UNIVERSIDADE ESTADUAL DE MONTES CLAROS

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Modelos de associação entre depressão e funções cognitivas: uma via bidirecional

Montes Claros – Minas Gerais
2021

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Modelos de associação entre depressão e funções cognitivas: uma vida bidirecional

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Às mais de 400 mil vítimas do Coronavírus e do descaso.

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Humildade como técnica é o seguinte: só se aproximando com humildade da coisa é que ela não escapa totalmente. Descobri este tipo de humildade, o que não deixa de ser uma forma engraçada de orgulho. Orgulho não é pecado, pelo menos não tão grave: orgulho é coisa infantil em que se cai como se cai em gulodice. Só que orgulho tem a enorme desvantagem de ser um erro grave, e, com todo o atraso que o erro dá à vida, faz perder muito tempo[1].

[1] LISPECTOR, Clarice. *A descoberta do mundo*. Editora Rocco - Rio de Janeiro, 1999.

RESUMO

Este trabalho teve como objetivo apresentar sob diferentes óticas modelos de associação entre a depressão e as funções cognitivas. Para isso, dois trabalhos foram desenvolvidos: o primeiro visou determinar o nível de associação entre os sintomas depressivos e habilidades cognitivas de idosos institucionalizados, e o segundo aborda uma hipótese neurobiológica de que a interação entre depressão e declínio cognitivo é mediada por corticosteroides, gerando um *downregulation* no BDNF. Em relação ao método, o primeiro estudo é de caráter transversal e contou com 69 idosos vivendo em Instituições de Longa Permanência para Idosos (ILPIs), com rastreamento de seus sintomas depressivos e sua performance física e cognitiva investigadas através de testes e escalas específicas. Assim, a Escala de Depressão Geriátrica (GDS) de 30 itens foi usada para categorizar os grupos entre aqueles com sintomas depressivos (score de 10 ou mais) e os assintomáticos. Sobre os testes cognitivos: O Mini Exame do Estado Mental (MEEM) foi usado para quantificar a cognição global, contendo 11 itens que avaliam domínios cognitivos como: orientação, memória, cálculo, linguagem e praxia. O teste de Fluência Verbal (FV) foi usado para avalir a fluência semântica e a função executiva através do número máximo de evocação de nomes de animais em 60 segundos. O Digit Span Forward (DSF) e o Digit Span Backward (DSB) foram usados para avaliar a memória de curto prazo e memória de trabalho, respectivamente. O DSF se trata da repetição de uma sequência numérica na mesma ordem dita e o DSB na ordem inversa. Sobre as avaliações físicas, foram usados o Teste de Marcha Estacionária de 2 minutos (TME2') e o Teste Sentar e Levantar (TSL). O primeiro avalia a resistência aeróbia do sujeito por meio do número máximo de passos completados em dois minutos. No segundo teste o sujeito deve sentar e levantar continuamente por 30 segundos, para estimar a resistência e a força dos membros inferiores. O segundo estudo traz como método a análise *in silico,* por meio da inserção de genes no banco de dados GeneCards, para explorar os genes que codificam proteínas associadas com a depressão e o declínio cognitivo. As siglas dos genes foram inseridas na base de dados de bioinformática String, para visualização da interação em rede. Entre os resultados, no primeiro estudo foi evidenciado que os idosos com pior performance física e cognitiva exibiram a presença de sintomas depressivos, sendo que aqueles com maior déficit na memória de curto prazo mostraram quase 5 vezes mais chances de apresentarem sintomas depressivos (OR=4.86; IC= 1,09;21,69). Na análise *in silico*, a rede de interações entre os genes sugeriu a associação entre depressão e declínio cognitivo mediados por fator inflamatório (TNF-α) associado aos precursores de hormônios glicocorticoides (POMC e CRH). Desse modo, ressalta-se a importância de entender melhor como a associação entre depressão e declínio cognitivo acontece, uma vez que tais mecanismos se retroalimentam e podem ser melhor explicados por um modelo integral que contemple as dimensões biológicas e psicológicas, a fim de proporcionar intervenções mais eficientes e que abordem o problema de modo holístico.

Palavras-chave: idosos; sintomas depressivos; cognição; institucionalização; desempenho físico.

ABSTRACT

This study aimed to present, under different perspectives, models of association between depression and cognitive functions. For this, two studies were developed: the first aimed to determine the level of association between depressive symptoms and the cognitive abilities of institutionalized older persons, and the second approaches a neurobiological hypothesis that the interaction between depression and cognitive decline is mediated by corticosteroids, generating a downregulation in the BDNF. Regarding the method, the first study is cross-sectional and involved 69 older adults living in Long-Term Care Facilities for the older persons (LTCFs), with tracking of their depressive symptoms and their physical and cognitive performance, investigated through tests and specific scales. Thus, the Geriatric Depression Scale (GDS) of 30 items was used to categorize the groups between those with depressive symptoms (score of 10 or more) and asymptomatic ones. About cognitive tests: The Mini Mental State Examination (MMSE) was used to quantify global cognition, containing 11 items that access cognitive domains such as: orientation, memory, calculation, language and praxis. The Verbal Fluency (VF) test was used to access semantic fluency and executive function through the maximum number of animal name recalls in 60 seconds. Digit Span Forward (DSF) and Digit Span Backward (DSB) were used to access short-term and working memory respectively. DSF is a repetition of a numerical sequence in the same order and DSB in reverse order. On the physical evaluations, the 2-minute Stationary Walking Test (2MST) and the Sit-to-Stand Test were used. The first one evaluates the subject's aerobic resistance by means of the maximum number of steps completed in two minutes. In the second test, the subject must sit and stand continuously for 30 seconds to estimate the functional capacity of the lower limbs. The second study uses *in silico* analysis as a method of inserting genes into the GeneCards database to explore the genes encoding proteins associated with depression and cognitive decline, in which these genes were inserted into the String bioinformatics database. for viewing network interaction. Among the results, in the first study, it was evidenced that the older adults with worse physical and cognitive performance exhibited the presence of depressive symptoms, and those with a greater deficit in short-term memory were 5 times more likely to have depressive symptoms (OR = 4.86; CI = 1.09; 21.69). In the *silico* analysis, the network of interactions between the genes suggested the association between depression and cognitive decline mediated by inflammatory factor (TNF-α) associated with precursors of glucocorticoid hormones (POMC and CRH).In this way, the importance of better understanding how the association between depression and cognitive decline occurs, since these mechanisms feedback each other and can be better explained by an integral model that contemplates the biological and psychological dimensions, in order to provide more efficient interventions that address the problem holistically.

Keywords: Aged; cognition; depressive symptoms; institutionalization; physical performance

LISTA DE ABREVIATURAS E SIGLAS

IBGE	Instituto Brasileiro de Geografia e Estatística
OMS	Organização Mundial da Saúde
WHO	World Health Organization
HPA	Hipotálamo-Pituitária-Adrenal
IPEA	Instituto de Pesquisa Econômica Aplicada
ILPI	Instituição de Longa Permanência para Idosos
MEEM	Mini Exame do Estado Mental
CID-10	Classificação Estatística Internacional de Doenças e Problemas Relacionados com a Saúde-10
DSM-5	Manual Diagnóstico e Estatístico de Transtornos Mentais-5
SD	Sintomas depressivos
AS	Assintomático
GDS	Escala de depressão geriátrica
FV	Fluência verbal
DSF	Digit span forward
DSB	Digit span backward
TME2	Teste de marcha estacionária de dois minutos
TC6’	Teste de caminhada de seis minutos
POMC	Opiomelanocortina
CRH	Hormônio liberador de corticotropina
TNF-α	Fator de necrose tumoral alfa
BDNF	Fator neurotrófico derivado do cérebro
APOE	Apolipoproteína E
MAPT	Proteína tau associada a microtúbulos
SLC6A4	Transportador de serotonina dependente de sódio
HTR2A	Receptor 5-hidroxitriptamina 2A
COMT	Catecol O-metiltransferase

SUMÁRIO

1 INTRODUÇÃO 13

2 OBJETIVOS 16

2.1 Objetivo Geral 16

2.2 Objetivos Específicos 16

4 MATERIAL E MÉTODO.....17

5 PRODUTOS 21

5.1 Artigo 1: Cognitive abilities of institutionalized older persons with depressive symptoms.....22

5.2 Artigo 2: Neurobiological hypotheses about the interaction between depression and cognitive decline *in silico* analysis.....41

6 CONCLUSÕES.....56

REFERÊNCIAS 57

APÊNDICES 60

ANEXOS 64

1 INTRODUÇÃO

De acordo com a Organização Mundial da Saúde (OMS), idoso é todo indivíduo com 60 anos ou mais[1]. Através de investimentos no cuidado à saúde e com os avanços tecnológicos, a demografia mundial vem sofrendo alterações, aumentando de 930.629.00, o que corresponde a 12,5% de idosos, em 2016 para 1.081.903.00 (13,70%) de indivíduos até o presente ano[2]. Nesse sentido, no Brasil a expectativa de vida do passou de 75,8 anos em 2016 para 76,6 anos em 2019 e o percentual atual de 14,5% da população considerada idosa tende a dobrar nas próximas décadas, segundo a Projeção da População divulgada em 2018 pelo Instituto Brasileiro de Geografia e Estatística[3,4].

Longevidade e envelhecimento saudável não são sinônimos[5] e com as alterações na funcionalidade, cognição e humor, a qualidade de vida dos idosos é diretamente impactada[6]. Assim, esse é um processo fisiológico permeado de características socioculturais e psíquicas, exigindo uma abordagem holística e interdisciplinar[4]. Entre os possíveis fatores causais da redução da qualidade de vida dessa população destaca-se a alta prevalência de depressão[7]. De forma clínica, pode-se dividir a presença de sintomas depressivos como episódico ou como transtorno depressivo recorrente[8]. Ambas as classificações são compostas por uma ampla gama de sintomas afetivos, neurovegetativos, cognitivos, em relação à volição, autovaloração e psicomotricidade. O humor triste e a anedonia são os sintomas mais marcantes[9]. O episódio é definido pela presença dos sintomas por pelo menos duas semanas e não mais que por dois anos e é classificado pela Classificação Internacional de Doenças (CID-11)[8] em leve, moderado ou grave de acordo com o número e intensidade dos sintomas. Porém, quando há mais de um episódio depressivo ao longo da vida, sem intercalação de episódios maníacos ou hipomaníacos, diz-se transtorno depressivo recorrente[8]. Dentre tais classificações, o transtorno depressivo maior representa a condição clássica desse grupo de transtornos, mas existem muitos subtipos clínicos[10]. Apesar dos avanços no entendimento da etiologia da depressão maior, nenhum mecanismo determinístico foi estabelecido para explicar todos os aspectos da doença, contudo algumas associações foram elucidadas, como a redução no volume do hipocampo, a mudança na ativação/conexão dos circuitos neuronais, as alterações nos principais sistemas neurobiológicos que mediam a resposta ao estresse, a contribuição genética de aproximadamente 35% e fatores psicossociais[11].

Na literatura já é estabelecida a associação entre sintomas depressivos e prejuízo cognitivo[12,13]. Através de funções especializadas como a orientação, a atenção e a memória,

dentre outras, a cognição é o que permite responder a estímulos externos com determinados objetivos[14]. Assim, com o envelhecimento há uma redução natural no desempenho cognitivo[13], principalmente em relação aos processos associados ao córtex pré-frontal[15]. Contudo, apesar da associação supracitada, não está completamente elucidado qual é fator de risco ou sintoma do outro ou ainda, se são consequência de fatores de risco compartilhados entre ambos[16]. Entre as hipóteses, destaca-se a sinalização disfuncional do eixo hipotálamo-pituitária-adrenal (HPA) e a perspectiva do modelo neuropsicológico cognitivo da depressão[17,18.] Assim, investigações que permitam identificar os fatores de risco e proteção relacionados ao declínio cognitivo se ampliam[18]. Entre esses se incluem a aptidão física e o aumento da capacidade cardiorrespiratória, que agem como contribuintes para a manutenção da função cognitiva[19]. Em conjunto, as alterações físicas, cognitivas e psíquicas decorrentes de alterações estruturais, neuroquímicas e psicossociais[6], impactam diretamente na capacidade funcional, dimensão base para a avaliação geriátrica[14]. A esses processos, algumas vezes, acrescenta-se a institucionalização do idoso, que por si só é um fator estressante, provocando uma quebra no seu processo adaptativo e podendo aumentar de duas a três vezes a prevalência da depressão nessa população[12,15]. No Brasil, até o ano de 2011, o número de idosos institucionalizados era de 83 mil, contando com 3.548 instituições pelo país, com a concentração de dois terços na região sudeste[20].

Dentre os idosos residentes em Instituições de Longa Permanência para Idosos (ILPIs), de acordo com um estudo de 2014[21] conduzido em 4 municípios brasileiros, 48.7% apresentavam sintomas depressivos. Outro estudo conduzido no nordeste do Brasil confirma a alta taxa de prevalência apontando o percentual de 45.77%[22]. Nesse sentido, ao comparar idosos institucionalizados com os da comunidade em geral, de acordo com um estudo de follow-up, o primeiro grupo apresentou maior declínio cognitivo após a institucionalização, com uma diferença de 0,7 pontos por ano no Mini Exame do Estado Mental (MEEM)[23]. Não é bem estabelecido o porquê do maior índice de declínio cognitivo entre os idosos institucionalizados, porém os fatores sociodemográficos, a falta de interação social, a redução ou falta de atividade física e o maior comprometimento funcional, além dos efeitos físicos e psicológicos da institucionalização são tidos como hipóteses[24,25].

Devido à transição demográfica a atenção aos processos de saúde da população idosa está em evidência. Assim, o modelo biopsicológico surge como um caminho possível para a integralização das dimensões biológicas e psicológicas. A partir daí, novas estratégias para um envelhecimento saudável podem ser pensadas.

2 OBJETIVOS

2.1 Objetivo geral:

Apresentar sob diferentes óticas (neuropsicológica e neurobiológica) modelos de associação entre a depressão e as funções cognitivas.

2.2 Objetivos específicos:

- Determinar a associação entre sintomas depressivos e funções cognitivas em idosos institucionalizados.
- Identificar a interação entre depressão e declínio cognitivo, mediados por fator inflamatório (TNF-α) associado aos precursores de hormônios glicocorticoides (POMC e CRH) que podem gerar um *downregulation* no BDNF.

4 MATERIAL E MÉTODO

A presente dissertação se desdobra em dois estudos, os quais são apresentados separadamente nesta seção. O primeiro estudo visou determinar o nível de associação entre os sintomas depressivos e as habilidades cognitivas de idosos institucionalizados. O segundo estudo aborda uma hipótese neurobiológica de que a interação entre depressão e declínio cognitivo é mediada por corticosteroides, gerando um *downregulation* no BDNF.

4.1 **Método do artigo 1**:

Cenário e participantes

Estudo transversal retrospectivo realizado a partir de um banco de dados (https://doi.org/10.6084/m9.figshare.14233928.v1) de pesquisas maiores realizadas entre 2015 e 2018 em quatro ILPIs brasileiras (três localizadas na cidade do Rio de Janeiro, estado do Rio de Janeiro, e uma localizada na cidade de Montes Claros, estado de Minas Gerais). No Rio de Janeiro as avaliações ocorreram no turno vespertino e em Montes Claros no turno matutino e vespertino, com alternância de dias entre testes neuropsicológicos e físicos para evitar viés de aferição.

Os participantes do estudo eram idosos, de ambos os sexos, com idade igual ou superior a 60 anos e que atendessem aos seguintes critérios de inclusão: i) ser residente em ILPI; ii) exibir comunicação preservada; iii) ausência de doenças pulmonares e cardíacas graves e debilitantes; iv) autorização médica; e v) ausência de comprometimento neurológico grave. Os participantes foram excluídos se apresentassem transtorno depressivo diagnosticado de acordo com os critérios do Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-5)[10], uma vez que a presença de depressão clínica influenciaria a investigação dos sintomas depressivos.

Distribuição de grupos

Os participantes do estudo foram alocados em dois grupos, de acordo com a presença de sintomas depressivos (SD) e assintomáticos (AS), na ausência de tais sintomas. Essa categorização foi feita de acordo com o ponto de corte da versão brasileira da Escala de Depressão Geriátrica (GDS na sigla em inglês)[26]. A GDS é um instrumento de autorrelato feito especificamente para rastrear a ocorrência de sintomas depressivos em idosos. É

composto por trinta perguntas com respostas binárias (sim ou não). Assim, indivíduos que atingiram pontuação igual ou superior a 10 foram alocados no grupo SD[26], enquanto os demais foram alocados no grupo AS.

Funções cognitivas

A versão brasileira do MEEM foi usada para quantificar a cognição global. O MEEM é composto por 11 itens e foi utilizado para identificar o nível cognitivo por meio da memória e evocação de curto prazo, orientação temporal e espacial, linguagem e habilidades visuoespaciais, cálculo e práxis. Os maiores valores da pontuação indicam maior desempenho cognitivo, com valor máximo de 30 pontos. Devido à influência do nível de escolaridade nos escores totais do MEEM, diferentes pontos de corte são adotados para os diferentes níveis de ensino[27]. Neste estudo, não houve estratificação por grau de escolaridade, pois esse instrumento foi utilizado apenas para caracterizar a amostra.

