ISSN 1980-5764

# Dementia & Neuropsychologia

Volume 16 • Number 2
June 2022
São Paulo • Brazil

OFFICIAL JOURNAL OF THE SCIENTIFIC DEPARTMENT OF COGNITIVE NEUROLOGY AND AGING OF THE BRAZILIAN ACADEMY OF NEUROLOGY

Congresso Brasileiro de Neurologia 2022
Fortaleza.CE

Caros Amigos,

É com muito prazer que convidamos a todos para o Neuro 2022, o XXX Congresso da Academia Brasileira de Neurologia, que será realizado aqui em Fortaleza entre os dias 21 a 24 de setembro do próximo ano.

Nós da Comissão Organizadora, atentos às condições epidemiológicas e sanitárias, planejamos um evento híbrido. Teremos o retorno de atividades presenciais para o número de participantes permitido pelas normas vigentes e faremos transmissão ao vivo para os que preferirem participar de forma virtual.

Esperamos vocês no Neuro 2022 para refletirmos a neurologia do Futuro através de estratégias inovadoras, abrindo o espaço de reconhecimento de toda a produção em neurociências de nosso país, a qual nos guiará pelos melhores caminhos futuros. Faremos isso a partir de quatro eixos principais: **Discutir, Rever, Abordar e Inovar**.

Iremos **Discutir** os dilemas éticos e os desafios como neurologistas; **Rever** temas importantes para a prática neurológica e seu ensino; **Abordar** os avanços dos últimos anos; e **Inovar** na maneira de agir, diagnosticar e tratar.

Com a participação de todos o debate em torno destes tópicos terá a consistência e a força necessária para melhorar o nosso exercício profissional e, por consequência, a neurologia em nosso País.

Além das belezas naturais de Fortaleza, queremos fazer do Neuro 2022 uma oportunidade ímpar para o tão desejado reencontro, seja de forma presencial ou virtual, e uma experiência transformadora inesquecível.

Acessem nosso site, www.neuro2022.com.br e contribuam com sugestões de temas.

Até lá.

Norberto Frota | Presidente do Congresso
Fernanda Maia | Secretária
Pedro Braga Neto | Tesoureiro
Manoel Sobreira | Coord. da Comissão Científica
João José Carvalho | Presidente de Honra

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# Dementia & Neuropsychologia

Volume 16 • Number 02
June 2022
São Paulo • Brazil

OFFICIAL JOURNAL OF THE SCIENTIFIC DEPARTMENT OF COGNITIVE NEUROLOGY AND AGING OF THE BRAZILIAN ACADEMY OF NEUROLOGY

**Indexed in**

PubMed (US National Library of Medicine National Institutes of Health)

SciELO (Scientific Electronic Library Online)

Scopus (The Largest Abstract and Citation Database of Peer-reviewed Literature)

SJR (SCImago Journal Rank)

LILACS (Literature on the Health Sciences in Latin America and the Caribbean)

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Edifício Top Towers Offices - Torre Sul - 04101-000
Telefone: (11) 5083-3876

Dementia & Neuropsychologia (ISSN1980-5764), the official scientific journal of the Cognitive Neurology and Aging Department of the Brazilian Academy of Neurology, is published by the Brazilian Academy of Neurology,a non-profit Brazilian association.
Regularly published on March, June, September, and December since 2007.

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Dementia & Neuropsychologia / Brazilian Academy of Neurology / Associação Neurologia Cognitiva e do Comportamento. -- v. 1, n. 1 (2007). -- São Paulo: Cognitive Neurology and Aging Department of the Brazilian Academy of Neurology and of the Brazilian Association of Geriatric Neuropsychiatry, 2007-

v.: il.

