UNIVERSIDADE FEDERAL DO PARÁ
INSTITUTO DE CIÊNCIAS BIOLÓGICAS
PROGRAMA DE PÓS-GRADUAÇÃO EM FARMACOLOGIA E BIOQUÍMICA

CAIO GUSTAVO LEAL DE NAZARÉ

POTENCIAL NEUROPROTETOR DA ATIVIDADE FÍSICA EM POPULAÇÕES RIBEIRINHAS DA AMAZÔNIA EXPOSTAS AO MERCÚRIO

BELÉM-PA

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RESUMO

O mercúrio é um metal altamente tóxico e está entre as três substâncias com maior potencial de ameaça à saúde humana. Sua espécie orgânica, o metilmercúrio, é especialmente perigosa para a saúde humana devido sua facilidade em atravessar barreiras biológicas. Sendo assim, o cérebro é um alvo crítico para o metilmercúrio, onde é capaz de causar distúrbios neurológicos, incluindo déficit motor, visual, auditivo, comportamental e cognitivo. As células gliais estão intimamente implicadas nos mecanismos que medeiam tais distúrbios, e podem atuar protegendo ou danificando o SNC, dependendo do contexto. Além disso, nenhum tratamento farmacológico mostrou-se eficaz contra intoxicação mercurial até então, e a literatura já mostrou que tanto o exercício físico quanto a atividade física são capazes de modular aspectos gliais envolvidos na fisiopatologia comum entre diversas condições neurológicas e intoxicação por metilmercúrio. Assim, uma abordagem potencialmente terapêutica e não-farmacológica, como exercício físico – e até mesmo a atividade física – seria conveniente para populações vulnerabilizadas que se encontram econômica, social e geograficamente em desvantagem, como as populações ribeirinhas amazônicas que estão cronicamente expostas ao metilmercúrio através da ingestão de peixes contaminados. Este trabalho tem por objetivo verificar se o perfil de atividade física pode influenciar a sintomatologia da intoxicação mercurial em ribeirinhos da região do lago de Tucuruí. Entrevistas foram realizadas para obter um perfil de atividade física e sintomas neurológicos autodeclarados, e mercúrio total foi mensurado a partir de amostras de cabelo. Nossos resultados apontam para uma possível e complexa relação entre os níveis de mercúrio capilar e a prática de atividade física, sugerindo que a prática de exercícios físicos pode ser uma alternativa viável a ser inserida no cotidiano.

Palavras-chave: Amazônia; ribeirinhos; metilmercúrio; MeHg; neurotoxicidade; sintomas neurológicos; exercício físico; Tucuruí.

ABSTRACT

Mercury is a highly toxic metal and is among the three substances with the greatest potential threat to human health. Its organic form, methylmercury, is particularly dangerous to human health due to its ability to easily cross biological barriers. The brain is a critical target for methylmercury, where it can cause neurological disorders, including motor, visual, auditory, behavioral, and cognitive deficits. Glial cells are closely involved in the mechanisms mediating such disorders and can either protect or damage the central nervous system (CNS), depending on the context. Moreover, no pharmacological treatment has proven effective against mercury intoxication to date, and literature has shown that both physical exercise and physical activity are capable of modulating glial aspects involved in the pathophysiology common to various neurological conditions and methylmercury intoxication. Thus, a potentially therapeutic and non-pharmacological approach, such as physical exercise – and even physical activity – would be particularly suitable for vulnerable populations who are economically, socially, and geographically disadvantaged, such as the riverine communities of the Amazon, who are chronically exposed to methylmercury through the consumption of contaminated fish. This study aims to assess whether physical activity profiles can influence the symptomatology of methylmercury intoxication in riverside residents of the Tucuruí Lake region. Interviews were conducted to obtain a profile of physical activity and self-reported neurological symptoms, and total mercury was measured from hair samples. Our results point to a possible and complex relationship between hair mercury levels and physical activity, suggesting that physical exercise may be a viable alternative to be included in daily life.

Keywords: Amazônia; riverine communities; methylmercury; MeHg; neurotoxicity; neurological symptoms; physical exercise; Tucuruí.

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LISTA DE SIGLAS E SÍMBOLOS

SIGLAS

AD - Alzheimer's Disease

AMPAR - α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor

APP - Amyloid Precursor Protein

ASGM - Artisanal and Small-Scale Gold Mining

ASK1 - Apoptosis Signal-Regulating Kinase 1

ATSDR - Agency for Toxic Substances and Disease Registry

BBB - Blood-Brain Barrier

BDNF - Brain-Derived Neurotrophic Factor

CD200 - Neuronal Immunoregulatory Molecule

CD200R - CD200 Receptor

CCL2 - Chemokine (CC motif) Ligand 2

CCR2 - C-C Chemokine Receptor Type 2

CNS - Central Nervous System

COX-2 - Cyclooxygenase 2

CONEP - Conselho Nacional de Ética em Pesquisa

CREB - Cyclic AMP Response Element-Binding Protein

CSF1R - Colony-Stimulating Factor 1 Receptor

DG - Dentate Gyrus

EAATs - Excitatory Amino Acid Transporters

ERK - Extracellular Signal-Regulated Kinase

GFAP - Glial Fibrillary Acidic Protein

Gpld1 - Glycosylphosphatidylinositol-Specific Phospholipase D1

GSH - Reduced Glutathione

HCAR1 - Hydroxycarboxylic Acid Receptor 1

Ho-1 - Heme Oxygenase-1

ICP-MS - Inductively Coupled Plasma Mass Spectrometry

ICF - Informed Consent Form

IGF-1 - Insulin-Like Growth Factor 1

IL-1β - Interleukin 1-beta

IL-6 - Interleukin 6

IL-10 - Interleukin 10

IKKβ - IκB Kinase Beta

IPAQ - International Physical Activity Questionnaire

IQR - Interquartile Range

LBD - Lewy Body Dementia

MAPK - Mitogen-Activated Protein Kinase

MEK - Mitogen-Activated Protein Kinase

MeHg - Methylmercury

MCI - Mild Cognitive Impairment

MS - Multiple Sclerosis

NF-kB - Nuclear Factor Kappa B

NF-κB - Nuclear Factor Kappa B

NMDAR - N-Methyl-D-Aspartate Receptor

Nqo-1 - Quinone Oxidoreductase-1

Nrf-2 - Nuclear Factor Erythroid 2-Related Factor 2

PI3 kinase - Phosphatidylinositol 3-Kinase

PI3K/Akt - Phosphatidylinositol 3-Kinase/Protein Kinase B

PD - Parkinson's Disease

PS1 - Presenilin 1

PTWI - Provisional Tolerable Weekly Intake

RIT1 - Ras-Like Without CAAX 1

ROCK - Rho-Associated Kinase

ROS - Reactive Oxygen Species

RNS - Reactive Nitrogen Species

STAT3 - Signal Transducer and Activator of Transcription 3

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

TBI - Traumatic Brain Injury

TMEM119 - Transmembrane Protein 119

TNF-α - Tumor Necrosis Factor-alpha

TREM2 - Triggering Receptor Expressed on Myeloid Cells 2

Trk - Tropomyosin Kinase Receptor

TrkB - Tropomyosin Receptor Kinase B

UNEP - United Nations Environment Programme

USEPA - U.S. Environmental Protection Agency

VEGF - Vascular Endothelial Growth Factor

WHO - World Health Organization

SÍMBOLOS

% - Porcentagem

°C - Graus Celsius

~ - Aproximadamente

µg - Micrograma

µg/g - Microgramas por grama

µg/mL - Microgramas por mililitro

µM - Micromolar

mg/kg - Miligramas por quilograma

mlO2/min - Mililitros de Oxigênio por Minuto

ng/g - Nanogramas por grama

ng/mL - Nanogramas por mililitro

p - Valor de significância estatística

ppm - Partes por milhão

r - Coeficiente de correlação de Spearman

SUMÁRIO

1. VISÃO INTEGRADORA DO PROBLEMA

O mercúrio é um metal toxico que afeta o ambiente e a saúde humana no mundo inteiro. Dentre as diversas formas de mercúrio, metilmercúrio é a mais tóxica, afetando diversos tecidos e órgãos, principalmente o cérebro (Crespo-Lopez et al., 2021). Embora a intoxicação mercurial seja um problema global, populações de algumas regiões apresentam um risco maior, por concentrarem atividades humanas intimamente envolvidas no manuseio desse metal (Basu et al., 2018). Dentre elas, as principais atividades relacionadas a emissão de mercúrio para o ambiente incluem a queima de combustíveis, o desmatamento, mineração artesanal e de pequena escala, manuseio impróprio de materiais contendo mercúrio e atividades industriais (Crespo-Lopez et al., 2022).

Na Amazônia, por exemplo, onde a atividade de mineração é intensa, uma alta prevalência de intoxicação mercurial já foi relatada na literatura. Os sintomas relacionados a tal intoxicação incluem dores de cabeça, perda de peso, fadiga, fraqueza muscular, tremores das mãos e pálpebras, perda parcial da função visual e auditiva, e até problemas cognitivos como perda de memória e distúrbios de aprendizagem (Santos-Sacramento et al., 2021).

Os sintomas neurológicos relacionados a intoxicação mercurial têm sido vastamente atribuídos a disfunções neuronais (Crespo-López et al., 2009; Ajsuvakova et al., 2020). Entretanto neurônios são apenas a metade da população celular cerebral. A outra parte é composta por células gliais, com a micróglia e os astrócitos tendo um papel expressivo no contexto da intoxicação mercurial. De fato, essas células estão envolvidas em uma gama de funções no cérebro, como manutenção da homeostase e defesa, e estão implicadas em variados mecanismos de neurotoxicidade mercurial (Crespo-Lopez et al., 2022). Essas células respondem, essencialmente, tamponando o mercúrio para torná-lo excretável pelo organismo, modulando o status imunológico para restaurar alterações deletérias, controlando o sistema redox cerebral e liberando fatores de crescimento, protegendo assim os neurônios e as

demais células do SNC dos efeitos neurotóxicos do mercúrio que, por fim, previnem eventos neuropatológicos (Ni et al., 2012; Augusto-Oliveira et al., 2019; Augusto-Oliveira et al., 2020). Por outro lado, quando a exposição mercurial é intensa e sustentada, as respostas de defesa glial podem ficar saturadas e assumir funções deletérias (seja por perder as funções de defesa ou ganhar funções anormais), contribuindo assim para o dano (Crespo-Lopez et al., 2022).

Desafortunadamente, até hoje, não há terapia farmacológica efetiva para a intoxicação por metilmercúrio, e a aplicação de determinados fármacos, como os quelantes, podem até elicitar efeitos deletérios (Risher and Amler, 2005; Kosnett, 2013). Este cenário é ainda mais preocupante considerando o contexto amazônico, no qual as populações se encontram geograficamente isoladas, desprovidas de fornecimento regular de energia elétrica, água potável e assistência médica de qualidade, e estão cronicamente expostas ao metilmercúrio no ambiente – principalmente através da ingestão diária de peixes contaminados (Arrifano et al., 2018a; Arrifano et al., 2018b; Machado et al., 2021). Ante o exposto acima, apostamos em uma abordagem terapêutica não-farmacológica, de baixo custo e acessível que tem se mostrado promissora em prevenir e/ou mitigar prejuízos cognitivos induzidos por inúmeras condições, quer sejam fisiológicas como envelhecimento, quer sejam patológicas como lesão cerebral traumática e doença de Alzheimer: a atividade física.

De fato, uma robusta literatura tem demonstrado que a atividade física planejada e estruturada, com finalidade de melhorar ou manter um ou mais componentes da aptidão física, também chamada de exercício físico (Dasso, 2019), tem potencial para melhorar déficits cognitivos induzidos patologicamente através da modulação da reatividade glial relacionada a neuroinflamação sustentada, produção e excreção de hormônios de crescimento, fatores de crescimento, expressão de fatores neuroprotetores e alteração do volume de regiões cerebrais chave (Larson et al., 2006; Hamer and Chida, 2009; Erickson et al., 2014; Colonna and Wang, 2016; Augusto-Oliveira and Verkhratsky,

2021). Os efeitos benéficos do exercício físico podem ser observados tanto na abordagem experimental quanto na clínica, e em todas as faixas etárias. No entanto, o protocolo de exercício adotado – como tempo de início, duração, intensidade e frequência – deve ser levado em consideração, pois os efeitos benéficos inerentes a eles são sempre dependentes do contexto, incluindo idade, gênero, espécie, região cerebral afetada, background genético, condição patológica pré-existente (Augusto-Oliveira et al., 2023).

Considerando que o exercício é capaz de modular positivamente os mesmos mecanismos fisiopatológicos gliais afetados pela intoxicação mercurial e que este pode representar uma alternativa terapêutica de baixo custo e de fácil acesso, é coerente sugerir, com a devida cautela, que a adoção de protocolos de exercício físico direcionados ou a adoção de um estilo de vida fisicamente ativo pode prevenir sintomas neurológicos induzidos por intoxicação mercurial em populações vulnerabilizadas como as indígenas, quilombolas e ribeirinhas que residem na Amazônia. É extremamente urgente traçar estratégias de mitigação para populações expostas ao mercúrio na Amazônia, considerando o contexto em que estão inseridas.

Assim, este trabalho foi está dividido em três capítulos, tendo dois deles sido publicado como artigo científico em periódicos internacionais. O primeiro se trata de uma revisão abrangente da literatura cobrindo o papel de células neurais chave no contexto da intoxicação por metilmercúrio – as células gliais. Estudos investigando esse organometal são extremamente relevantes haja vista que o metilmercúrio é um dos principais poluentes liberados no ambiente amazônico com potencial deletério para a saúde de indivíduos pertencentes as comunidades residindo tanto em áreas mais próximas de seu manuseio quanto mais afastadas. Considerando que não há tratamento eficaz para os efeitos gerados pela intoxicação por metilmercúrio, a atividade/exercício físico surge com uma abordagem terapêutica potencialmente promissora em mitigar tais efeitos. O segundo capítulo traz também uma revisão abrangente da literatura,

reunindo e discutindo criticamente achados que destacam o potencial do exercício físico em melhorar a cognição através da modulação da neurogênese, neuroinflamação e remodelamento estrutural mediados por células gliais em contextos tanto fisiológicos quanto patológicos. Mesmo que ainda não tenha sido investigado se a atividade física ou exercício físico são capazes de influenciar os sintomas clínicos da intoxicação mercurial, apostamos nessa abordagem porque, possivelmente, exercício físico e a toxicidade do metilmercúrio têm os mesmos alvos celulares e moleculares. Assim, nosso terceiro capítulo baseia-se na premissa de que a atividade/exercício físico é potencialmente capaz de mitigar os sintomas clínicos elicitados pela intoxicação mercurial em ribeirinhos da Amazônia expostos cronicamente ao metal.

2. ARTIGO I: NEUROTOXICIDADE DO MERCÚRIO: O PAPEL DAS CÉLULAS GLIAIS

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Review

Methylmercury neurotoxicity: Beyond the neurocentric view

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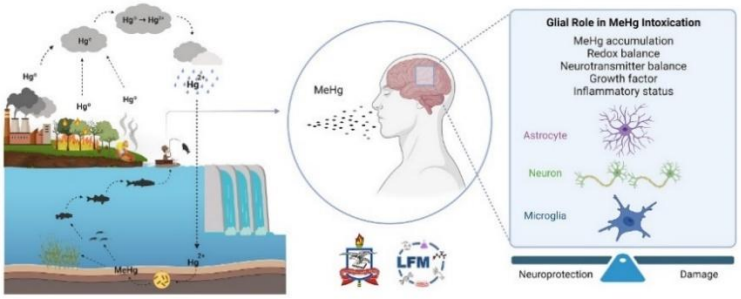
HIGHLIGHTS

- MeHg is a highly neurotoxic global pollutant.
- Besides neuron, glial cells are critical in MeHg neurotoxicity.
- Glia modulate MeHg-induced glutamatergic, oxidative, and immunological dysfunction.
- Glial roles in MeHg neurotoxicity depend on the context.
- Future studies must consider key aspects including dose, exposure and brain area.

GRAPHICAL ABSTRACT



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ABSTRACT

Mercury is a highly toxic metal widely used in human activities worldwide, therefore considered a global public health problem. Many cases of mercury intoxication have occurred in history and represent a huge challenge nowadays. Of particular importance is its methylated form, methylmercury (MeHg). This mercurial species induces damage to several organs in the human body, especially to the central nervous system. Neurological impairments such as executive, memory, motor and visual deficits are associated with MeHg neurotoxicity. Molecular mechanisms involved in MeHg-induced neurotoxicity include excitotoxicity due to glutamatergic imbalance, disturbance in calcium homeostasis and oxidative balance, failure in synaptic support, and inflammatory response. Although neurons are largely affected by MeHg intoxication, they only represent half of the brain cells. Glial cells represent roughly 50 % of the brain cells and are key elements in the functioning of the central nervous system. Particularly, astrocytes and microglia are deeply involved in MeHg-induced neurotoxicity, resulting in distinct neurological outcomes depending on the context. In this review, we discuss the main findings on astroglial and microglial involvement as mediators of neuroprotective and neurotoxic responses to MeHg intoxication. The literature shows that these responses depend on chemical and morphophysiological features, thus, we present some insights for future investigations, considering the particularities of the context, including time and dose of exposure, brain region, and species of study.

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1. Introduction

Mercury is a highly toxic metal found in all ecosystems and widely distributed through natural and anthropogenic processes (WHO, 2021). Emissions of this metal by human activities represent a toxicological risk for both environment and human health (UNEP, 2013; Ha et al., 2017; Crespo-Lopez et al., 2021).

According to the United Nations, in 2015, East and Southeast Asia, South America and Sub-Saharan Africa led the emissions of mercury into the atmosphere from fuel burning, industrial sectors, product use, and artisanal and small-scale gold mining (ASGM) (UNEP, 2019). Together, these regions account for 73 % of global mercury emissions into the air (UNEP, 2019). Plumes of thousands of kilometers in size have been detected over these regions, and both Africa and South America present elevated dry and wet deposition of mercury (UNEP, 2019).

Mercury is currently third among the chemical substances of greatest concern to public health (ATSDR, 2022). Worryingly, people worldwide are exposed to mercury at some level, which may vary within and between different countries and regions (Basu et al., 2018). A recent systematic review and meta-analysis found the highest estimated blood mercury in 2015 in South America and the lowest in Europe (Sharma et al., 2019). However, it is important to stress that some populations, especially gold miners and traditional populations living in highly contaminated areas such as the Amazon region, are at increased risk of mercury exposure, mainly due to the massive growing of ASGM activities and through contaminated fish intake (Basu et al., 2018, Crespo-Lopez et al., 2022a,b). Recent systematic reviews confirmed that human exposure to this metal in South America, especially in the Amazonian traditional communities, are among the highest levels in the world (Basu et al., 2018; Sharma et al., 2019). Furthermore, among populational groups, indigenous people present more than six times the median blood mercury of the general population, being even higher than that found in ASGM or dental workers (Basu et al., 2018). In the Amazon, traditional populations (indigenous, riverine and African-descendants) present a close contact with the surrounding environment, being more sensible to any environmental alterations. These traditional populations consume around 10 meals per week containing 160–430 g of fish each (Hacon et al., 2020). The most recent data on piscivorous fish sold in Amazonian markets for human consumption have demonstrated a mercury mean of 0.603 μg/g (Basta et al., 2023), meaning that only 200 g of fish could be enough (0.603 μg/g × 200 g = 120.6 μg of mercury) to exceed the provisional tolerable weekly intake of methylmercury (MeHg), 100 μg, recommended by the World Health Organization (WHO) (WHO, 2017). Of note, the genetic makeup of some populations may increase susceptibility to mercury intoxication and the deleterious effects associated with mercury exposure (Arrifano et al., 2018; Crespo-Lopez et al., 2023b). Worryingly, mercury emissions into the air from anthropogenic sources have recently increased (Steenhuisen and Wilson, 2019; UNEP, 2019), and anthropogenic actions in the Amazon over the last years are likely mobilizing mercury worldwide and increasing its bioavailability to humans (Crespo-Lopez et al., 2023a).

The organic specie of mercury, MeHg, is the most toxic compound of this metal (UNEP, 2019). It easily penetrates the food chains, where it undergoes processes of bioaccumulation and biomagnification (WHO, 2021). Indeed, compared to inorganic mercury, MeHg exert stronger cytotoxic effects, triggering apoptotic cascade in neurons even in low-level exposure (Lohren et al., 2015). Considering this distinct toxicity, speciation analysis seems to be a critical step to investigate mercurial intoxication (Krupp et al., 2016).

MeHg is the most experimentally investigated species, especially due to its ability to cross biological barriers including the blood-placental barrier and the blood-brain barrier (BBB), making it the most toxic mercury species for humans (Crespo-Lopez et al., 2021, 2022a,b). Attention should be given to the dose in experimental research, aiming to mimic actual contexts of human intoxication and ensure translational relevance (Crespo-Lopez et al., 2022a,b).

Most of the MeHg ingested is absorbed in the gastrointestinal tract, metabolized in the liver, and excreted mainly in the bile and feces (WHO, 2008; Crespo-Lopez et al., 2022a,b). Excretion through the hair represents 10 %, but this matrix is widely used to monitor individual MeHg levels due to its strong correlation with brain mercury levels, besides providing a history of the individual exposure (WHO, 2008; Branco et al., 2021; Crespo-Lopez et al., 2021). Through the bloodstream, MeHg is distributed to all organs of the body (Crespo-Lopez et al., 2022a,b), with the central nervous system (CNS) as the main target, where it can cause severe disturbances (Arrifano et al., 2021). Due to the high affinity for cysteine sulfhydryl groups, MeHg is able to form a molecular complex similar to methionine, mimicking it, and easily crossing the BBB, preferentially accumulating in glial cells, especially astrocytes and microglia (Ni et al., 2012; Ajsuvakova et al., 2020; Arrifano et al., 2021).