O teste de Fluência verbal (FV), foi usado para avaliar a fluência semântica (parte da memória de longo prazo que lida com significados, símbolos e palavras) e função executiva (analisada através da perda de iniciativa, perseverança ou quebra de regras) [28,29,30]. Nesse teste, o sujeito é solicitado a evocar o maior número de animais em 60 segundos. O número total de animais lembrados é a pontuação final[31].

O *Digit span forward* (DSF) e *Digit span backward* (DSB) foram usados para avaliar memórias de curto prazo e de trabalho, respectivamente. Os participantes foram solicitados a repetir as sequências numéricas ditas pelo avaliador na mesma ordem (DSF). Ao contrário, no DSB a sequência numérica dita pelo avaliador deve ser repetida na ordem inversa pelos participantes. Cada sequência, em ambos os testes, equivale a um ponto e a pontuação total é de 14 pontos. Se um participante repetir 6 ou mais dígitos em ordem direta, sua memória de curto prazo é classificada como normal. Já na ordem inversa, se o indivíduo conseguir repetir pelo menos 4 dígitos, sua memória de trabalho é classificada como normal[32].

Capacidade física

Utilizou-se o teste de Marcha estacionária de dois minutos (TME2) e o teste Sentar-e-Levantar para avaliar a capacidade física. O primeiro teste é uma proposta alternativa ao teste de caminhada de seis minutos (TC6) por ter maior viabilidade de aplicação em pequenos espaços, como os disponibilizados para este estudo. O TME2 avalia a resistência aeróbia do indivíduo por meio do número máximo de passos realizados em dois minutos a

partir do comando sonoro do avaliador. A altura mínima do joelho apropriada deve atingir um ponto médio entre a patela e a espinha ilíaca ântero-posterior. A pontuação total é registrada por um pesquisador treinado para contar quantas vezes o joelho direito atinge a altura indicada. A classificação é feita de acordo com o sexo e a idade, mas é considerada como zona de risco pontuação inferior a 65 passos para homens e mulheres[33,34]. O teste Sentar-e-Levantar começa com o sujeito sentado em uma cadeira, os pés apoiados no chão e os braços cruzados na altura do peito. Ao sinal sonoro do avaliador, o participante deve levantar-se e sentar-se continuamente até que seja dado um comando para parar. O número máximo de movimentos concluídos em 30 segundos estima a capacidade funcional dos membros inferiores. A classificação é feita de acordo com o sexo e a idade, porém, é considerada como zona de risco menos que 8 levantamentos não assistidos para homens e mulheres[34].

Análise estatística

Os dados são apresentados como média ± desvio padrão para variáveis com distribuição normal e como mediana (mínimo e máximo) para variáveis não-paramétricas. O teste de Shapiro-Wilk foi usado para determinar a normalidade dos dados. O teste T-independente e o teste de Mann-Whitney foram usados para comparar os dois grupos (AS e SD) em relação às variáveis quantitativas, de acordo com os pressupostos conceituais. Um teste de regressão logística binária foi realizado para verificar se as variáveis cognitivas e de desempenho físico, de acordo com suas categorias, poderiam predizer sintomas depressivos. O nível de significância foi estabelecido em $p \leqq 0,05$. Todas as análises foram realizadas no SPSS® versão 21.0.

Declaração de ética

Este estudo faz parte de dois grandes projetos que foram aprovados pelo Comitê de Ética em Pesquisa da Universidade Federal Fluminense (protocolo 1.287.659 / 2013) e Universidade Estadual de Montes Claros (protocolo 2.398.863 / 2017). Todos os voluntários assinaram o termo de consentimento livre e esclarecido para participar do estudo.

4.2 **Método do artigo 2**:

Este estudo foi elaborado com base em análise *in silico.* O banco de dados GeneCards (https://www.genecards.org) foi usado para explorar os genes que codificam as proteínas associadas à depressão e declínio cognitivo. Com base na literatura sobre a interação entre depressão e declínio cognitivo[35,36,37], os termos pró-opiomelanocortina (POMC), hormônio liberador de corticotropina (CRH), TNF-α e BDNF foram inseridos no GeneCards, resultando na recuperação de outros genes, como apolipoproteína E (APOE), proteína tau associada a microtúbulos (MAPT), transportador de serotonina dependente de sódio (SLC6A4), receptor 5-hidroxitriptamina 2A (HTR2A) e Catecol O-metiltransferase (COMT).

Os genes mencionados acima foram inseridos no banco de dados *String* (https://string-db.org), que aborda os genes e suas proteínas com interações em rede. A espécie considerada para o estudo foi a Homo Sapiens. Cada ligação proteína-proteína recebe uma certa "pontuação", que indica a veracidade da interação de acordo com as evidências publicadas. As interações encontradas tiveram escores acima de 0,40 e são classificadas como de média confiança, sendo o valor de p considerado significativo quando $\leq 0{,}05$.

As ligações encontradas foram analisadas de acordo com as cores dos símbolos da rede de interação, em que as linhas coloridas mostram interações moleculares, enquanto as linhas cinzas apresentam associações co-mencionadas nos resumos do PubMed. Assim, as linhas azuis significam ligação direta entre os genes; linhas amarelas - regulação da transcrição; linha roxa - catálise; linha preta - reação; setas - ativação; círculo - interação não especificada; e traço vermelho - inibição.

5 PRODUTOS TÉCNICO-CIENTÍFICOS GERADOS

5.1 **Produto 1**: *PHYSICAL AND COGNITIVE ABILITIES OF INSTITUTIONALIZED OLDER PERSONS WITH DEPRESSIVE SYMPTOMS*. Periódico: Frontiers Psychology. Artigo submetido e em processo de resposta aos revisores.

5.2 **Produto 2**: *NEUROBIOLOGICAL HYPOTHESES ABOUT THE INTERACTION BETWEEN DEPRESSION AND COGNITIVE DECLINE: AN IN SILICO ANALYSIS.* Periódico: CNS & Neurological Disorders – Drug targets. Artigo em construção.

5.1 PRODUTO 1

COGNITIVE ABILITIES OF INSTITUTIONALIZED OLDER PERSONS WITH DEPRESSIVE SYMPTOMS

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Abstract:

Objective: To determine the level of association between depressive symptoms and cognitive abilities of institutionalized older adults.

Methods: This is a cross-sectional study that enrolled 69 older adults, living in a long-term care facility. Investigation of depressive symptoms in all individuals was performed using the geriatric depression scale. Physical and cognitive tests were performed to assess their association with depressive symptoms.

Results: Depressive symptoms were identified in 35 individuals. Older adults with worse cognition and physical performances were associated with the presence of depressive symptoms (MMSE ($t(61) = 2.36$; $p < 0.05$) and 2MST ($t(53) = 3.12$; $p < 0.05$). Short-term memory and working memory tests presented worse results in individuals with depressive symptoms (DSF: $U = 402.00$; $p < 0.05$ and DSB: $U = 341.00$; $p < 0.05$). Older adults with low and normal DSF scores were 5 times more likely to exhibit depressive symptoms.

Conclusion: It is highlighted the importance of physical and cognitive intervention strategies in long-term care institutions to older adults in order to reinforce cognition and physical abilities. Notably, a deficit in short-term memory ability might increase the risk to develop depressive symptoms in older adults.

Keywords: Aged; cognition; depressive symptoms; institutionalization; physical fitness.

INTRODUCTION

Changes resulting from technological advances and health care have been modified the demographics in the world. In four decades, the world population aged 60 or over will increase from approximately 800 million to 2 billion[1]. In line with the global trend, the number of Brazilian older persons grew 18% in 5 years, from 25.4 million in 2012 to over 30 million in 2017[2].

According to the World Health Organization, the definition of older is not universally applicable. The definition can vary by country, culture, and gender, as such these events contribute to the aging process. In Brazil, the Elderly Statute considers older adults to be 60 years of age or older. Still, the United Nations Organization establishes differences between the older adults in developed and developing countries, being that in the first case, people aged 65 and over, and in the second, as in the case of Brazil, those aged 60 or more.[3,4,5]

This transition in the age structure has attracted attention to the preservation of functional skills, especially for the older adults, since these individuals usually have physical and cognitive impairments, increasing the risk of dependence[6,7]. Thus, aging is understood as a physiological process covered with sociocultural and psychic characteristics, and its approach is complex and interdisciplinary[8]. However, unsuccessful aging affects the functionality, cognition and mood, impairing the quality of life of older adults[9]. The aforementioned factors reduce the quality of life of older adults and increase the prevalence of depression[10].

Despite advances in understanding the etiology of depressive disorder, no mechanism has been established to explain all aspects of the disease. However, some mechanisms have been hypothesized, such as i) the reduction in the volume of the hippocampus, ii) the change in the activation/connection of neuronal circuits which mediate the stress response (e. g. HPA axis), iii) the genetic contribution and iv) psychosocial factors, such as significant losses (e.g. death of a loved one, job loss), lack of social support and other illnesses[11]. In addition to these factors, there are theories that address cognitive and behavioral models of depression. In Beck's cognitive model, the central role of beliefs incorporated into cognitive schemas for the development of depression and other disorders is believed. Thus, negative cognitive biases in the interpretation of events related to themselves, the world, and the future cause to explain depressive symptoms[12,13]. Still, Seligman's theory of helplessness

addresses the impact on cognition, motivation, and emotions when the subject in the face of a challenging situation repeatedly fails to conduct himself. In this way, the subject believes that there is no relationship between his actions and responses and is unmotivated, creating avoidance patterns. Such a negative emotional state could then give rise to depressive symptoms[14].

Individuals with depressive symptoms usually exhibit cognitive impairment[15]. Cognition allows us to achieve certain goals through specialized functions that enable the ability to think, remember, feel, perceive and respond to external stimuli[16]. There is a decrease in cognitive performance during aging, which does not necessarily affect everyday activities[17]. Thus, the cognitive condition of the older population is a reflection of the cumulative process of cognitive decline, not necessarily resulting in neurocognitive disorders or cognitive impairments that significantly impact their functionality[18,19].

Thereby, efforts to identify risk and protective factors related to cognitive decline have been a frequent concern. Aging is still the biggest risk factor for neurocognitive disorders since with it there is an increased risk of neurodegenerative, cerebrovascular, and cardiovascular diseases that directly impact cognition[20]. In this sense, a great quantity of cardiovascular risk factors has been investigated and, among them, physical fitness has been recommended as a useful intervention aiming to optimize cognitive aging[21]. Longitudinal neurocognitive performance is associated with baseline cardiorespiratory fitness and memory appears to be a substantially affected domain[22].

It should be noted that depression, cognitive and physical impairments have been related to dependency and institutionalization of older adults[13,23]. The prevalence of depression among community-dwelling older adults is in the range of 2 to 10% for patients with minor depression, however, up to 50% of the older adults in nursing homes are depressed[23]. Institutionalization *per se* is a stressor, increasing from two to three times the prevalence of depression in this population[16,25]. Also, cognitive decline is highly prevalent in these populations when compared to community-dwelling older persons[26]. According to a follow-up study among a group of institutionalized and community older adults, the first group presented a greater cognitive decline after institutionalization with a difference of 0.7 points per year in the MMSE (Mini-Mental State Examination)[27]. The reasons for a greater cognitive decline among institutionalized older adults are not completely elucidated in the literature, but it is believed that physical and psychological effects of institutionalization, sociodemographic factors, social isolation, reduction or lack of physical activity leading to

greater functional impairment, in addition to own depressive symptoms[26,27,28]. In fact, conducting research at the LTCFs in Brazil is difficult to manage due to the lack of structural and human resources, in addition to the possible losses of subjects that occur during the course of the research. A possible solution is to track the symptoms of the older people at the time of entry into the LTCF and try to conduct periodic reevaluations, however, obstacles are still likely to happen.

Therefore, along with the increase in life expectancy of individuals, there is the increased necessity of focusing on the healthy aging process[1]. Added to this, is complex the relation between depression and cognitive decline. Since, despite the different theories as to how this association and its mechanisms happen, mostly in the literature researches has shown depressive symptoms as predictors of cognitive decline[29,30,31]. In the present study, we aim to contribute to the discussion by addressing another possibility: Can cognitive impairment be a predictor of depressive symptoms in institutionalized older adults?

METHODS

Setting and participants

This is a retrospective cross-sectional study carried out from a database (https://doi.org/10.6084/m9.figshare.14233928.v1) of larger research performed between 2015 and 2018 in four Brazilian LTCFs (three located in Rio Janeiro city, Rio de Janeiro state, and one located in Montes Claros city, Minas Gerais state). In Rio de Janeiro the evaluations took place in the afternoon shift and in Montes Claros in the morning and afternoon shift with alternating days between neuropsychological and physical tests to avoid measurement bias.

Participants of this study were of both genders, aged 60 years old or over. The following inclusion criteria were applied: i) being a resident of an LTCF for older adults; ii) to exhibit preserved communication; iii) absence of severe and debilitating lung and heart disease; iv) medical authorization; and v) absence of severe neurological impairment. Participants were excluded if they presented diagnosed depressive disorder according to the DSM-5 (Diagnostic and statistical manual of mental disorders-5) criteria.

Groups of study

Participants of this study were allocated in two groups according to the presence of depressive symptoms (DS) and those as asymptomatic ones (AS). That categorization was

made by transforming the numerical variable from the Brazilian version of the Geriatric Depression Scale (GDS)[32] into a categorical one. GDS is a self-report instrument made specifically for screening the occurrence of depressive symptoms in older adults. It consists of thirty questions with binary answers (yes or no). Individuals who reached a score equal to or greater than 10 were allocated to the DS group[32]. The sensitivity and specificity of GDS 30 were 83 % and 57 % respectively and the test presents a moderate reliability (kappa= 0.48; p= 0.04)[32].

Cognitive functions tests

The Brazilian version of the MMSE was used to quantify global cognition. MMSE consists of 11 items and was used to identify the cognitive level through memory and short-term evocation, temporal and spatial orientation, language and visuospatial skills, calculus, and praxis. The higher values of the score indicate greater cognitive performance, with a maximum value of 30 points. Due to the influence of education level on the total MMSE scores, different cut-off points are adopted for different levels of education[33]. In this present study, there was no stratification according to the level of education since this instrument was only used to characterize the sample. The MMSE test has a reliability coefficient of (R = 0.90), classified as high[34]. According to the Medcal software, the sensitivity of the MMSE was 37% and the specificity was 91%.

Verbal Fluency (VF), was used to assess semantic fluency (part of the long-term memory that deals with meanings, symbols, and words) and executive function (analyzed through the loss of initiative, perseverance, or breaking rules)[20,35,36]. In this test, the subject is asked to evoke the largest number of animals within 60 seconds. The total number of animals remembered is the final score[37]. The reliability of VF is 99% classified as high[38]. Sensitivity of 76% and specificity was 44% according of the Medcal software.

Digit span forward (DSF) and Digit span backward (DSB) were used to assess short-term memory and working memory, respectively. Both tests have high reliability coefficients (Fisher Z = 0.90)[39,40]. In the DSF test participants were asked to repeat numeric sequences said by the assessor in the same order. Otherwise, in the DSB the numerical sequence said by the assessor should be repeated in the reverse order by the participants. Each sequence, in both tests, is equivalent to one point and the total score is 14 points. If a participant repeats 6 or more digits in direct order, his/her short-term memory is classified as normal. Meanwhile in the reverse order, if the individual is able to repeat at least 4 digits,

his/her working memory is classified as normal[41]. The sensitivity of the DSF was 82% and the specificity was 52%. The DSB sensitivity was 40% and the sensitivity was 93%. Tests performed according to Medcal software.

Thus, for this study in relation to cognition, executive functions were considered, especially: memory, language, decision making, and inhibitory control.

Physical capability

We used the stationary gait test of two minutes (2MST) and the Sit-to-stand Test to assess the physical capability. The first test is an alternative proposal of the six-minute walk test (6MWT) as it has greater feasibility of application in small spaces, such as those made available for the present study. The 2MST evaluates the aerobic endurance of the individual through the number maximum of steps complete in two minutes from the buzzer evaluator. The appropriate minimum knee height should reach a midpoint between the patella and the anteroposterior iliac spine. The total score is recorded by a trained researcher to count how many times the right knee reaches the indicated height. The classification is made according to sex and age, but it is considered as a risk zone less than 65 steps for men and women[42,43]. The Sit-to-stand Test begins with the subject sitting in a chair, feet flat on the floor and arms crossed at chest level. The sound signal evaluator, the participant must get up and sit continuously until a command is given to stop. The maximum number of completed movements in 30 seconds estimates the functional capability of the lower limbs. The classification is made according to sex and age, however, it is considered as a risk zone less than 8 unassisted stands for men and women[43,44]. Thus, these instruments aim to assess aerobic endurance and muscle strength of the lower limbs to determine functional physical capacity.