Published in English, 4 times per year.
ISSN 1980-5764

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# SUMÁRIO

https://doi.org/10.1590/1980-5764-DN-2022-V001

# Individual integrity and public morality in scientific publishing

Sergio Della-Sala[1]

**ABSTRACT.** Science and science reporting are under threat. Knowingly or not, researchers and clinicians are part of this debacle. This is not due so much to the notorious replication crisis, as to our acceptance of lowering common morality for personal gains, including the widespread, deprecable phenomenon of predatory publishing. Rather than fiercefully countering this loathsome practice, academics are accepting, often supporting a masquerade solution: paying several thousand dollars to publish for all their own papers. This new policy will create a disparity across richer and poorer disciplines; will result in concentrating even more in the hands of large, rich, Western institutions, also penalising younger researchers; will kill observational studies and exploratory research; and will make disseminating science depending more on finances than on quality. This article calls for the full awareness of the academic community on the risks of the current situation in scientific publishing.

**Keywords:** Open Access Publishing; Predatory Publishers; Plan-S; Integrity; Scientific Publishing.

**INTEGRIDADE INDIVIDUAL E MORALIDADE PÚBLICA NA PUBLICAÇÃO CIENTÍFICA**

**RESUMO.** A ciência e os relatórios científicos estão ameaçados. Conscientemente ou não, pesquisadores e médicos fazem parte desse desastre. Isso não se deve tanto à notória crise de replicação, mas à nossa aceitação de rebaixar a moralidade comum para ganhos pessoais, incluindo o fenômeno generalizado e depreciável da publicação predatória. Em vez de combater ferozmente essa prática repugnante, os acadêmicos estão aceitando, muitas vezes até apoiando uma solução de disfarce: pagar vários milhares de dólares para publicar seus próprios artigos. Essa nova política criará uma disparidade entre as disciplinas mais ricas e mais pobres, resultará na concentração ainda maior nas mãos de grandes e ricas instituições ocidentais, penalizando também os pesquisadores mais jovens; matará os estudos observacionais e a pesquisa exploratória e fará com que a divulgação científica dependa mais das finanças do que da qualidade. Este artigo apela à plena consciência da comunidade acadêmica sobre os riscos da situação atual da publicação científica.

**Palavras-chave:** Publicação de Acesso Aberto; Editores Predatórios; Plano-S; Integridade; Publicação Científica.

## INTRODUCTION

Science and science reporting are under threat. Knowingly or not, researchers and clinicians are part of this debacle. This is not due so much to the notorious replication crisis[1], as to our acceptance of lowering common morality for personal gains[2]. This article aimed at urging our community to raise its morality bar to rescue itself from the abyss of ridicule towards which we are heading at full speed. I first list behaviours that we should all avoid or abide with, and then I discuss in more detail the current situation in publishing, which calls for the full awareness of the academic community.

## MANUSCRIPT ETIQUETTE

### Aim at good science not at "good results"

Chris Chambers, describing the current methodological sins hampering the thoroughness of scientific publications, laid out his forthright manifesto on how to avoid the pitfalls of favouring "good results" over good science. The most frequent of such drawbacks are summarised in Table 1; see also the guidance offered by the Committee on Publication Ethics (COPE), the International Committee of Medical Journals Editor (ICMJE), the NIH Office of Research Integrity (ORI),

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on January 20, 2022; Accepted on January 24, 2022.

