextual memory. Results are expressed as mean ± standard deviation (SD). *p<0.05 between groups

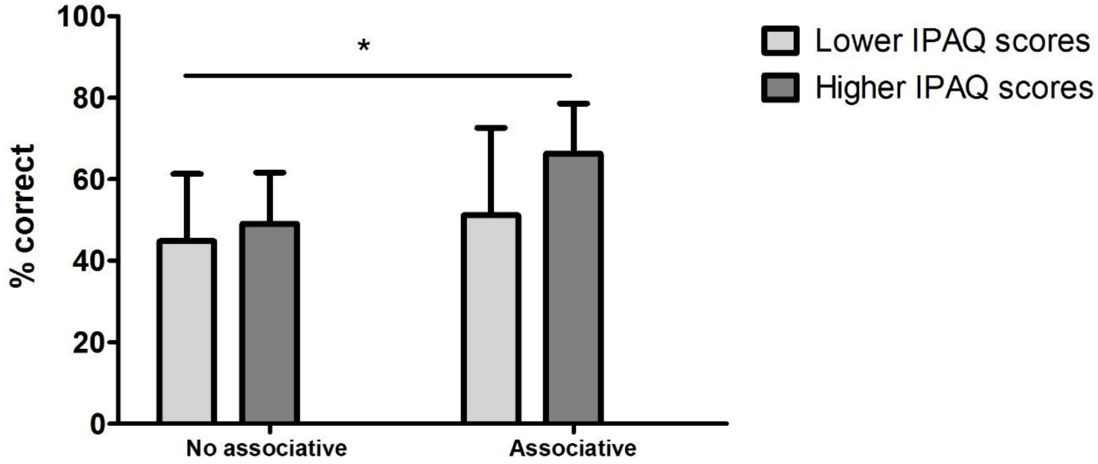

Fig 2. Effects of physical activity levels on context recognition under two encoding conditions. Results are expressed as mean ± standard deviation (SD). *p<0.05 between groups

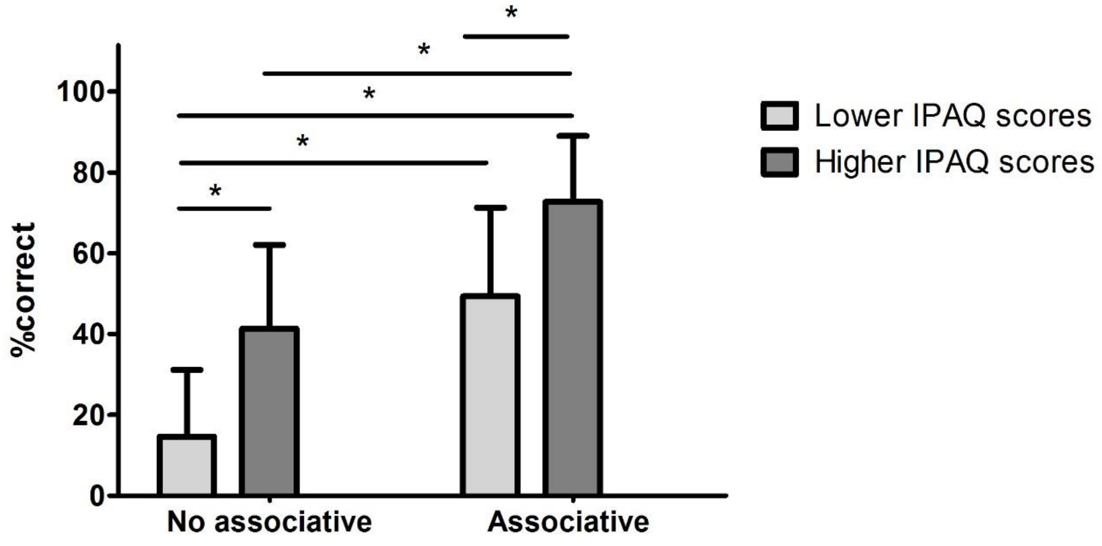

Fig 3. Effects of physical activity levels on context free recall under two encoding conditions. Results are expressed as mean ± standard deviation (SD). *p<0.05 between groups

CAPÍTULO IV

4 CONSIDERAÇÕES FINAIS

5 PERSPECTIVAS

4 CONSIDERAÇÕES FINAIS

O objetivo da pesquisa foi avaliar os efeitos do estilo de vida (quanto às atividades social, intelectual e física) sobre diferentes componentes cognitivos e níveis de BDNF.

A análise transversal de uma amostra de idosos saudáveis identificou uma relação positiva entre a atividade física e os níveis de BDNF bem como um efeito benéfico da atividade física sobre a memória contextual incidental e a reserva cognitiva. Entretanto, não foram observados efeitos da atividade intelectual ou da interação social sobre os níveis de BDNF ou sobre a performance cognitiva.

4.1 ATIVIDADE FÍSICA E NÍVEIS DE BDNF

A análise da relação entre atividade física e BDNF mostrou que o grupo com menor nível de atividade física também apresentou menores níveis de BDNF. Os resultados estão pertinentes com estudos intervencionais que observaram que a prática de atividade física moderada tem efeitos favoráveis sobre os níveis de BDNF em idosos (COELHO et al., 2013; ERICKSON et al., 2011).