All instruments, cognitive and physical tests used in the study followed their respective application protocols[33,35,36,37,41,42,43]. Therefore, all instructions were given to the participants orally. The auditory acuity was established informally and only individuals with preserved communication skills were included in the study. Still, participants requiring orthosis could use it while performed subtasks of the MMSE, minimizing bias. However, it is important to appraise that hearing loss is associated with psychosocial impairments, which can impair autonomy, cause isolation and worsen quality of life, even causing depressive symptoms[45].

Statistical analysis

Based on the reference by Thakur and Blazer (2008)[46], was used a 35% prevalence of depressive symptoms in institutionalized older persons. A finite population of 309 individuals was considered, the precision of 5%, and the proportion of events of 35%. The sample was estimated at 164 subjects. To perform the calculation the Sample Size Calculator tool from the Australian Bureau of Statistics was used. In addition to those that did not fit the inclusion criteria, adds up the difficulties related to conducting research at LTCFs such as the high turnover, deaths, lost information due to the gaps in the medical records, and data loss in testing applications only 69 individuals were evaluated.

Data are presented as mean ± standard deviation for normally distributed variables and as a median (min and max) for variables without normal distribution. The Shapiro-Wilk test was used to determine the normality of the data. Independent T-test and Mann-Whitney test were used to compare the two groups: asymptomatic (AS) and depressive symptoms (DS), as appropriate. A hierarchical binary logistic regression test was performed to verify whether the cognitive variables could predict depressive symptoms since these data were transformed into categorical variables. Since aerobic capacity interferes with depressive symptoms and cognitive functions, this variable was used as a control. The level of significance was established at $p < 0.05$. All analyzes were performed using SPSS® version 21.0.

Ethics statement

This study is a part of two large projects which were approved by the Research Ethics Committee of the Universidade Federal Fluminense (protocol 1.287.659/2013) and Universidade Estadual de Montes Claros (protocol 2.398.863/2017). All volunteers signed the informed consent to participate in the study.

RESULTS

Sixty-nine older adults participated in this present study. Figure 1.

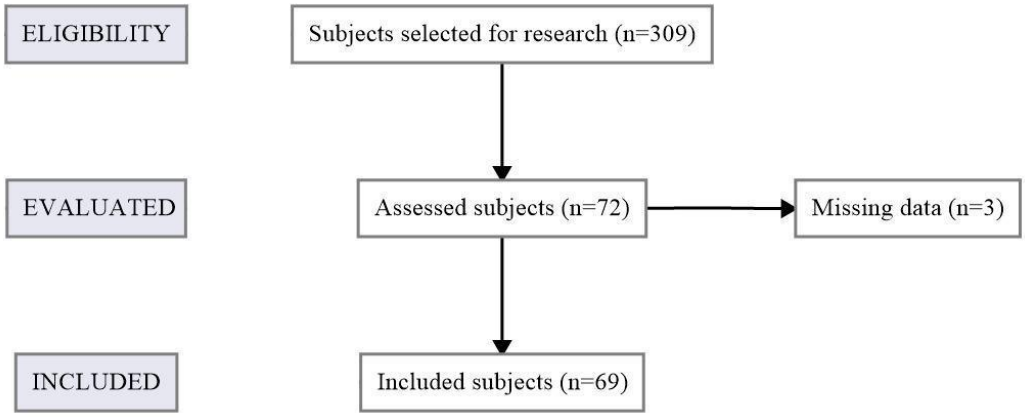

Figure 1 Flowchart of the study selection protocol.

Regarding the medication intake, all of the participants used three or more, with emphasis on the use of antihypertensives, benzodiazepines, and anxiolytics/antidepressants.

In concern to the occurrence of depressive symptoms, 34 individuals were classified as asymptomatic (AS) and 35 participants showed depressive symptoms (DS). AS group had a score of 5.36 ± 2.13 on GDS, while older adults of the DS group had a value of 17.56 ± 4.08 on GDS. Sociodemographic data are displayed in Table 1.

Table 1 - Characteristics and cognitive and physical performance in institutionalized asymptomatic (AS) and symptomatic (DS) older adults.

Variable	AS (n = 34)	DS (n = 35)	p-value
GDS$_{(score)}$	5.36 ± 2.1	17.56 ± 4.08	< 0.01$^{\#}$
AGE$_{(years)}$	81.05 ± 8.01	83.38 ± 7.57	0.22$^{\#}$
BODY MASS$_{(kg)}$	68.98 ± 17.42	68.53 ± 17.03	0.94$^{\#}$
HEIGHT$_{(m)}$	1.56 ±0.09	1.53 ±0.07	0.44$^{\#}$
MMSE	20.79 ± 5.27	17.14 ± 7.42	0.02$^{\#}$
DSF	6.00 (1, 10)	4.00 (0, 10)	0.01*
DSB	3.00 (0, 7)	2.00 (0, 7)	< 001*
VF	9.59 ± 4.95	8.18 ± 4.71	0.24$^{\#}$
Sit-to-Stand	7.28 ± 2.56	6.04 ± 2.36	0.06$^{\#}$
2MST	38.50 ± 16.67	26.00 ± 12.58	< 0.01$^{\#}$

Data presented with mean ± standard deviation (s.d.). $^{\#}$Independent T-test. Data presented with median, minimum and maximum. *U-test. ($p \leq 0.05$).

The homogeneity of ages between groups is especially relevant considering that age can negatively influence the subject's cognitive ability[16,25]. The data obtained through the independent T-test showed a difference between the groups with and without depressive symptoms, according to the results of the MMSE variables (t (61) = 2.36; p <0.05) and 2MST (t (53) = 3.12; p <0.05) shown in Table 2.

Table 2- Binary logistic regression showing the relationship between cognitive functions and depressive symptoms in institutionalized older adults (Cox & Snell R^2=0.261; Nagelkerke R^2=0.347).

Variable	β	WALD	OR	CI95%	p-value
DSF	1.582	4.300	4.86	1.09; 21.69	0.03
DSB	-.586	0.506	0.55	0.11; 2.79	0.47

Aerobic capacity was used as a control covariate: 2MST (OR = 0.93, p = <0,01). The cutoff points of 6 and 4 were used respectively for the DSF and DSB tests[26].

These results demonstrate that older adults with depressive symptoms show worse cognitive and physical performance when compared to those with no symptoms.

Older adults with depressive symptoms showed lower short-term memory and working memory than asymptomatic ones DSF (U = 402.00, p < 0.05) and DSB (U = 341.00, p < 0.05), indicating that cognitive functions influence depressive symptoms (Table 1).

These outcomes were consolidated according to the results from binary logistic regression made on cognitive performance as predictor of depressive symptoms. The results pointed that the older adults with scores below normal in DSF (score < 6) are 5 times more likely to have depressive symptoms. However, the other variables were not significant predictors of depressive symptoms. These findings are detailed in Table 2.

DISCUSSION

This study evidenced short-term memory as the main cognitive function influencing depressive symptoms. According to the literature, people with major depression may present a deficit in several cognitive processes such as memory, attention, processing speed, and learning, in addition to a negative cognitive bias in the understanding of information[47,48].

Regarding short-term memory, this can be understood by the human capacity to retain a limited amount of information for a short period of time[49]. Working memory, on the other hand, is the combination of sustaining attention and immediate memory that is used to achieve a specific goal and carry out behavior [49]. To differentiate between short-term memory and working memory, it must be understood that working memory is fully active and requires effort when maintaining mental operations for a short period, "working" constantly[50].

About the association between depressive symptoms and cognitive impairment in institutionalized older adults a recent study[25] showed results that corroborating the idea that as higher is the score obtained in the GDS, the greater is the cognitive impairment. In the comparison between the GDS and the Cambridge Cognitive Test, a tool used in the study that also assesses the cognitive performance of the older adults, a negative Pearson correlation ($r = -0.471$; $p = 0.004$) was found for the group of older adults considered independent, indicating that as the score of one instrument increases, the other decreases.

It is noteworthy that although the variables working memory and global cognition did not show a significant p-value, these were important to improve the initial model (without independent variables), increasing its predictive power from 50% to 72,2%. These variables were statistically significant before in the association with depressive symptoms in older patients in this study and the literature[16,17,48]. Moreover, aerobic capacity was used as a control variable with significant influence on the model $p<0.05$. This result can be explained by a study of 2012[16], also with institutionalized older adults, once an increase in the incidence of depressive symptoms was associated with impaired functional capacity ($r = -0.306$, $p = 0.021$), explaining that as one of the elements increases, the other reduces. Another study indicates that physical impairment is a risk factor for depression[51].

It should be noted that, in the context of institutionalization, the older adults are limited by various factors of the LTCFs, such as the rigidity of routine, reduced social functions, the absence of situations that require decision-making, the limitation of the physical space that result in a loss of autonomy and put you in a situation of physical, cognitive and emotional fragility[16]. We emphasize that being an old adult is different in developed and developing countries[5] and that the prevalence of depression varies due to cultural factors and assessment methods. However, in Brazil, studies claim that among institutionalized older persons, the prevalence of depression is approximately 50% (48.7% and 45.7%)[52,53], following the trend of developed countries like the United States of America[54].

The aging process is natural and inevitable, causing several structural, functional, social, and psychic changes, resulting from the interaction of several intrinsic and extrinsic factors. Understanding these changes in cognitive functions, which are related to depressive symptoms, can be useful in preventing depressive symptoms by monitoring cognitive impairment, resulting in greater longevity, quality of life, and less burden to public coffers[25]. Regarding physical performance, this should be understood within a context of functionality and autonomy, since its decline may be associated with the onset of depressive symptoms[16]. Likewise, considering better mental health should also be considered with the absence or minimization of depressive symptoms can promote an improvement in physical and cognitive ability[55,56].

When it comes to the older population, depression is under-diagnosed and under-treated, either because its symptoms permeate neurodegenerative diseases, making a differential diagnosis difficult, or because its symptoms are considered part of unsuccessful aging[57]. Consequently, with the progressive enhancement in the population aging and the risk of depression, this issue will become a public health problem. The problem is added that with the increase in aging, there is an increase in the institutionalization of this part of society[25], and studies have already addressed that compared to older adults in the community, those who live in LTCF have a higher prevalence of depressive symptoms, cognitive impairments, and functional deficits[9,16,25,57].

Although the association between depression and cognitive decline is well established in the literature, it is not clear whether cognitive decline is a risk factor for depression, a symptom of it, or a consequence of risk factors that are shared between both[33]. Many studies point to depression as a risk factor for dementia[58,59,60,28], however, 20% of subjects with dementia develop depression[61]. Added to this is the perspective of the cognitive neuropsychological model of depression that brings with it the idea that the negative affective bias plays a central role in the development and maintenance of depression[62,63]. In order to collaborate in this matter, this study discussed cognition as a predictor of depression, since even with the remission of the episode of major depression, deficits in selective attention, working memory, and long-term memory remain[64]. Therefore, it is important to consider both pathophysiological pathways and their clinical implications for better treatment guidance.

In this sense, this study aimed to promote a better understanding of the possible associations of depressive symptoms and cognitive ability being controlled by aerobic capacity. This is a reaffirmation study to increase the range of evidence in this line of studies.

This association between low short-term memory and depressive symptoms may occur via hippocampal atrophy[65]. Memories that carry a relationship with the hippocampus are the most affected in depressed patients as they undergo changes mediated by stress, decreased neurogenesis, and neurodegeneration[66]. Considering the classic segmentation of the hippocampus which is - CA1-CA4, dentate gyrus, subiculum, molecular layer, and tail - these substructures present a reduction in volume, mainly in the left lateral region, with the exception of the molecular layer, which presents an increase[65]. Such findings confirm the importance of CA1-CA4 and dentate regions, which are important circuits for the functions of pattern separation and completion and neurogenesis[65]. Thus, the atrophy of these regions in depression may be associated with impaired short-term memory. However, as such mechanisms were not investigated in the present study, we should interpret this as a speculation.

Limitations include the lack of sociodemographic data and the loss of anthropometric data (37), but without prejudice to the reliability of the results. The lack of stratification of the MMSE requires a cautious interpretation of the results. Some included individuals were diagnosed with depression according to the physician in each LTCF. However, none validated criteria (e. g. DSM-5) was used as an instrument to provide the diagnosis. Thus, these persons were not excluded from the sample, probably limiting our results. Also, it is added that with aging the prevalence of sensory deficits increases and these can negatively impact cognitive performance, which may result in overestimating cognitive decline[67], requiring further investigation of how such deficits are associated with cognitive functions. About the limitations surrounding the Brazilian LTCFs most are philanthropic and do not have sufficient human resources to manage services and information, causing limitations in conducting research at these institutions. Thus, the results of this study cannot be generalized, once the planned sample was not reached, once a large number of older adults were excluded due to the incapacities to be evaluated. Still, considering the heterogeneity of issues that vary among the older adults aged 60, 80, or more, a multidimensional approach that considers the peculiarities of each age group is necessary to guide both diagnosis and treatment in order to offer a more appropriate care plan for the situations that concern each older person in these periods[68].

Finally, a prospective study investigating the incidence of depression and cognitive impairment in institutionalized older adults should be carried out, since in this research we do not intend to establish whether institutionalization is what favors such declines

or if people with previous commitments are more hospitalized. However, it is pointed out that there is a need to intensify the care provided by the LTCFs so that they favor the autonomy of the older adults through cognitive, physical, and social stimulation.

CONCLUSION

The present study demonstrated that short-term memory and working memory would be associated with the development of depressive symptoms in institutionalized older adults. The results indicate the importance of seeking intervention strategies in these institutions aimed at strengthening these capabilities, especially concerning short-term memory, whose deficit would be associated with an approximately 5 times greater risk of developing depressive symptoms.

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Authorship Contributions

All authors contributed equally to develop this study.

Disclosure of Conflicts of Interest

The authors declare no conflict of interest.

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5.2 PRODUTO 2

NEUROBIOLOGICAL HYPOTHESES ABOUT THE INTERACTION BETWEEN DEPRESSION AND COGNITIVE DECLINE *IN SILICO* ANALYSIS.

Depressive and neurocognitive disorders have a mutual influence through their neuropathological pathways. Studies reveal that 25 to 40% of older persons diagnosed with depression may exhibit mild cognitive impairment[1]. Like the older adult with stress-related disorders, they are at an increased risk of vascular dementia and Alzheimer's disease[2].

Psychosocial stress throughout life can promote a neurotoxic environment with the accumulation of corticosteroid hormones, insoluble proteins, and pro-inflammatory cytokines. In the case of chronic depression in the older adult, the main neuropathological process shows an increase in the activity of the hypothalamic-pituitary-adrenal axis (HPA) with the excess production of corticosteroids[3]. On the other hand, the main neurobiological theories of cognitive decline in the older adult report the accumulation of insoluble proteins, such as β-amyloid and Tau[4]. Both depression and cognitive decline are also associated with the phenomenon of chronic inflammation with aging (inflammaging), which promotes the accumulation of pro-inflammatory cytokines, such as interleukins and tumor necrosis factors (TNF)[5]. Together, these neuropathological pathways promote neurodegeneration of the prefrontal cortex, amygdala, insula, and hippocampus, presenting an important role in the association of depressive symptoms and cognitive decline[3,6].

Hippocampal atrophy caused by the accumulation of neurotoxic substances can produce a vicious and disruptive cycle on the HPA axis, stimulating both depressive symptoms and cognitive decline[7]. The chronic release of inflammatory cytokines can also increase the expression of glutamate receptors and reduce the expression of serotonergic, dopaminergic, and insulin receptors, increasing cerebral glial and metabolic dysfunction[8,9]. The deleterious effects of these changes also affect brain structure and function, through the inhibition of protein synthesis and the downregulation of neurotrophic factors[10]. Thus, regardless of the neuropathological pathway, neurodegeneration and neural inflammation can perpetuate depression and cognitive decline.

Given the diverse neuropathological pathways involved in this matter, understanding the relationship between depression and cognitive decline may have important implications for early diagnosis and treatment. Therefore, the present study aims to reinforce

the hypothesis about the interaction of depression with cognitive decline through an *in silico* analysis. Therefore, the present study through *in silico* analysis proposes as a hypothesis about the interaction of depression, cognitive decline, corticosteroids (POMC and CRH), genes that encode proteins (APOE, MAPT, SLC6A4, HTR2A, COMT) and cytokines (TNF -α) that would cause a downregulation in the BDNF.

Mechanisms of depression

The first hypothesis related to the pathophysiology of major depressive disorder (MDD) considered the mechanisms of the main antidepressants, building a so-called monoaminergic theory[11]. Changes in the levels of serotonin, norepinephrine, and dopamine would be responsible for the disease, despite that, the depletion of these neurotransmitters is not enough to explain it[12].

Subsequently, the role of the receptors was the subject of intense research. The increased expression of 5HT1a autoreceptors is related to depressive symptoms and the opposite happens to their heteroreceptors[13]. The same occurs with 5HT1b autoreceptors, which are related to the reactivity to stress and its heteroreceptors, related to possible hippocampal neurogenesis and antidepressant action[14]. An overactivity of 5HT-2c heteroreceptors can contribute to the same etiology of depression as evidenced by the abnormal increase in the expression of these receptors in suicide victims[14]. The 5-HT4 heteroreceptor polymorphism is associated with susceptibility to depression, whereas the 5-HT7 heteroreceptors mediate interactions between the serotonergic system and the HHA / HPA axis, with the agonism of the receptors increasing the hippocampal expression of glucocorticoid receptors[12].