**Table 1.** Common unwise practice that should be avoided in reporting scientific data.

| Bad practice/misconduct | Description |
|---|---|
| p-hacking | Fishing for statistically significant results, massaging the data, cherry-picking them, or adding unplanned participants or data points to rich statistical significance[4] |
| HARKing | Hypothesising after results are known. Writing the introduction and spelling out the study predictions after the data have been collected |
| Low statistical power | Not collecting enough data, or dispersing them in salami publications, favouring quantity of papers over their quality |
| Ignoring the effects of different analyses | Not being aware that little differences in scoring, pre-processing, analysing the data result in large conclusions differences[5] |
| Lacking definitions | Assuming common understanding of terms or concepts[6] |
| Framing study within loose assumptions | Lack of appreciation of the difference between intuitive hunches and a sound path between predictions and outcome[7] |
| Pushing for novelty | Considering replications as mundane and wanting in intellectual adroitness |
| Knowingly publishing poor data | Influencing appointments, promotions and workload with quantity, rather than quality[8] |
| Publication bias | Hiding, rejecting or not attempting to publishing null results or negative findings |
| Not data sharing | Being secretive about one's own data due to fear of being caught wrong |
| Statistical fallacies | Using easy statistics rather than proper statistics |
| Not retracting | Unearthing errors and not retracting the paper in fear of public shame |
| Owning findings | Failing to appreciate that once published, findings belong to the community; criticisms are raised to results and not to authors (unless fraudulent). Verifications should be welcome[9] |
| Plagiarism | Lifting material from available literature without proper citation, including rephrasing, translating from a foreign text and reproducing own material (self-plagiarism)[10] |
| Misappropriation | Mentioning someone else's ideas without the appropriate acknowledgement via citation of the original work |
| Misleading | Exaggerating the reach of the study, e.g. by gilding the titles of the paper, spuriously widening its real claims[8] |
| Hiding conflicts | Not declaring possible conflicts of interests of authors or sponsors |

the Guidelines for Responsible Conduct Regarding Scientific Communication of the Society for Neuroscience (SfN) or the Publication Practices & Responsible Authorship by the American Psychological Association (APA).

## Data of published papers should be posted, always

Anyone skimming through the daily list of dubious papers, highlighted by the laudable Retraction Watch, should be alarmed by the sheer volume of blunder and fabrication tarnishing scientific articles. One way to contrast this dangerous drift is to require that all data on which a report is based be made available for scrutiny, re-analyses and criticisms. Authors should honour this golden rule, reviewers should demand to see the data, editors should insist that they be transparent, and publishers should assist their archiving in accessible repositories.

## Honorary authorship should be avoided

Too often, names are added to the list of authors, even if their contribution does not qualify them as authors. An author of a scientific paper is anyone who contributed substantially to the study, by designing it, collecting considerable amount of the data reported, analysing or interpreting them. All authors are accountable for the content of the manuscript they sign. Anybody else associated with the study should be acknowledged for their specific work, but not listed as an author, see, for instance, the recommendation of the ICMJE or the criteria laid out by CRediT (Contributor Roles Taxonomy). In particular, authorship should not be offered as an honorary homage to someone in a position of power, nor should it be used as a bargaining chip to obtain career or other advantages. In short, an author is someone who actively partook to the study, practically or conceptually; hence, for example, offering access to a

group of patients does not qualify the clinician as author (although there is some ambiguity as to what it qualifies as "resources" in CRediT). Moreover, if used thoroughly and systematically, CRediT may also provide a mechanism to reveal any unbalanced division of tasks and workload due to gender or other personal demographics of the researchers involved in the study[11].

### Ethical approval should be detailed

Ethics is relevant. Which ethics body approved the reported study or permitted the report of the observation should always be explicit in the manuscript. Avoid the cliché of simply parroting the mantra phrase, "The study received ethical approval and is conducted according to the Declaration of Helsinki." Be specific and consider ethics as integral part of the study process[12], not a bureaucratic hurdle to overcome[13].

### Dissemination should be responsible

Scientists and clinicians blame journalists for poor science reporting in the media. However, often exaggeration in the news is due to the researchers bragging about their findings in academic press releases[14]. Researchers should publicise their results responsibly, showing their interest without embellishing them or overstating their reach. This becomes particularly relevant when promoting the outcome of an individual study, which has not been vetted by other laboratories or thoroughly replicated. Science should be disseminated only when is based on solid evidence[15], and the reports should be comprehensible without trying too hard to be smart or sensationa[16].

### Peer review should be protected

The idea generally held about reviewing is that it would benefit from an overhaul, changing its status from a quasi-hobby to a mandatory duty of each academic. Reviewing (and editorial) time should figure in the workload models of universities, it should be taught formally to early career researchers, and possibly it should be financially rewarding for the individuals or their institutions[17].