The main neurological symptoms of MeHg poisoning include attention and memory deficits, motor, visual and verbal impairments (Santos-Sacramento et al., 2021), which are manifested even at low-levels exposure (Karagas et al., 2012; Prpić et al., 2017; Loan et al., 2023). Associating these mechanism and pathological changes with exact mercury concentrations is a tricking issue due to the numerous confusing factors involving mercury intoxication (age, genetic background, gender, and time of exposure, among others). However, as a possible approach, we recently discussed and proposed (Crespo-Lopez et al., 2022a,b) mercury doses of translational relevance for in vivo models, based on reference and critical doses for humans already established by the WHO and the U.S. Environmental Protection Agency (USEPA). For instance, the LOAEL/Benchmark doses[1] of MeHg weekly consumption in humans according to WHO and USEPA are 35 and 7.7 μg/kg, respectively, which would be approximately equivalent to 215.83 and 47.48 μg/kg in rats (Crespo-Lopez et al., 2022a,b). Furthermore, reference doses (i.e., maximum weekly intake) recommended by both organizations are 1.6 μg/kg and 0.7 μg/kg, respectively, which may be equivalent to 9.87 and 4.32 μg/kg in rats (Crespo-Lopez et al., 2022a,b). Although these animal equivalent doses are not precise measurements, they represent means for achieving more predictive and reliable comparisons between human exposure and in vivo models (Crespo-Lopez et al., 2022a,b).

At the cellular and molecular level, such symptoms result from the diverse toxic mechanisms such as disturbances in oxidative balance – either reducing the antioxidant defense or increasing the production of reactive species (Farina and Aschner, 2017; Crespo-López et al., 2019; Arrifano et al., 2021), disturbance in glutamate and γ-aminobutyric acid (GABA) signaling (Ayensu et al., 2009, Farina et al., 2011, T. Yang et al., 2020), disturbance in calcium homeostasis (Colón-Rodríguez et al., 2020) and mitochondrial activity (Shao et al., 2019).

Glial cells, such as astrocytes and microglia, considered key elements for the CNS homeostasis and defense, are closely related to functions mentioned above (Ni et al., 2012; Arrifano et al., 2021; Crespo-Lopez et al., 2022a,b), performing crucial roles in MeHg-induced neurotoxic events. Noteworthy, the involvement of glial cells in MeHg intoxication was last reviewed in 2012 (Ni et al., 2012), and much has been learned since then. For example, although astrocytes and microglia share many common features, they differ concerning cellular function and on their role in MeHg-mediated toxicity (Fig. 1), resulting in distinct neurological outcomes depending on the context (Table 1) (Arrifano et al., 2021, Crespo-Lopez et al., 2022a,b). Oligodendrocytes represent a numerous and important glial cells group, however, literature covering their

[1] Estimated critical doses (Benchmark dose or low observed adverse effect level, LOAEL) are those causing detectable adverse effects related to neurological alterations; reference doses are those corresponding to the provisional tolerable weekly intake recommended by each organization, i.e., the maximum weekly MeHg consumption without apparent adverse effects. For more details, see Crespo-Lopez et al. (2022a,b).

involvement in MeHg intoxication is rather sparse [for recent review please see Crespo-Lopez et al., 2022a,b]. Here we focus on astrocytes and microglia as key modulators in MeHg intoxication.

2. Methylmercury neurotoxicity: a neurocentric view

Neurons, the best-known and most extensively studied neural cellular component, are severely affected by mercury intoxication (Crespo-López et al., 2009). MeHg, the most neurotoxic mercurial species, damages neuronal cytoskeleton, reducing neurite outgrowth and cell viability (Ferraro et al., 2009; Pierozan et al., 2017). Binding to free sulfhydryl groups present at both ends and on the surface of microtubules, MeHg impairs the assembly and stability, ultimately causing cell death and tissue disturbance (Vogel et al., 1985; Ajsuvakova et al., 2020). Indeed, microtubules are important components of the stability of the eukaryotic organic cytoskeleton and, along with actin and intermediate filaments, mediate the transport of organelles, vesicles, neurite growth, proliferation and cell migration and division (Rolls et al., 2021). Interestingly, using human neuronal culture (H9 cell line), it was found that MeHg intoxication leads to microRNAs deregulation, disrupting critical pathways related to neuronal differentiation including axon guidance and neurotrophin-regulated signaling (Pallocca et al., 2014).

In addition to affecting cell structure and viability, MeHg interferes with dopaminergic (Ke et al., 2020), GABAergic (Basu et al., 2010) and glutamatergic (Juárez et al., 2002; Farina et al., 2003) synaptic transmissions. Particularly considering the latter, the most investigated

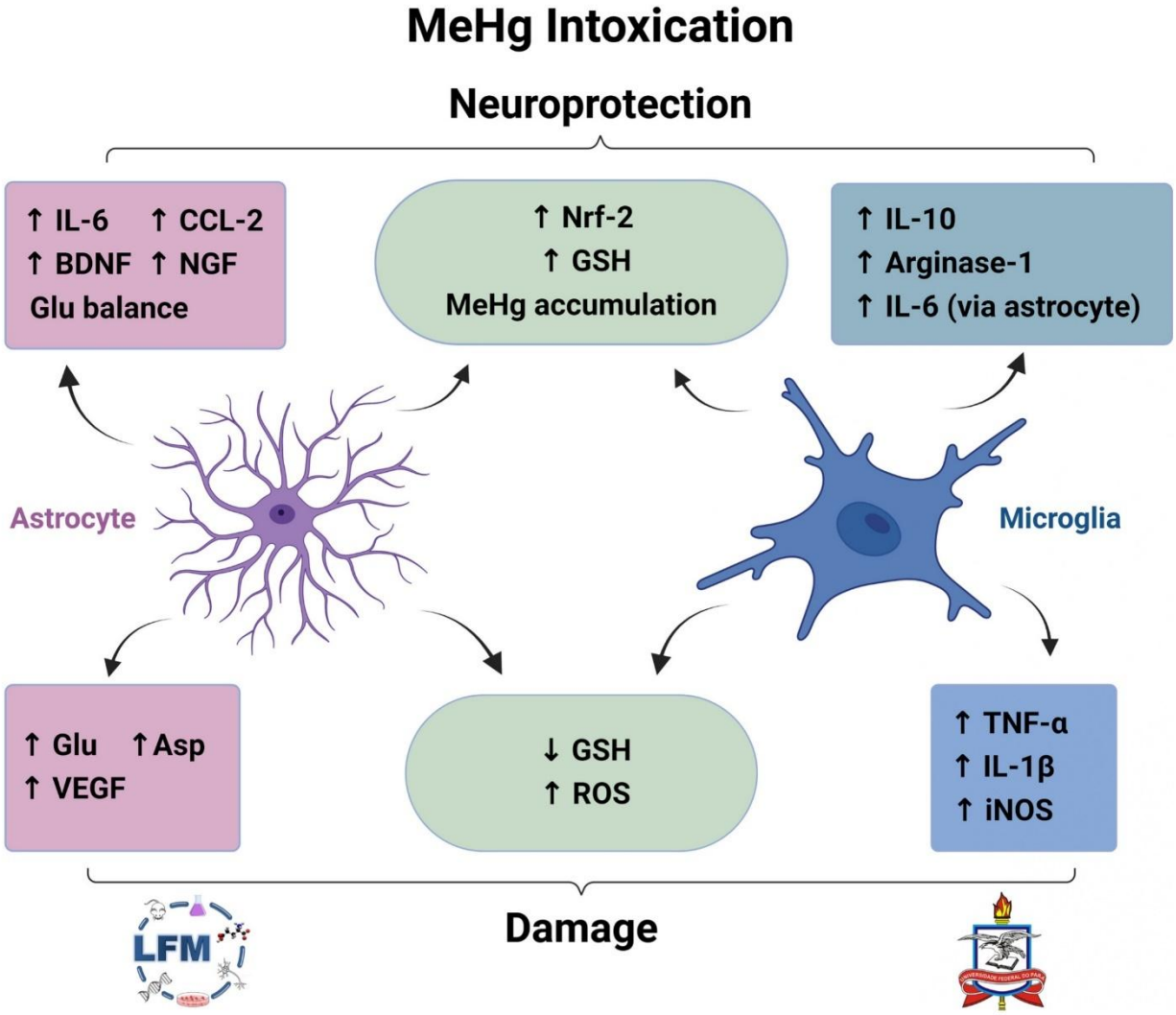

Fig. 1. Glial involvement in MeHg-mediated toxicity. Mechanisms underlying neuroprotection performed by both astrocytes and microglia involve the regulation of antioxidant enzymes and metal storage. Astrocytes promote neuroprotection by the release of cytokines, chemokines, growth factors, and glutamate balance. Microglia contribute to neuroprotection through cytokines (including astrocytes-mediated cytokines) and metalloenzymes. Damage mediated by astrocytes and microglia includes loss of their functions or gain of abnormal functions, such as inhibition of antioxidant enzymes and increased formation of reactive oxygen species. Mechanisms underlying astrocyte-induced damage include neurotransmitter imbalance and release of growth factor. Microglia contribute to damage through cytokines and cytokine-activated enzymes. IL-6, interleukin 6; IL-10, interleukin 10; IL-1β, interleukin 1-β; CCL-2, chemokine (CC motif) ligand 2; TNF-α, tumor necrosis factor-α; iNOS, inducible nitric oxide synthase; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; Nrf-2, erythroid nuclear factor linked to factor 2; GSH, glutathione; ROS, reactive oxygen species; Glu, glutamate; Asp, aspartate; MeHg, methylmercury. Created with BioRender.

Table 1
Glial involvement in MeHg-induced neurotoxicity.

Glial involvement in MeHg-induced neurotoxicity							
Glial cell	Model	Brain region	Exposure via	MeHg treatment dose	Time of treatment	Main results	Reference
Astrocytes	Primary astrocytic culture from newborn (1-day-old) Sprague–Dawley rats	Cerebral cortices	In vitro	1, 5 and 10 μM	1 and 6 h	Treatment with MeHg (5 and 10 μM) for 1 or 6 h caused an increase in the levels of markers of oxidative damage and concentration-dependent reduction in the inner mitochondrial membrane potential. Furthermore, it decreased mRNA expression coding for glutamine transporters (SNAT3/SN1 and ASCT2) at the highest concentration (10 μM). It suggests that exposure to MeHg induces increased mitochondrial membrane permeability, alterations in glutamine/glutamate cycling, increased ROS formation, and consequent oxidative injury.	Yin et al., 2007
	Primary astrocytic culture from newborn Sprague–Dawley rats	Cerebral hemispheres	In vitro	0 to 5 × 10^{-4M}	30 min	Reduced uptake of L-glutamate and D-aspartate at MeHg concentrations as low as 10^{-5} M. Dose- and time-dependent increase in the efflux of both excitatory amino acids after MeHg exposure.	Aschner et al., 1993
	Mutant CHO-K1 cell line (DdB7)	–	In vitro	0, 5 and 10 μM	6 h	Exposure to MeHg distinctly affects the predominantly astrocytic glutamate transporters, GLAST and GLT-1. For example, increased expression of GLT-1 mRNA (but not GLAST) after 6 h of treatment (5 or 10 μM MeHg); Increased levels of GLAST transporter proteins (5 or 10uM MeHg); and low levels of GLT-1 transporter proteins (5 μM MeHg); and inhibits glutamate uptake by GLAST, while increasing GLT-1 activity by 5 or 10 μM MeHg.	Mutkus et al., 2005
	Primary astrocytic culture from newborn Sprague–Dawley rats	Cerebral hemispheres	In vitro	0 to 5 × 10^{-4M}	30 min	MeHg (10^{-5M}) inhibited the initial rate of uptake (1 min) of the Na+-dependent L-glutamate.	Aschner et al., 1990
	Wistar rats	Frontal, central, and occipital brain regions, and cerebellum	Oral	20 ppm	1 to 4 weeks	Subacute MeHg intoxication (up to 4 weeks) induced cerebellar damage confirmed by extravasation of endogenous IgG and decreased expression of RECA-1. Furthermore, it induced BBB damage by up-regulating astrocytic VEGF in the cerebellum and occipital lobe.	Takahashi et al., 2017
	Co-culture of human neuronal cell line (SH-SY5Y) and astrocytic-like cell line (D384).	–	In vitro	1 to 2.5 μM	24 to 48 h	Mitochondrial dysfunction was significantly mitigated in neurons co-cultured in the presence of astrocytes at concentrations from 1.75 to 2.5 μM.	De Simone et al., 2017
	Primary mono- and co-culture of astrocytes and neurons from (1 and 7-day-old) mice.	Cortex and cerebellum	In vitro	5, 10, 25 and 50 μM	24 h	MeHg did less damage to the mitochondrial and cell membrane integrity of cerebellar astrocytes compared to cortical astrocytes. Furthermore, in co-cultures of neurons and cerebellar astrocytes exposed to a low dose of MeHg, neurons showed fewer alterations compared to the respective cell type in monoculture. This suggests that astrocytes may protect neurons against MeHg toxicity.	Morken et al., 2005
	Primary mono- and co-culture of astrocytes and neurons from fetal (17- to 18-day-old) and newborn (1-day-old) Sprague–Dawley rats.	Cerebral cortices	In vitro	1 and 10 μM	6 h	MeHg (10 μM) altered the concentration of amino acids (serine, glycine, and alanine) in astrocytes and cortical neurons. Glutamate concentration	Yin et al., 2009

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Table 1 (*continued*)

Glial involvement in MeHg-induced neurotoxicity							
Glial cell	Model	Brain region	Exposure via	MeHg treatment dose	Time of treatment	Main results	Reference
						decreased only in neurons at the same MeHg concentration. The decrease in neurons was fully reversed when these cells were co-cultured with astrocytes.	
	Primary astrocytic culture from newborn (1-to 2-day-old) Wister rats	Cerebral cortices	In vitro	10 μM	6 h	MeHg (10 μM for 6 h) activates 38 transcription factors and Nfr-2 (an antioxidant response element, which has been reported to act on MeHg detoxification.	Takemoto et al., 2016
	Primary astrocytic culture from newborn (1-day-old) rats	Cerebral hemispheres	In vitro	0.01, 0.1, 1, 5 and 10 μM	6 h	MeHg activated Nrf2 and its downstream antioxidant system in neonatal rat primary astrocytes. Nrf2 function is regulated by PI3 kinase. Furthermore, inhibition of the PI3 kinase resulted in decreased cellular glutathione and increased cell death to high-dose MeHg (5 μM).	Wang et al., 2009
	Primary astrocytic culture from newborn (1-day-old) Sprague–Dawley rats	Cerebral cortices	In vitro	±10 μM	30 min	Adequate intracellular GSH levels and selective antioxidants promote protective effects against MeHg-induced oxidative stress in primary astrocyte cultures.	Shanker et al., 2005
	Primary astrocytic culture from newborn (1-to 2-day-old) Wistar rats	Cerebral cortices	In vitro	3 and 10 μM	24 h	Conditioned medium of MeHg-treated astrocytes (MCM) attenuated neuronal cell death induced by MeHg. Furthermore, BDNF and NGF homodimers as well as an increase in the expression of these factors were detected in astrocyte culture.	Takemoto et al., 2015
	ICR mice	Inferior colliculus	Oral	4 mg/kg/day	1 to 8 weeks	MeHg induced motor incoordination within 6 weeks of exposure. Furthermore, Astrocytes exposed to MeHg increased the expression of BDNF in the inferior colliculus (IC), suggesting that astrocytic brain-derived neurotrophic factor is a potent protectant in the IC.	Ishihara et al., 2019
	Primary astrocytic culture from newborn Wistar rats	Cerebral cortices	In vitro	0.1, 1 and 3 μM	1, 2, 6 and 12 h	MeHg stimulates the release of astrocytic ATP that auto-stimulates P2Y1 receptors to regulate IL-6 (via p38 MAP kinase), thus protecting neurons against MeHg.	Noguchi et al., 2013
	Human astrocytoma cell line (1321N1)	–	In vitro	10 μM	0, 3, 6, 12, and 24 h	MeHg induced CCL-2 expression in human astrocytes by activating the transcription factor NF-kB.	Kim et al., 2012
	Adult Wistar rats	Visual cortex	Oral gavage	0.04 mg/kg/day	60 days	Chronic MeHg intoxication (low dose) induced reactive state in astrocytes (cell body hypertrophy and swelling and shortening and thickening of cell dendrites). Besides, the decreased levels of NADPH-d neuropil labeling.	Freire et al., 2020
Astrocytes and microglia	Primary culture of astrocytes and microglia isolated from newborn (1-day-old) Sprague-Dawley rats	Cerebral cortices	In vitro	0.1, 1 and 5 μM	>6 h	Both astrocytes and microglia store intracellular MeHg, form ROS by GSH depletion, and can trigger antioxidant defense by activating Nfr-2. However, Microglia store more MeHg, have a lower basal level of GSH, and form more ROS, besides initiating antioxidative defense in a shorter time and dose of treatment with MeHg compared to astrocytes.	Ni et al., 2011
	Primary culture of astrocytes and microglia isolated from newborn Wistar rats or C57BL/6 mice.	Cerebral cortices	In vitro	0.01, 0.1, 1, and 3 μM	0, 3 and 24 h	Low concentration of MeHg (0.1 μM) stimulates exocytosis of microglial ATP (via p38 MAPK- and vesicular nucleotide transporter-dependent	Shinozaki et al., 2014

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Table 1 (*continued*)

Glial involvement in MeHg-induced neurotoxicity							
Glial cell	Model	Brain region	Exposure via	MeHg treatment dose	Time of treatment	Main results	Reference
						mechanisms) which stimulates P2Y1 astrocystic receptors to regulate IL-6 and protect neurons against low concentrations of MeHg.	
	Neoplastic mono- and co-cultures of astrocyte and microglia from newborn rats	–	In vitro	10^{-10M} to 10 − 6 M	5 and 10 days	Exposure to MeHg induces microglia reactive state. Furthermore, interaction between reactive microglia and astrocyte (as evidenced by aggregate formation) may increase local IL-6 levels and promote neuroprotection.	Eskes et al., 2002
Microglia	Sprague Dawley rats (7-weeks-old)	Dorsal root nerves and spinal cord	Oral	1 mg/kg/day	0, 1, 2, 3, and 4 weeks	Treatment with fasudil induced a protective microglial state (evidenced by a decrease in the expression of TNF-α, iNOS, IL-6 and IL-1ß, and an increase in the expression of arginase-1 and IL-10) capable of recovering axonal degeneration and neural dysfunction induced by chronic exposure to MeHg.	Fujimura et al., 2019
	Adult monkeys (*Macaca fascicularis*)	Cortex of the calcarine sulcus and occipital pole	Oral	50 μM/kg/day	6, 12 and 18 months	Chronic exposure to non-toxic doses of MeHg induced microglial reactivity in the brain of monkeys.	Charleston et al., 1994
	Primary microglial culture from newborn (0- and 1-day-old) and organotypic slice culture from posnatal (5- and 7-day-old) C57BL/6J Wild-type mice.	Cerebral cortices	In vitro/in situ (organotypic slice culture)	0.1 μM	24 and 96 h/ 3 weeks (in situ)	Chronic exposure to MeHg induced a neurotoxic microglial state, as evidenced by reduced process motility, retraction of hypertrophic processes and cell bodies, as well as increases in iNOS and TNF-α levels. Rho-kinase (ROCK) was found to be key for controlling microglial reactivity and neurotoxicity. Furthermore, MeHg-induced neuronal damage was increased in the presence of ROCK-mediated neurotoxic microglia.	Shinozaki et al., 2019
	Microglial cell line (BV-2) and primary microglial culture from newborn (2-day-old) C57BL/6 mice.	Cerebral cortex and cerebellum	In vivo (subcutaneou)/in vitro	25 mg/kg (in vivo)/0, 5, 10 and 20 μM (in vitro)	7 days (in vivo)/0, 1, 2, 4 and 6 h (in vitro)	MeHg-induced mitochondrial ROS formation promoted TNF-α expression in primary microglia and microglia lineage BV-2 and neuronal cell death via ASK1 activation and p38 MAPK phosphorylation.	Toyama et al., 2021
	Microglial cell line (N9)	–	In vitro	2 ng/mL and 2 μg/mL	3, 6, 12, 24 and 48 h	Low dose of MeHg-HSA (2 ng/mL) induced cell proliferation, high levels of nitric oxide (NO) and intracellular Ca2+, besides to suppressing the release of inflammatory mediators such as TNF-α and IL-1ß, without cytotoxic effects; while higher doses (2 μg/mL) of MeHg-HSA induced an increase in the release of TNF-α and IL-1ß, promoting cell death and cytotoxic effects on N9 cells. Furthermore, ERK/MAPKs and STAT3 signaling pathways are related to MeHg-HSA hormesis in N9 cells.	Tan et al., 2019a
	Microglial cell line (BV-2)	–	In vitro	0.01, 0.1, 1 and 10 μM	1 h	MeHg (10 μM) induced necrotic-like cell death and suppression of IL-6, TNF-α, iNOS immunoreactivity, and release of NO, besides decreasing the metabolic activity of BV-2 cells.	Martins et al., 2022

signaling pathway and a critical target of MeHg-induced neurotoxicity [for a review see Aschner et al., 2007], MeHg inhibits glutamate uptake and stimulates its release into the synaptic cleft, increasing extracellular levels of this neurotransmitter leading to excitotoxicity (Farina et al., 2013). This enhanced extracellular glutamate concentration exacerbates any previous excitotoxic event by overactivation of the *N*-methyl-D-aspartate receptors (NMDAR) and GluA2-subunit-lacking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), which increases calcium influx into neuron (Pivovarova and Andrews, 2010; Sceniak et al., 2020). MeHg also affects neuronal function by blocking sodium and calcium channels, disrupting synapse transmission and neuronal excitability as observed in CA1 area of rat hippocampus (Gutiérrez et al., 2018). Interestingly, although disruption of calcium signaling and glutamate dyshomeostasis may contribute separately to MeHg toxicity, they are inter-related events (Farina et al., 2013; T. Yang et al., 2020).

In addition to affecting calcium and glutamate signaling, MeHg can induce neuroinflammation by releasing neuronal inflammatory mediators. Increased levels of "pro-inflammatory" cytokines such as interleukin 1-β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α) and interferon-gamma (IFN-γ), and decreased levels of the "anti-inflammatory" cytokine interleukin 10 (IL-10), as well as increased levels of caspase-1, caspase-3 and caspase-8 (which are involved in cell death) were detected in vitro after MeHg exposure (Algarve et al., 2019).