A dysfunction of the HPA axis in MDD is well documented, and this correlation is more consistent when considering childhood traumas[15]. This occurs because of a reduction in the function and expression of glucocorticoid receptors, which impair the negative feedback of the axis and keep cortisol releasing high[16]. Hypercortisolemia reduces the immunomodulatory function of the axis, increasing proinflammatory cytokines expression and reducing anti-inflammatory factors, which cause a decrease in the neurogenesis[17]. However, it is not clear whether these changes in the peripheral immune system are risk factors or the result of major depressive disorder[18].

Besides the aforementioned neuroendocrine effects, pro-inflammatory cytokines cause effects on the synthesis, release, and reuptake of all neurotransmitters (serotonin,

dopamine, norepinephrine, and glutamate) associated with affective disorders[18]. Inflammation also occurs through mechanisms mediated by toll-like receptors Type 4 that activates NF-kB, inflammasomes (producing IL-1B and IL-18), increased permeability of the blood-brain barrier through IL-6 and TNF as well as changes in the gut microbiota[19]. In addition to the influences of peripheral immunity, immune cells of the central nervous system such as microglia are activated and astrocytes atrophied (with negative consequences on synaptogenesis and increase on neurotoxicity)[20].

An important factor in the communication between the microbiota, the inflammatory factors, and the HPA axis is the vagus nerve that exerts a bi-directional function in controlling mood and the immune response through information on internal organs by their afferences (forming one component of the gut-brain axis) and efferences (part of the parasympathetic system)[21]. It acts as an intermediary in the influence of the effects of colonic inflammation and the beneficial effects of probiotics[22]. This mechanism is displayed in the Figure 01.

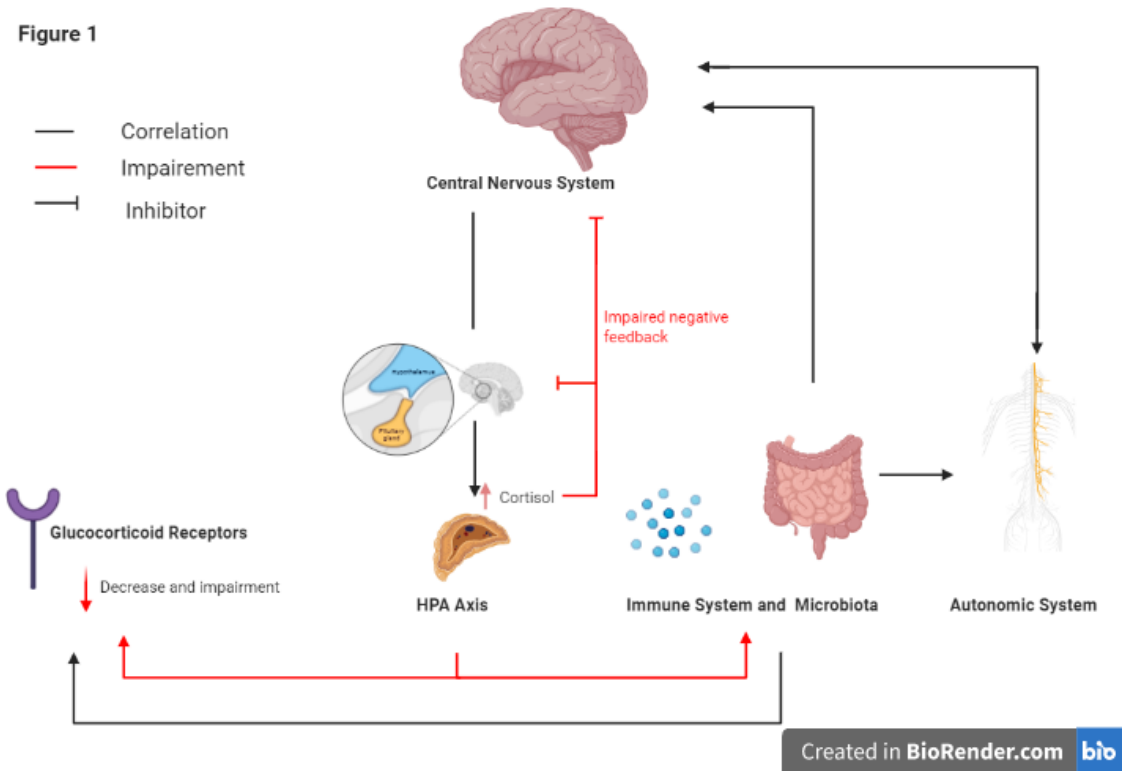

Fig. 1. Mechanisms of depression. Gut-brain axis and the bidirectional function of the vagus nerve mediating mood and immune responses.

Also, more recent studies highlight that low levels of irisin, a hormone produced endogenously during continuous physical exercise, may be involved in the development of

depressive symptoms[23]. This is due to the fact that irisin is an inducer of BDNF expression through the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a)/fibronectin type III domain containing 5 (FNDC5) pathway[24]. Thus, lower concentrations of irisin would imply a lower expression of BDNF and, consequently, a reduction in its neuroprotective functions.

The relationship between inflammation and cognitive decline

Neuroinflammation is a protective mechanism to restore the damaged glial cells and neuronal cells in the CNS. Mild activation of microglia and astrocytes usually indicates neuroprotection and improves the early symptoms of neurodegeneration, strong activation of inflammatory mechanisms, however, leads to overproduction of cytokines, which promotes neurodegeneration[25]. Excessive inflammatory responses are detrimental in the brain, since neurons are damaged or degenerated, they are unable to be repaired or regenerated in the CNS[26]. Chronic neuroinflammation plays an important role in the onset and progression of neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and Multiple Sclerosis (MS)[27]. Depression also produces neuroinflammation by increasing proinflammatory mediators released from inflammatory cells[28].

An important factor for neuroinflammation is the activation of the P2X7-NLRP3 inflammasome cascade. The NLRP3 is part of the inflammasome family, which cleaves multiple substrates implicated in inflammation or cell death[29]. NLRP3 is expressed in both peripheral immune and microglial cells. Under physiological conditions, inflammasome-induced IL-1β expression is essential as trophic support to promote long-term potentiation and memory formation[30]. However, at high levels, IL-1β becomes excitotoxic, alters synaptic activity[31], and modulates monoaminergic and glutamatergic synaptic transmission[32].

The P2X7 receptor expression has been reported in almost all cellular lineages making up the brain tissue, including oligodendrocytes, astrocytes, microglia, and neurons[33,34]. In addition, the stimulation of P2X7 receptors participates in the synthesis/secretion of inflammatory cytokines and is a key factor in neuroinflammation[35,36]. P2X7 receptors improve the inflammatory cytokine response performed by IL-1β, IL-6, and tumor necrosis factor-α (TNF-α)[37]. Collectively, these data suggest that the mechanism of microglial activation via P2X7-NLRP3 inflammasome cascade is an explanation for this neurobiological process in the pathophysiology of depression[38].

It has been previously shown that major depressive disorder (MDD) patients exhibited higher levels of IL-6 and TNF-α in the blood and cerebrospinal fluid[39,40]. In addition, the expression of IL-1β, IL-6, and TNF-α was also increased in postmortem brain samples from suicide victims that suffered from depression[41].

Another study[42] investigated the levels of the pro-inflammatory and anti-inflammatory cytokines in antidepressant drug-naïve patients with MDD. Compared to healthy controls, patients with MDD had significantly higher levels of IL-1β, IL-10, and TNF-α, but significantly lower levels of IL-8. There were linear correlations between IL-1β, TNF-α, and IL-8, and the severity of depression, as well as between IL-8 and anxiety level in patients with a comorbid anxiety disorder. Compelling evidence suggests that stress-evoked mood disorders are partially related to the dysfunction of the inflammatory system, and the elevation of inflammatory components contributes to depression and may even worsen it further[43,44,45]. The cascade of the inflammatory process is shown in Figure 2.

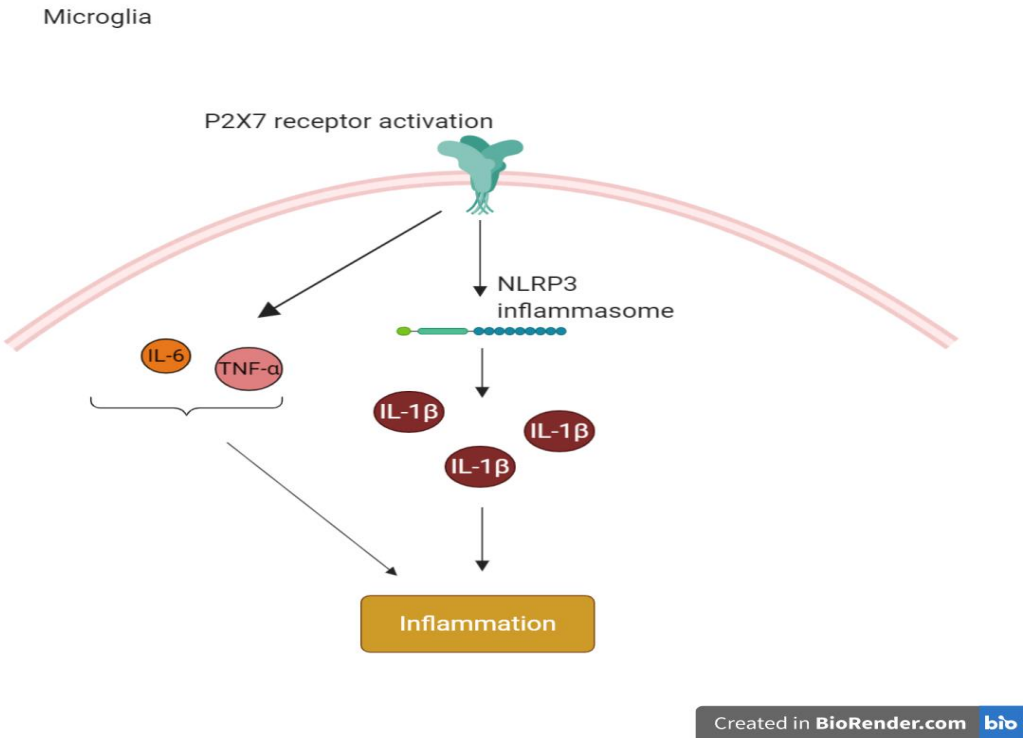

Fig. 2. Activation of the neuroinflammatory cascade of the P2X7-NLRP3 inflammasome participating in the neurobiological process in the pathophysiology of depression.

Chronic stress, affective disorder and cognitive impairment

Persons with mood disorders have changes in immunological biomarkers and premature senescence[46]. Faced with external stressors, the brain activates its stress system causing neuroendocrine changes in an attempt to reach homeostasis and readaptation. However, if these adaptive responses are inadequate or are prolonged over time, exaggerated inflammatory reactions may arise causing damage to the organism[46].

In stressful situations, the hypothalamus secretes the corticotrophin-releasing hormone (CRH), stimulating the release of adrenocorticotrophic hormone (ACTH) by the pituitary gland and resulting in the adrenal glucocorticoid: cortisol[47]. The exacerbated inflammatory reaction may be associated with a dysfunction in the HPA axis (hypothalamus-pituitary-adrenal) leading to hypercortisolemia[48]. Through chronic stress and the inflammatory processes generated from it, there is a loss in the negative feedback of the HPA axis during the production of cortisol leading to the resistance of glucocorticoid receptors and thus to the hyperactivation of the axis[17].

Chronic stress affects not only mood and affection but also impairs cognitive performance via learning and memory[47]. Studies show that continuous exposure to stressors increases the plasma level of tumor necrosis factor (TNF)[50,51,52] and associates inflammatory cytokines with damage in memory and learning[53].

In this sense, glucocorticoids play an important role in metabolic, immunological and behavioral regulation[47,48] and changes in their levels are associated with autoimmune, somatic, metabolic and psychiatric diseases, such as depression[48].

Gene network analyzes

To explore genes that encode proteins associated with depression and cognitive decline, the GeneCards database (https://www.genecards.org) was used. Based on the literature on the interaction between depression and cognitive decline, the terms pro-opiomelanocortin (POMC), corticotropin-releasing hormone (CRH), TNF-α and BDNF have been inserted into GeneCards, resulting in the recovery of other genes, such as Apolipoprotein E (APOE), Microtubule-associated protein tau (MAPT), Sodium-dependent serotonin transporter (SLC6A4), 5-hydroxytryptamine receptor 2A (HTR2A), Catechol O-methyltransferase (COMT).

The genes mentioned above were inserted into the String database (https://string-db.org) that addresses the genes and their interactions in a network. The species considered for this study were Homo Sapiens. Significant specific and non-specific interactions were found in the genetic interaction network generated in the String (PPI enrichment p-value: 7.08e-14). Each protein-protein bond receives a certain "score" that indicates the veracity of the interaction according to the published evidence. The interactions found had scores above 0.40 and are classified as average confidence. The links found were analyzed according to the colors of the interaction network symbols, in which the colored lines show molecular interactions, while the gray lines show associations co-mentioned in the PubMed abstracts. Thus, the blue lines signify a direct link between the genes. Figure 3 shows the genes found in the String.

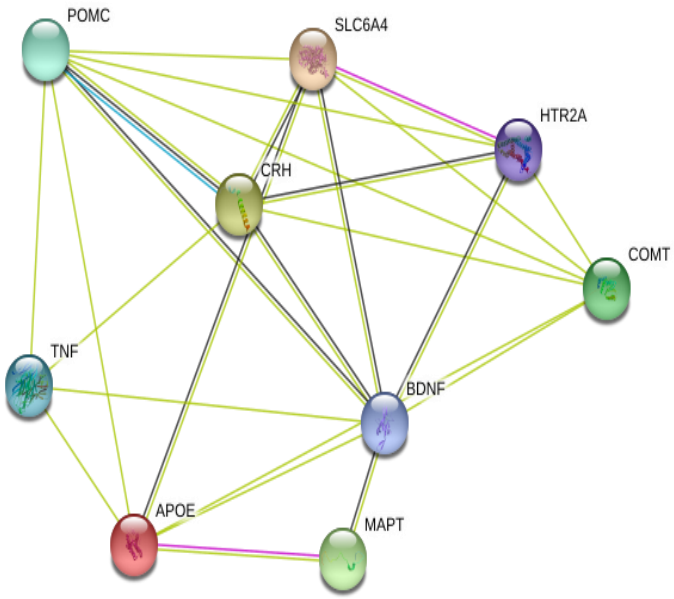

Fig. 3. Genes network found at String. Bindings among genes POMC, TNF, APOE, CRH, MAPT, BDNF, SLC6A4, HTR2A, COMT is shown. Color lines show molecular interactions, while grey lines show no molecular interactions but associations co-mentioned in PubMed abstracts. Yellow lines: regulation of transcription. Purple line: catalysis. Black line: reaction. Arrows: activation. Circle: unspecified interaction and red line: inhibition

For the purpose of more detailed analysis, molecular interactions were considered. Since the study mainly addresses the hypothesis of downregulation in the BDNF, the direct interactions with it are highlighted, as shown in Figure 4 below:

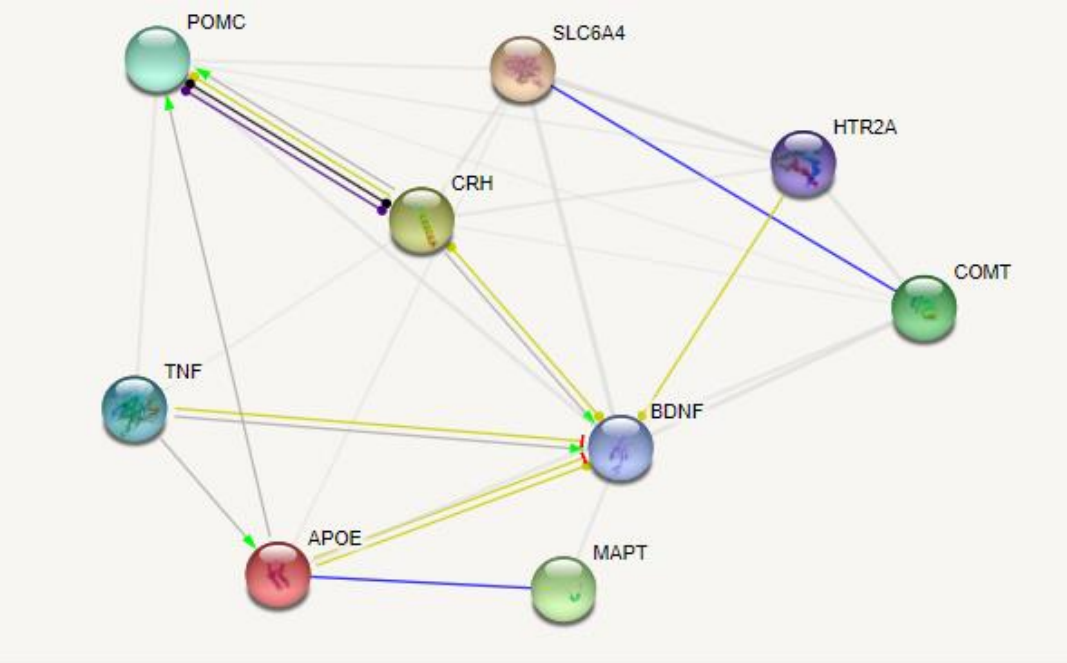

Fig. 4. Specific network among genes related BDNF found at String. Blue lines mean direct binding among genes. Yellow lines: transcriptional regulation. Purple line: catalysis. Black line: reaction. Grey lines: show no molecular interactions. Arrows: activation. Circle: unspecified interaction. Red trace: inhibition.