4.2 ATIVIDADE FÍSICA E DESEMPENHO COGNITIVO

Nossas análises não indicaram relação entre atividade física e desempenho nas tarefas de atenção, memória operacional e função executiva, conforme descrito no artigo I. Tal resultado pode ser explicado pelas características da amostra, que era composta de idosos saudáveis ou, até mesmo, pela pouca sensibilidade dos testes cognitivos em identificar pequenas diferenças no desempenho. Portanto, consideramos necessário verificar a relação entre atividade física e cognição através de uma tarefa mais sensível, a de memória contextual incidental.

Os resultados obtidos no artigo II mostraram que maiores níveis de atividade física favoreceram o desempenho dos idosos nas tarefas evocação livre e reconhecimento da memória contextual. Complementarmente, quando maiores níveis de atividade física foram aliados a uma estratégia de codificação associativa, o benefício sobre o desempenho da memória contextual (reconhecimento e evocação livre) foi ainda maior, sendo mais evidente na tarefa de evocação livre.

4.3 LIMITAÇÕES DO ESTUDO

O presente estudo possui alguns fatores limitantes, dentre os quais, o tamanho da amostra que não foi suficientemente grande para que houvesse maior estratificação das atividades sociais e intelectuais do estilo de vida. O intervalo pequeno de dados nos questionários de avalição desses dois aspectos representou outra limitação para o estudo. Talvez um intervalo de dados mais amplo possibilitasse a identificação dos efeitos dos componentes social e intelectual. É relevante mencionar também a utilização do Questionário Internacional de Atividade Física-Forma longa (IPAQ-L) para avaliar o nível de atividade física dos sujeitos uma vez que, há controvérsia quanto à utilização desse questionário em idosos (DE FÁTIMA CABRAL et al., 2017; MILANOVIĆ et al., 2014), pois ele ainda não foi validado para utilização nessa população.

4.4 PONTOS FORTES DO ESTUDO

Um dos pontos fortes dessa investigação foi o cuidado que tivemos em testar a relação entre os escores no IPAQ-L e os resultados no teste de consumo máximo de oxigênio (VO_2max). A análise identificou uma associação entre a pontuação no IPAQ-L e os valores de VO_2max considerando razoável a utilização do IPAQ-L ao longo do estudo para avaliação dos níveis de atividade física praticados pelos idosos.

Outro aspecto relevante, foi a avaliação das atividades sociais, intelectuais e físicas em uma mesma amostra. Isso possibilitou averiguar individualmente a relação de cada uma das atividades com os níveis de BDNF e a performance cognitiva, além disso, foi possível controlar a influência dos demais aspectos do estilo de vida por análise de covariância. No artigo I, ao dividirmos os sujeitos de acordo com níveis de atividade física, identificamos que o grupo do primeiro quartil do IPAQ-L (com menor nível de atividade física) possuía menor nível de BDNF e, também, apresentava maior nível de interação social. Contudo, quando a atividade social foi inserida como covariável não conseguiu alterar o desfecho.

Em nossas análises controlamos diferentes variáveis capazes de interferir no desempenho cognitivo e níveis de BDNF. Além das características que estudos desse tipo geralmente levam em consideração (escolaridade, níveis socioeconômicos, escores no Mini Exame do Estado Mental, sintomas depressivos), avaliamos, ainda, os níveis de cortisol, a qualidade do sono e as queixas subjetivas de memória. Foram identificadas algumas diferenças entre os grupos, porém, as mesmas não alteraram o desfecho dos resultados obtidos para a relação entre BDNF e atividade física.

4.5 CONCLUSÕES

Nossos resultados demonstram que além de modular os níveis de BDNF, a atividade física é capaz de favorecer a reserva cognitiva e o desempenho em tarefas de memória incidentais.

Complementarmente, os níveis de atividade intelectual e social de idosos saudáveis parecem estar concentrados num intervalo relativamente estreito, o que não permitiu a identificação de seus efeitos em estudos transversais nessa população.

5 PERSPECTIVAS

Uma vez que, o conhecimento a respeito dos mecanismos moleculares moduladores dos efeitos do estilo de vida sobre a cognição ainda é fragmentário, é importante examinar o papel de outras moléculas. Fatores neurotróficos, como NT3, NGF, Fator de crescimento semelhante a insulina-1 (IGF-1) e Fator de crescimento de fibroblasto- 2 (FGF-2) são candidatos interessantes a serem investigados em experimentos futuros, visto que, estudos em animais sugerem que eles podem estar envolvidos na associação entre estilo de vida e cognição (GÓMEZ-PINILLA; DAO; SO, 1997; NAKAJIMA et al., 2010; NEEPER et al., 1996; PHAM et al., 2002).

Para melhor avaliar os efeitos das atividades sociais e intelectuais, seria interessante realizar um estudo de intervenção, incluindo idosos com nível muito baixo de atividade física e, então separá-los em grupos de acordo com as práticas realizadas: sociais, intelectuais ou manutenção do mesmo padrão de atividades físicas.

Ademais, seria muito importante utilizar medidas mais sensíveis dos diferentes aspectos do estilo de vida em investigações futuras. Para a avaliação da atividade física poderiam ser incluídos pedômetros e acelerômetros que são amplamente utilizados e possuem vantagens sobre a utilização de questionários como o IPAQ-L (HARRIS et al., 2009). Quanto às atividades sociais e intelectuais seria interessante o emprego de questionários mais sensíveis, que abordassem além da frequência, o tempo de exposição dos sujeitos a cada uma das atividades sociais ou intelectuais realizadas.

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