Indeed, MeHg can induce neuronal cell death through both apoptotic and necrotic pathways, depending on the intensity of the insult. For example, in the primary culture of cerebellar granule cells, exposure to 5–10 μM of MeHg for 1 hour induced necrotic cell death, while exposure to lower concentrations such as 0.5 to 1 μM of MeHg for 18 hour induced apoptotic cell death (Castoldi et al., 2000). Further, in primary cultures of cortical neurons from neonatal rats exposed prenatally to 4 mg/kg of MeHg (through the mother), MeHg induced cell death by apoptosis, while at a higher dose (8 mg/Kg) MeHg induced cell death by both apoptosis and necrosis (Ferraro et al., 2009). The mechanisms by which MeHg activates necrotic pathways in neuronal cells are still uncertain, however, in addition to intensity of the insult, they depend on the cell type, cellular defense mechanisms (Ferraro et al., 2009, L. Yang et al., 2020).

Furthermore, prenatal MeHg exposure may increase neuronal differentiation of fetal radial glial precursor through CREB phosphorylation, besides increasing cortical neurogenesis and interfering in neuronal trajectories during cell migration (Loan et al., 2023). These MeHg-induced neuronal alterations led to impaired communication, reduced sociability, and increased restrictive and repetitive behaviors in young adult rats (Loan et al., 2023). Considering adult neurogenesis, MeHg seems to affect numerous molecular mechanisms in neural stem cells including apoptosis, mitochondrial dysfunction, and cell cycle progression, with potential effects on cognitive function (Faustman et al., 2002; Raposo et al., 2020; Abbott and Nigussie, 2021).

MeHg intoxication affects neurons significantly, including disturbances in neuronal structure and function, neurotransmitter imbalance, inflammatory mediators, and even cell death, which lead to major

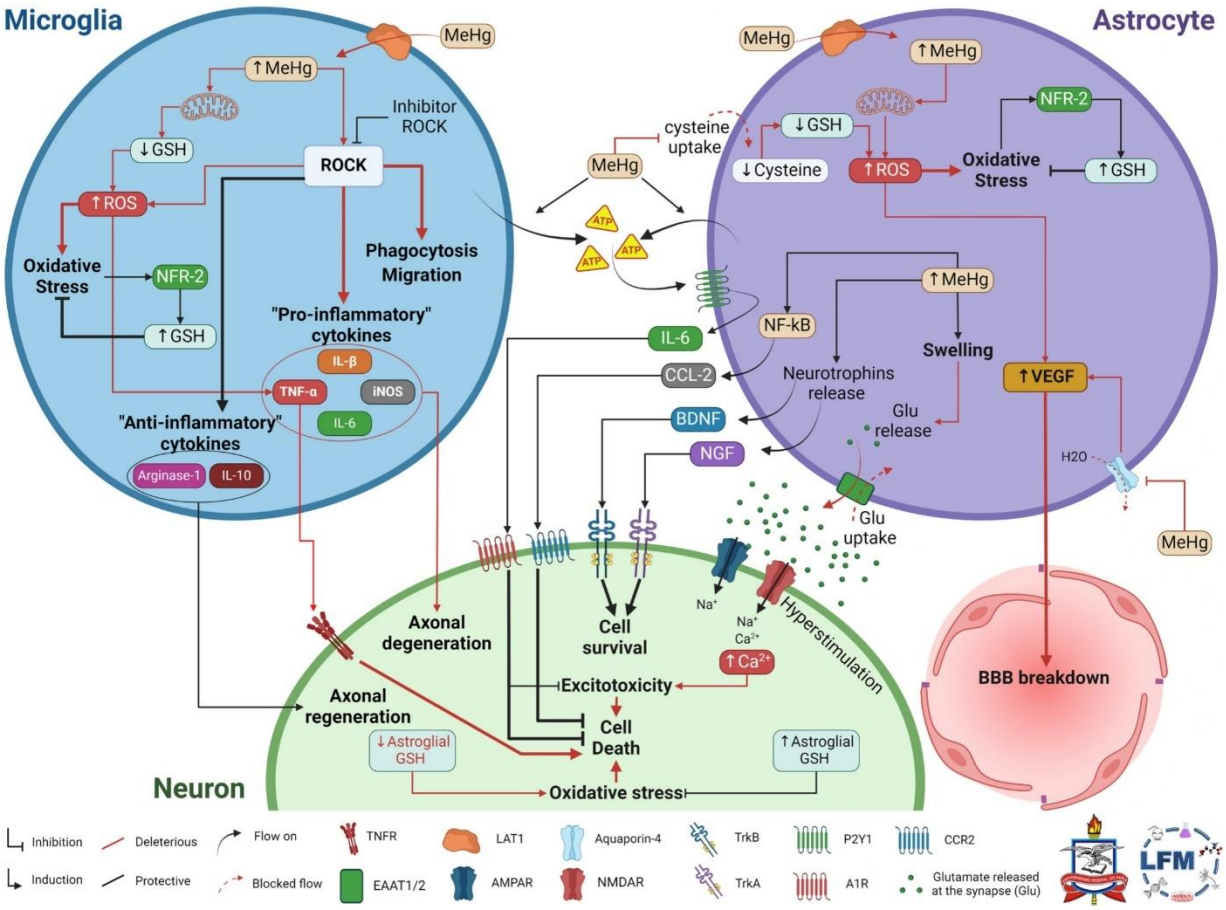

Fig. 2. Diagram of complex biochemical pathways involved in the neuroprotective and deleterious roles of glial cells in MeHg neurotoxicity. Created with BioRender.

effects such as altered cognition and behavior (Sokolowski et al., 2013; Tian et al., 2016; Wu et al., 2016; Shinoda et al., 2019; T. Yang et al., 2020). However, neurons only constitute half of the brain cells. The remaining 50 % is comprised of glial cells, which play a crucial role in the functioning of the CNS (Augusto-Oliveira et al., 2020; Verkhratsky et al., 2021; Arrifano et al., 2022; Augusto-Oliveira et al., 2022). Among the glial cells, astrocytes and microglia are particularly implicated in the MeHg-induced neurotoxicity, acting as protective or aggravating agents of the toxic effects of MeHg (Fig. 2) (Arrifano et al., 2021; Crespo-Lopez et al., 2022a,b).

3. Astrocytes and methylmercury

3.1. Astroglial physiopathology

Astrocytes comprise the main glial cells responsible for CNS homeostasis (Kriegstein and Alvarez-Buylla, 2009; Augusto-Oliveira et al., 2020; Verkhratsky et al., 2020). As electrically silent cells, they respond to the extracellular environment through a diversity of receptors that elicit fluctuations of cytosolic ions tightly organized in space and time (Semyanov et al., 2020; Verkhratsky et al., 2020; Arrifano et al., 2021). Thus, these cells are involved in several events such as water and potassium transport, maintenance of the BBB, oxidative balance, neurotransmitter uptake and metabolism and release of inflammatory mediators, ultimately modulating synapse plasticity, cognition and animal behavior (Augusto-Oliveira et al., 2020; Verkhratsky et al., 2020; Arrifano et al., 2021). This functional diversity is closely related to its molecular and morphological diversity (Augusto-Oliveira et al., 2020).

Astrocytes are widely diverse cells, exhibiting differential transcriptional and proteomic profiles that are brain region-, time- and species-dependent (Chai et al., 2017; John Lin et al., 2017; Morel et al., 2017). Of note, this distinct gene expression is closely related to astroglial functions (Chai et al., 2017), and it has been used to identify astroglial subpopulations (Batiuk et al., 2020). In fact, the comparison between astroglial mRNAs from different brain regions suggests that the gene expression is different between regions (Doyle et al., 2008; Bayraktar et al., 2020)., Consequently, the coding pattern of proteins as neuropeptides, glycoproteins, Na+ and K+ channels, glutamate and GABA receptors, glutamate and glycine transporters, and also chemical reactions as synthesis of nitric oxide and GABA are different either (Zhang and Barres, 2010). In the cerebellum, astrocytic gene expression is modulated by the adjacent mature neurons, suggesting that the astrocyte-neuron communication would have an important role in the molecular diversity of astrocytes (Farmer et al., 2016). Cortical astrocytes, for example, exhibit molecular patterns which are specific to each layer of the cortex, and according to the different astrocyte-neuron interactions in each layer (Lanjakornsiripan et al., 2018).

Morphologically, astrocytes are extremely complex cells with high diversity in both soma and branch; numerous processes, ranging from short and thick to long and thin branches, compose an intricate arborization that covers part of the synapses held by neurons and blood vessels, in addition to maintaining contact with other glial cells (Zhou et al., 2019; Augusto-Oliveira et al., 2020; Arrifano et al., 2022). Expression of specific markers characterizes this diversity in astrocytic morphology, including the expression of glial fibrillary acidic protein (GFAP), calcium-binding protein β (S100β), glutamine synthetase (GS), and excitatory amino acid transporters (EAATs), among others (Augusto-Oliveira et al., 2020; Escartin et al., 2021). The GFAP, the oldest and most used marker (Eng et al., 1971; Hol and Pekny, 2015), is expressed at different levels in astrocytes depending on cellular maturation and brain region, and under both physiological and pathological conditions (Savchenko et al., 2000; Augusto-Oliveira et al., 2020). For example, white matter astrocytes express higher GFAP levels than gray matter astrocytes (Cahoy et al., 2008). Additionally, expression of astroglial markers may be modulated by pathological and lifestyle contexts, as the case for GFAP (Sofroniew, 2020).

Astrocytes under pathological conditions perform roles contributing to both deleterious and benefic outcomes in several pathological contexts, either i) preserving the nervous tissue and essential functions of the CNS including maintenance of the antioxidant system, neurotransmitters balance and regulation of BBB permeability or; ii) losing their functions and/or gaining abnormal functions, thus contributing to neuronal damage and pathological disorders including neurodegenerative diseases (Escartin et al., 2021) and neurotoxicity induced by xenobiotics such as MeHg (Farina et al., 2011; Malfa et al., 2014; Arrifano et al., 2021, 2022).

3.2. Astrocytes in MeHg intoxication

Most of the scientific literature investigating astroglial involvement in mercury neurotoxicity focuses on MeHg effects, the most toxic species of mercury for the CNS. Astrocytes present high affinity for MeHg, accumulating it inside the cell (Ni et al., 2011). The presence of neutral L-type amino acid transporter system (LAT1) in its cell membrane contributes to the intracellular storage of MeHg through the MeHg-L-cysteine conjugate, which is structurally similar to the endogenous substrate of LAT1, L-methionine (Simmons-Willis et al., 2002; Yin et al., 2008).

Within astrocytes, MeHg interacts with reduced glutathione (GSH), forming an excretable complex, which decreases GSH levels and increases reactive oxygen species (ROS) production, leading to oxidative stress (Fig. 2) (Farina et al., 2011). Of note, MeHg can raise ROS levels, mediated by alterations in several MAP kinase-related signaling pathways including ERK1/2, p38MAPK and SAPK/JNK (Sasaki et al., 2023). GSH is the main antioxidant defense, neutralizing ROS and xenobiotic molecules (Ni et al., 2011), and promoting the maintenance of the intracellular redox state (Shanker and Aschner, 2001). In addition to the direct interaction, MeHg interferes with GSH synthesis by inhibiting the uptake of its precursors (cystine and cysteine) in astrocytes; considering that astrocytes play an important role in supplying GSH precursors to neurons, the antioxidant defense of neurons is compromised by reducing GSH levels and making neurons more susceptible to MeHg intoxication (Shanker and Aschner, 2001; Allen et al., 2002).

MeHg also interferes with one of the fundamental astrocytic roles in the CNS homeostasis: the metabolism and uptake of neurotransmitters from the synaptic cleft (Farina et al., 2011; Mahmoud et al., 2019). Astrocytes are the main responsible for removing extracellular neurotransmitters from the synaptic space, using two types of transporters: Na+-dependent and Na+-independent membrane transporters (Lehre and Danbolt, 1998; Anderson and Swanson, 2000; Mahmoud et al., 2019). The Na+-dependent transporter captures most of the synaptic cleft neurotransmitters (Rose et al., 2018). In addition to uptake less quantity of neurotransmitters, the Na+-independent transporter captures cystine, which is a crucial substrate for the antioxidant response (Anderson and Swanson, 2000).

In the event of MeHg exposure, the metal inhibits EAATs, increasing the concentration of extracellular glutamate that hyper stimulates neuronal receptors causing excitotoxicity (Fig. 2) (Aschner et al., 1993; Yin et al., 2007). This decreased astroglial uptake of glutamate by MeHg compromises astroglial GSH content, also contributing to neurotoxicity (Mutkus et al., 2005; Augusto-Oliveira et al., 2020; Arrifano et al., 2021). Furthermore, MeHg intoxication can stimulate the efflux of excitatory amino acids, glutamate and aspartate, mediated by astrocytic swelling (Aschner et al., 1990; Mullaney et al., 1994), aggravating neuronal damage by excitotoxicity (Aschner et al., 1993).

Additionally, astrocytes express vascular endothelial growth factor (VEGF), a potent regulatory factor in vascular growth and development (Nesic et al., 2010; Hirooka et al., 2013). Increased expression of VEGF can amplify permeability in systemic vessels and even in the BBB, leading to hypersensitivity, leakage, and edema (Fig. 2) (Ferrara et al., 2003; Takahashi and Shimohata, 2019). Recently, it was observed that MeHg may induce VEGF overexpression in astrocytes, in which two

alternative pathways may be involved: (i) regulation of hypoxia-inducible factor 1α-mediated by MeHg-induced ROS; or (ii) MeHg-induced aquaporin 4 water channels inhibition (Takahashi et al., 2017).

Although not yet investigated, part of the MeHg-induced neurotoxicity may be associated with a possible disturbance in calcium signaling in astrocytes, as observed in motor neurons; MeHg-mediated increase in intracellular calcium concentration has been reported in motor neurons both from human pluripotent stem cells, through AMPAR (Colón-Rodríguez et al., 2020), and from the spinal cord of mice, through NMDAR and voltage-gated calcium channels (Ramanathan and Atchison, 2011). Calcium plays a fundamental role in cellular functions (Berridge et al., 2003), but the excess in the cytoplasm can activate cell death pathways (Berridge et al., 2000). It is not yet known whether MeHg intoxication disturbs calcium homeostasis in astrocytes, so this discussion opens an interesting window for further investigation.

Other studies have found neuroprotective roles of astrocytes against MeHg (Arrifano et al., 2021). For example, neurons co-cultured with astrocytes show higher resistance to MeHg when compared to isolated cultures (of neurons or astrocytes) (Morken et al., 2005; De Simone et al., 2017). A similar study, using primary cultures of rat cerebral cortices, suggests that astrocytes can attenuate MeHg-induced glutamatergic imbalance in neurons (Yin et al., 2009).

A possible mechanism underlying the neuroprotective role of astrocytes in MeHg intoxication is the astrocytic expression of erythroid nuclear factor linked to factor 2 (Nfr-2) in response to MeHg-induced oxidative stress (Fig. 2) (Ni et al., 2011). Once activated, Nfr-2 is translocated to the nucleus and upregulates a series of antioxidant proteins promoting neuroprotection (Toyama et al., 2007; Wang et al., 2009; Takemoto et al., 2016). Inhibition of Nfr-2 or its abnormal expression can aggravate MeHg intoxication, leading to cell death (Toyama et al., 2007; Ni et al., 2011). Activation of Nfr-2 increases the GSH synthesis and protects neurons and astrocytes against MeHg-induced oxidative stress, consequently protecting brain tissue and function (Shanker et al., 2005; Ni et al., 2011).

Astrocytes also synthesize and release neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Schwartz and Nishiyama, 1994). By binding to tropomyosin kinase (Trk) receptors A and B, respectively, these neurotrophins induce autophosphorylation of the intracellular tyrosine kinase domain, activating a signaling pathway for cell survival and neuronal protection (Fig. 2) (Takemoto et al., 2015; Odaira et al., 2019). Indeed, the upregulation of BDNF and NGF prevents neuronal cell death induced by excitotoxicity (Lin et al., 1996; Almeida et al., 2005). Recently, it was reported that the MeHg-induced NGF and BDNF release in astrocytes would attenuate neuronal cell death (Takemoto et al., 2015), protecting the auditory system (Ishihara et al., 2019), which suggests a protective role for astrocytes against MeHg-induced neurotoxicity.

Besides trophic factors, astrocytes release inflammatory factors such as cytokines and chemokines (Choi et al., 2014; Chen et al., 2015), that may mediate protective mechanisms against MeHg-induced neuronal damage. For example, IL-6 released by astrocytes in response to ATP released by astrocytes or microglia stimulates neuronal adenosine 1 receptors, which are autoreceptors, inhibit synaptic signaling and, consequently, neuronal hyperstimulation (Fig. 2) (Noguchi et al., 2013; Shinozaki et al., 2014). Curiously, the release of astrocytic IL-6 mediated by microglial ATP may lead to an earlier and more sensitive neuroprotective response to lower concentrations of MeHg (Shinozaki et al., 2014), suggesting that the interaction between astrocytes and microglia may trigger a better adapted response to MeHg intoxication. Besides IL-6, MeHg induces chemokine (CC motif) ligand 2 (CCL2) overexpression in astrocytes through activation of the transcription nuclear factor-kappa B (NF-kB) (Fig. 2) (Kim et al., 2012), which can trigger an inflammatory response against MeHg neurotoxicity. Blocking CCL2 signaling by inhibiting C—C chemokine receptor type 2 (CCR2) increases neuronal cell death in MeHg intoxication (Godefroy et al., 2012).

Despite these findings, further studies are needed on the mechanisms and components involved in astrocyte-mediated inflammatory responses towards MeHg-induced damage. Perhaps the interactions between astrocytes represent just one of several adaptive strategies of the CNS against neurotoxicity promoted by toxic metals.

4. Microglia and methylmercury

4.1. Microglial physiopathology

Microglia are the most responsive immune cells in the CNS, responding quickly to disturbances in the nervous environment (Augusto-Oliveira et al., 2019). They derive from primitive macrophages that migrate to the neural tube early in embryonic development before BBB formation (Ginhoux et al., 2010; Stremmel et al., 2018). In adulthood, microglia seem to promote self-renewal through a finely tuned region- and age-dependent balance between proliferation and apoptosis without additional recruitment of cells from the circulating monocytes (Askew et al., 2017). The density of microglial cells is approximately 7 % of total non-neuronal cells and it remains relatively similar among mammalian species (including rodents, carnivores, marsupials, and primates) and different brain structures, although such density may vary between cortical white and gray matter (Dos Santos et al., 2020).

Microglia are involved in several events such as inflammation, stroke, neurodegenerative diseases, brain homeostasis and cognitive processes, ultimately influencing animal behavior (Augusto-Oliveira et al., 2019; Augusto-Oliveira et al., 2022). Such extensive participation in both physiological and pathological processes in the nervous system reflects the great diversity of receptors that these cells express in their membranes, including receptors for neuromodulators, receptors for neurotransmitters and immunoreceptors (Garaschuk and Verkhratsky, 2019). The wide range of microglial receptors allows these cells to be highly sensitive to the brain environment and to orchestrate an appropriate response to any homeostatic disturbance (Colonna and Butovsky, 2017; Verkhratsky et al., 2021). For instance, by detecting a harmful stimulus, microglia can release chemical mediators that signal the recruitment and proliferation of new microglial cells, as well as phagocytosis of pathogens, injured cells, and/or cellular debris (Thameem Dheen et al., 2007; Shinozaki et al., 2019).

Microglia have idiosyncratic and highly varied morphology in both physiological and pathological contexts (Augusto-Oliveira et al., 2022). In the healthy brain, the predominant microglial state is the surveilling microglia, characterized by a small cell body and elongated, branched and mobile processes that constantly monitor the nervous environment, scanning the extracellular space and checking the functioning of adjacent cells, ready to respond to the smallest disturbances (Augusto-Oliveira et al., 2022). By detecting disturbances in CNS homeostasis, microglia undergo a shift from surveillance to a reactive state, in which they may present a less complex morphology, characterized by shortening and thickening of the processes and a wider cell body (Sierra et al., 2016). The morphology of this reactive microglia may also vary according to the type, intensity, and region of the disease or injury, in which their morphologies are associated with distinct gene expression profiles (Paolicelli et al., 2022).

The transcriptional profile of human microglia is quite heterogeneous compared to that of other species, although many primate species retain a central gene program typical of microglia (Geirsdottir et al., 2019). The combined analysis of single-cell techniques (RNA sequencing and mass cytometry) revealed that the microglial transcriptional profile is brain region-, age-, disease-dependent (Sankowski et al., 2019, Y.L. Tan et al., 2019, Augusto-Oliveira et al., 2022). In the healthy CNS, molecular profile of microglia is based on a region-dependent spectrum of expression of microglia-specific genes such as ionized calcium-binding adapter molecule 1 (Iba-1), purinergic receptor P2YR12, transmembrane protein 119 (TMEM119) and colony-stimulating factor receptor (CSF1R) (Sankowski et al., 2019). In the pathological CNS, the

microglial molecular profile is based on a context-dependent spectrum of microglial genes expression including, but not limited to, TREM2, APOE, CD11c, CD68, CD86, CD45, CX3CR, CD16 and CD32 (Böttcher et al., 2018; Hoshi et al., 2019; Paolicelli et al., 2022).

4.2. Microglia in MeHg intoxication

It is well established that microglia are involved in mercury toxicity (Garg and Chang, 2006; Sakamoto et al., 2008) and, similar to astrocytes, microglia tend to accumulate intracellular MeHg which, when depleted of GSH, may generate oxidative stress and consequently cell death (Fig. 2) (Ni et al., 2011). Recently, it was discovered that, as astrocytes, microglia also express LAT1 in their membrane, which allows them to capture and accumulate MeHg (Huttunen et al., 2019). Another aspect similar to astrocytes is that microglia express antioxidant genes such as hemeoxygenase-1 (Ho-1), cysteine/glutamate transporter (xCT), and quinone oxidoreductase-1 (Nqo-1) that encode detoxifying proteins from Nrf-2 activation (Ni et al., 2011; Jimenez-Blasco et al., 2015). Even non-toxic doses of MeHg can elicit reactivity in both microglia (Charleston et al., 1994; Lapham et al., 1995) and astrocytes (Freire et al., 2020).

Despite the similarities, microglia respond more quickly to MeHg than astrocytes. For example, in vitro microglial Nrf-2 upregulation occurs 1 min after MeHg exposure and Nrf-2 nuclear translocation is detected after 10 min of treatment, whereas, in astrocytes, the Nrf-2 upregulation takes 6 h of exposure to be evident, in addition to requiring higher MeHg concentration (Ni et al., 2011). The early microglial response to MeHg may be related to its greater ability to store MeHg, generate more ROS, and lower basal GSH level compared to astrocytes (Ni et al., 2011).