Evidence suggests that the immune system plays a large role in modulating memory, learning, and mood[53]. Through the high production of proinflammatory cytokines and prostaglandins, imbalances in the neurophysiological actions of immunological processes cause damage to both cognition and the psychological scope[46,53,54].

Among morphological and functional changes during chronic inflammatory processes, studies have already revealed that in patients with cognitive decline or mood disorders, levels of the Brain-Derived Neurotrophic Factor (BDNF) are reduced when compared to people without these pathologies[56]. Such neutrophin plays a central role in neurogenesis, synaptogenesis, and neuronal integrity and is a potential neurobiological mediator of processes dependent on external stimuli such as life, memory and learning experiences[55,57].

Studies have already shown that continuous exposure to stress increases levels of pro-inflammatory cytokines such as TNF-α in the hippocampus and plasma[48,58,59]. In the silica analysis of the molecular action, after the TNF transcription process, it generates an inhibitory effect on the BDNF (score: 0.45). Such analysis is in line with other results that bring the effect of reducing the level of BDNF in the increased presence of TNF[60].

In the same sense, Apolipoprotein E (APOE E2, E4) and BNDF are associated in relation to cognition (score: 0.45). The APOE gene is presented in the literature as a predictor of cognitive impairment, which may increase or decrease the risk of dysfunction[61]. Its actions are related to axonal growth and formation, synaptic remodeling and neurogenesis of the hippocampus, directly impacting the formation of memory, learning and neuronal repair[62]. The APOE e4 allele of this gene is linked to an increased risk of developing mild cognitive decline until Alzheimer's disease (AD)[61]. However, the presence of the APOE e2 allele has protective and delaying effects on AD[61]. Thus, it is possible that the double interaction between APOE and BDNF, shown in the computational model, makes reference to the two alleles previously mentioned since after the transcription of the APOE gene, an inhibitory and a non-specific action on BDNF is seen.

Regarding the association identified between the HTR2A gene and BDNF (score: 0.40), the influence of serotonin receptor agonists on BDNF expression is already well established[63]. During a stressful event, the HPA axis and the stress response can be modulated via the serotonergic pathway[64]. In this case, serotonin (5HT) interacts with the pre and postsynaptic receptors, respectively 5HT1A and 5HT2A, mediating the regulation of BDNF and contributing to the effects of stress[65]. It is known that the interaction occurs after transcriptional regulation, but the non-specificity of the action between the receptor and neutrophin may be due to the fact that it depends on the location in the brain since: in a stress situation, the 5HT2A receptor agonist decreases the expression of BDNF mRNA in the dentate gyrus of the hippocampus and in the parietal cortex and in other neocortical areas there is an increase in this expression[63].

However, the association that is most evident is between CRH, POMC and BDNF, with an expression score of 0.53 and an activation score of 0.56 between CRH and BDNF. It is known that the synthesis and secretion of CRH are dysfunctional due to stressful situations in the HPA axis[66]. Since the CRH acts on the anterior lobe of the pituitary gland to initiate the synthesis of the POMC protein[67], it can cause changes in its transcriptional regulation (score: 0.64), in addition to a bidirectional interaction in the process of catalysis (score: 0.91) or reaction (score: 0.91). However, the type of interaction suffered is not specified by the model. Likewise, there is a bidirectional interaction between CRH and BDNF that is also nonspecific, but that can point to the bidirectional relationship between depression and inflammation[46]. Such bidirectional relationship between depression and inflammation is also seen between the HPA axis and the TNF-α system since the TNF system stimulates the

HPA axis while the axis suppresses the activity of the TNF system[68], thus reinforcing this hypothesis feedback. Cytokines, such as TNF disrupt the interaction of corticosteroids and its receptors, increasing hypercortisolemia.

Final considerations

Depression is one of the most prevalent and disabling mental illnesses in the world[69], however, its molecular mechanism is not completely unveiled. In the older adult, depression is accompanied by structural and functional changes in the frontal lobes and their connections with the limbic and striated system, resulting in 30-40% of older persons with depression and undiagnosed who have cognitive impairments[70].

Thus, unraveling the possible molecular interactions can help in the diagnostic accuracy and in the treatment offered[57]. The hypothesis of this study is based on clinical observations and analysis on silica, pointing out that the interaction between depression and cognitive decline is mediated mainly by corticosteroids and cytokines, especially CRH, POMC and TNF. Thus, these mediators would cause a downregulation in the BDNF.

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6 CONCLUSÕES

O primeiro trabalho reforça a importância da estimulação cognitiva e física de idosos institucionalizados uma vez que a memória de curto prazo, a memória de trabalho e a capacidade cardiorrespiratória estão associadas ao desenvolvimento de sintomas depressivos nessa população. No que se refere à memória de curto prazo, seu déficit pode estar associado a um risco cerca de 5 vezes maior de desenvolver sintomas depressivos, direcionando maior atenção para o fortalecimento dessa função cognitiva.

O segundo trabalho reforça a hipótese, baseada em observações clínicas e análises in sílico, que a interação entre depressão e declínio cognitivo é mediada principalmente por corticosteroides e citocinas, principalmente CRH, POMC e TNF, e que esses mediadores causariam um *downregulation* no BDNF.

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APÊNDICE(S)

APÊNDICE A – Termo de Consentimento Livre e Esclarecido

CONSENTIMENTO LIVRE E ESCLARECIDO- Voluntário da Pesquisa

Nome do voluntário: _____

RG: _____ Data de nascimento ___/___/___

Responsável legal (quando for o caso) _____

RG do responsável legal: _____

Projeto: EFEITO DE DIFERENTES PROGRAMAS DE EXERCÍCIO FÍSICO SOBRE O PERFIL INFLAMATÓRIO, RESPOSTA HORMONAL, DESEMPENHO FUNCIONAL E SAÚDE MENTAL DE IDOSOS INSTITUCIONALIZADOS E NÃO INSTITUCIONALIZADOS

Objetivo: O(a) senhor(a) está sendo convidado para participar de uma pesquisa para avaliar as possíveis modificações cognitivas, comportamentais, motoras e funcionais de idosos, além de alterações em componentes do sangue e da saliva. Nesta pesquisa, caso o(a) senhor(a) seja residente em instituição de longa permanência para idosos (ILPI), todos os procedimentos serão realizados em sua instituição. Portanto, não precisará deslocar-se a outro local para participar.

Haverá testes de avaliação de memória, atenção, concentração, capacidades simples de cálculo e entendimento de tarefas, além de perguntas sobre as suas atividades de vida diária, testes de equilíbrio, marcha (caminhada), força de preensão (força na mão) e coleta de sangue e saliva. A pesquisa não envolverá qualquer custo ao senhor(a). Para que haja segurança na sua participação, o médico responsável pela ILPI deverá autorizar seu engajamento na pesquisa.

Riscos: Os riscos envolvidos nesses procedimentos são baixos, mas podem ocorrer alterações da pressão arterial como aumento ou diminuição da mesma durante os testes físicos, podendo ocasionar tontura, enjoo e dores na cabeça. As avaliações de testes psicológicos não trazem desconfortos a não ser algum problema com a sua própria avaliação do desempenho. As coletas de sangue e saliva serão realizadas por profissionais qualificados, o que reduz o risco de intercorrências.

Atendimento: Caso o(a) senhor(a) venha a apresentar algum sintoma ou problema durante as avaliações, elas serão interrompidas e o(a) senhor(a) será encaminhado(a) à emergência do hospital mais próximo. Além disso, o médico responsável será comunicado imediatamente.

Confidencialidade: Todas as informações coletadas no estudo são confidenciais e o seu nome não será divulgado em momento algum. Toda e qualquer informação será utilizada somente para fins acadêmicos.

Benefícios: A sua participação poderá trazer benefícios através dos resultados das avaliações que serão anexadas ao seu prontuário para que a equipe que lhe atende possa fazer o necessário a partir daí. Além disso, o projeto contribuirá para a divulgação de novos recursos no atendimento ao idoso.

Liberdade para interromper a participação: A qualquer momento o(a) senhor(a) pode interromper sua participação no presente estudo sem que isso implique em prejuízo na sua relação com a instituição ou com os profissionais da mesma ou qualquer outro tipo de prejuízo.

Direito de imagem: estou ciente de que poderão ser realizadas fotografias e filmagens de minha pessoa e autorizo a reprodução das mesmas para fins acadêmicos.

Eu afirmo que li (ou que me foram lidas), entendi as informações do estudo acima citado e estou suficientemente informado a respeito do mesmo.

Identificação do responsável pelo estudo:

Prof. Renato Sobral Monteiro Junior (CREF 024869-G/RJ) – Doutorando (Programa de Pós-graduação Stricto Sensu em Neurologia – Neurociências da Universidade Federal Fluminense)

E-mail: renatoprofedfis@hotmail.com

Estrada do Cabuçu de Baixo, 800, Guaratiba, Rio de Janeiro, RJ, BL 25 CS 15.

Fone: (21) 9244-7872

Dr. Osvaldo José Moreira Nascimento – Coordenador do Programa de Pós-graduação Stricto Sensu em Neurologia – Neurociências da Universidade Federal Fluminense

Centro de Ciências Médicas, Hospital Universitário Antônio Pedro.
Rua Marques do Paraná 330 (Hospital Universitário Antonio Pedro)
Centro, Niterói, RJ - Brasil
Telefone: (021) 22354855
Fax: (021) 22354855

Comitê de Ética em Pesquisa da UFF

Rua Marquês do Paraná 303, 4° andar , prédio anexo ao Hospital Universitário Antônio Pedro.
Telefone: (21) 2629-9189 (21) 7621-2867

_____ _____

Assinatura do participante ou responsável legal Testemunha

_____ _____

Assinatura do pesquisador Data

APÊNDICE B – Termo de Consentimento Livre e Esclarecido

CONSENTIMENTO LIVRE E ESCLARECIDO
PARA PARTICIPAÇÃO EM PESQUISA

Título da Pesquisa: EFEITO DO EXERCÍCIO BASEADO EM REALIDADE VIRTUAL NA SAÚDE MENTAL, DESEMPENHO FÍSICO, QUALIDADE MUSCULAR, PERFIL INFLAMATÓRIO E ATIVIDADE CEREBRAL DE IDOSOS INSTITUCIONALIZADOS: EXPERIMENTO CONTROLADO, RANDOMIZADO E DUPLO-CEGO

Instituição Promotora: Universidade Estadual de Montes Claros – UNIMONTES
Patrocinador: não se aplica
Coordenador: Renato Sobral Monteiro Junior

Atenção:
Antes de aceitar participar desta pesquisa, é importante que o responsável pela Instituição leia e compreenda a seguinte explicação sobre os procedimentos propostos. Esta declaração descreve o objetivo, metodologia/ procedimentos, benefícios, riscos, desconfortos e precauções do estudo. Também descreve os procedimentos alternativos que estão disponíveis e o seu direito de interromper o estudo a qualquer momento. Nenhuma garantia ou promessa pode ser feita sobre os resultados do estudo.

1. **Objetivo:** O objetivo do presente projeto é investigar os efeitos do treinamento físico com e sem realidade virtual na saúde mental, desempenho físico e perfil inflamatório de idosos institucionalizados.

2. **Metodologia/ procedimentos:** O (a) senhor(a) está sendo convidado para participar de uma pesquisa para avaliar as possíveis modificações cognitivas, comportamentais, motoras e funcionais de idosos, além de alterações em componentes do sangue e saliva. Além disso, serão realizadas imagens por meio de ultrassonografia (imagens de tecidos muscular, adiposo e conectivo ou conjuntivo; e fluxo sanguíneo cerebral) e tomografia. Nesta pesquisa, caso o(a) senhor(a) seja residente em instituição de longa permanência para idosos (ILPI), todos os procedimentos serão realizados em sua instituição. Portanto, não precisará deslocar-se a outro local para participar.
   Haverá testes de avaliação de memória, atenção, concentração, capacidades simples de cálculo e entendimento de tarefas, além de perguntas sobre as suas atividades de vida diária, testes de equilíbrio, marcha (caminhada), força de preensão (força na mão), coleta de sangue e saliva, exames de ultrassonografia e eletroencefalografia. A pesquisa não envolverá qualquer custo ao senhor(a). Para que haja segurança na sua participação, o médico responsável pela ILPI deverá autorizar seu engajamento na pesquisa.

3. **Justificativa:** Pretende-se iniciar a construção de um conhecimento sólido sobre as estratégias de intervenção com exercício físico para idosos institucionalizados, de modo que possam ser detectadas possíveis alterações positivas:
   a) Nos componentes da função motora
   b) Na autonomia funcional

c) Nas funções cognitivas
d) Nos aspectos comportamentais
e) Nos aspectos fisiológicos

4. **Benefícios:** A sua participação poderá trazer benefícios através dos resultados das avaliações que serão anexadas ao seu prontuário para que a equipe que lhe atende possa fazer o necessário a partir de ent. Além disso, o projeto contribuirá para a divulgação de novos recursos no atendimento ao idoso.

5. **Desconfortos e riscos:** Estou ciente de que os riscos associados a minha participação no projeto estão relacionados às possíveis respostas decorrentes dos testes de capacidade funcional ou das sessões de treinamento, como pequena elevação da frequência cardíaca e da pressão arterial. Em todas as avaliações estarão presentes profissionais de saúde capacitados para o suporte básico à vida, sendo de total responsabilidade do pesquisador principal o suporte a intercorrências durante os procedimentos, incluindo acompanhamento.

6. **Danos:** Não se aplica.

7. **Metodologia/ procedimentos alternativos disponíveis:** A qualquer momento o(a) senhor(a) pode interromper sua participação no presente estudo sem que isso implique em prejuízo na sua relação com a instituição ou com os profissionais da mesma ou qualquer outro tipo de prejuízo.

8. Confidencialidade das informações: estou ciente de que poderão ser realizadas fotografias e filmagens de minha pessoa e autorizo a reprodução das mesmas para fins acadêmicos.

9. Consentimento: Li e entendi as informações precedentes. Tive oportunidade de fazer perguntas e todas as minhas dúvidas foram respondidas a contento. Este formulário está sendo assinado voluntariamente por mim, indicando meu consentimento para a participação desta instituição/ empresa, até que eu decida o contrário. Receberei uma cópia assinada deste consentimento. E que o mesmo só poderá ser aprovado nesta instituição após aprovação no Comitê de Ética da Instituição fomentadora da pesquisa.

Nome do participante	Assinatura do participante	Data
Nome da testemunha	Assinatura da testemunha	Data
Renato Sobral Monteiro Junior		31/08/2017
Nome do coordenador da pesquisa	Assinatura do coordenador da pesquisa	Data

ENDEREÇO DO PESQUISADOR: Rua São Bento, 119, Todos os Santos – apt. 302, Montes Claros/MG, 39400-627

TELEFONE: (38) 988042715

ANEXO(S)

ANEXO A – Parecer do Comitê de Ética e Pesquisa/Universidade Federal Fluminense

FACULDADE DE MEDICINA DA UNIVERSIDADE FEDERAL FLUMINENSE/ FM/ UFF/ HU

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Exercício físico, saúde física e mental de idosos em instituições de longa permanência.

Pesquisador: Renato Sobral Monteiro Junior
Área Temática:
Versão: 4
CAAE: 21556613.4.0000.5243
Instituição Proponente: Programa de Pós Graduação em Neurologia / Neurociências
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.178.067
Data da Relatoria: 07/08/2015

Apresentação do Projeto:
Trata-se de uma emenda, justificada pela "Adição de um membro à equipe de pesquisa e armazenamento dos dados das avaliações para posterior publicação."

As intervenções sofrida pelos participantes da pesquisa são: jogos com movimentos corporais interagindo com realidade virtual em duas dimensões e jogos com movimentos corporais sem interação com realidade virtual

Objetivo da Pesquisa:
Objetivo Primário:
Investigar os efeitos do treinamento físico com e sem realidade virtual nas funções cognitiva eexecutiva de idosos institucionalizados e não institucionalizados.
Objetivo Secundário:
Investigar os efeitos do treinamento com e sem realidade virtual na autonomia funcional e equilíbrio, no perfil inflamatório, força e aspectos comportamentais de idosos institucionalizados e não institucionalizados.