The process of peer reviewing is not perfect, does not prevent despicable errors, and does not impede very bad research from entering the literature[18]. Yet, if carried out conscientiously, it is the best quality control system we have for the scientific literature[19]. The process is as good as we make it. All researchers should do their share in reviewing papers in their field and should do so according to the golden rule that, when wearing the reviewer's hat, they should behave as they would like others to behave when they are at the receiving end (wearing the author's hat). Hence, reviewers should offer their feedback reasonably fast[20] and should use a polite tone, be honest in their appraisal, and clear in their requests[21].

The scientific community should resist the pressure to shortening reviewing time to deadlines incompatible with thoroughness. In Commencement Address at Harvard, Aleksandr Solzhenitsyn stated that, "Hastiness and superficiality are the psychic diseases of the 20$^{th}$ century, and more than anywhere else this disease is reflected in the press" (1978)[22]. This warning duly applies to the current urgency imposed by serious publishers of carrying out editorial duties fast rather than well. This is imposed to compete with the speed at which low-quality outlets are willing to accept papers for publication, often with no questions asked, provided their fees are paid (see below). Genuine publishers should ring-fence quality instead of entering this deranged marketplace.

Indeed, the publishing arena is now marred with the problem of a deluge of below-par publications in unscrupulous outlets. Let us trace our steps to analyse how we got here.

## SCIENTIFIC PUBLISHING: A WRONG TURN

### Plan S

At the end of 2018, the initiative *cOAlition S*, launched *Plan S* which establishes the principle that academic journals should gradually increase the quota of papers they publish in Open Access (OA) starting at the beginning of 2022. The outcome of this policy is that publishing each single academic paper will be charged several thousand dollars. Individual researchers, agencies funding their work, or the institution where they operate will have to bear such expenses. The reaction of the academic world has not been to fight against this decision, rather individual universities, institutions, learned societies and even individual research groups are trying to navigate the system by establishing bilateral deals with the publishing houses, allowing their affiliated researchers to publish their papers at discounted fees. These deals involve packages including a fixed number of papers that each group will be allowed to publish with a particular publisher at no extra cost. The benefit would be that all published material will be made available to everyone in OA.

However, the new policy will also carry severe consequences: (1) Institutions will not cover the entire costs of publications, part of which will have to be met by individual researchers, creating a disparity across richer and poorer disciplines[23]; (2) Publishing rights

will be concentrated even more in the hands of large, rich, Western academic institutions, excluding researchers who carry out their studies in less privileged institutions around the world; (3) Observational studies, single cases, exploratory research, serendipitous findings, or any study not fully funded by granting bodies but also position papers, viewpoints, discussions, and commentaries will be discouraged; (4) Younger researchers with less access to large amounts of financial support for their research will be penalised, forcing them to team up with wealthier colleagues to see their results published[24]; and (5) Publishing will depend more on the availability of finances than on the quality of the work, distorting the concept of merit for careers, appointments and promotions.

This proves to be a typical case of the so-called Cobra Effect, which bedevils well-intended policies that fail to properly consider their unintended consequences.

## The cobra effect

The cobra effect loosely refers to unintended and unforeseen consequences of policies designed in good faith and with the view of bettering the current situation[25]. The term was originally introduced by Siebert[26] to deride the unpredicted effects of poorly thought through financial incentives. It is based on a likely apocryphal anecdote about an attempt by the British Governor of colonial India to reduce the number of snakes roaming the street of New Delhi. He ruled that any citizen bringing to the city hall a dead cobra would get a cash reward. In no time the streets were cleared of snakes. However, people liked the relatively easy money, and began to breed cobras in their backyards, to then kill them to cash them in. The British authorities felt ridiculed, and abruptly stopped any reward for serpents' carcasses. Indians did not know what to do with the cobras in their garden cages and freed them. The outcome was that there were many more cobras gliding through the streets of New Delhi than when the original rule had been introduced. The unforeseen consequences of OA resonate with the Cobra Effect.