In addition, microglia may interact with astrocyte and promote a joint response to MeHg. In 3-D cultures of brain cells treated with MeHg, reactive microglia-astrocytes interaction increases local IL-6 release, triggering astrocytic reactions which may protect neurons against MeHg toxicity (Eskes et al., 2002). Interleukin-6 neuroprotection has been previously reported in hippocampal neurons against cell death induced by glutamatergic excitotoxicity (Yamada and Hatanaka, 1994). Also, the release of other cytokines such as arginase-1 and IL-10 by microglia has already been reported to promote the restoration of MeHg-induced axonal degeneration (Fig. 2) (Fujimura et al., 2019).

Chemokines release may also be involved in the microglial response to MeHg. The chemokines CCL3 and CCL4, also known as macrophage inflammatory proteins 1α and 1β, respectively (Gamo et al., 2008), are synthesized and released in the CNS by glia (Simpson et al., 1998) and target the CCR1 and CCR5 chemokine receptors (Ren et al., 2010). In the MeHg-exposed mouse brain, the expression of CCL3 and CCL4 genes is upregulated, which can mediate MeHg-induced CNS damage (Kim et al., 2013). Some transcription factors activated by lipopolysaccharides (LPS) and hydrogen peroxide, such as NF-kB, are involved in the CCL4 expression, while other transcription factors are also playing their role in this process (Takahashi et al., 2018). It is presumable that the CCL4 expression is induced by MeHg because of the activation of those other transcription factors, as a cell protective response to MeHg exposure, decreasing neuronal damage. Further studies are necessary to better understand the role of microglial chemokines in MeHg intoxication.

Microglial response via inflammatory mediators such as TNF-α, interleukins, and chemokines can promote repair of injured tissue or exacerbate the injury depending on the context (Kettenmann et al., 2011; Augusto-Oliveira et al., 2019; Verkhratsky et al., 2021). For instance, the MeHg-induced reactive microglia state may lead to neurodegeneration and neuronal damage through the microglial release of inflammatory mediators via Rho-kinase (ROCK) signaling (Fig. 2) (Shinozaki et al., 2019). Different pathways may be involved in ROCK activation in microglia, such as MeHg-mediated caspase-3 activation or arachidonic acid release with downstream prostaglandin induced by MeHg (Shinozaki et al., 2019). Blockade of ROCK signaling by inhibitors (Y-27632 and Fasudil) restores axonal degeneration and prevent neuronal cell death by inducing a "protective" microglial phenotype characterized by decreased TNF-α, inducible nitric oxide synthase (iNOS), IL-1β, and IL-6 expression and increased arginase-1 activity and IL-10 expression (Fujimura et al., 2019). Furthermore, through the ASK1/p38MAPK signaling pathway, MeHg-induced mitochondrial ROS formation might promote microglial TNF-α release and, consequently, neuronal cell death (Toyama et al., 2021).

Interestingly, the dose and duration of exposure modulate the outcomes of microglial reactivity in MeHg intoxication (Shinozaki et al., 2014, 2019). Low MeHg concentration (2 ng/mL) conjugated to human serum albumin (MeHg-HSA) promotes cell proliferation, high levels of nitric oxide (NO) and intracellular calcium in N9 microglia cell line, besides to suppressing the inflammatory mediators (TNF-α and IL-1β, among others) release, preventing cytotoxicity; otherwise, higher dose (2 μg/mL) of MeHg-HSA increases the TNF-α and IL-1β release from N9 microglia, causing cell death (Q. Tan et al., 2019). Further, in microglial BV-2 cell line, acute treatment with high MeHg concentration (10 μM) induces necrotic-like cell death and suppression of IL-6 and TNF-α (Martins et al., 2022). However, low MeHg concentration treatment (100 nM), for 24 h, stimulates a neuroprotective microglial state (Shinozaki et al., 2014). Interestingly, the chronic exposure to the same MeHg dose induces neurotoxic microglial state (Shinozaki et al., 2019). Indeed, acute exposure to high doses and chronic exposure to relatively low doses can lead to microglial inflammatory response, motivating distinct microglial inflammatory responses, which in turn, can either prevent or mitigate damage to neurons or aggravate previous pathological events and cause harmful effects on neurons (Thameem Dheen et al., 2007; Toyama et al., 2021; Martins et al., 2022).

The role of microglial cytokines and chemokines in MeHg-induced toxicity is hardly understood and the literature has shown different results in under different conditions (Table 1). Several aspects such as the animal/in vitro model, duration of exposure, and dose may interfere with the outcome of the microglial response to MeHg intoxication, being imperative that these features must be selected according to their translational meaning (Crespo-Lopez et al., 2022a,b).

5. Conclusion

In this review, we discuss the involvement of two glial types, astrocytes and microglia, in MeHg-induced neurotoxicity and highlight the similarities and differences between the protective and deleterious roles played by these cells. It is evident the massive involvement of astrocytes and microglia in pathophysiological responses to MeHg intoxication, although the exact microglial and astrocytic components and mechanisms driving the diversity of glial responses to MeHg neurotoxicity are just beginning to be understood. Noteworthy, particularities such as context, time and dose of exposure, brain region, and species seem to drive the way of glial cells response to MeHg intoxication. Finally, further investigations on glial involvement in MeHg intoxication to decipher such particularities can pave the way to better understand how MeHg affects the CNS and to develop new mitigating therapies to MeHg-induced neurotoxicity.

CRediT authorship contribution statement

Caio Gustavo Leal-Nazaré: Writing – review & editing, Writing – original draft, Conceptualization. **Gabriela P. Arrifano:** Writing – review & editing, Funding acquisition. **Amanda Lopes-Araújo:** Writing – review & editing. **Leticia Santos-Sacramento:** Writing – review & editing. **Jean Ludger Barthelemy:** Writing – review & editing. **Isabela Soares-Silva:** Writing – review & editing. **Maria Elena Crespo-Lopez:** Writing – review & editing, Funding acquisition. **Marcus Augusto-Oliveira:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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3. ARTIGO 2: O EXERCÍCIO REMODELA O CÉREBRO: ALTERAÇÕES MOLECULARES, CELULARES E ESTRUTURAIS ASSOCIADAS A MELHORIAS COGNITIVAS

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Exercise Reshapes the Brain: Molecular, Cellular, and Structural Changes Associated with Cognitive Improvements

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Abstract
Physical exercise is well known as a non-pharmacological and holistic therapy believed to prevent and mitigate numerous neurological conditions and alleviate ageing-related cognitive decline. To do so, exercise affects the central nervous system (CNS) at different levels. It changes brain physiology and structure, promoting cognitive improvements, which ultimately improves quality of life. Most of these effects are mediated by neurotrophins release, enhanced adult hippocampal neurogenesis, attenuation of neuroinflammation, modulation of cerebral blood flow, and structural reorganisation, besides to promote social interaction with beneficial cognitive outcomes. In this review, we discuss, based on experimental and human research, how exercise impacts the brain structure and function and how these changes contribute to cognitive improvements. Understanding the mechanisms by which exercise affects the brain is essential to understand the brain plasticity following exercise, guiding therapeutic approaches to improve the quality of life, especially in obesity, ageing, neurodegenerative disorders, and following traumatic brain injury.

Keywords Physical activity · Memory · Neuroinflammation · Alzheimer's disease · Adult neurogenesis · Brain volume · Cerebral blood flow

Introduction

Exercise, different from physical activity (any bodily movement produced by skeletal muscles), is a planned and structured physical activity purposefully focused on improvement or maintenance of physical fitness, which is a set of attributes either health- or skill-related [1]. Exercise impacts the whole body and affects the central nervous system in many ways (Fig. 1); it increases the heart rate thus pumping more oxygen to the brain, and induces hormonal, growth factor and inflammatory mediators release, besides brain structural changes; all these effects reflect neuroplasticity, which is intimately associated with cognitive improvements. Cognition is widely defined as a set of mental processes involved in acquiring knowledge and handle it through perceiving, recognising, understanding, and reasoning, which eventually leads to changes in behaviour.

Animal studies mainly provide information about exercise-induced cellular and molecular changes, which are associated with cognitive functions (Fig. 2). These changes include synaptogenesis [2], angiogenesis [3], adult neurogenesis [4], and inflammatory response [5], which are associated with cognitive performance as assessed by numerous behavioural tasks. In human studies, exercise effects on CNS and cognition are mainly associated with brain structural changes (i.e. volume) and modulation in serum growth factors [6]. However, it is important to consider that some exercise protocol details such as duration and intensity have contradictory effects on CNS. Also, the exact molecular signalling pathways underlying this modulation promoted by exercise have not yet been defined, as well as how this might impact brain function and neurodegenerative diseases prevention and treatment.

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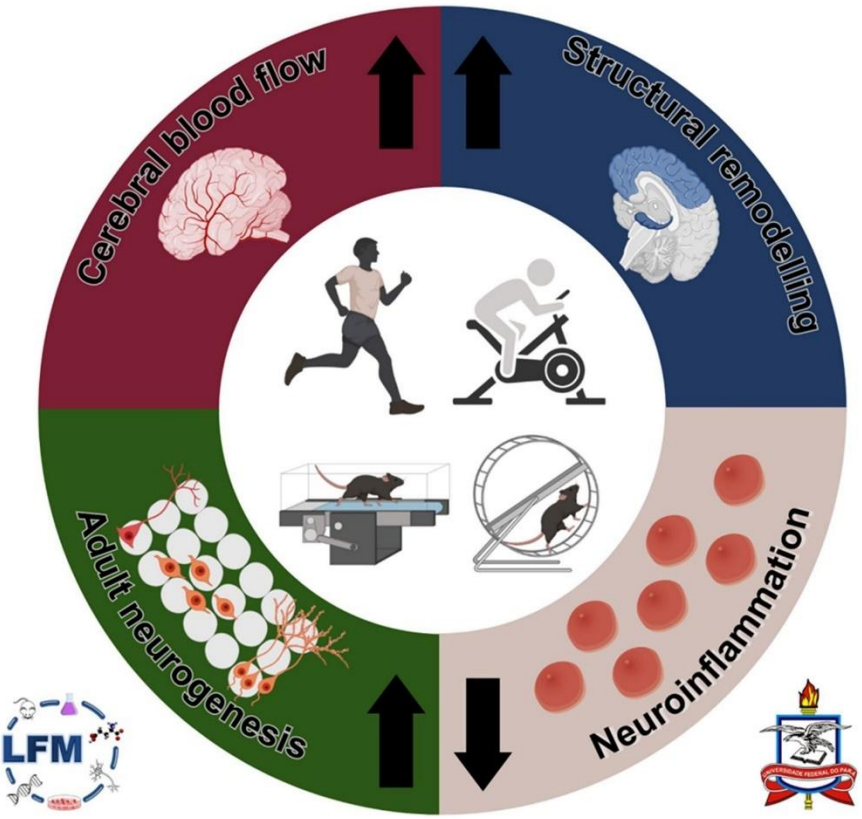

Fig. 1 Effects of exercise on brain cellular, molecular, and structure. Exercise is believed to positively impact the brain, being recommended as an adjuvant polytherapy for several neurological conditions both for preventing and mitigating them. As a potent stimulus, exercise modulates brain functions through molecular, cellular, and structural changes ultimately affecting cognition. Created with Biorender

We shall start our narrative by analysing how exercise affects brain physiology due to the cellular and molecular changes (influencing adult neurogenesis and inflammatory status) and alterations of cerebral blood flow, associated with improved cognitive processes (Table 1). Additionally, we discuss how exercise affects structural reorganisation of different brain areas and the association between this structural reorganisation and cognitive performance in humans. Finally, we briefly ponder on how future studies could circumvent potential pitfalls that could bias the conclusions, making it difficult both accurate interpretation and replication of results.

Exercise-Induced Cellular and Molecular Changes Influencing Cognitive Performance

Exercise Modulates Adult Hippocampal Neurogenesis and Cognition

Among the most challenging cellular changes induced by exercise, adult neurogenesis arises as an important event with therapeutic applications associated with cognitive improvements. As we shall see bellow, exercise-induced adult neurogenesis is controlled by a series of growth factors, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF), and is positively associated with several aspects of cognition including different types of memory, learning, and executive functions.

Adult neurogenesis occurs in all species investigated so far, from fishes to mammals, with some debate considering its extent and function in humans [32]. Neurogenesis in the adult brain is strongly associated with cognitive improvements specially learning and memory processes [33]. The generation, survival, and integration of new neurons into pre-stablished circuits are complex events which depend on favourable environment and are profoundly influenced by exercise.

Initially, it was shown that enriched environment, with all its inherent aspects such as social interaction, learning tasks, inanimate stimuli, and exercise, induced adult neurogenesis [34]. Later, by separating elements from enriched environment, it was possible to demonstrate that voluntary exercise alone is sufficient to increase cell proliferation and survival of new neurons in the dentate gyrus (DG) of mice [35]. To assess rather accurately the influence of exercise on adult neurogenesis, mice were housed in four groups in cages with

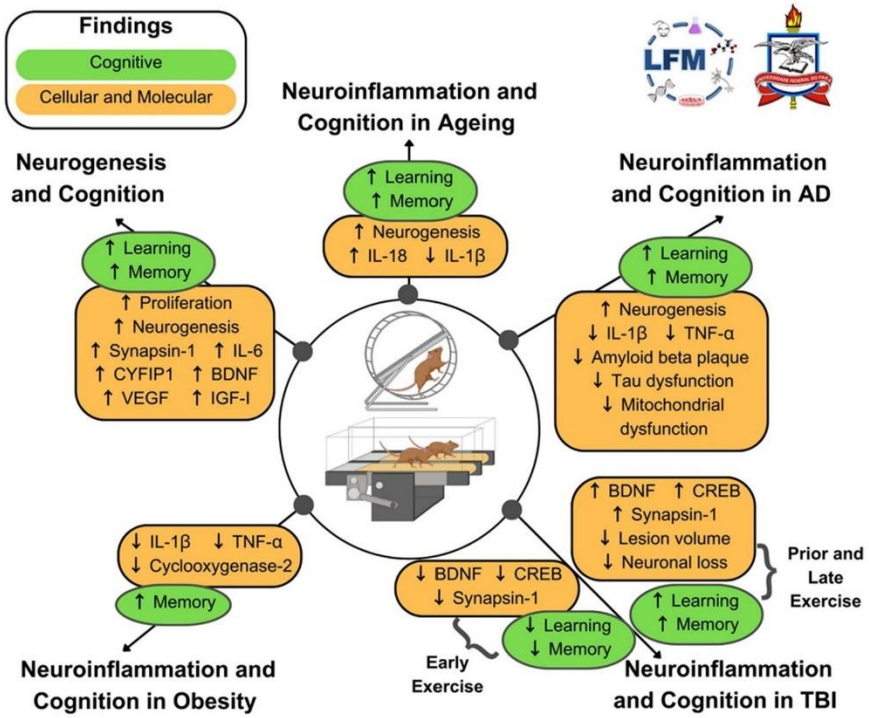

Fig. 2 Exercise-induced molecular, cellular, and cognitive changes in experimental models. Exercise induces increase or decrease of several molecules involved in cognitive functions according to experimental models. In ageing, exercise improves cognition through increased neurogenesis, IL-18 and decreased IL-1β. In AD models, exercise induces a reduction of Aβ plaques, Tau dysfunction, mitochondrial dysfunction, IL-1β, and TNF-α, besides to increase neurogenesis improving cognition. Following TBI, early exercise (performed in early stage after lesion) reduces BDNF, CREB, and Synapsin-1, contributing to cognitive deficits. On the other hand, prior (performed before de lesion) or late (beginning late after lesion) exercise increases the expression of these molecules, besides to reduce neuronal loss and lesion volume, contributing to cognitive improvements. In obesity models, exercise reduces IL-1β, TNF-α, and cyclooxygenase-2, contributing to cognitive improvements. Finally, exercise seems to positively impact adult neurogenesis through several molecules including VEGF, BDNF, IGF-1, IL-6, and Synapsin-1, which is associated with improved cognition. Created with Biorender

the same size: control, running (standard cage plus running wheel), and enriched environment with and without running wheels. Only groups with exercise available displayed increased cell proliferation, neuron survival, and neurotrophin levels, thus suggesting exercise as an essential mediator of BDNF levels and adult hippocampal neurogenesis [36].

Either controlled or voluntary exercise in running wheels enhances both adult hippocampal neurogenesis and memory process [37]. By increasing adult neurogenesis and reorganising new neurons in pre-existing neural circuitry, exercise impacts cognitive processes such as improvements in contextual, spatial, and temporal information [38]. In ageing mice, improved cognition such as spatial learning following voluntary exercise (running wheels for 21, 35, and 49 days) occurs due to DG connectivity, particularly DG-Cornu Ammonis 3 and the DG-medial entorhinal cortex connections in the dorsal hippocampus, which is dependent on neurogenesis [8]. Short-term running wheel exercise (running wheels for 5 days) can reorganise circuits of 1-week old adult neurons, influencing their numbers, morphology, and excitatory synaptic inputs [39]. More recently, it was found that these morpho-functional changes in newborn granule neurons are long-term and result in enhanced synaptic plasticity [40]. Also, chronic exercise (running wheels for 3–4 weeks) accelerates 3 weeks old neuron development in aged mice, impacting neuron born at the onset, during and in the end of exercise period [41].

These important effects of exercise in the adult neurogenesis seem to be mainly mediated by neurotrophic factors including BDNF, IGF-1, and VEGF [42], which are increased by exercise in both rodents and humans and associated with the improvements in cognitive processes including faster reaction time, better attention, learning, and memory [43, 44]

BDNF is primarily synthesised during the exercise through PGC-1α/FNDC5 pathway [45]; it is essential to hippocampal exercise-mediated neurogenesis, synapse plasticity, and cognitive improvements by regulating critical

Table 1 Exercise-induced molecular, cellular, and cognitive changes in experimental models

Brain area	Specie	N	Mean age	Physical activity tests	Physical activity	Duration	Cognitive tests	Molecular and cellular findings	Cognitive findings	Reference
Neurogenesis and cognition										
Dentate gyrus	C57Bl/6 mice	50	8 weeks	Running wheel	Voluntary and controlled exercise	14 days	Water maze	Increased neurogenesis	Improved spatial memory performance	[7]
Dentate gyrus	C57Bl/6 mice		24 months	Running wheel	Voluntary exercise	21, 35, or 49 days	Active place avoidance	Grater hippocampal volume and increased neurogenesis-dependent dentate gyrus connections	Improved spatial learning	[8]
Dentate gyrus	Wistar rats	~72	10 weeks	Treadmill running (high-intensity intermittent/interval (HIIT) and moderate-intensity continuous (MICT))	Controlled exercise	4 weeks	Water maze	Increased neurogenesis and protein levels of BDNF signalling	Improved spatial memory	[9]
Dentate gyrus	5×FAD APP/PS1 doubly transgenic mice	_	6–8 weeks	Running wheel	Controlled and Voluntary exercise	3 h	Delayed non-matching to place/eight-arm radial arm maze/Y-maze	Exercise-induced neurogenesis increased levels of BDNF, IL-6, FNDC5, and synaptic markers	Improved memory	[10]
Dentate gyrus	Sprague Dawley rats	62	1 week	Running wheel	Controlled exercise	3 weeks	Open field test/water maze	Increased neurogenesis and BDNF–pCREB signalling in the sham irradiation	Prevented radiation-induced cognitive deficits and increased hippocampus-dependent learning and memory	[11]
Dentate gyrus	C57/BL6 mice and IGF-I deficient mutant mice	30	3 months	Treadmill running	Controlled exercise	4 weeks	Morris water maze	There was no improvement in impaired neurogenesis in mutant mice	Improved spatial learning	[12]

Table 1 (continued)

Brain area	Specie	N	Mean age	Physical activity tests	Physical activity	Duration	Cognitive tests	Molecular and cellular findings	Cognitive findings	Reference
Dentate gyrus, CA1, and CA3	Sprague Dawley rats	28	_	Running wheel	Voluntary exercise	5 days	Morris maze	Selectively increased IGF-I mRNA levels and proteins levels of BDNF and its precursor (pro-BDNF)	Improved memory	[13]
Hippocampus	Rats	_	_	Treadmill running	Controlled exercise	6 weeks	Morris water maze	Increased VEGF levels in muscle fibres. Reduced both SOD and MDA levels in muscle fibres	Improved learning and memory	[14]
Dentate gyrus, CA1 and visual cortex	Long Evans rats	24	40 days	Running wheel	Voluntary exercise	10 days	Object displacement/object replacement tests	Prevented neuronal apoptosis	Prevented impairment in spatial and visual memory	[15]
Ischemic penumbra	C57BL/6 mice	84	_	Treadmill running	Controlled exercise	7 and 14 days	Eight-arm radial arm maze	Increased expression of caveolin-1, VEGF, BDNF, synapsin I, and CYFIP1. Improved synaptic morphology	Improved spatial learning performance	[16]
Dentate gyrus	C57BL/6 mice	_	8 weeks	Treadmill running	Controlled exercise	6 weeks	Eight-arm radial arm maze	Moderate exercise increased cell proliferation, survival, neuronal differentiation, and migration. Intense exercise promoted neuronal differentiation and migration, as well as lower expressions of VEGF, BDNF, IGF1, and erythropoietin	Moderate exercise improved the performance in spatial pattern separation	[17]

Table 1 (continued)

Brain area	Specie	N	Mean age	Physical activity tests	Physical activity	Duration	Cognitive tests	Molecular and cellular findings	Cognitive findings	Reference
Hippocampus	C57BL/6 J mice	_	24 months	Running wheel	Voluntary exercise	7, 21, 28, 35, 42, and 49 days	Active place avoidance/ barnes maze	Increased GH hormone levels and neurogenesis	Exercise in specific duration (35 days) reversed the learning deficit in aged	[18]
Neuroinflammation and cognition in ageing										
Ventral hippocampi and frontal cortices	Fischer 344 rats	6	18 months	Running wheel	Voluntary exercise	12 weeks	Water maze/ inhibitory avoidance	Increased neurogenesis and IL-18 and GRO-KC levels. Decreased IL-1β expression and serum leptin along with serum MCP-1 (CCL2) levels	Improved learning and memory performance	[19]
Hippocampus and cortex	C57BL/6 mice	_	4 and 18 months	Treadmill running	Controlled exercise	10 days	Object displacement/object replacement tests	Prevented the increase in microglial glycolysis, glycolytic capacity and PFKFB3, as well as decreased β-galactosidase and p16INK4A expression	Improved spatial memory performance	[20]
Hippocampus	Mice	_	3 and 18 months	Running wheel	Voluntary exercise	6 weeks	Radial-arm water maze/ contextual fear conditioning	Increased neurogenesis and plasma concentration of the liver enzyme Gpld1	Improved learning and memory performance	[21]