Endereço: Rua Marquês de Paraná, 303 4º Andar
Bairro: Centro **CEP:** 24.030-210
UF: RJ **Município:** NITEROI
Telefone: (21)2629-9189 **Fax:** (21)2629-9189 **E-mail:** etica@vm.uff.br

Continuação do Parecer: 1.178.067

Avaliação dos Riscos e Benefícios:

Riscos:

Todo programa de intervenção por atividade física gera um risco. Entretanto não é comum ocorrerem eventos adversos durante a prática de exercícios. Por se tratarem de idosos, todo o suporte necessário será fornecido, como a supervisão de até 3 profissionais por atendimento, além da presença de equipe multiprofissional nos locais, o que garante a redução dos riscos ao máximo. Os possíveis eventos adversos são: tontura e visão turva.

Benefícios:

De acordo com o cenário apresentado e principalmente considerando a necessidade da saúde pública para elaboração de novas estratégias com positivo custo x benefício no atendimento ao idoso, o presente projeto apresenta uma nova perspectiva de abordagem no treinamento preventivo e tratamento de idosos institucionalizados. Além disso, poucos estudos na literatura investigaram os efeitos desse método de exercícios nessa
população. Os estudos com essa característica avaliaram componentes físicos isoladamente, o que não necessariamente significa melhora da autonomia funcional. O cruzamento das informações associadas ao desempenho funcional e aos aspectos neuropsicológicos e comportamentais pode aumentar a consistência dos achados e relacioná-los aos efeitos positivos do exercício físico no cérebro, especialmente se
correlacionados aos mecanismos fisiológicos. No Brasil, até o momento nenhum estudo verificou esses parâmetros em idosos institucionalizados, o que aumenta a relevância do presente projeto, uma vez que esta iniciativa visa melhorar a saúde dos idosos com a perspectiva de reduzir os gastos públicos com internação e tratamentos dispendiosos. Este projeto pretende iniciar a construção de um conhecimento sólido sobre as estratégias de intervenção com exercício físico para idosos institucionalizados, de modo que possam ser detectadas possíveis alterações positivas: a) Nos componentes da função motora b) Na autonomia funcional c) Nas funções cognitivas d) Nos aspectos comportamentais e) Nos aspectos fisiológicos.

Comentários e Considerações sobre a Pesquisa:

O projeto foi aprovado em reunião do colegiado em 31 de outubro de 2013, conforme Parecer Consubstanciado do CEP 458834 de 15 de novembro de 2013. O pesquisador apresenta uma Emenda, devidamente justificada, não alterando em nada o escopo do trabalho, incluindo as

FACULDADE DE MEDICINA DA UNIVERSIDADE FEDERAL FLUMINENSE/ FM/ UFF/ HU

Continuação do Parecer: 1.178.067

Intervenções anteriormente analisadas por este CEP.

Considerações sobre os Termos de apresentação obrigatória:
Foi apresentado o termo referente a emenda

Recomendações:
–

Conclusões ou Pendências e Lista de Inadequações:
Aprovado

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:

NITEROI, 10 de Agosto de 2015

Assinado por:
ROSANGELA ARRABAL THOMAZ
(Coordenador)

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Bairro: Centro **CEP:** 24.030-210
UF: RJ **Município:** NITEROI
Telefone: (21)2629-9189 **Fax:** (21)2629-9189 **E-mail:** etica@vm.uff.br

ANEXO B – Parecer do Comitê de Ética e Pesquisa/Universidade Estadual de Montes Claros

UNIVERSIDADE ESTADUAL DE MONTES CLAROS - UNIMONTES

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITO DO EXERCÍCIO BASEADO EM REALIDADE VIRTUAL NA SAÚDE MENTAL, DESEMPENHO FÍSICO, QUALIDADE MUSCULAR, PERFIL INFLAMATÓRIO E ATIVIDADE CEREBRAL DE IDOSOS INSTITUCIONALIZADOS: EXPERIMENTO CONTROLADO, RANDOMIZADO E DUPLO-CEGO

Pesquisador: Renato Sobral Monteiro Junior

Área Temática:

Versão: 2

CAAE: 75755917.0.0000.5146

Instituição Proponente: Universidade Estadual de Montes Claros - UNIMONTES

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.398.863

Apresentação do Projeto:

Caracteriza-se por ser um experimento controlado e randomizado com alocação de grupos paralelos. A população deste estudo será composta por idosos de três instituições de longa permanência (ILPI) na cidade de Montes Claros (MG) e de outras ILPIs de cidades vizinhas, caso necessário. Critério de inclusão: ser residente de instituição de longa permanência para idosos. Critério de Exclusão: serão excluídos os indivíduos que apresentarem: a) histórico pregresso de cardiopatia grave, sem liberação médica para realizar esforço físico; b) lesões musculoesqueléticas agudas que impossibilite a realização dos exercícios; c) sequelas graves de acidente vascular encefálico ou doenças neurodegenerativas em estágio avançado; e d) capacidade de entender e atender comandos simples que impossibilite a aplicação da intervenção. Idosos que não tenham condição de realizar as atividades propostas apenas participarão do levantamento de informações epidemiológicas. As intervenções serão aplicadas em dois grupos, sendo: 1) exercícios com realidade virtual e 2) exercícios sem realidade virtual. A duração do programa será de dois meses (2 vezes por semana) e os idosos serão avaliados no início e no final do estudo. As variáveis de interesse serão obtidas com os seguintes instrumentos: coleta e análise de sangue, posturografia estática computadorizada, análise cinemática da marcha, testes funcionais, avaliação neuropsicológica, medida de fluxo sanguíneo cerebral e espessura muscular (ambas com

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Bairro: Vila Mauricéia **CEP:** 39.401-089
UF: MG **Município:** MONTES CLAROS
Telefone: (38)3229-8180 **Fax:** (38)3229-8103 **E-mail:** smeiccseb@gmail.com

ultrassonografia) e tomografia computadorizada de crânio. A duração do projeto será de quatro anos. Testes e Procedimentos que serão realizados: Bioimpedância que consiste na aplicação de uma corrente elétrica imperceptível de 500 a 800 mA e 50 kHz que é aplicada pelos eletrodos distais na mão e no pé, e captada pelos eletrodos proximais, no pulso e tornozelo. Antropometria: a coletada dos dados referente à composição corporal será realizada uma semana antes dos participantes ingressarem no programa. Será avaliada a massa corporal e estatura. Fragilidade: a síndrome da fragilidade ocorre por meio de um "fenótipo" com cinco componentes mensuráveis objetivamente. Função cognitiva global será avaliada pelo Mini-mental State Examination 7, 19. Este exame é composto por 11 itens, que são divididos em duas seções: 1) respostas verbais, orientação, memória e atenção; e 2) leitura e escrita. Função executiva será avaliada pelo Floor Maze Test 20. Trata-se de um teste que avalia a capacidade de memória episódica, planejamento e tomada de decisão, em que o indivíduo elabora uma estratégia de percurso para um labirinto bidimensional. Além disso, será aplicado o Trail Making Test A, nesse teste são apresentados círculos numerados de 1 a 25, distribuídos aleatoriamente, onde o sujeito deve ligar os círculos em ordem crescente. Para a Memória será utilizado o Digit Span Test. Esse instrumento é um subteste da escala de inteligência Wechsler para adultos, WAIS-R. Espessura muscular: será utilizado o ultrassom Logic E da marca GE Healthcare com as funções: Power Doppler Imaging, Power Doppler Imaging, que permite detectar fluxo sanguíneo lento, Easy 3D, que permite realizar exames e reconstruir uma imagem volumétrica e a função B-Color que permite adicionar tons de cor para melhorar a amplificação dos contrastes. Fluxo sanguíneo cerebral: durante o teste os indivíduos permanecerão sentados a 45º. As sessões de Doppler transcraniano funcional serão realizadas com aparelho GE LOgiq P5, com transdutor convexo 2 a 5 MHz–4C, transdutor endocavitário 4 a 11 MHz–E8C e transdutor linear 4 a 13 MHz–12L. Para avaliação do fluxo sanguíneo cerebral será utilizado o protocolo de Doppler transcraniano. Desempenho funcional: tratamento dos dados medidas de tendência central e dispersão de acordo com a natureza dos dados paramétricos ou não paramétricos.

Objetivo da Pesquisa:

O objetivo do projeto é investigar os efeitos do treinamento físico com e sem realidade virtual na saúde mental, desempenho físico e perfil inflamatório de idosos institucionalizados.

Avaliação dos Riscos e Benefícios:

Riscos:

UNIVERSIDADE ESTADUAL DE MONTES CLAROS - UNIMONTES

Continuação do Parecer: 2.398.983

O pesquisador descreve que existe um pequeno risco relacionado às possíveis respostas decorrentes dos testes de capacidade funcional ou das sessões de treinamento como: pequena elevação da frequência cardíaca e da pressão arterial. Em todas as avaliações estarão presentes profissionais de saúde capacitados para o suporte básico à vida, sendo de total responsabilidade do pesquisador principal o suporte a intercorrências durante os procedimentos. O pesquisador descreve ainda que os idosos somente poderão participar do estudo mediante liberação do médico responsável de cada instituição.

Benefícios:

A participação do idoso institucionalizado poderá trazer benefícios através dos resultados das avaliações que serão anexadas ao seu prontuário para que a equipe que lhe atende possa fazer o necessário à partir desses dados. Além disso, o projeto contribuirá para a divulgação de novos recursos no atendimento ao idoso institucionalizado.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante que poderá contribuir para estabelecer novas direções de pesquisa na área, de modo a prestar um cuidado mais direcionado e a divulgação de novos conhecimentos.

Considerações sobre os Termos de apresentação obrigatória:

Adequados

Recomendações:

Apresentação de relatório final por meio da plataforma Brasil, em "enviar notificação".

Conclusões ou Pendências e Lista de Inadequações:

Aprovado.

Considerações Finais a critério do CEP:

O projeto respeita os preceitos éticos da pesquisa em seres humanos, sendo assim somos favoráveis à aprovação do mesmo.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação

Endereço: Av.Dr Rui Braga s/n-Camp Univers Prof° Darcy Rib
Bairro: Vila Mauricéia **CEP:** 39.401-089
UF: MG **Município:** MONTES CLAROS
Telefone: (38)3229-8180 **Fax:** (38)3229-8103 **E-mail:** smeicosta@gmail.com

UNIVERSIDADE ESTADUAL DE MONTES CLAROS - UNIMONTES

Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_984466.pdf	31/10/2017 12:55:29		Aceito
Declaração de Instituição e Infraestrutura	TCI2510.pdf	31/10/2017 12:55:05	LUCIANA MENDES OLIVEIRA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEMOD.docx	31/10/2017 12:54:42	LUCIANA MENDES OLIVEIRA	Aceito
Folha de Rosto	FOLHADEROSTO.pdf	04/09/2017 20:27:01	LUCIANA MENDES OLIVEIRA	Aceito
Declaração de Pesquisadores	TERMODERESPONSABILIDADE.doc	31/08/2017 22:32:59	LUCIANA MENDES OLIVEIRA	Aceito
Projeto Detalhado / Brochura Investigador	PROJETOILPIsCEPFINAL.doc	31/08/2017 21:01:48	LUCIANA MENDES OLIVEIRA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

MONTES CLAROS, 25 de Novembro de 2017

Assinado por:
SIMONE DE MELO COSTA
(Coordenador)

Endereço: Av Dr Rui Braga s/n-Camp Univers Profª Darcy Rib
Bairro: Vila Mauricéia **CEP:** 39.401-089
UF: MG **Município:** MONTES CLAROS
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ANEXO C – instrumentos de avaliação

Escala de Depressão Geriátrica – GDS-30

ESCALA GERIÁTRICA DE DEPRESSÃO (GDS 30)

Yesavage e tal (1983) "Development and validation of geriatric depression scale" J. Psychiatric Res. 17:37-49

NOME:_____

IDADE: _____ **DATA DE NASCIMENTO:**_____/_____/_____

RESPONDA **SIM** OU **NÃO** CONSOANTE SE TEM SENTIDO DE HÁ UMA SEMANA PARA CÁ:

	S	N
01. Está satisfeito(a) com a sua vida?		1
02. Pôs de lado muitas das suas atividades e interesses?	1	
03. Sente a sua vida vazia?	1	
04. Fica muitas vezes aborrecido(a)?	1	
05. Tem esperança no futuro?		1
06. Anda incomodado(a) com pensamentos que não consegue afastar?	1	
07. Está bem disposto(a) a maior parte do tempo?		1
08. Tem medo que lhe vá acontecer alguma coisa de mal?	1	
09. Sente-se feliz a maior parte do tempo?		1
10. Sente-se muitas vezes desamparado(a)?	1	
11. Fica muitas vezes inquieto(a) e nervoso(a)?	1	
12. Prefere ficar em casa, em vez de sair e fazer coisas novas?	1	
13. Preocupa-se muitas vezes com o futuro?	1	
14. Acha que tem mais problemas de memória do que as outras pessoas?	1	
15. Pensa que é bom estar vivo(a)?		1
16. Sente-se muitas vezes desanimado(a) e abatido(a)?	1	
17. Sente-se inútil?	1	
18. Preocupa-se muito com o passado?	1	
19. Acha a vida interessante?		1
20. É difícil para si começar novas actividades?	1	
21. Sente-se cheio(a) de energia?		1
22. Sente que a sua situação é desesperada?	1	
23. Pensa que a situação da maioria das pessoas é melhor que a sua?	1	
24. Aflige-se muitas vezes com pequenas coisas?	1	
25. Sente muitas vezes vontade de chorar?	1	
26. Tem dificuldade em se concentrar?	1	
27. Gosta de se levantar de manhã?		1
28. Prefere evitar encontrar-se com muitas pessoas?	1	
29. Tem facilidade em tomar decisões?		1
30. O seu pensamento é tão claro como era dantes?		1

Digit Span

Digits Forward		Pass-Fail
1	5-8-2	
	6-9-4	
2	6-4-3-9	
	7-2-8-6	
3	4-2-7-3-1	
	7-5-8-3-6	
4	6-1-9-4-7-3	
	3-9-2-4-8-7	
5	5-9-1-7-4-2-8	
	4-1-7-9-3-8-6	
6	5-8-1-9-2-6-4-7	
	3-8-2-9-5-1-7-4	
7	2-7-5-8-6-2-5-8-4	
	7-1-3-9-4-2-5-6-8	

Digits Backward		Pass-Fail
1	2-4	
	5-8	
2	6-2-9	
	4-1-5	
3	3-2-7-9	
	4-9-6-8	
4	1-5-2-8-6	
	6-1-8-4-3	
5	5-3-9-4-1-8	
	7-2-4-8-5-6	
6	8-1-2-9-3-6-5	
	4-7-3-9-1-2-8	
7	9-4-3-7-6-2-5-8	
	7-2-8-1-9-6-5-3	

MEEM – Mini Exame do Estado Mental

Pontuação Máxima	Pontuação do paciente	MEEM
5		**Orientação temporal**: Dia _____, mês ____, ano ____, dia da semana ____, horas _____ (0 a 5).
5		**Orientação espacial**: Local (específico) _____, Pais, _____,bairro _____, cidade ___, estado _____(0 a 5).
3		**Registro**: repetir: cadeira ____, sapato _____, bicicleta _____.
5		**Cálculo**: 100-7=93 _____; 93-7=86 _____, 86-7=79 _____; 79-7=72 _____; 72-7=65 _____(0 a 5) **ou** MUNDO: O, D, N, U, M:
3		**Memória recente**: Quais foram as três palavras que te pedi para repetir? _____(0 a 3)
9		**Linguagem:** ▪ Nomear dois objetos: caneta _____e relógio _____ (0 a 2) ▪ Repetir a expressão “nem aqui, nem ali, nem lá” (0 a 1) _____ ▪ Comando de três estágios: apanhar esta folha de papel com a mão direita, dobrar ao meio e coloca-la no chão _____(0 a 3) ▪ Ler e executar (feche os olhos) _____(0 a 1) ▪ Escrever uma frase completa _____(0 a 1) ▪ Copiar o diagrama: _____(0 a 1)
30		**Obs:**

MANUSCRIPT FORMATTING GUIDELINES – FRONTIERS IN PSYCHOLOGY

1. General standards

1.1. Article Type

Frontiers requires authors to carefully select the appropriate article type for their manuscript and to comply with the article type descriptions defined in the journal's "Article Types" page, which can be seen from the "For Authors" menu on any Frontiers journal page. Please pay close attention to the word count limits.

1.2. Templates

If working with Word please use our Frontiers Word templates. If you wish to submit your article as LaTeX, we recommend our Frontiers LaTeX templates.

For LaTeX files, please ensure all relevant manuscript files are uploaded: .tex file, PDF, and .bib file (if the bibliography is not already included in the .tex file).

During the Interactive Review, authors are encouraged to upload versions using "Track Changes." Editors and reviewers can only download the PDF file of the submitted manuscript.

1.3. Manuscript Length

Frontiers encourages the authors to closely follow the article word count lengths given in the "Article Types" page of the journals. The manuscript length includes only the main body of the text, footnotes, and all citations within it, and excludes the abstract, section titles, figure and table captions, funding statement, acknowledgments, and references in the bibliography. Please indicate the number of words and the number of figures and tables included in your manuscript on the first page.

1.4. Language Editing

Frontiers requires manuscripts submitted to meet international English language standards to be considered for publication.

For authors who would like their manuscript to receive language editing or proofreading to improve the clarity of the manuscript and help highlight their research, Frontiers recommends the language-editing services provided by the following external partners:

Editage

Frontiers is pleased to recommend the language-editing service provided by our external partner Editage to authors who believe their manuscripts would benefit from professional editing. These services may be particularly useful for researchers for whom English is not the primary language. They can help to improve the grammar, syntax, and flow of your manuscript prior to submission. Frontiers authors will receive a 10% discount by visiting the following link: https://editage.com/frontiers/.

The Charlesworth Group

Frontiers recommends the Charlesworth Group's author services, who has a long-standing track record in language editing and proofreading. This is a third-party service for which Frontiers authors will receive a 10% discount by visiting the following link: https://www.cwauthors.com/frontiers/.

Frontiers **推荐您使用在英**语语言编辑和校对领域具有悠久历史和良好口碑的查尔斯沃思作者服务。此项服务由第三方为您提供，Frontiers **中国作者通**过此链接提交稿件时可获得 10**%的特**别优惠: www.cwauthors.com.cn/frontiers/.

Note that sending your manuscript for language editing does not imply or guarantee that it will be accepted for publication by a Frontiers journal. Editorial decisions on the scientific content of a manuscript are independent of whether it has received language editing or proofreading by the partner services, or other services.

1.5. Language Style

The default language style at Frontiers is American English. If you prefer your article to be formatted in British English, please specify this on the first page of your manuscript. For any questions regarding style, Frontiers recommends authors to consult the Chicago Manual of Style.

1.6. Search Engine Optimization (SEO)

There are a few simple ways to maximize your article's discoverability. Follow the steps below to improve search results of your article:

- include a few of your article's keywords in the title of the article;
- do not use long article titles;
- pick 5 to 8 keywords using a mix of generic and more specific terms on the article subject(s);
- use the maximum amount of keywords in the first 2 sentences of the abstract;

- use some of the keywords in level 1 headings.

1.7. CrossMark Policy

CrossMark is a multi-publisher initiative to provide a standard way for readers to locate the current version of a piece of content. By applying the CrossMark logo Frontiers is committed to maintaining the content it publishes and to alerting readers to changes if and when they occur. Clicking on the CrossMark logo will tell you the current status of a document and may also give you additional publication record information about the document.

1.8. Title

The title should be concise, omitting terms that are implicit and, where possible, be a statement of the main result or conclusion presented in the manuscript. Abbreviations should be avoided within the title.

Witty or creative titles are welcome, but only if relevant and within measure. Consider if a title meant to be thought-provoking might be misinterpreted as offensive or alarming. In extreme cases, the editorial office may veto a title and propose an alternative.

Authors should try to avoid, if possible:

- titles that are a mere question without giving the answer;
- unambitious titles, for example starting with "Towards," "A description of," "A characterization of," "Preliminary study on;"
- vague titles, for example starting with "Role of…," "Link between…," "Effect of..." that do not specify the role, link, or effect;
- include terms that are out of place, for example the taxonomic affiliation apart from species name.

For Corrigenda, Book Reviews, General Commentaries, and Editorials, the title of your manuscript should have the following format:

- "Corrigendum: Title of Original Article"
- "Book Review: Title of Book"
- General Commentaries
    - "Commentary: Title of Original Article"
    - "Response: Commentary: Title of Original Article"
- "Editorial: Title of Research Topic"

The running title should be a maximum of 5 words in length.

1.9. Authors and Affiliations

All names are listed together and separated by commas. Provide exact and correct author names as these will be indexed in official archives. Affiliations should be keyed to the author's name with superscript numbers and be listed as follows: Laboratory, Institute, Department, Organization, City, State abbreviation (only for United States, Canada, and Australia), and Country (without detailed address information such as city zip codes or street names).

Example: Max Maximus[1]

[1] Department of Excellence, International University of Science, New York, NY, United States.

Correspondence:

The Corresponding Author(s) should be marked with an asterisk in the author list. Provide the exact contact email address of the corresponding author(s) in a separate section.

Example: Max Maximus

maximus@iuscience.edu

If any authors wish to include a change of address, list the present address(es) below the correspondence details using a unique superscript symbol keyed to the author(s) in the author list.

Equal contributions:

The authors who have contributed equally should be marked with a symbol (†) in the author list of the doc/latex and pdf files of the manuscript uploaded at submission.

Standard statements to include in the author list:

Equal contribution	These authors have contributed equally to this work
First authorship	These authors share first authorship
Senior authorship	These authors share senior authorship
Last authorship	These authors share last authorship
Equal contribution & First authorship	These authors have contributed equally to this work and share first authorship
Equal contribution & Senior authorship	These authors have contributed equally to this work and share senior authorship
Equal contribution & Last authorship	These authors have contributed equally to this work and share last authorship

Example: Max Maximus 1†, John Smith2† and Barbara Smith1

†These authors have contributed equally to this work and share first authorship

1.10. Consortium/Group and Collaborative Authors

Consortium/group authorship should be listed in the manuscript with the other author(s).

In cases where authorship is retained by the consortium/group, the consortium/group should be listed as an author separated by "," or "and,". The consortium/group name will appear in the author list, in the citation, and in the copyright. If provided, the consortium/group members will be listed in a separate section at the end of the article.

For the collaborators of the consortium/group to be indexed in PubMed, they do not have to be inserted in the Frontiers submission system individually. However, in the manuscript itself, provide a section with the name of the consortium/group as the heading followed by the list of collaborators, so they can be tagged accordingly and indexed properly.

Example: John Smith, Barbara Smith and The Collaborative Working Group.

In cases where work is presented by the author(s) on behalf of a consortium/group, it should be included in the author list separated with the wording "for" or "on behalf of." The consortium/group will not retain authorship and will only appear in the author list.

Example: John Smith and Barbara Smith on behalf of The Collaborative Working Group.

1.11. Abstract

As a primary goal, the abstract should render the general significance and conceptual advance of the work clearly accessible to a broad readership. In the abstract, minimize the use of abbreviations and do not cite references, figures or tables.

For Clinical Trial articles, please include the Unique Identifier and the URL of the publicly accessible website on which the trial is registered.

1.12. Keywords

All article types require a minimum of 5 and a maximum of 8 keywords.

1.13. Text

The entire document should be single-spaced and must contain page and line numbers in order to facilitate the review process. The manuscript should be written using either Word or LaTeX. For templates, see 1.2. Templates.

1.14. Nomenclature

- The use of abbreviations should be kept to a minimum. Non-standard abbreviations should be avoided unless they appear at least four times, and defined upon first use in the main text. Consider also giving a list of non-standard abbreviations at the end, immediately before the Acknowledgments.
- Equations should be inserted in editable format from the equation editor.
- Italicize gene symbols and use the approved gene nomenclature where it is available. For human genes, please refer to the HUGO Gene Nomenclature Committee (HGNC). New gene symbols should be submitted here. Common alternative gene aliases may also be reported, but should not be used alone in place of the HGNC symbol. Nomenclature committees for other species are listed here. Protein products are not italicized.
- We encourage the use of Standard International Units in all manuscripts.
- Chemical compounds and biomolecules should be referred to using systematic nomenclature, preferably using the recommendations by IUPAC.
- Astronomical objects should be referred to using the nomenclature given by the International Astronomical Union provided here.
- Life Science Identifiers (LSIDs) for ZOOBANK registered names or nomenclatural acts should be listed in the manuscript before the keywords. An LSID is represented as a uniform resource name (URN) with the following format: urn:lsid:<Authority>:<Namespace>:<ObjectID>[:<Version>]

For more information on LSIDs please see the Code section.

1.15. Sections

The manuscript is organized by headings and subheadings. The section headings should be those appropriate for your field and the research itself. You may insert up to 5 heading levels into your manuscript (i.e.,: 3.2.2.1.2 Heading Title).

For Original Research articles, it is recommended to organize your manuscript in the following sections or their equivalents for your field:

INTRODUCTION

Succinct, with no subheadings.

MATERIALS AND METHODS

This section may be divided by subheadings and should contain sufficient detail so that when read in conjunction with cited references, all procedures can be repeated. For experiments reporting results on animal or human subject research, an ethics approval statement should be included in this section (for further information, see the Bioethics section.)

RESULTS

This section may be divided by subheadings. Footnotes should not be used and must be transferred to the main text.

DISCUSSION

This section may be divided by subheadings. Discussions should cover the key findings of the study: discuss any prior research related to the subject to place the novelty of the discovery in the appropriate context, discuss the potential shortcomings and limitations on their interpretations, discuss their integration into the current understanding of the problem and how this advances the current views, speculate on the future direction of the research, and freely postulate theories that could be tested in the future.

For further information, please check the descriptions defined in the journal's "Article Types" page, which can be seen from the "For Authors" menu on any Frontiers journal page.

1.16. Acknowledgments

This is a short text to acknowledge the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors. Should the content of the manuscript have previously appeared online, such as in a thesis or preprint, this should be mentioned here, in addition to listing the source within the reference list.

1.17. Contribution to the Field Statement

When you submit your manuscript, you will be required to briefly summarize in 200 words your manuscript's contribution to, and position in, the existing literature in your field. This should be written avoiding any technical language or non-standard acronyms. The aim should be to convey the meaning and importance of this research to a non-expert. While Frontiers evaluates articles using objective criteria, rather than impact or novelty, your statement should frame the question(s) you have addressed in your work in the context of the current body of knowledge, providing evidence that the findings—whether positive or negative—contribute to progress in your research discipline. This will assist the Chief Editors to determine whether your manuscript fits within the scope of a specialty as defined in its mission statement; a detailed statement will also facilitate the identification of the editors and reviewers most appropriate to evaluate your work, ultimately expediting your manuscript's initial consideration.

Example Statement on: Markram K and Markram H (2010) The Intense World Theory – a unifying theory of the neurobiology of autism. Front. Hum. Neurosci. 4:224. doi: 10.3389/fnhum.2010.00224

Autism spectrum disorders are a group of neurodevelopmental disorders that affect up to 1 in 100 individuals. People with autism display an array of symptoms encompassing emotional processing, sociability, perception and memory, and present as uniquely as the individual. No theory has suggested a single underlying neuropathology to account for these diverse symptoms. The Intense World Theory, proposed here, describes a unifying pathology producing the wide spectrum of manifestations observed in autists. This theory focuses on the neocortex, fundamental for higher cognitive functions, and the limbic system, key for processing emotions and social signals. Drawing on discoveries in animal models and neuroimaging studies in individuals with autism, we propose how a combination of genetics, toxin exposure and/or environmental stress could produce hyper-reactivity and hyper-plasticity in the microcircuits involved with perception, attention, memory and emotionality. These hyper-functioning circuits will eventually come to dominate their neighbors, leading to hyper-sensitivity to incoming stimuli, over-specialization in tasks and a hyper-preference syndrome. We make the case that this theory of enhanced brain function in autism explains many of the varied past results and resolves conflicting findings and views and makes some testable experimental predictions.

2. Figure and Table Guidelines

2.1. CC-BY Licence

All figures, tables, and images will be published under a Creative Commons CC-BY licence, and permission must be obtained for use of copyrighted material from other sources (including re-published/adapted/modified/partial figures and images from the internet). It is the responsibility of the authors to acquire the licenses, follow any citation instructions requested by third-party rights holders, and cover any supplementary charges.

For additional information, please see the Image Manipulation section.

2.2. Figure Requirements and Style Guidelines

- Frontiers requires figures to be submitted individually, in the same order as they are referred to in the manuscript; the figures will then be automatically embedded at the end of the submitted manuscript. Kindly ensure that each figure is mentioned in the text and in numerical order.
- For figures with more than one panel, panels should be clearly indicated using labels (A), (B), (C), (D), etc. However, do not embed the part labels over any part of the image, these labels will be replaced during typesetting according to Frontiers' journal style. For graphs, there must be a self-explanatory label (including units) along each axis.
- For LaTeX files, figures should be included in the provided PDF. In case of acceptance, our Production Office might require high-resolution files of the figures included in the manuscript in EPS, JPEG or TIF/TIFF format.
- In order to be able to upload more than one figure at a time, save the figures (labeled in order of appearance in the manuscript) in a zip file and upload them as 'Supplementary Material Presentation.'

Please note that figures not in accordance with the guidelines will cause substantial delay during the production process.

2.2.1. Captions

Captions should be preceded by the appropriate label, for example "Figure 1." Figure captions should be placed at the end of the manuscript. Figure panels are referred to by bold capital letters in brackets: (A), (B), (C), (D), etc.

2.2.2. Image Size and Resolution Requirements

Figures should be prepared with the PDF layout in mind. Individual figures should not be longer than one page and with a width that corresponds to 1 column (85 mm) or 2 columns (180 mm).

All images must have a resolution of 300 dpi at final size. Check the resolution of your figure by enlarging it to 150%. If the image appears blurry, jagged or has a stair-stepped effect, the resolution is too low.

- The text should be legible and of high quality. The smallest visible text should be no less than 8 points in height when viewed at actual size.
- Solid lines should not be broken up. Any lines in the graphic should be no smaller than 2 points wide.

Please note that saving a figure directly as an image file (JPEG, TIF) can greatly affect the resolution of your image. To avoid this, one option is to export the file as PDF, then convert into TIFF or EPS using a graphics software.

2.2.3. Format and Color Image Mode

- The following formats are accepted: TIF/TIFF (.tif/.tiff), JPEG (.jpg), and EPS (.eps) (upon acceptance).
- Images must be submitted in the color mode RGB.

2.2.4. Chemical Structures

Chemical structures should be prepared using ChemDraw or a similar program. If working with ChemDraw please use our Frontiers ChemDraw template. If working with another program please follow the guidelines given below:

- Drawing settings: chain angle, 120° bond spacing, 18% width; fixed length, 14.4 pt; bold width, 2.0 pt; line width, 0.6 pt; margin width, 1.6 pt; hash spacing, 2.5 pt. Scale 100% Atom Label settings: font, Arial; size, 8 pt.
- Assign all chemical compounds a bold, Arabic numeral in the order in which the compounds are presented in the manuscript text.

2.3. Table Requirements and Style Guidelines

- Tables should be inserted at the end of the manuscript in an editable format. If you use a word processor, build your table in Word. If you use a LaTeX processor, build your table in LaTeX. An empty line should be left before and after the table.

- Table captions must be placed immediately before the table. Captions should be preceded by the appropriate label, for example "Table 1." Please use only a single paragraph for the caption.
- Kindly ensure that each table is mentioned in the text and in numerical order.
- Please note that large tables covering several pages cannot be included in the final PDF for formatting reasons. These tables will be published as supplementary material.

Please note that tables which are not according to the guidelines will cause substantial delay during the production process.

2.4. Accessibility

Frontiers encourages authors to make the figures and visual elements of their articles accessible for the visually impaired. An effective use of color can help people with low visual acuity, or color blindness, understand all the content of an article.

These guidelines are easy to implement and are in accordance with the W3C Web Content Accessibility Guidelines (WCAG 2.1), the standard for web accessibility best practices.

A. Ensure sufficient contrast between text and its background

People who have low visual acuity or color blindness could find it difficult to read text with low contrast background color. Try using colors that provide maximum contrast.

WC3 recommends the following contrast ratio levels:

- Level AA, contrast ratio of at least 4.5:1
- Level AAA, contrast ratio of at least 7:1

Level	AA
Contast ratio 4.6:1	

Level	AA
Contast ratio 9.5:1	

You can verify the contrast ratio of your palette with these online ratio checkers:

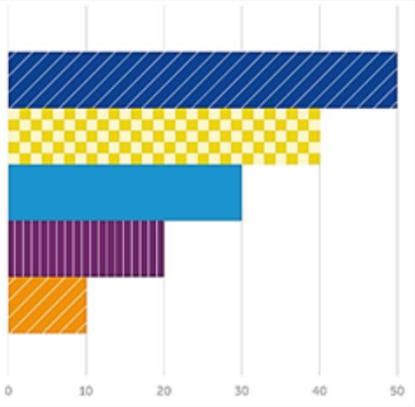
- WebAIM
- Color Safe

B. Avoid using red or green indicators

More than 99% of color-blind people have a red-green color vision deficiency.

C. Avoid using only color to communicate information

Elements with complex information like charts and graphs can be hard to read when only color is used to distinguish the data. Try to use other visual aspects to communicate information, such as shape, labels, and size. Incorporating patterns into the shape fills also make differences clearer; for an example please see below:



3. Supplementary Material

Data that are not of primary importance to the text, or which cannot be included in the article because they are too large or the current format does not permit it (such as videos, raw data traces, powerpoint presentations, etc.), can be uploaded as Supplementary Material during the submission procedure and will be displayed along with the published article. All supplementary files are deposited to Figshare for permanent storage and receive a DOI.

Supplementary Material is not typeset, so please ensure that all information is clearly presented without tracked changes/highlighted text/line numbers, and the appropriate caption is included in the file. To avoid discrepancies between the published article and the supplementary material, please do not add the title, author list, affiliations or correspondence in the supplementary files.