Table 1 (continued)

Brain area	Specie	N	Mean age	Physical activity tests	Physical activity	Duration	Cognitive tests	Molecular and cellular findings	Cognitive findings	Reference
Neuroinflammation and cognition in Alzheimer's disease										
Hippocampus	APP/PS1 double-transgenic mice and C57BL/6 mice	6	3 months	Treadmill running	Controlled exercise	12 weeks	Morris water maze/novel object recognition	Inhibited Aβ generation and delayed microglia-associated Aβ deposition. Suppressed the "pro-inflammatory" microglial state and supported the "anti-inflammatory"	Prevented deficits in spatial learning and memory	[22]
Hippocampus and cortex	Triple transgenic AD (3xTg-AD) mice	10	3 months	Treadmill running	Controlled exercise	12 weeks	Morris water maze/passive avoidance	Decreased levels of Aβ plaque burden and neuroinflammation and mitochondrial dysfunction, as well as increased neurogenesis	Improved performance in spatial learning and memory	[23]
Hippocampus and prefrontal cortex	Triple transgenic AD (3xTg-AD) mice	16	9 months	1-m ladder	Controlled exercise	4 weeks	Y-maze/novel object recognition	Decreased levels of Aβ plaque, hyperphosphorylated tau deposits, and TNF-α level	Improved performance in recognition and memory	[24]
Hippocampus	Tg2576 mice and C57Bl6/SJL mice	12	16–18 months	Running wheel	Voluntary exercise	3 weeks	Radial-arm water maze	Reduced levels of TNF-α and IL-1β, as well as increased IFN-γ, CD40, MHC II, CD11c, and MIP-1α markers. Decreased soluble Aβ40 and soluble fibrillar Aβ	Improved spatial learning	[25]

Table 1 (continued)

Brain area	Specie	N	Mean age	Physical activity tests	Physical activity	Duration	Cognitive tests	Molecular and cellular findings	Cognitive findings	Reference
Hippocampus	Tg2576 mice and C57Bl6/SJL mice	6	15–19 months	Running wheel	Voluntary exercise	3 weeks	Radial-arm water maze	Increased CXCL1 and CXCL12 markers	Improved spatial learning	[26]
Neuroinflammation and cognition following traumatic brain injury (TBI)										
Hippocampus	Sprague Dawley rats	72/2	_	Running wheel	Voluntary exercise	0–6 days post-TBI and 14–20 days post-TBI	Water maze	Late exercise increased BDNF, CREB and synapsin1 levels, while early exercise decreased CREB and synapsin1 levels	Late exercise improved learning and memory performances, while early exercise impaired learning and memory performances	[27]
Hippocampus	C57BL/6 mice	_	10 weeks	Running wheel	Voluntary exercise	4 weeks beginning at 1 week and 5 weeks post-TBI	Morris water maze/reversal morris water maze/open field/novel object recognition/tail-suspension	At 5 weeks post-TBI decreased lesion volume but not at 1 week post-TBI	5 weeks post-TBI decreased working and retention memory impairment	[28]
Hippocampal subregions, cortex, and thalamus	C57BL/6NT mice	23	10 weeks	Running wheel	Voluntary exercise	4 weeks prior to TBI	Morris water maze/reversal morris water maze/open field/novel object recognition/tail-suspension	Decreased lesion volume, neuronal loss, microglial activation, and key apoptotic pathways	Improved learning and memory performance	[29]

Table 1 (continued)

Brain area	Specie	N	Mean age	Physical activity tests	Physical activity	Duration	Cognitive tests	Molecular and cellular findings	Cognitive findings	Reference
Obesity-induced neuroinflammation and cognition										
Hippocampus and cerebral cortex	Sprague Dawley rats	10	20 weeks	Treadmill running	Controlled exercise	8 weeks	Passive avoidance	It cancelled the increase in TNF-α and IL-1β and cyclooxygenase-2 levels induced by the high-fat diet. It upregulated Bcl-2 expression and suppressed Bax expression	Improved working memory	[30]
Hippocampus and cerebral cortex	C57BL/6 J (B6) mice	–	2–12 months	Running wheel	Voluntary exercise	15 days	Open field/ spontaneous alternation/ novel spatial recognition	Prevented white matter damage and neuroinflammation	Prevent working memory déficit	[31]

steps such as differentiation and neuronal survival [46]. Importance of BDNF to adult neurogenesis and associated cognitive performance such as learning and memory was demonstrated by numerous models including BDNF knockdown [47] and ablation of the gene encoding high-affinity receptor for BDNF (tropomyosin kinase receptor B, TrkB) in the hippocampus [48], both models resulting in disrupted adult neurogenesis and memory deficits. Recently, rats exposed to moderate- and high-intensity intermittent exercise for 4 weeks showed increased hippocampal neurogenesis, enhanced protein levels of hippocampal BDNF, and improved spatial memory, suggesting that exercise-induced neurogenesis and cognitive improvements are associated with BDNF signalling [9]. Interestingly, pharmacological induction of adult neurogenesis and elevated levels of BDNF mimicked the beneficial effects of exercise in cognitive function such as spatial pattern separation and retention memory in a mouse model of Alzheimer's disease (AD) [10].

In a rat model of whole-brain irradiation-induced cognitive impairment, running exercise (forced running for 3 weeks in a motor riven running wheel) induced both neurogenesis and cognitive improvements via BDNF-mediated pathway as quantified by open field and Morris water maze tests [11]. Of note, despite the link between BDNF, adult neurogenesis, and exercise in humans is not completely understood, studies demonstrate that aerobic exercise increases BDNF levels in diseased and normal individuals [49, 50], and indicate that BDNF mediates exercise-induced cognitive improvements including executive functions assessed by task-switch paradigm [51].

Besides BDNF, IGF-1 is critical to brain plasticity and adult neurogenesis. The main source of IGF-1 is outside of the brain and exercise is critical to its protective and plastic functions in the brain [52]. Circulating IGF-1 levels are quickly increased by exercise [53], which is essential for exercise-induced adult neurogenesis and cognitive processes. In fact, mutant mice with low levels of serum IGF-1 showed disrupted adult hippocampal neurogenesis and spatial memory deficits, which were not improved by exercise [12]. Interestingly, exogenous IGF-1 administration restored neurogenesis and ameliorated cognitive deficits in response to exercise [12]. One of the mechanisms underlying IGF-1-mediated adult neurogenesis involves the RIT1/Akt/Sox2 cascade [54]; disruption on Akt signalling impairs exercise-mediated adult neurogenesis and synaptic plasticity [55, 56]. Additional evidence indicates points of convergence between IGF-1 and BDNF signalling related to exercise effects on hippocampal plasticity, which could influence adult neurogenesis and cognition [42]. For instance, in response to exercise, BDNF signalling is potentiated by IGF-1, and exercise-induced BDNF signalling is inhibited following IGF-1 blockade, which reduces the expression of synaptic proteins [13].

Additionally, in cultured hippocampus, BDNF signalling is reinforced through IGF-1-induced neuronal levels of TrkB [57].

Furthermore, VEGF emerges as another neurotrophic factor influenced by exercise and necessary for exercise-induced adult hippocampal neurogenesis [58]. VEGF is an angiogenic factor with neurogenic functions both in vitro and in vivo, stimulating proliferation of adult hippocampal neurons through three distinct cascades, MEK/ERK- and P13K/Akt-dependent-, caveolin-1/VEGF, and VEGF-C/VEGFR-3 signalling [59–61]. Thus, VEGF signalling links hippocampal activity to neurogenesis, neuronal plasticity, learning and memory [62, 63], and exercise [64]. In fact, peripheral VEGF is required for hippocampal response to exercise [65], and blocking it from entering the brain inhibits exercise-induced adult hippocampal neurogenesis in mice [66]. Also, regular treadmill exercise (30 min daily, 3 days a week for 6 weeks) increased VEGF levels in both soleus and gastrocnemius muscles, which was correlated with hippocampal learning assessed by Morris water maze in rats [14]. Interestingly, in the mice brain, mRNA and proteins levels of VEGF are increased by exercise only in the hippocampus [67] and occur via lactate receptor HCAR1 [68].

Recent pharmacological approach in experimental models provides evidence that reinforces the role of VEGF on exercise effects. The pharmacological inhibition (oral application of a tyrosine kinase inhibitor) of VEGF signalling prevented the exercise-induced neurogenesis and visual and spatial memory improvements [69]. Similar findings were found in mice after ischemic injury; treadmill exercise (30 min/day, 5 days/week during 1 or 3 weeks) improved neurogenesis and cognitive function such as spatial learning abilities; these benefits were prevented by administration of selective VEGF receptor 2 (VEGFR2) inhibitor [16]. Of note, while fatiguing exercise induced only adult neurogenesis with no spatial discrimination and no changes in hippocampal levels of BDNF and VEGF, moderate exercise induced adult neurogenesis, increased levels of hippocampal BDNF and VEGF, and cognitive improvement as assessed by radial arm maze task [70], shedding some light on the need to investigate and normalise studies considering exercise protocols aiming at better understand the effects of exercise on cognition.

Beyond these three growth factors, exercise also modulates adult neurogenesis and cognition through modulation of growth hormone (GH) levels; the blockade of GH receptors or depletion of newborn neurons prevented exercise-induced cognitive improvement in aged female mice [18]. Noteworthy, these benefits of exercise only occur for a specific duration (35 days of exercise), with shorter (21 days) or longer periods (45 days) proving ineffective [18].

Exercise Modulates Neuroinflammation and Cognition

The inflammatory response occurring within the CNS is mainly mediated by cytokines and chemokines that are mostly produced by glial cells. The intensity of this response may vary according to the context, either physiological (i.e. ageing) or pathological (i.e. neurodegeneration, neurotrauma, obesity), and its duration has critical impacts on neurological outcomes [71]. Although short-term inflammation represents an essential role for orchestrating immune response aimed at CNS defence, sustained inflammatory response may contribute to tissue and cell damage and numerous associated deficits including cognitive impairments [72, 73]. Growing evidence supports exercise as an extrinsic modulator of inflammatory mediators that may contribute to prevent or mitigate cognitive decline in different contexts including normal ageing, ageing-related neurodegenerative diseases, neurotrauma, and obesity.

Exercise Modulates Neuroinflammation in Ageing

Ageing process is accompanied by a chronic low-grade inflammatory status known as "inflammageing", with upregulation of numerous "pro-inflammatory" mediators such as tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), ciclooxigenase 2 (COX-2), and inducible nitric oxide synthase (iNOS) to name a few [74]. The main source of these "pro-inflammatory" mediators in the aged brain are primed microglia, which are more responsive to immunological challenges and drive exaggerated neuroinflammatory response [75, 76]. Since cognitive ageing is intimately associated with neuroinflammation [77], reducing microglial reactivity is of particular importance to inhibit or mitigate ageing-related neuroinflammation and preserving cognitive processes.

In this context, exercise emerges as a contributor to modulate microglial reactivity inhibiting neuroinflammation by increasing the expression of "anti-inflammatory" mediators and decreasing the expression of "pro-inflammatory" mediators [78, 79]. For example, CD200, a neuronal immunoregulatory factor that inhibits microglial reactivity, and its ligand, microglial CD200R [80], are both increased by exercise (treadmill running) in the mouse brain [81]. In addition, exercise induces brain expression of IL-1Ra (antagonist of IL-1β) [82], which has higher affinity with IL-1R than IL-1β (a key player in immune dysregulation and cognitive vulnerability in ageing brain, mainly released by primed microglia) [83]. Thus, by interfering with IL-1β signalling, exercise may contribute to modulate neuroinflammation and improve cognition. In fact, aged rats showed reduced hippocampal IL-1β signalling, as well as improved memory processes following daily exercise for 12 weeks [19]. Besides the

reduction of ageing-related increase in hippocampal IL-1β expression (mRNA and protein), the number of senescent microglia and restoration of microglial metabolic homeostasis has been recently suggested as an alternative mechanism for the cognitive improvement assessed by novel object recognition and object displacement tests, which is associated with exercise in the aged brain [20].

Exercise also modulates peripheral inflammatory mediators, which influences neuroinflammation in elderly, thus modulating ageing-related cognitive decline [84]. For instance, in elderly individuals, 16 weeks of multimodal exercise was associated with decreased peripheral "pro-inflammatory" cytokines, increase in peripheral levels of BDNF, and improved cognition assessed by Montreal Cognitive Assessment test [85]. Interestingly, higher intensity of exercise and lower serum TNF-α levels were associated with greater total brain volume in older humans [86, 87], while sedentary older people displayed smaller lateral prefrontal cortex and hippocampus volume, and worse performance in cognitive tests, including Clock test, Mini-Mental State Examination test, and questionaries regarding memory, orientation, and executive functions, compared to physically active elderly [88]. In old mice, exercise-induced benefits on cognition seem to be mediated by liver-to-brain axis [21]. Plasma concentrations of glycosylphosphatidylinositol (GPI)-specific phospholipase D1 (Gpld1), an enzyme derived from liver, are high following exercise, and correlate with cognitive improvements. Of note, serum levels of Gpld1 were found increased in active, healthy elderly humans [21].

Finally, exercise seems to be determinant for successful ageing (determined by absence of depressive symptoms, disability, respiratory symptoms, systemic conditions such as cancer and coronary artery disease and cognitive impairment) [89], ultimately improving quality of life and well-being in elderly individuals [90].

Exercise Modulates Neuroinflammation and Cognition in Alzheimer's Disease

Exercise, as previously shown, is a well stablished anti-ageing holistic therapy inversely associated with risk for neurodegenerative diseases [91]. In line with this view, clinical studies have demonstrated that exercise is associated with reduced risk for dementia and AD among people over 65 years [92] and a widely recommended powerful strategy for preventing and combating AD [93]. Although its effects modulating neuroinflammation in AD are widely studied [94], the precise type, intensity, frequency, or duration of the exercise to be protective against AD remains to be better investigated [95]. It is important to note that neuroinflammation is a central characteristic of AD [96], with critical roles in AD brain such as in neuronal plasticity, hippocampal neurogenesis, and brain networking connectivity, essential for cognition [97–99]. In the AD context, exercise modulates neuroinflammation through numerous pathways including the expression of triggering receptor expressed on myeloid cells 2 (TREM2), an immunoglobulin receptor mainly expressed by microglia in the brain [100]. Soluble TREM2 plays a protective role against AD, suggesting the increase of soluble TREM2 as a potential therapy for AD [101]. Interestingly, 16 weeks of mild to moderate exercise (treadmill, stationary bike, cross training) was associated with increased soluble TREM2 measured in cerebrospinal fluid in AD patients [102].

Although animal models cannot accurately replicate human AD, a considerable body of experimental evidence has provided relevant information about the role of exercise in AD-induced pathophysiology [94, 103, 104]. For example, in an AD model using amyloid precursor protein (APP)/PS1 double-transgenic mice, 12 weeks of treadmill exercise reduced neuroinflammation as quantified by decreased inflammatory mediators such as TNF-α and IL-1β, reduced amyloid beta accumulation in the hippocampus, and preserved cognitive function assessed by Morris water maze and novel object recognition tests [105]. Using another AD mouse model (3xTg mice), treadmill exercise for 12 weeks induced a reduction of amyloid beta plaque burden, hyper-phosphorylated tau, neuroinflammation, and increased cognitive performance assessed by Morris water maze and passive avoidance tests [23]. Similar results were found applying a shorter exercise training (4 weeks) in the same 3xTg mice model of AD; exercise led to a reduction of amyloid beta and hyperphosphorylated tau deposits, down-regulation of TNF-α in the prefrontal cortex, and upregulation of "anti-inflammatory" interleukin 10 (IL-10) in the hippocampus, besides improved cognitive performance in Y-maze and novel object recognition tests [24].

Even short-term exercise was able to reduce neuroinflammation and improve cognitive functions in an AD model; 3 weeks of running wheel reduced hippocampal levels of TNF-α and IL-1β in the Tg2576 mouse model as compared to wild type mice levels, a response coincident with improved cognition assessed by radial-arm water maze, reference/long-term, and working short-term memory tests [25]. In addition, the same exercise program in the same model resulted in an altered neuroinflammatory profile with increased mRNA levels of CXCL1 and CXCL12, molecules involved in neuroprotection against hippocampal amyloid beta, and neuron-glia/neuron-neuron communication, respectively [26]. Furthermore, this exercise program improved spatial memory in these transgenic animals as compared to sedentary controls [26]. Taking these data together, exercise is highly recommended as a beneficious adjuvant for preventing and combating AD-associated cognitive dysfunctions.

Noteworthy, considering exercise effects on neurodegenerative diseases, this review focuses on AD since it is the most common neurodegenerative disease worldwide. In fact, about 6 million people live with AD only in the USA [106]. However, it is important to note that exercise positively affects cognitive functions in many other neurodegenerative diseases. In Parkinson's disease (PD), for example, a recent systematic review of randomised controlled trials has found that exercise promotes significant cognitive improvements in PD patients, including cognitive function, processing speed, sustained attention, and mental flexibility [107]. Additionally, it was found that treadmill exercise (60 min, 3 times a week for 24 weeks) promoted the best results on cognitive functions of PD patients [107]. In multiple sclerosis (MS), an autoimmune and neurodegenerative disease, exercise also seems to positively impacts cognitive functions; a recent systematic review of randomised trials recommends that MS patients be engaged in multimodal exercise, at least 3 times a week for best results in cognitive functions [108]. Also, they found that a worse basal MS status, or the older the patients, the greater effect on cognitive function [108]. In other neurodegenerative diseases such as Lewis body dementia (LBD), much less is known about how exercise affects cognitive functions. In fact, the first trial investigating exercise effects on cognition in individuals diagnosed with LBD was recently published [109]. This study showed that exercise promoted improvements in cognition and functional independence in participants, although the authors recognise that further studies with larger samples and high-quality trials are necessary for further evaluation of exercise as potential non-pharmacological intervention [109]. Future experimental and clinical studies should investigate mechanistic aspects of exercise and potential cognitive and behavioural improvements in neurodegenerative diseases.

Exercise Modulates Neuroinflammation and Cognition Following Traumatic Brain Injury

Traumatic brain injury (TBI) is a non-degenerative and non-congenital insult to the brain and is recognised as a global public health problem, with a high incidence of neurological disorders. Despite the causal relationship not being entirely known, it has been suggested that neuroinflammatory response exacerbates the TBI-induced pathophysiology leading to physical and neurological conditions including cognitive deficits [110].

In this scenario, microglia seem to be the main player in TBI-associated neuroinflammation through release of numerous inflammatory mediators, driving progressive lesion expansion, loss of myelin, neurodegeneration, and cognitive disfunction [111, 112]; microglial deletion, 1 month after TBI, to remove chronically reactive hypertrophic microglia and subsequent repopulation by ramified microglia, resulted in reduced neuroinflammation, neurodegeneration, and improved cognition in rats [113]. In this scenario, exercise exerts important roles following TBI by modulating microglial reactivity [78] and neuroinflammatory status, which is a determinant for neurological outcomes and ultimately the quality of life. Interestingly, the timing of exercise initiation seems to be critical for some neurological outcomes. In contrast to late intervention, it has been long suggested that exercise intervention administered too soon following TBI may increase brain damage and the odds of adverse outcomes [114]. In fact, while late exercise (14–20 postinjury days) induced an increase of BDNF, cyclic adenosine monophosphate response element-binding protein (CREB) synapsin 1 levels and recovered cognitive function assessed by water-maze training in rats, early initiation of exercise (0–6 postinjury days) induced a decrease of CREB and synapsin 1 levels besides impaired cognitive performance in learning and memory tests [27].

The neuroinflammatory response following TBI, which is initially aimed at defending the brain tissue and physiology, is further exacerbated and to a large extent responsible for sustaining secondary brain damage, neurodegeneration, and cognitive deficits in the TBI prognose [115, 116]. Therefore, preventing the secondary inflammatory phase rather than avoiding the first phase would be at the core of the beneficial effect of exercise in TBI. In mice, late exercise beginning at 5 weeks (not early — 1 week) after TBI reduced deficits in working and retention memory; this cognitive improvement was associated with modulation of inflammatory cascades and neurogenesis [28]. Late exercise also reduced microglial reactivity resulting in decreased levels of "pro-inflammatory" TNF-α and increased levels of "anti-inflammatory" IL-10 [28].

Additionally, late exercise led to increased BDNF, IGF-1, and CREB gene expression, besides increased hippocampal neurogenesis compared to control animals [28]. In contrast to late exercise, early exercise (1 week) increased microglial reactivity and associated inflammatory responses, failing in rescue cognitive outcomes as assessed by Morris water maze and reversal Morris water maze tests [28].

Reinforcing regular active lifestyle, pre-conditioning training seems to be efficient for preventing neuroinflammation following TBI. Rats exposed to 4 weeks of running before TBI displayed reduced neuroinflammation and were protected against motor deficit [117]. In a shorter model of pre-conditioning (voluntary running during 3 weeks before TBI), exercise positively modulated neuroinflammation by increasing mRNA expression of anti-inflammatory markers and decreasing mRNA expression of "pro-inflammatory" markers [118]. In addition, using a similar model of preconditioning, exercise activated multiple antiapoptotic pathways improving synaptic plasticity and cognitive function [29]. From a metabolic point of view, experimental data

revealed that favourable changes in the hepatic oxidative-inflammatory status elicited by exercise exerted prophylactic effects on acute hyperglycaemia and cerebral inflammatory response induced by severe TBI [119].

An important pathway by which exercise modulates neuroinflammation following TBI seems to be through IL-6 release. In fact, compelling evidence suggests beneficial effects of IL-6 release following TBI [120, 121]. The release of this interleukin is closely related to the duration of the exercise and can reach up to fivefold the basal levels after exercise in the human brain [122]. Brain release of IL-6 is usually followed by "anti-inflammatory" events such as production of IL-1Ra and IL-10 [123], while deficiency of IL-6 is associated with increased levels of IL-1β and cognitive dysfunction, with poor behavioural performance as assessed by open field, rotarod and NeuroScreen tests in mice following TBI [124]. All in all, regular exercise or late intervention would be essential for both prevention and mitigation of TBI-induced neuroinflammation and related adverse outcomes including motor and cognitive aspects.