The Supplementary Material can be uploaded as Data Sheet (Word, Excel, CSV, CDX, FASTA, PDF or Zip files), Presentation (PowerPoint, PDF or Zip files), Image (CDX, EPS, JPEG, PDF, PNG or TIF/TIFF), Table (Word, Excel, CSV or PDF), Audio (MP3, WAV or WMA) or Video (AVI, DIVX, FLV, MOV, MP4, MPEG, MPG or WMV).

For Supplementary Material templates (LaTeX and Word), see our Supplementary Material templates.

4. References

- All citations in the text, figures or tables must be in the reference list and vice-versa.

- The names of the first six authors followed by et al. and the DOI (when available) should be provided.
- The reference list should only include articles that are published or accepted.
- Unpublished data, submitted manuscripts or personal communications should be cited within the text only, for the article types that allow such inclusions.
- For accepted but unpublished works use "in press" instead of page numbers.
- Data sets that have been deposited to an online repository should be included in the reference list. Include the version and unique identifier when available.
- Personal communications should be documented by a letter of permission.
- Website URLs should be included as footnotes.
- Any inclusion of verbatim text must be contained in quotation marks and clearly reference the original source.
- Preprints can be cited as long as a DOI or archive URL is available, and the citation clearly mentions that the contribution is a preprint. If a peer-reviewed journal publication for the same preprint exists, the official journal publication is the preferred source. See the Preprints section for more information.

4.1. Science, Engineering and Humanities and Sustainability Journals

(Full list of journals and corresponding reference style)

4.1.1. In-text Citations

- For works by a single author, include the surname, followed by the year.
- For works by two authors, include both surnames, followed by the year.
- For works by more than two authors, include only the surname of the first author followed by et al., followed by the year.
- For Humanities and Social Sciences articles, include the page numbers.

4.1.2. Reference List

ARTICLE IN A PRINT JOURNAL

Sondheimer, N., and Lindquist, S. (2000). Rnq1: an epigenetic modifier of protein function in yeast. Mol. Cell. 5, 163-172.

ARTICLE IN AN ONLINE JOURNAL

Tahimic, C.G.T., Wang, Y., Bikle, D.D. (2013). Anabolic effects of IGF-1 signaling on the skeleton. Front. Endocrinol. 4:6. doi: 10.3389/fendo.2013.00006

ARTICLE OR CHAPTER IN A BOOK

Sorenson, P. W., and Caprio, J. C. (1998). "Chemoreception," in The Physiology of Fishes, ed. D. H. Evans (Boca Raton, FL: CRC Press), 375-405.

BOOK

Cowan, W. M., Jessell, T. M., and Zipursky, S. L. (1997). Molecular and Cellular Approaches to Neural Development. New York: Oxford University Press.

ABSTRACT

Hendricks, J., Applebaum, R., and Kunkel, S. (2010). A world apart? Bridging the gap between theory and applied social gerontology. Gerontologist 50, 284-293. Abstract retrieved from Abstracts in Social Gerontology database. (Accession No. 50360869)

WEBSITE

World Health Organization. (2018). E. coli. https://www.who.int/news-room/fact-sheets/detail/e-coli [Accessed March 15, 2018].

PATENT

Marshall, S. P. (2000). Method and apparatus for eye tracking and monitoring pupil dilation to evaluate cognitive activity. U.S. Patent No 6,090,051. Washington, DC: U.S. Patent and Trademark Office.

DATA

Perdiguero P, Venturas M, Cervera MT, Gil L, Collada C. Data from: Massive sequencing of Ulms minor's transcriptome provides new molecular tools for a genus under the constant threat of Dutch elm disease. Dryad Digital Repository. (2015) http://dx.doi.org/10.5061/dryad.ps837

THESES AND DISSERTATIONS

Smith, J. (2008) Post-structuralist discourse relative to phenomological pursuits in the deconstructivist arena. [dissertation/master's thesis]. [Chicago (IL)]: University of Chicago

PREPRINT

Smith, J. (2008). Title of the document. Preprint repository name [Preprint]. Available at: https://persistent-url (Accessed March 15, 2018).

4.1.3. Resources

Chicago Manual of Style

Frontiers Science Endnote Style

Frontiers Science, Engineering and Humanities Bibstyle

4.2. Health, Physics, and Mathematics Journals

(Full list of journals and corresponding reference style)

4.2.1. In-text Citations

- Please apply the Vancouver system for in-text citations.
- In-text citations should be numbered consecutively in order of appearance in the text—identified by Arabic numerals in the parenthesis for Health articles and in square brackets for Physics and Mathematics articles.

4.2.2. Reference List

ARTICLE IN A PRINT JOURNAL

Sondheimer N, Lindquist S. Rnq1: an epigenetic modifier of protein function in yeast. Mol Cell (2000) 5:163-72.

ARTICLE IN AN ONLINE JOURNAL

Tahimic CGT, Wang Y, Bikle DD. Anabolic effects of IGF-1 signaling on the skeleton. Front Endocrinol (2013) 4:6. doi: 10.3389/fendo.2013.00006

ARTICLE OR CHAPTER IN A BOOK

Sorenson PW, Caprio JC. "Chemoreception,". In: Evans DH, editor. The Physiology of Fishes. Boca Raton, FL: CRC Press (1998). p. 375-405.

BOOK

Cowan WM, Jessell TM, Zipursky SL. Molecular and Cellular Approaches to Neural Development. New York: Oxford University Press (1997). 345 p.

ABSTRACT

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, editor. Genetic Programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3–5; Kinsdale, Ireland. Berlin: Springer (2002). p. 182–91.

WEBSITE

World Health Organization. E. coli (2018). https://www.who.int/news-room/fact-sheets/detail/e-coli [Accessed March 15, 2018].

PATENT

Pagedas AC, inventor; Ancel Surgical R&D Inc., assignee. Flexible Endoscopic Grasping and Cutting Device and Positioning Tool Assembly. United States patent US 20020103498 (2002).

DATA

Perdiguero P, Venturas M, Cervera MT, Gil L, Collada C. Data from: Massive sequencing of Ulms minor's transcriptome provides new molecular tools for a genus under the constant threat of Dutch elm disease. Dryad Digital Repository. (2015) http://dx.doi.org/10.5061/dryad.ps837

THESES AND DISSERTATIONS

Smith, J. (2008) Post-structuralist discourse relative to phenomological pursuits in the deconstructivist arena. [dissertation/master’s thesis]. [Chicago (IL)]: University of Chicago

PREPRINT

Smith, J. Title of the document. Preprint repository name [Preprint] (2008). Available at: https://persistent-url (Accessed March 15, 2018).

CNS & Neurological Disorders - Drug Targets

Formerly: Current Drug Targets - CNS & Neurological Disorders

ONLINE MANUSCRIPT SUBMISSION

An online submission and tracking service *via* Internet facilitates a speedy and cost-effective submission of manuscripts. Manuscripts and the full thematic issues must be submitted online *via* Bentham's Manuscript Processing System (MPS) at **https://bentham.manuscriptpoint.com/journals/cnsnddt** / **View Submission Instructions**

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The principal/corresponding author will be required to submit a Copyright Letter along with the manuscript, on behalf of all the co-authors (if any). The author(s) will confirm that the manuscript (or any part of it) has not been published previously or is not under consideration for publication elsewhere. Furthermore, any illustration, structure or table that has been published elsewhere must be reported, and copyright permission for reproduction must be obtained.

For all online submissions, please provide soft copies of all the materials (main text in MS Word or Tex/LaTeX), figures / illustrations in TIFF, PDF or JPEG, and chemical structures drawn in ChemDraw (CDX) / ISISDraw (TGF) as separate files, while a PDF version of the entire manuscript must also be included, embedded with all the figures / illustrations / tables / chemical structures *etc*. It is advisable that the document files related to a manuscript submission should always have the name of the corresponding author as part of the file name, i.e., "Cilli MS text.doc" , "Cilli MS Figure 1" *etc*.

It is imperative that before submission, authors should carefully proofread the files for special characters, Greek letters, tables, references and images, to ensure that they appear in proper format.

References, figures, tables, chemical structures *etc*. should be referred to in the text at the appropriate place where they have been first discussed. Figure legends/captions should also be provided.

A successful electronic submission of a manuscript will be followed by a system-generated acknowledgement to the principal/corresponding author. Any queries therein should be addressed to **info@benthamscience.net**.

MANUSCRIPT PREPARATION

The manuscript should be written in English in a clear, direct and active style. All pages must be numbered sequentially, facilitating in the reviewing and editing of the manuscript.

MICROSOFT WORD TEMPLATE

It is advisable that authors prepare their manuscript using the template available on the Web, which will assist in preparation of the manuscript according to Journal's Format. **Download the Template**.

SECTIONS IN MANUSCRIPTS

Manuscripts submitted for research and review articles in the journal should be divided into the following sections

- Title
- Title Page
- Structured Abstract
- Graphical Abstract
- Keywords
- Text Organization
- Conclusion
- List of Abbreviations (if any)
- Consent for Publication
- Conflict of Interest
- Acknowledgements
- References
- Appendices
- Figures/Illustrations (if any)
- Chemical Structures (if any)
- Tables (if any)
- Supportive/Supplementary Material (if any)

Title

The title of the article should be precise and brief and must not be more than 120 characters. Authors should avoid the use of non-standard abbreviations and question marks in titles. The first letter of each word should be in capital letters except for articles, conjunctions and prepositions.

As recommended by the Reporting guidelines information about the study should be a part of the title (particularly for randomized or clinical trials, systematic reviews and meta analyses).

Authors should also provide a short 'running title with no more than 80 characters'. Title, running title, byline, correspondent footnote, and keywords should be written as presented in the original manuscript

Title Page

Title page should include paper title, author(s) full name and affiliation, corresponding author(s) names complete affiliation/address, along with phone, fax and email.

Structured Abstract

The abstract of an article should be its clear, concise and accurate summary, having no more than 250 words, and including the explicit sub-headings (as in-line or run-in headings in bold). Use of abbreviations should be avoided and the references should not be cited in the abstract.

Ideally, each abstract should include the following sub-headings, but these may vary according to requirements of the article.

All the original research articles, systematic reviews and meta analyses must be accompanied with a structured abstract. Ideally, each abstract should include the following sub-headings, but these may vary according to requirements of the article.

- Background
- Objective
- Methods
- Results
- Conclusion

The clinical trial studies should have the registration number at the end of the study.

Graphical Abstract

A graphic should be included when possible with each manuscript for use in the Table of Contents (TOC). This must be submitted separately as an electronic file (preferred file types are EPS, PDF, TIFF, Microsoft Word, PowerPoint and CDX *etc*.). A graphical abstract, not exceeding 30 words along with the illustration, helps to summarize the contents of the manuscript in a concise pictorial form. It is meant as an aid for the rapid viewing of the journals' contents and to help capture the readers' attention. The graphical abstract may feature a key structure, reaction, equation, *etc*. that the manuscript elucidates upon. It will be listed along with the manuscript title, authors' names and affiliations in the contents page, typeset within an area of 5 cm by 17 cm, but it will not appear in the article PDF file or in print.

Graphical Abstracts should be submitted as a separate file (must clearly mention graphical abstract within the file) online *via* Bentham's Manuscript Processing System.

Keywords

6 to 8 keywords must be provided. Choose important and relevant keywords that researchers in your field will be searching for so that your paper will appear in a database search. The keywords should be contained in the title and they should appear several times in the article. In biomedical fields, MeSH terms are a good 'common vocabulary' source to draw keywords from **https://www.nlm.nih.gov/mesh/meshhome.html**.

Text Organization

The main text should begin on a separate page and should be divided into separate sections. The manuscript should be divided into title page, abstract and the main text. The text may be subdivided further according to the areas to be discussed, which should be followed by the Acknowledgements and Reference sections. The Review Article should mention any previous important recent and old reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The authors are advised to present and discuss their observations in brief.

For Research Articles the manuscript should begin with the title page and abstract followed by the main text, which must be structured into separate sections as **Introduction, Materials**

and Methods, Results, Discussion, Conclusion, Ethics Approval and Consent to Participate, Human and Animal Rights, Conflict of Interest, Acknowledgements and References .

All randomized clinical trials must include a flow diagram and authors should provide a completed randomized trial checklist (see CONSORT Flow Diagram and Checklist; **www.consort-statement.org**) and a trial protocol.

For case reports, the authors should follow the **CARE guidelines** . The **CARE checklist** should be submitted as a separate file.

The manuscript style must be uniform throughout the text and 10 pt Times New Roman font should be used. The full term for an abbreviation should precede its first appearance in the text unless it is a standard unit of measurement. The reference numbers should be given in square brackets in the text. Italics should be used for Binomial names of organisms (Genus and Species), for emphasis and for unfamiliar words or phrases. Non-assimilated words from Latin or other languages should also be italicized *e.g. per se, et al. etc.*

SECTION HEADINGS
Section headings should be numbered sequentially, left aligned and have the first letter capitalized, starting with the introduction. Sub-section headings however, should be in lower-case and italicized with their initials capitalized. They should be numbered as 1.1, 1.2, *etc*.

INTRODUCTION
The Introduction section should include the background and aims of the research in a comprehensive manner.

MATERIALS AND METHODS
This section provides details of the methodology used along with information on any previous efforts with corresponding references. Any details for further modifications and research should be included. Sufficient details should be provided to the reader about the original data source in order to enable the analysis, appropriateness and verification of the results reported in the study. It is important for the Methods Section should be sufficiently detailed in respect of the data presented, and the results produced from it. This section should include all the information and protocol gathered for the study at the time when it was being written. If the study is funded or financially supported by an organization to conduct the research, then it should be mentioned in the Methods Section. Methods must be resultoriented. The statement regarding the approval by an independent local, regional or national review committee (*e.g.* name of ethic committee and institutional review board) should be part of the Methods Section.

EXPERIMENTAL
Repeated information should not be reported in the text of an article. A calculation section must include experimental data, facts and practical development from a theoretical perspective.

RESULTS
Results should be precise.

DISCUSSION
This should explore the significance of the results of the work, present a reproducible procedure and emphasis the importance of the article in the light of recent developments in the field. Extensive citations and discussion of published literature should be avoided.

The Results and Discussion may be presented together under one heading of “Results and Discussion”. Alternatively, they may be presented under two separate sections (“Results” section and “Discussion” Sections). Short sub- headings may be added in each section if required.

CONCLUSION

A small paragraph summarizing the contents of the article, presenting the final outcome of the research or proposing further study on the subject, may be given at the end of the article under the Conclusion section.

FUNDING

The authors need to declare the funding sources of their manuscripts clearly by providing the name of the funding agency or financial support along with allotted grant/award number in round brackets (if applied), for instance, “This work was financially supported by [Name of the funding agency] (Grant number XXX).

Similarly, if a paper does not have any specific funding source, and is part of the employment of the authors, then the name of the employer will be required. Authors will have to clearly state that the funder was involved in writing, editing, approval, or decision to publish the article.

Greek Symbols and Special Characters

Greek symbols and special characters often undergo formatting changes and get corrupted or lost during preparation of manuscript for publication. To ensure that all special characters used are embedded in the text, these special characters should be inserted as a symbol but should not be a result of any format styling (Symbol font face) otherwise they will be lost during conversion to PDF/XML.

Authors are encouraged to consult reporting guidelines. These guidelines provide a set of recommendations comprising a list of items relevant to their specific research design. Chemical equations, chemical names, mathematical usage, unit of measurements, chemical and physical quantity & units must conform to SI and Chemical Abstracts or IUPAC.

All kinds of measurements should be reported only in International System of Units (SI).

Appendices

In case there is a need to present lengthy, but essential methodological details, appendices must be used, which can be a part of the article. An appendix must not exceed three pages (Times New Roman, 10 point fonts, 900 max. words per page).The information should be provided in a condensed form, ruling out the need of full sentences. A single appendix should be titled APPENDIX, while more than one can be titled APPENDIX A, APPENDIX B, and so on.

Supportive/Supplementary Material

We do encourage to append supportive material, for example a PowerPoint file containing a talk about the study, a PowerPoint file containing additional screenshots, a Word, RTF, or PDF document showing the original instrument(s) used, a video, or the original data (SAS/SPSS files, Excel files, Access Db files *etc*.) provided it is inevitable or endorsed by the journal's Editor.

Supportive/Supplementary material intended for publication must be numbered and referred to in the manuscript but should not be a part of the submitted paper. In-text citations as well as a section with the heading "Supportive/Supplementary Material" before the "References"

section should be provided. Here, list all Supportive/Supplementary Material and include a brief caption line for each file describing its contents.

Any additional files will be linked to the final published article in the form supplied by the author, but will not be displayed within the paper. They will be made available in exactly the same form as originally provided only on our Web site. Please also make sure that each additional file is a single table, figure or movie (please do not upload linked worksheets or PDF files larger than one sheet). Supportive/ SupplementaryMaterial must be provided in a single zipped file not larger than 4 MB.

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List of Abbreviations

If abbreviations are used in the text at least 3 times, they should be defined in the list of abbreviations.