Exercise Modulates Obesity-Induced Neuroinflammation and Cognition

Exercise has long been known as an efficient tool for weight control in overweight and obese individuals, being instrumental to prevent and treat different levels of obesity [125–127]. Systematic reviews have revealed cognitive dysfunction in obese adults, including attention, memory, and decision making, among others [128, 129]. The most recent systematic review and meta-analysis reveals that exercise improves numerous domains of cognition including working memory, cognitive flexibility, and nonverbal and spatial ability in both obese children and adolescents [129]. These beneficial effects can be extended to obese adults [130] and elderly, ultimately improving quality of life [131]. Of note, exercise also improves cognition, as assessed by several neuropsychological tests, in obese elderly with metabolic syndrome [132] and glucose intolerance [133], both risk factors for dementia.

Experimental evidence in rodent suggests potential mechanisms underlying beneficial effects of exercise on cognition in obesity, with a central role for inflammation. Obesity has been classically considered an inflammatory condition [134], which has been recently linked to alterations in microbiota [135]. Obesity-associated systemic inflammation drives hypothalamic inflammation, which causes dysfunctional hypothalamic outputs to other parts of the brain eventually associated with cognitive dysfunction (Reviewed in: [136]). In humans, obese adults showed hypothalamic damage associated with inflammatory markers and cognitive dysfunction [137]. In mice, exercise (treadmill running) protected the hypothalamus against high-fat-induced inflammation by reducing microglial reactivity and improving glucose tolerance [138], besides to improve metabolic function by preserving hypothalamic neurons and enhancing leptin and insulin sensitivity [139]. Insulin and leptin resistance can be induced by obesity-induced inflammation, which may contribute to cognitive dysfunction [140, 141]. By modulating IL-6 and IL-10 "anti-inflammatory" activity, exercise may contribute to increase hypothalamic insulin and leptin sensitivity through IKKβ/NF-kβ signalling in rats [142]. These hormonal alterations could represent exercise-induced neuroprotection, ultimately improving brain tissue and cognitive health [143].

Regarding the obesity-associated neuroinflammation, other areas of the brain, including the prefrontal cortex, amygdala, and hippocampus, are also affected. In rats, obesity induced by high-fat diet resulted in increased levels of TNF-α, IL-1β, and cyclooxygenase-2 in the hippocampus, which were revoked by treadmill exercise [30]. Moreover, exercise (30 min/day for 5 consecutive days on a motorised treadmill) improved working memory and ability in a passive avoidance task when compared to sedentary obese rats [30]. Recently, it was reported that exercise prevents both obesity-associated neuroinflammatory response and consequent white matter damage associated with excessive phagocytosis of myelin by myeloid cells, and associated memory deficits such as spatial working memory and novel spatial recognition [31].

Additionally, microglia seem to actively contribute to obesity-induced cognitive disfunction through phagocytosis of synapses; partial knockdown of receptor of fractalkine (chemokine serving as a "find me" cue for microglia) prevented microglial reactivity and cognitive decline in obese mice [144]. Considering that exercise inhibits microglial reactivity [78, 145], exercise could contribute to prevent obesity-induced cognitive dysfunction by modulating microglial behaviour.

Exercise Modulates Cerebral Blood Flow and Cognition

Cerebral blood flow is tightly regulated by cerebral autoregulation, and the traditional belief was that it remained stable and largely unaffected by external stimuli such as exercise [146, 147]. However, this view has been challenged by studies indicating that exercise induces global and regional increase of cerebral blood flow [148–151]. A systematic review and meta-regression analysis reported increased cerebral blood flow in the prefrontal cortex, a brain region involved in executive functions, associated with moderate and intense exercise in healthy individuals [152]. More recently, a study in preadolescent children (7- to 9-year-old) revealed that exercise is not associated with cerebral

blood flow in brainstem, but it is associated with higher hippocampal cerebral blood flow, a brain region intimately involved in cognitive processes such learning and memory [153]. The most compelling studies associating exercise, increased cerebral blood flow, and cognition improvements were performed in healthy and diseased elderly [154–158].

A study with only healthy old women (50- to 90-year-old) has found a strong association between exercise, cerebrovascular blood flow, and cognitive processes including executive functions as measured by neuropsychological batteries including verbal fluency, spatial reasoning, and memory tests, suggesting that, at least partially, exercise would be associated with beneficial effects on cognition mediated by increased cerebral blood flow [154]. Indeed, robust evidence from animal studies and data from studies with adult humans over 50 years indicates numerous ways by which exercise influences cerebral vasculature improving neuroplasticity and cognitive processes [159]. In 60- to 70-year-old apparently healthy men, 8 weeks of aerobic exercise were associated with increased cerebral blood flow in the prefrontal lobe, particularly the subcallosal and anterior cingulate gyrus, and improvements on executive functions [156]. In healthy low-active middle-aged and older adults (mean age 65.9 years), 6-month of aerobic exercise was associated with increased cerebral blood flow and improvements in verbal fluency but not in memory [157]. Interestingly, shorter term aerobic exercise (12 weeks) in healthy adults (57- to 75-year-old) increased cerebral blood flow in the anterior cingulate region and in both left and right hippocampus, associated with improved immediate and delayed memory performance [155].

The brain is an organ with relative high-energy density demands; the adult human brain, for example, although accounts for only ~ 2% of the entire body mass, it accounts for ~ 20% (~ 49 ml O_2 per minute) of the total oxygen consumption at rest [160]. In this scenario, reduced cerebral blood flow may compromise neuronal function and cognitive processes; it represents an increased risk for dementia in general population [161], being predictive of conversion from mild cognitive impairment (MCI) to dementia among elderly [162]. Comparing MCI and healthy individuals, 12 weeks of aerobic exercise (30-min sessions of moderate-intensity treadmill walking per week) improved verbal fluency and working memory in both groups. However, while these cognitive improvements were associated with increased cerebral blood flow in healthy individuals, in MCI individuals, verbal fluency was associated with decreased cerebral blood flow in the left insula and anterior cingulate cortex [163]. Noteworthy, MCI individuals showed increased cerebral blood flow in the left insula at baseline compared to healthy ones, which is hypothesised to reflect a neurovascular compensatory response supporting compromised neural network [164]. A subsequent study with MCI individuals (mean age 66.4 years) showed that 12 months of aerobic exercise (25-to 30-min training, 3 times per week) increased cerebral blood flow in the anterior cingulate cortex associated with memory improvement measured by Wechsler Memory Scale-Revised [158]. Potential discrepancies in the results could be due to the different type of exercise among other factors, since cerebral haemodynamic response is dependent on type of exercise [165]. Overall, these data suggest that beneficial effects of exercise on cognition are mediated by increased and reorganisation of cerebral blood flow, and that although the nature of vascular response may differ, exercise has potential to improve cerebrovascular dynamics and ultimately brain health and cognition.

Exercise-Induced Structural Changes Associated with Cognitive Improvements in Humans

The effects of exercise on brain structures are well-documented [1, 86, 166–168], and evidence using image techniques and cognitive tests in humans suggests that exercise-induced brain structural changes are associated with cognitive improvements through lifespan (Table 2). The importance of exercise for brain structure and function may also be noted in sedentary people, who present reduced hippocampal volume and white matter hyperintensities such as gliosis, demyelination, and axonal loss, which are associated with cognitive impairment [189–191].

Literature suggests that exercise effects on human brain and cognition are most prominent in elderly and children [192], although recent studies indicate that even a single session of moderate intensity exercise is associated to hippocampal connectivity and memory improvement in young adult humans [174, 193]. Most of protocols used to assess exercise in humans include treadmill, walking or running, and cycle ergometer, while brain volume is assessed by magnetic resonance imaging, and cognitive performance by several protocols including memory tasks (i.e. work, spatial, episodic, relational, verbal memory), intelligence and attention tests, processing speed, and several executive function tasks (Table 2). Notably, the effects of exercise are not uniform across brain regions [194], being more consistent in areas related to memory and executive functions such as hippocampus and prefrontal cortex [167].

Hippocampus represents the most investigated brain area regarding exercise effects on CNS. For example, several works in children, adults, and elderly have shown an association between exercise, greater hippocampal volume, and better cognitive performance including improved spatial, relational, verbal, and episodic memory (Table 2). Regarding prefrontal cortex, increased volume and thickness are often associated with exercise and better executive functions, working memory, and attentional performances (Table 2).

Table 2 Exercise-induced brain structural changes and cognitive improvement in humans

Brain area	N	Age (years)	Mean age	Sex	Physical activity	Duration	Cognitive tests	Structural findings	Cognitive findings	Reference
Cortex frontal, parietal, temporal and occiptal	48	9-10 years old	9.97	M/F	Treadmill	2 min until volitional exhaustion.	Wide Range Achievement Test (WRAT-3)	Decreased gray matter thickness in superior frontal cortex, superior temporal areas, and lateral occipital cortex	Better arithmetic performance	[169]
Hippocampus	49	9-10 years old	10	M/F	Treadmill	2 min until volitional exhaustion	Kaufman Brief Intelligence test	Greater Hippocampal Volume	Improved Relational Memory Performance	[170]
Basal Ganglia	55	9-10 years old	10	M/F	Treadmill	2 min until volitional exhaustion	Kaufman Brief Intelligence and Attention Tests.	Greater dorsal striatum (i.e; left caudate nucleus and bilateral putamen)	Improved Attention	[171]
Basal Ganglia	32	9-10 years old	10	M/F	Treadmill	2 min until volitional exhaustion	Modified version of the Eriksen flanker task	Greater volume of basal ganglia	Increased flanker accuracy and increased cognitive flexibility.	[172]
Hippocampus	34	15-18 years old	16.4	M	Treadmill	until volitional exhaustion	Rey Auditory Verbal Learning Test and Virtual Morris Water MazeTask	Greater hippocampal volume	Better learning on the virtual Morris Water Task	[173]
Hippocampus, Precuneus, subiculum, lingual gyrus, occipital gyrus and parahippocampus	18	18-34 years old	20.03	M	Pedal	30 min at a cardiac frequency of 65% of their FcMax or warmed up for 2 min at 50% FcMax then the load was progressively increased over 1 min to reach 75% FcMax (for 5 days)	Hippocampus-dependent associative memory task	Increased hippocampal activity	Higher memory performance	[174]

Table 2 (continued)

Brain area	N	Age (years)	Mean age	Sex	Physical activity	Duration	Cognitive tests	Structural findings	Cognitive findings	Reference
Hippocampus	36	_	20.85	F	Cycle ergometer	10 min	Mnemonic Discrimination Task.	Increased activity in the hippocampus and the surrounding regions, as well as increased coupling between the hippocampus and cortical regions	Improves hippocampal memory function. Improved Pattern Separation	[175]
Hippocampus	38	18-35 years old	25.7	M/F	Treadmill, Running and weightlifting	20 to 30 minutes a day, 3 days a week, for 12 weeks	Task Materials and Stimuli and Task Procedure	Increased hippocampal volume (in the left dentate gyrus/CA3 subregion)	Improvement in the mnemonic discrimination performance	[176]
corpus callosum, bilateral superior longitudinal fasciculus, bilateral internal and external capsule, bilateral uncinate fasciculus, the corticospinal tract, and cerebellar peduncles	1206	_	28.8	M/F	Walking	2 min	NIH Cognition Total Composite Score	Greater volume of the corpus callosum, bilateral superior longitudinal fasciculus, bilateral internal and external capsule, bilateral uncinate fasciculus, the corticospinal tract, and cerebellar peduncles	Enhanced global cognitive function	[177]
Cortex	132	20-67 years old	40.4	M/F	Stretching/toning, electronic-braked cycle ergometer	4 sessions per week for 6 months	Neuropsychological batteries	Increased cortical thickness in left caudal middle frontal cortex Brodmann area	Increased executive function	[178]

Table 2 (continued)

Brain area	N	Age (years)	Mean age	Sex	Physical activity	Duration	Cognitive tests	Structural findings	Cognitive findings	Reference
Hippocampus	10	25-59 years old	41	M/F	Cycle ergometer, cycling, running or walking	30 min (week 1–4), 40 min (week 5–8), 50 min (week 9–12)	Rey Auditory Verbal Learning Task (RAVLT) and the Spatial Pattern Separation Task (SPST) [39]	Greater left Hippocampal Volume	Increase in immediate verbal memory performance	[179]
Ventricles, Frontal lobe, Dorsolateral prefrontal córtex, Cingulate córtex, Parietal lobe, Precuneus, Temporal lobe and Hippocampus	104	50-70 years old	57.67	M/F	sportive walking (walking in order to exercise), sport/dancing, gardening, climbing stairs, walking, and cleaning the house	Self-reported physical activity status for the last 6 months (<2 h/week/≥5 h/week or 2.5 h/week)	Executive function; Memory; Visuospatial Function; Language and Attention-Speed.	Increased volume of the temporal lobe in men and the dorsolateral prefrontal cortex and temporal lobe in women.	Improved executive function, working memory and sleep quality.	[180]
left prefrontal and cingulate cortex, temporal lobe and hippocampus	62	50–72 years old	60.2	M/F	Nordic walking Gymnastics (stretching, limbering, and toning)	Minimum of 3 sessions of 50 min per week for 6 months	Tests of general intellectual functioning, attention, verbal fluency, digit spans, and verbal and visuospatial memory	Increase in local gray matter volume in prefrontal and cingulate cortex and occipital cortex	Memory score increase	[181]
Basal ganglia	179	59-81 years old	66	M/F	Treadmill	_	Task Switching and Flanker Task	Increased volume of caudate nucleus, putamen and globus pallidus	Higher accuracy rates in the executive function	[182]
Hippocampus	158	60-80 years old	66.49	M/F	Physical Activity Scale for the Elderly Treadmill	-	Spatial memory	Greater preservation of hippocampal volume	Increased Accuracy and faster spatial memory and fewer episodes of forgetting.	[183]
Hippocampus	165	59-81	66.55	M/F	Treadmill	_	Spatial Memory	Greater Hippocampal Volume	Improved Spatial Memory Performance	[184]

Table 2 (continued)

Brain area	N	Age (years)	Mean age	Sex	Physical activity	Duration	Cognitive tests	Structural findings	Cognitive findings	Reference
Hippocampus	120	55-80 years old	66.55	M/F	Walking	It started with 10 min and increased weekly by 5 min, until reaching 40 min in the last week (week 7).	Spatial Memory	Greater anterior hippocampus volume	Improved spatial memory performance	[185]
Prefrontal cortex	142	58-81 years old	66.6	M/F	Treadmill	_	Stroop Task (attention and inhibitory control) and Spatial Working Memory Assessment	Greater Prefrontal Cortex Volume	Improved Attention and Spatial Working Memory Performance	[186]
Hippocampus and Prefrontal Cortex	58	64-78 years old	Study: 68.40 Control: 68.97	M/F	Cycle ergometer	volitional exhaustion or when the self-perceived exertion was rated 15 or above at baseline, and 17 at follow-up (3 days a week for 6 months)	Episodic Memory; Processing speed; Executive function; Reasoning and Visuospatial ability	Greater Cortical Thickness and Hippocampal Volume	Improved Episodic Memory, Processing Speed and Executive Function	[187]
Medial Temporal Lobe	26	60–89 years old	Median: 71.0	M/F	Walking	2 weeks	Memory; Attention and information-processing speed and Executive functioning	Thicker Fusiform Gyrus and Parahipocampal Cortex	Improved Attention and Information-Processing Speed	[188]

Additionally, other brain areas have been investigated; exercise was associated with greater volume of basal ganglia and improved executive functions and cognitive flexibility. Also, exercise was associated with thicker medial temporal lobe and improved attention (Table 2).

Conclusion and Future Directions

Although there is a massive body of evidence demonstrating that exercise is associated with improved cognition evolving numerous mechanisms throughout life in healthy and pathological contexts as previously discussed, high heterogeneity among studies investigating these effects represents a common limitation and a potential bias in the literature.

Numerous systematic reviews and meta-analysis have shown that heterogeneity of nature of studies may account, at least in part, for conflicting results since relationship between exercise and cognition depends on the cognitive task assessed, age, gender, time of intervention, and the exercise protocol performed [195–200]. In humans, for example, a recent systematic review and meta-analysis has found, at least in older adults, the absence of a linear relationship between exercise and cognition, with different types of exercises inducing different dose–response associations [201]. Also, the authors estimated minimal and optimal doses for several types of exercise, indicating superior effects of resistance exercises over other modalities [201]. Additionally, the dose–response relationships between exercise and cognition are distinct in older adults with and without cognitive impairments, indicating that short and high frequency exercise programs may elicit better cognitive results in the former group [202]. Finally, the sample sizes should be carefully discussed since it was recently shown that works using dozens or few hundreds of people present statistical underpower, resulting in inflated effect sizes and replication failures [203]. In small samples, the variability across population accounts for replication failures; as samples sizes increase into thousands of participants, both replication rates and effect size inflation start to improve [203].

In this context, it is of particular importance for the field to standardise study methods, including exercise protocols (i.e. modality, design, intensity, and duration), intervention time (i.e. before or after diagnosis of injury or neurodegenerative disease), study group (i.e. age, gender, and health condition), interference controls (including control groups, inclusion/exclusion criteria), cognitive functions (what and how they are assessed), and assessment time of outcome (i.e. during, post-exercise, and how long after exercise interventions). Furthermore, especially considering human studies, it is essential to work on large samples (thousands of participants); since there is high heterogeneity among people, a large sample is essential for accurate conclusions and replication of results.

Careful application and normalisation of the above research methods can allow us to answer key questions that can drive to future directions of research, e.g. What type of exercise/exercise protocol should be recommended to promote cognitive improvement/recovery? When would it be best to practice such an exercise? How often and for how long? Which group of people would the practice of a certain exercise benefit? Research in line with answering these questions would make it possible for people to benefit from a personalised exercise program, according to individual particularities or groups of people. All in all, the complex relationship between exercise and different cognitive aspects needs to be carefully assessed to allow us to better understand how exercise can affect cognitive functions in different contexts. This knowledge has the potential for supporting the development of future effective and accurate non-pharmacological interventions aiming cognitive improvement/preservation, and prevention of ageing- and disease-associated cognitive decline.

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4. ARTIGO 3: ATIVIDADE FÍSICA: UMA ESTRATÉGIA REALÍSTICA CONTRA NEUROTOXICIDADE MERCURIAL EM POPULAÇÕES RIBEIRINHAS DA AMAZÔNIA

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Abstract

Mercury is a toxic metal present worldwide. South America is the second region on mercury emissions into the environment, especially the Amazon region, where intense gold exploration activities are concentrated and which, combined with deforestation, biomass burning and the construction of hydroelectric dams, draw a serious scenario of mercury contamination in the region. In fact, recent studies have already demonstrated, in riverine populations, the occurrence of neurological symptoms and mercury concentrations are so high that they easily exceed the limits established by international health agencies. Considering that these populations are mostly isolated, socioeconomically vulnerable and the absence of proper pharmacological intervention against mercury intoxication in such scenario, this work proposes investigating the potential of lifestyle-related physical activity to mitigate or prevent both mercury accumulation and neurological symptoms reported by individuals chronically exposed to mercury in riverine communities. For this, individuals from communities in the region of Lake Tucuruí, Pará State, were interviewed to survey the profile of physical activity and self-reported neurological symptoms. Further, hair samples were extracted for mercury quantification. This study revealed high mercury exposure in an Amazonian population, with men presenting significantly higher concentrations. We found no correlation between general physical

activity and self-reported clinical symptoms or mercury concentrations. However, individuals who exercised more frequently (5-7 times/week) presented significantly lower mercury concentrations. Future investigations with robust methodologies are crucial to elucidating these relationships and associated health outcomes.

Introduction

Mercury contamination is a public health problem present worldwide. South America is the second region that emits the most mercury into the environment, mainly through artisanal mining activities, namely artisanal and small-scale gold mining (ASGM) (UNEP, 2019). In the Amazon region, this activity corresponds to 78.5% of the mercury emission by ASGM in South America and 27% in the entire world (Galvis, 2020). Most of the Amazon territory is in Brazil (Legal Amazon), where the largest and one of the oldest areas of ASGM, the Tapajós Basin region, can be found (Berzas Nevado et al., 2010; Crespo-Lopez et al., 2021).

Large amounts of elemental mercury vapor are emitted into the atmosphere during the gold purification process, which consists of heating mercury-gold amalgams (Crespo-Lopez et al., 2021). In clouds, elemental mercury is partially transformed into inorganic mercury, which can travel long distances and precipitate with rain, reaching vegetation, water bodies, and sediments (Crespo-Lopez et al., 2021). Of note, the Amazon rainforest, the largest tropical forest in the world, plays a crucial role in the fixation and uptake of atmospheric mercury (Figueiredo et al., 2018). Thus, deforestation harms the sequestration of atmospheric mercury, and the increasing fires throw it back into the air. Interestingly, biomass burning is the second largest source of mercury emission in this region (Crespo-Lopez et al., 2021).

In addition, the building of large projects, such as dams for Hydroelectric Power Plants, increases the dynamism of mercury in the Amazon environment for two main reasons: (I) the creation of

physicochemical conditions conducive to the proliferation of methanogenic bacteria capable of biotransforming the inorganic mercury present in soil, water, and sediment into MeHg (Gomes et al., 2019); and (II) interference in the migration of piscivorous fish, which favors the bioaccumulation and biomagnification of this metal *in loco* (Crespo-Lopez et al., 2021).

The human populations residing in this region, including riverine populations, indigenous people, quilombolas, rural and remote communities, and residents of areas close to mining, are constantly exposed to large concentrations of mercury through the consumption of contaminated fish (Hacon et al., 2020; Crespo-Lopez et al., 2021; Santos-Sacramento et al., 2021), especially carnivorous fish such as mandubé, pirarucu, tucunaré, and trairão which, because they are at the top of the food chain, accumulate the highest levels of mercury (Hacon et al., 2020). According to the World Health Organization (WHO), is tolerable a weekly intake of 1.6 µg of MeHg per kilogram of body weight (provisional tolerable weekly intakes – PTWI) (WHO, 2008), however, considering the high levels of MeHg found in fish from this region and that these populations, especially riverine populations, usually eat several meals based on this fish weekly, the WHO limit can be extrapolated easily (Hacon et al., 2020; Crespo-Lopez et al., 2021).

In fact, previous studies have already shown high concentrations of mercury in the hair of riverine populations in the Amazon (Nevado et al., 2010; Marques et al., 2013; Hacon et al., 2014; Arrifano et al., 2018c). A recent review analyzed 34 articles focused on the main river basins of the Amazon (Tapajós, Tocantins, and Madeira) and found that mercury concentrations measured in these populations exceeded two to ten times the values recommended by both the WHO (2,300 ng/g) and the United States Environmental Protection Agency (1,000 ng/g), with the main neurological symptoms manifested being cognitive, visual, motor, somatosensory, and emotional deficits (Santos-Sacramento et al., 2021). It is noteworthy that these symptoms are closely related to altered glial cell functions, which represent key components for CNS

homeostasis and defense (Yin et al., 2007; Takahashi et al., 2017; Fujimura et al., 2019; Shinozaki et al., 2019).

It must also be considered that a large part of the riverine populations of the Amazon live far from large urban centers, in small communities near rivers; they live from manual subsistence activities; they are exposed to contamination by improperly discarded substances; they live in conditions with little or no basic sanitation, electricity and/or access to medical services; and frequent school dropout (Arrifano et al., 2018a; Machado et al., 2021). This scenario is particularly worrying because it makes it difficult to develop intervention strategies for these populations that are chronically exposed to high concentrations of mercury (Crespo-Lopez et al., 2022).

A possible strategy that is easily accessible and low financial cost would be to encourage the practice of physical activity/exercise, since, to date, no drug has been effective in combating mercury neurotoxicity (Aaseth et al., 2015; Aaseth et al., 2018; Bjørklund et al., 2019). Although, at the outset, physical activity and exercise allude to distinct phenomena (Dasso, 2019), both can imply positive changes for brain health (Di Liegro et al., 2019; Bonanni et al., 2022). In fact, physical exercise is known to induce cognitive improvements and positively affect quality of life, as well as prevent and mitigate neurological disorders (Augusto-Oliveira et al., 2023). In line with this, physical activity can positively impact brain plasticity, preventing cortical atrophy, improving brain and cognitive function (Erickson et al., 2013). It is noteworthy that no data has been found in the literature concerning physical activity practices. Therefore, considering the geographic, social and economic scenario of these populations, the practice of physical activities related to their lifestyle (such as commuting from home to work, games ball, swimming, performing domestic and/or work-related tasks) may represent an important therapeutic target capable of reducing or preventing the impacts caused by exposure to mercury. Once the potential impacts that physical activity and/or physical exercise have on individuals exposed to mercury are known, it would be possible to design

strategies and protocols to assist in the prevention and mitigation of problems caused by this metal.

Therefore, the objective of this study is to outline a physical activity profile of riverine populations from islands of Lake Tucuruí and to assess whether the physical activity they engage in can prevent the symptoms reported by riverine populations environmentally exposed to mercury.

Material and Methods

The data and samples used in the present study were retrieved from previous expeditions of the research group and treated as follows.

Study Population and Location

This study included volunteer riverine populations from communities near Lake Tucuruí (-3.800897, -49.811848), whose formation took place from the construction of the fifth largest hydroelectric plant in the world, the Tucuruí Hydroelectric Power Plant. For this study, we selected 202 adult individuals (over 18 years of age) who have lived in riverine communities for at least two years and who consume fish five times or more per week.

Ethical Aspects

This study followed the guidelines for reporting STROBE observational studies (Von Elm et al., 2007) and the ethical principles of the Declaration of Helsinki for research in human beings. It was submitted for approval by the National Council for Ethics in Research with Human Beings – CONEP (CAAE nº 43927115.4.0000.0018). The individuals signed an Informed Consent Form (ICF) as a criterion for participation in the study.

Data and Sample Collection

A previous announcement of the project was made through visits, meetings and communications with community health agents. The

samples and data of each volunteer participant were collected using meeting places and public spaces in the communities, such as schools. Explanations/clarifications about the purposes of the study were provided to the participants. After the volunteers' consent have been recorded via the ICF, an interview was conducted with everyone to apply the symptom and physical activity questionnaires. All questions were read aloud by the applicator/researcher, explained and exemplified when necessary. The data collected from the participants includes name, gender, age, neurological symptoms presented by the participant at the time of the interview, and the participants' physical activity profile related to their routines (household chores, work, leisure, and moving from one place to another). In addition, hair samples of approximately 0.1 g were collected from the occipital region and stored in paper envelopes until analysis.

Physical Activity Profile

The physical activity profile was obtained from the volunteers' self-reports. Individuals who reported engaging in any physical activity at least once a week were termed as "physically active" and were divided into four groups based on the weekly frequency of their physical activity; whereas individuals who reported not practicing any physical activity weekly, such as not even once a week regularly, were termed "sedentary". It is noteworthy that we adopted these two terms only to separate our two different groups since the data collected in our research do not meet the appropriate criteria that define "physically active" and "sedentary" behaviors established in the literature (WHO, 2010; Ainsworth et al., 2011; Tremblay et al., 2017), although the precise meaning of "sedentary behavior" is still under scientific discussion (Magnon et al, 2018). In addition, the frequency of activities was determined based on how many times per week individuals reported engaging in each activity.

Quantification of Mercury in Human Hair

Total mercury present in the hair samples was quantified by inductively coupled plasma mass spectrometry (ICP-MS), as previously described (Arrifano et al., 2018b; Lopes-Araújo et al., 2023).

Statistical Analysis

The normality of the data was analyzed using the D'Agostino-Pearson test. Parametric and non-parametric data were represented as mean and standard deviation or median and interquartile ranges, respectively. Prevalence was tested using the Chi-square test or Fisher's exact test when appropriate. Between-group differences were analyzed using the Mann-Whitney test and correlations using Spearman's Rank Correlation test. The P-value < 0.05 was considered significant in all analyses.

Results and Discussion

A total of 202 participants were included in this study. Of these, 75 were male and 127 were female, 96 were between 26 and 45 years of age and only 87 responded to the self-reported clinical symptoms questionnaire (Table 1).

Table 1. Demographic characteristics and median hair mercury concentrations (ng/g) of the study population stratified into groups: general population, physically active individuals, sedentary individuals, and respondents to the clinical symptom questionnaire. The values expressed as percentages indicate the prevalence between genders.

Parameters	General population (n = 202)	Physically active (n = 92)	Sedentary (n = 110)	Clinical symptom (n = 87)
Men	75 (37%)	42 (46%)	33 (30%)	36 (41%)
Women	127 (63%)	50 (54%)	77 (70%)	51 (59%)
Age (median)	41	42.5	39	43
Hair mercury (median ng/g)	8,189	8,481	7,339	7,452

Of the participants, 46% reported practicing daily physical activities (Figure 1A). We found that the reported activities fell into three

broad types (Figure 1B): Leisure (80%), which included activities such as running, gym, swimming, and soccer; Work (18%), including fishing, rowing, mowing, and weeding; and Household (2%), including sweeping the house, washing clothes and general household chores. Further, the five most frequently reported types of physical activity included walking (42), soccer (22), swimming (17), mowing (12), and running (10) (Figure 2). This differs from previous observations, which reported that occupation-related activities were the only type of physical activity practiced by Amazonian populations (Machado et al., 2021). Interestingly, leisure-time physical activity has been reported to provide greater health benefits compared to physical activities performed in home or work settings (Janssen and Voelcker-Rehage, 2023). Moreover, it tends to be more prevalent in physical environments that are conducive to leisure, such as those with sidewalks, bike paths, trails, parks, and lower traffic density (Gao et al., 2015; Van Cauwenberg et al., 2018), as is also observed in our study region.

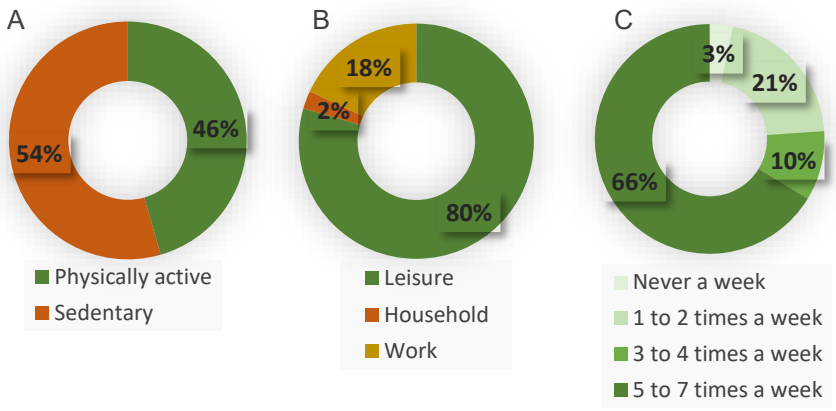

Figure 1. Physical activity profile of the study population. (A) Proportion of physically active versus sedentary individuals; (B) distribution of the three most frequently reported types of physical activity; and (C) distribution of participants according to four different weekly frequencies of physical activity.

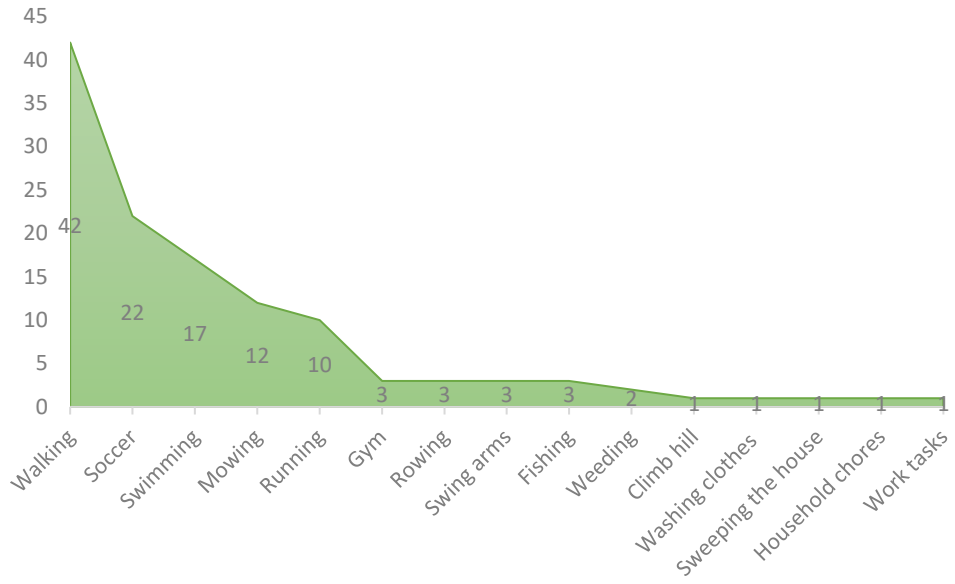

Figure 2. Frequency of types of physical activity reported by participants. Walking was the most reported activity (n = 42), followed by soccer (n = 22), swimming (n = 17), mowing (n = 12), and running (n = 10). Less frequent activities included gym workouts, rowing, swinging arms, fishing, and weeding (each n = 3), as well as other occasional tasks such as climbing hills, washing clothes, sweeping the house, household chores, and work-related tasks (each n = 1).

On the other hand, the marked discrepancy between leisure and work or household physical activity prevalences (Figure 1B) may be associated with methodological issues inherent to the use of a non-standardized questionnaire, which may have led individuals to misunderstand what it means to be “physically active”; or it may be related to limitations faced by these populations, such as the difficulty some respondents have in understanding the questions, especially considering that some of them are illiterate. These factors make data collection particularly challenging. In addition, the weekly frequency of physical activity of the individuals was classified as never a week (for activities performed sporadically), 1 to 2 times a week, 3 to 4 times a week, and 5 to 7 times a week (Figure 1C).

Our results showed that the most frequently reported type of physical activity was leisure (IC 95%, 71.3–86.3) and most participants engaged in physical activity 5 to 7 times per week (IC 95% 55.7–75.8). Nonetheless, most individuals were sedentary (IC 95%, 47.3–61.5). The

higher prevalence of sedentary individuals may be related to mercury exposure-induced deficits in motor function. Indeed, mercury exposure has been reported to impair motor function by disrupting myogenesis, myotube formation, myotendinous junctions, neuromuscular junctions, and satellite cell differentiation (Tam and Rand, 2024). Comparatively, a recent study with birds demonstrated that short-term exposure mercury can potentially affect bird´s flight biomechanic, weakening endurance through reduced flight efficiency (Seewagen et al., 2022).

In this study, the median hair mercury concentration of the general population was 8,189 ng/g (mean = 9,674 ng/g, ranging from 0.483 to 29,830 ng/g), with only 19 individuals showing hair mercury concentrations within the limits recommended by international health agencies (1,000 - 2,300 ng/g) (WHO, 2008).This finding is consistent with the mean hair mercury concentrations generally found in Brazilian Amazonian populations (>6,000 ng/g) (Castro and Lima, 2018) and daily fish consumers (>10,000 ng/g) (WHO, 2008). Our results reveal 132 (65.3%) individuals with mercury concentrations above 6,000 ng/g and 85 (42.1%) above 10,000 ng/g, confirming that the population residing along the lake of the Tucuruí Hydroelectric Power Plant reservoir is potentially exposed to a high mercury burden (Arrifano et al., 2018c). In fact, mercury exposure among people living in riverine communities in the Amazon is among the highest in the world due to the daily ingestion of fish contaminated with the metal (Basu et al., 2018; Sharma et al., 2019; Crespo-Lopez et al., 2021).

Furthermore, chronic exposure to mercury in the Amazon has been shown to cause various clinical symptoms, including disturbances in hearing, vision and motor function (such as tremors, lack of coordination, muscle weakness, loss of balance, numbness, and limb paralysis) (Harada et al., 2001; Fillion et al., 2011; Peplow and Augustine, 2014; Costa Junior et al., 2017; Lacerda et al., 2020), which are classic symptoms of Minamata disease observed in the 1953 episode in Japan (Ekino et al., 2007).

Similarly, our research found that self-reported clinical symptoms closely resemble those documented in the literature. Among the most frequently reported were *chronic or frequent headaches* (61), *dizziness* (56), *muscle weakness* (55), *anxiety* (45), *blurred vision* (44), *numbness* (43), *tremors* (43), *hand/foot tremors* (35), *memory loss* (34), *lip and eyelid tremors* (30), *tinnitus* (21), *and speech disorders* (9) (Figure 3).

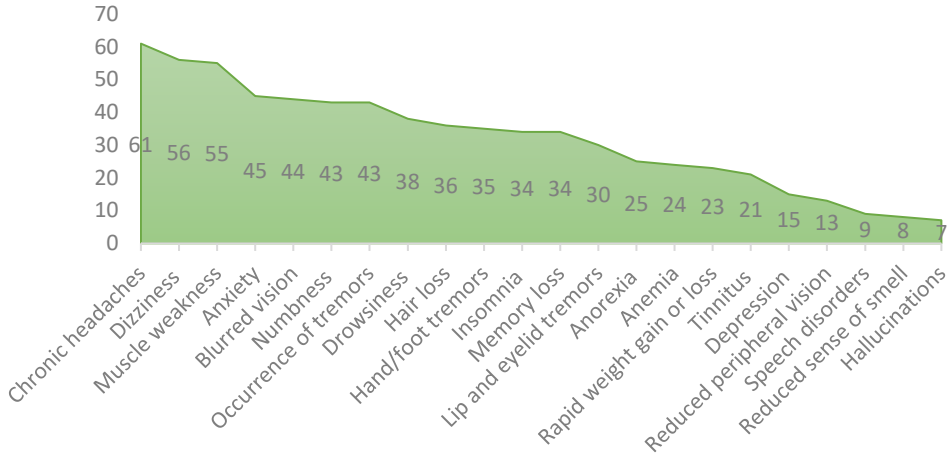

Figure 3. Frequency of self-reported clinical symptoms among study participants potentially associated with chronic mercury exposure. The most reported symptoms included headaches, dizziness, muscle weakness, and blurred vision. Values on the vertical axis represent the number of individuals who reported each symptom.

Moreover, we found a positive but very weak correlation between hair mercury concentration and the occurrence of self-reported symptoms ($r = 0.18$, $p = 0.09$) (Figure 4).

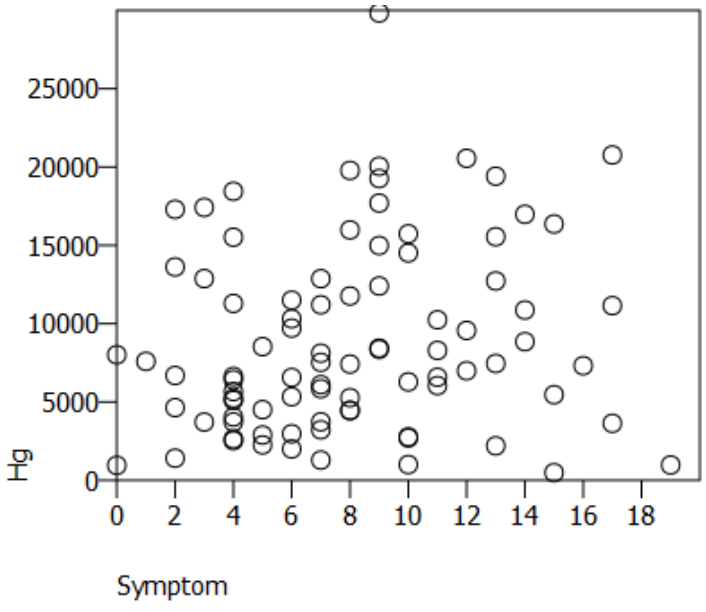

Figure 4. Scatterplot showing the relationship between hair mercury concentration (Hg) and the number of self-reported symptoms. Each point represents one individual. Although a slight positive trend is observable, the dispersion of points indicates a very weak Spearman's correlation between the variables, consistent with statistical results (r = 0.18, p = 0.09).

We hypothesize that a single mercury measurement is not sufficient to demonstrate a potential relationship between hair mercury concentrations and negative clinical outcomes, as mercury concentrations may vary according to factors that influence the exposure burden to the metal, such as the availability of alternative protein sources (affecting the amount of fish consumed); preference for fish species at a given trophic level; and seasonal variations in the occurrence of certain fish species (Oliveira et al., 2010; Hacon et al., 2020; Vasconcellos et al., 2021; Basta et al., 2023). Additionally, the biological half-life of mercury in the body is as short as approximately 30 to 60 days (Park and Zheng, 2012). It has also been shown that the half-life of mercury in hair is around 40 to 50 days (Caito et al., 2018). Thus, the hair mercury concentration measured in an individual in time A may be completely different from that recorded in time B. Therefore, periodic monitoring is recommended to build an exposure history for the individual or population. It is noteworthy that genetic polymorphisms may potentially influence the pharmacokinetics and pharmacodynamics of mercury, leading to greater accumulation in the body and increasing the susceptibility of certain populations to develop more severe clinical outcomes (Arrifano et al., 2018b; Perini et al., 2021).

Additionally, a comparative analysis of hair mercury concentrations between male and female participants revealed a statistically significant difference, with men exhibiting notably higher mercury concentrations (median = 11,289 ng/g) compared to women (median = 6,688 ng/g) ($p < 0.0001$) (Figure 5).

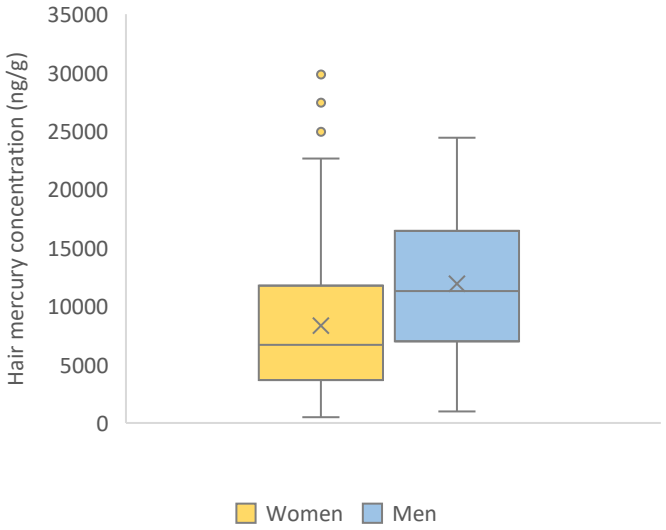

Figure 5. Boxplot comparing hair mercury concentrations (ng/g) between women and men in the study population. The median concentration for men was 11,289 ng/g (IQR: 7,507–17,103 ng/g; mean = 13,388 ng/g), while for women it was 6,688 ng/g (IQR: 4,517–10,164 ng/g; mean = 8,831 ng/g). Statistical comparison using the Mann–Whitney U test indicated a significant difference between groups (p = 0.0001). Boxes represent the interquartile range (IQR), with the horizontal line within each box indicating the median; whiskers extend to 1.5 times the IQR, and individual dots represent outliers. Means are indicated by a "x".

This difference may reflect sex-related behavioral or physiological factors, such as differences in dietary habits – although research investigating sex-dependent differences in fish consumption patterns in these populations is scarce – or in mercury metabolism and excretion pathways. A recent study conducted with Munduruku Indigenous communities found that fish consumption varies by gender and age, with men accounting for approximately 45% of the fish available for consumption, compared to 35% by women, and adults consuming around 80%, in contrast to 20% by younger individuals (Vasconcellos et al., 2021). In general, men require a higher caloric intake than women due to their greater body mass and faster metabolic rate (ATSDR, 1999; BRASIL, 2022).

Experimental studies suggest that the distribution, retention, metabolism, and excretion of mercury might be sex-dependent (Thomas et al., 1987; Mergler et al., 2007; Pittman et al., 2020). Males tend to retain higher concentrations of mercury compared to females, whereas females generally exhibit greater mercury excretion through both feces and urine (Thomas et al., 1987). These differences may be attributed, at least in part, to variations in the expression of renal transporters, such as organic anion transporters OAT1 and OAT3, which are involved in mercury uptake and excretion (Pittman et al., 2020). These findings highlight the importance of considering sex differences as a potential modifier in studies assessing mercury exposure and its associated health risks.

Conversely, no statistically significant differences were found between hair mercury concentrations of physically active (median = 8,481 ng/g; IQR: 5,137–15,316) and sedentary individuals (median = 7,339 ng/g; IQR: 4,074–13,951) (p = 0.3) (Figure 6). Stratified analysis by sex also showed no significant differences: among males, the medians were 11,246 ng/g (active) and 11,496 ng/g (sedentary) (p = 0.9); and among females, 7,417 ng/g (active) and 6,151 ng/g (sedentary) (p = 0.56).

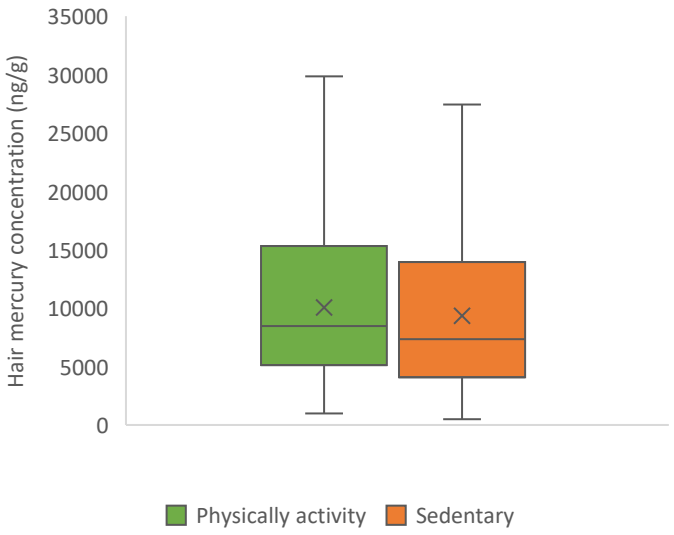

Figure 6. Boxplot comparing hair mercury concentrations (ng/g) between physically activity and sedentary individuals. The median concentration for

physically activity was 8,481 ng/g (IQR: 5,137–15,316 ng/g; mean = 10,052 ng/g), while for sedentary it was 7,339 ng/g (IQR: 4,074–13,951 ng/g; mean = 9,358 ng/g). Statistical comparison using the Mann–Whitney U test indicated no significant difference between groups (p = 0.3). Boxes represent the interquartile range (IQR), with the horizontal line within each box indicating the median; whiskers extend to 1.5 times the IQR. Means are indicated by a "x".

This result may be related to the limited design of the questionnaire, which – as a preliminary version – did not follow the standards of validated and widely used instruments such as the International Physical Activity Questionnaire (IPAQ) and the Global Physical Activity Questionnaire (GPAQ) (Sember et al., 2020). IPAQ was the first instrument developed to assess and monitor physical activity levels in a way that allows for international comparability across countries and regions (Sember et al., 2020). It has been validated and tested for reliability among Brazilian adults (Matsudo et al., 2001). Alternatively, the GPAQ was developed by the WHO as the recommended instrument for assessing physical activity within the STEPwise surveillance framework (WHO, 2021, 2024). It has been implemented in more than 120 countries (Riley et al., 2016), and is the most widely adopted tool for physical activity surveillance worldwide (WHO, 2011).

Both questionnaires record "total physical activity," encompassing various components such as intensity, duration, and frequency of activity (Sember et al., 2020; WHO, 2021). The GPAQ does this by assessing three domains: occupational physical activity, transport-related physical activity, and physical activity during leisure time (WHO, 2021). The IPAQ, in addition to covering these three domains, also includes physical activity related to household tasks (Wolin et al., 2008). Thus, both provide a comprehensive physical activity profile capable of estimating energy expenditure and determining whether an individual is physically active, inactive or sedentary (WHO, 2010; Tremblay et al., 2017; Sember et al., 2020; Herrmann et al., 2024).

Because these are standardized tools that help minimize potential biases arising from cultural variations across countries and regions, and enhance the reproducibility, robustness, and consistency of research data (Bauman et al., 2009), their use should be considered to support studies investigating the potential role of physical activity or exercise in mitigating mercury-induced adverse clinical outcomes.

Despite this, when comparing individuals who reported engaging in physical activity 1–2 times per week with those who reported doing so 5–7 times per week, we found significantly lower hair mercury concentrations in individuals with higher frequency of physical activity (median = 8,361 ng/g; IQR: 4,456–12,562) compared to those with lower frequency (median = 14,633 ng/g; IQR: 5,898–20,045) ($p = 0.02$) (Figure 7).

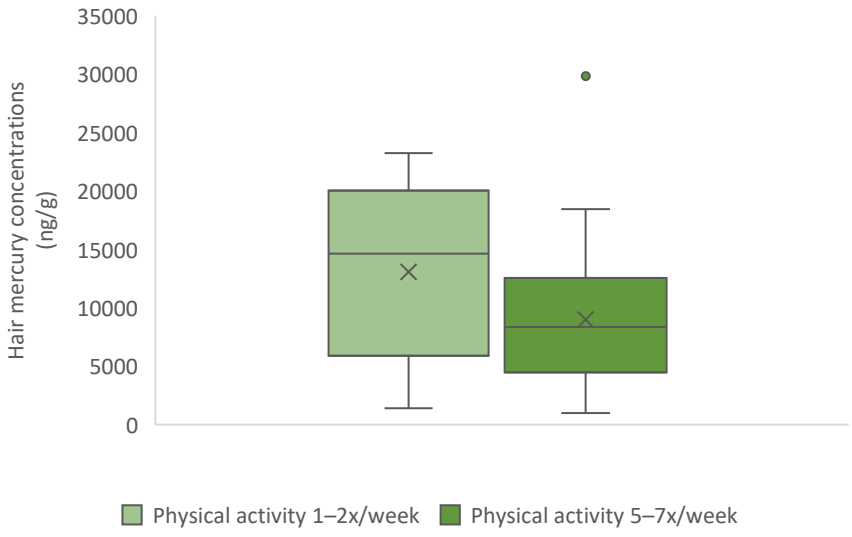

Figure 7. Boxplot illustrating the comparison of hair mercury concentrations (ng/g) between individuals engaging in low-frequency (1–2 times/week) and high-frequency (5–7 times/week) physical activity. The median concentration for low-frequency group was 14,633 ng/g (IQR: 5,898–20,045 ng/g; mean = 13,075 ng/g), while for high-frequency group it was 8,361 ng/g (IQR: 4,456–12,562 ng/g; mean = 8,978 ng/g). Statistical comparison using the Mann–Whitney U test indicated a significant difference between groups ($p = 0.02$). Boxes represent the interquartile range (IQR), with the horizontal line within each box indicating the median; whiskers extend to 1.5 times the IQR, and individual dots represent outliers. Means are indicated by a "x".

A recent study demonstrated that engaging in moderate or light physical activity at least three days per week may reduce the incidence of cognitive impairments, including memory loss and executive dysfunction, in middle-aged and older adults (Liu et al., 2025). Moreover, spending 150 minutes or more of physical activity per week – regardless of intensity – was associated with a lower prevalence of cognitive impairment (Liu et al., 2025). Indeed, physical activity can attenuate neuroinflammation in older adults, potentially preventing cognitive decline (Corlier et al., 2018). For instance, physically active individuals have been shown to exhibit lower peripheral levels of “pro-inflammatory” cytokines, greater total brain volume, and improved cognitive functions such as memory, orientation, and executive function, compared to sedentary individuals (Braskie et al., 2014; Nascimento et al., 2014; Papenberg et al., 2016). Comparatively, a recent study suggested that practicing moderate-intensity physical activity 3–4 times per week for 30–45 min for more than 12 weeks was positively correlated with enhanced cognition in adults with Alzheimer disease (Zhou et al., 2022).

Additionally, the adoption of certain physical activity protocols – particularly considering the type, duration and, intensity of the physical activity – differently modulates the body’s redox balance and antioxidant defenses (Abed et al., 2011; Pingitore et al., 2015; Fritzen et al., 2019). For example, engaging in acute or high-intensity physical exercise may increase oxidative stress levels and impair antioxidant capacity (Abed et al., 2011; Meng and Su, 2024), with greater pronounced effects observed in sedentary individuals (McGinley et al., 2009). Moreover, unaccustomed and/or exhaustive exercise can lead to increased ROS and oxidative stress-related tissue damage (He et al., 2016).

Oxidative stress might potentially modulate inflammation, leading to neurodegenerative disturbances, diabetes, cardiovascular diseases, chronic diseases, Alzheimer disease, and ageing (Leyane et al., 2022; Verhaegen et al., 2022; Kıran et al., 2023). Furthermore, practicing physical exercise leads to the natural muscle production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) due to the

abnormal release of electrons from the mitochondrial electron transport chain, leading to oxidative stress (Espinosa et al., 2023). However, oxidative stress has a dual nature, damaging at high levels and regulating at low levels (Pizzino et al., 2017; Meng and Su, 2024). Indeed, chronic or regular physical exercise-induced low levels of oxidative stress may lead to genetic adaptations, which increases antioxidant capacity (Powers and Jackson, 2008; Lu et al., 2021; Souza et al., 2022). Interestingly, the same effect can be observed in moderate-intensity exercises (Parker et al., 2014; Zuo et al., 2015).

According to the WHO, adults aged 18 to 64 should engage in at least 150 minutes per week (2 hours and 30 minutes) of moderate-intensity aerobic physical activity or 75 minutes per week (1 hour and 15 minutes) of vigorous-intensity aerobic physical activity, performed in bouts of at least 10 minutes (Bull et al., 2020). Although our study did not assess the intensity or duration of each physical activity session, it is reasonable to suggest that individuals reporting 5–7 sessions per week may be closer to meeting the minimum physical activity levels recommended by the WHO, and therefore may have lower capillary mercury concentrations.

Although a broad body of evidence supports that physically active individuals exhibit better health-related fitness levels and improved clinical outcomes (Li, 2016), including enhanced cognitive function (Zhou et al., 2022; Iso-Markku et al., 2024), delayed aging (Gajewski and Falkenstein, 2016; Erickson et al., 2022), and reduced risk of stroke (Ghozy et al., 2022; Cowan et al., 2023), cardiovascular disease (Dhuli et al., 2022), and other non-communicable diseases (Geidl et al., 2020), we found a weak and non-significant correlation between physical activity and the number of self-reported symptoms (r = –0.07, p = 0.53) (Figure 8A). Moreover, a positive and weak correlation was also observed between physical activity and hair mercury concentrations, consistent with no significance (r = 0.12, p = 0.27) (Figure 8B).

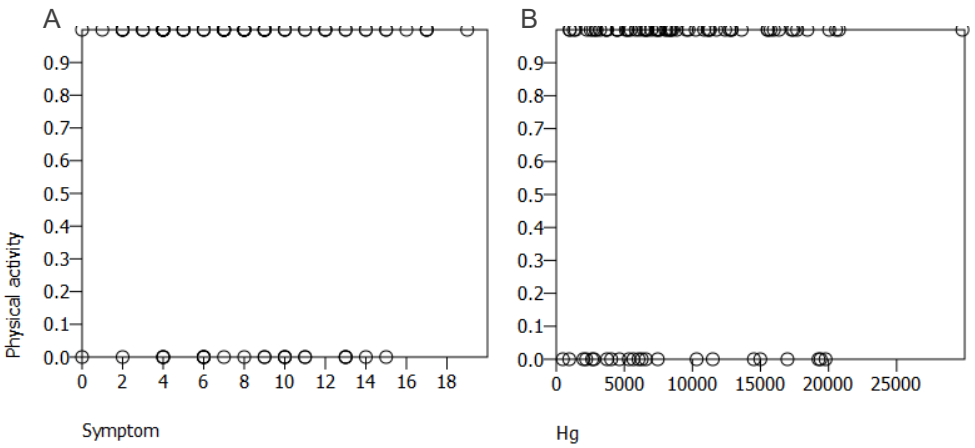

Figure 8. Scatterplot showing the relationship between physical activity (binary variable, in which 1 = practices physical activity and 0 = does not practice physical activity) and the number of self-reported symptoms (A) and the relationship between physical activity (binary variable) and hair mercury concentrations (Hg) (B). Each point represents one individual. The distribution of data points in both graphs suggests a very weak and non-significant spearman's correlation between variables (A, r = –0.07, p = 0.53; B, r = 0.12, p = 0.27).

As previously discussed, our study has some limitations that may introduce potential biases. These include the use of a non-standardized physical activity questionnaire, which consequently generated inconclusive data regarding the population's physical activity profile. Additionally, the relatively low number of volunteers participating in the study and the societal context of the population, notably the relevant occurrence of illiteracy among some individuals, are also weaknesses. However, considering that data on physical activity or exercise in Amazonian riverine populations and their possible health implications are still quite scarce, our preliminary findings point to interesting observations for future studies. Determining the physical activity profile of riverine populations exposed to mercury in the Amazon is only the first step in developing potentially effective strategies – such as physical exercise protocols – to mitigate the adverse effects elicited by exposure to this metal. Such protocols, when adapted to the population's context, could be a valuable tool to adopt in a more comprehensive approach, providing realistic recommendations for a healthier and safer lifestyle.

Conclusion

This study involving 202 participants, with a significant portion aged 26-45, revealed high concentrations of hair mercury, with a median concentration of 8.189 ng/g, far exceeding the recommended limits by international health agencies. While nearly half of the participants reported engaging in daily physical activities, these were overwhelmingly leisure-based. Methodological limitations, specifically the use of a non-standardized questionnaire, and the occurrence of some illiterate individuals may have influenced the observed discrepancy between leisure and work/household physical activity.

Additionally, the significantly higher hair mercury concentrations in male participants compared to females is likely related to distinct sex-related metabolism and dietary patterns. However, further studies are needed to test whether this hypothesis is true. Moreover, an interesting finding was that no direct significant correlation was found between overall physical activity status (active vs. sedentary) and hair mercury concentrations, nor between physical activity and self-reported symptoms, although a noteworthy observation emerged: individuals engaging in physical activity 5-7 times per week exhibited significantly lower hair mercury concentrations compared to those active only 1-2 times per week. This suggests that a higher frequency of physical activity might play a role in relation to mercury concentration – a hypothesis that needs to be further investigated with more robust methodologies, especially with a standardized international questionnaire. The very weak positive correlation found between hair mercury concentration and the occurrence of self-reported clinical symptoms, commonly associated with chronic mercury exposure, also requires further exploration with additional sampling that allows for the construction of a history of mercury exposures.

Overall, these findings underscore the significant mercury exposure in this Amazonian population and highlight a potential, although complex, interplay between physical activity frequency and

mercury burden. Future research employing standardized assessment tools and larger cohorts is crucial to confirm these preliminary observations and to elucidate the mechanisms underlying the relationship between physical activity, mercury exposure, and associated health outcomes in this vulnerable population.

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5. CONCLUSÕES INTEGRADORAS

As populações ribeirinhas da Amazônia estão historicamente expostas ao mercúrio presente no ambiente, notadamente em decorrência da atividade garimpeira, das queimadas florestais e do consumo diário de peixes contaminados (Crespo-Lopez et al., 2022). Diversos estudos demonstram que essas populações apresentam concentrações de mercúrio no cabelo significativamente superiores aos limites recomendados por agências internacionais de saúde – especialmente entre indivíduos que consomem peixe diariamente (WHO, 2008; Castro and Lima, 2018). Esse panorama é preocupante e destaca a urgência de se elaborar estratégias alternativas e viáveis voltadas a essas comunidades.

A partir de uma revisão abrangente da literatura, observamos que há evidências consistentes de que as células gliais desempenham um papel central no contexto da intoxicação por metilmercúrio, por meio de diversos mecanismos homeostáticos e de defesa celular envolvidos em desfechos tanto protetivos quanto deletérios. As nuances desse envolvimento glial variam de acordo com o contexto, incluindo fatores como idade, espécie, carga de exposição e a área do sistema nervoso afetada – aspectos que influenciam diretamente a forma como esses mecanismos são ativados (Leal-Nazaré et al., 2024).

Além disso, nossa revisão da literatura aponta o exercício físico como uma estratégia terapêutica viável, com potencial para melhorar a cognição em condições fisiológicas e patológicas, por meio da modulação glial da neurogênese, da neuroinflamação e do

remodelamento estrutural (Augusto-Oliveira et al., 2023). Curiosamente, diversos mecanismos gliais modulados positivamente pelo exercício físico também são negativamente afetados pelo metilmercúrio, sugerindo a existência de vias comuns entre os efeitos benéficos do exercício e os efeitos tóxicos do mercúrio.

Como ponto de partida, nosso estudo preliminar utilizou dados coletados em expedições anteriores a comunidades ribeirinhas situadas às margens do lago da Usina Hidrelétrica de Tucuruí, no estado do Pará, com o objetivo de traçar um perfil da atividade física local e verificar se o status da atividade física é capaz de influenciar nos sintomas clínicos relatados pelos indivíduos do estudo. Os resultados sugerem que a população estudada está altamente exposta ao mercúrio, com medianas de mercúrio capilar acima dos limites internacionais. Além disso, o perfil de atividade física dessa população, nunca antes avaliado, indica que a prática de exercícios físicos é uma alternativa viável a ser inserida no cotidiano. Embora parte dos nossos resultados apontem para uma direção contrária do que esperávamos, observamos uma possível e complexa relação entre os níveis de mercúrio capilar e a prática de atividade física.

São necessários novos estudos para verificar se a atividade física pode, de fato, prevenir ou mitigar sintomas clínicos decorrentes da exposição ao mercúrio. Para isso, recomenda-se o uso de ferramentas mais robustas, amostras populacionais mais abrangentes e uma atenção especial às particularidades socioculturais das comunidades envolvidas. Ainda, mais do que a atividade física, seria crítico investigar o potencial de protocolos de exercícios físicos na prevenção/mitigação dos sintomas da intoxicação mercurial. Adicionalmente, é fundamental a realização de ensaios experimentais que confirmem se as células gliais estão diretamente envolvidas nos possíveis efeitos protetivos da atividade física, assim como a identificação dos mecanismos moleculares e celulares por trás dessa interação.

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7. COMPROVANTE DE SUBMISSÃO/ACEITE DE ARTIGO CIENTÍFICO

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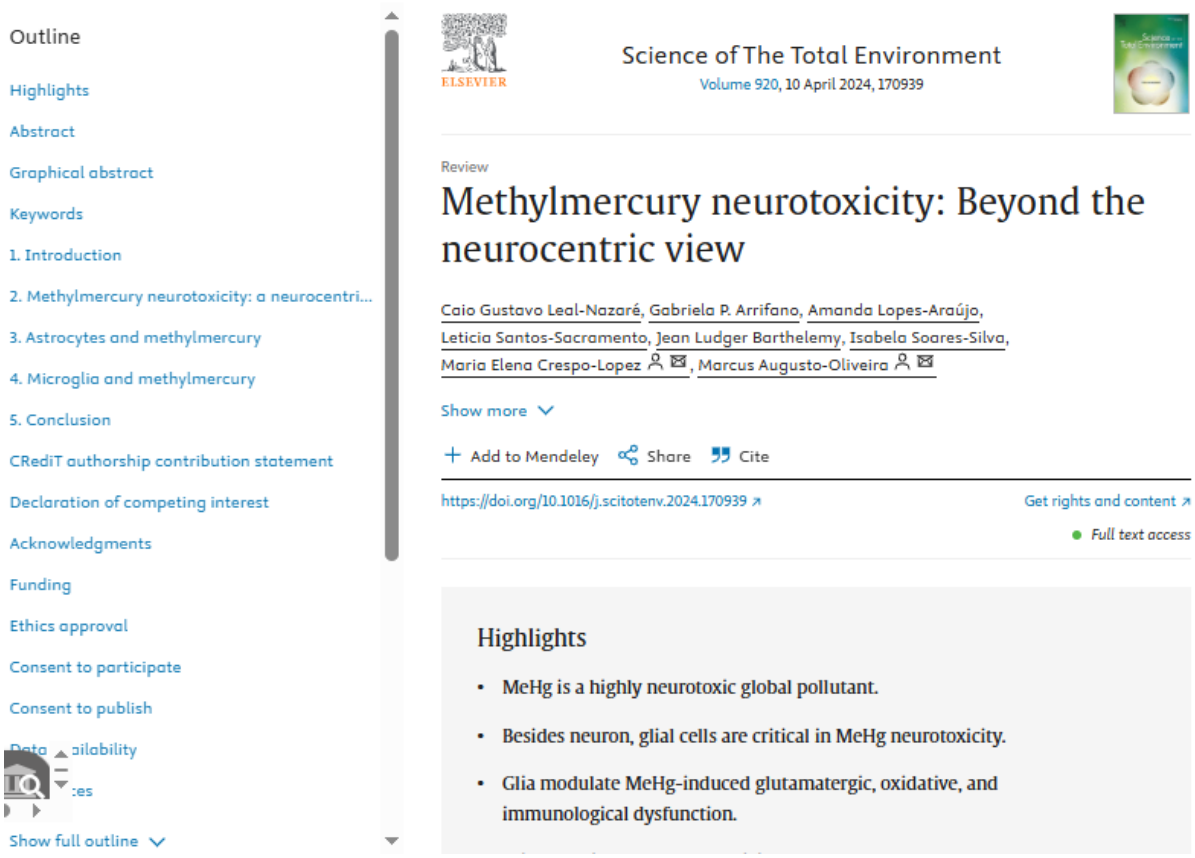

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Review

Methylmercury neurotoxicity: Beyond the neurocentric view

Caio Gustavo Leal-Nazaré, Gabriela P. Arrifano, Amanda Lopes-Araújo, Leticia Santos-Sacramento, Jean Ludger Barthelemy, Isabela Soares-Silva, Maria Elena Crespo-Lopez, Marcus Augusto-Oliveira

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Highlights

- MeHg is a highly neurotoxic global pollutant.
- Besides neuron, glial cells are critical in MeHg neurotoxicity.
- Glia modulate MeHg-induced glutamatergic, oxidative, and immunological dysfunction.

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Home › Molecular Neurobiology › Article

Exercise Reshapes the Brain: Molecular, Cellular, and Structural Changes Associated with Cognitive Improvements

Published: 31 July 2023

Volume 60, pages 6950–6974, (2023) Cite this article

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Abstract

Physical exercise is well known as a non-pharmacological and holistic therapy believed to prevent and mitigate numerous neurological conditions and alleviate ageing-related cognitive decline. To do so, exercise affects the central nervous system (CNS) at different levels. It changes brain physiology and structure, promoting cognitive improvements, which ultimately improves quality of life. Most of these effects are mediated by neurotrophins release, enhanced adult hippocampal neurogenesis, attenuation of neuroinflammation, modulation of cerebral blood flow, and structural reorganisation, besides to promote social interaction with beneficial cognitive outcomes. In this review, we discuss, based on experimental and human research, how exercise impacts the brain

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Abstract

Introduction

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