## Open Access

Publishing in OA is on the increase. The lofty founding principles of OA were to counter the power and fight against the revenues of established, private publishing houses by making freely available all papers reporting studies funded by public money[27]. Initially, the idea was based both on the naïve concept that online publishing would not cost much, and that such costs could be sustained by international agencies sponsoring scientific publication world-wide like modern Mecenates.

However, there is no such a thing as a free lunch, and soon it became clear that the authors themselves had to fork out the expenses of OA, hence draining resources from the research process itself. Moreover, far from decreasing the market dominance of the established publishing companies, OA boosted their income by adding authors' publishing fees to the subscriptions (the so-called "hybrid-journal" format), whilst increasing academic costs. The most harmful outcome of OA though has been paving the way to predatory publishing.

## Predatory publications

Predatory publishing is a pandemic that has infected science dissemination[28]. It is based on the OA model, whereby authors pay for the privilege of seeing their work in print, but, unlike the original OA vision, without the essential quality controls (Figure 1). These journals do not run proper peer-review processes, nor do they exert a sound editorial checking[29]. The model is very much like that of vanity press: pay-to-publish. Anything gets published, as hilariously demonstrated by the wonderfully goliardic article by two American scientists, who fed up with the constant email solicitations to submit their work to one or another such journals, eventually submitted a paper composed only of the sentence "Get me off your f***ing mailing list" repeated for 10 pages and illustrated by figures and graphs using the same text[30]. The roll-call of such imaginative hoaxes is long and ever increasing (see "List of scholarly publishing stings" in Wikipedia), proving beyond

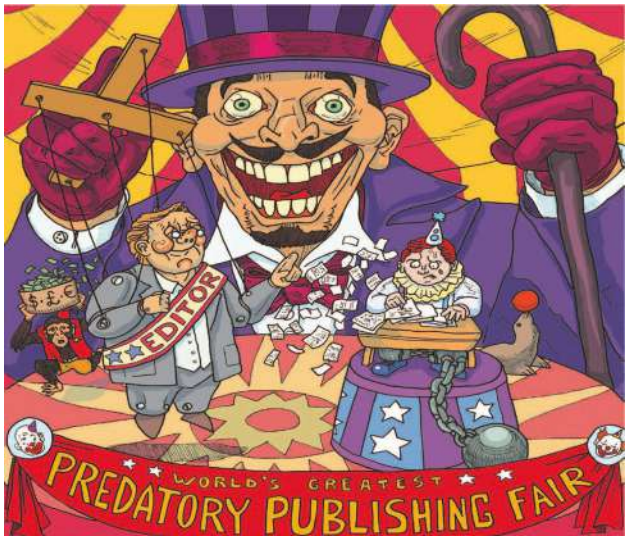


**Figure 1.** The cover illustration of *Cortex*, vol. 90, May 2017, drawn by Dario Battisti, depicting "The circus of predatory publishing." Available from: https://www.sciencedirect.com/science/article/pii/S0010945217301090. Accessed on: Jan 18, 2022.

doubt that hundreds of journals operate below morally acceptable quality standards, and making a mockery of serious science.

Yet, blinded by their hubris[31], or unashamed of taking shortcuts to boost their cv[32], or allured by pecuniary gains[33], researchers fall prey to or collude in these scams. They do not notice, or ignore, the flimsiness of the facades supporting these enterprises[34], including fake impact factors[35] and fake (or incompetent) editorial boards[36]. They are not deterred by the sloppy or non-existent vetting offered by these outlets. On the contrary, predatory publishers conquer larger and larger slices of the market, and paradoxically since these articles are OA, they end up being quoted even more than solid studies in non-OA journals[37]. The existence of such predatory outlets has also nurtured the phenomenon of paper mills, which offer shoddy, patchwork manuscripts for sale to unprincipled authors wishing to advance career effortlessly[38].

The advent of these predatory outlets represents a real menace to the integrity of science dissemination[39]. The only way to dissuade scientists and academics from this immoral practice would be to make disadvantageous to publish in or edit for scam journals, which should count as a negative factor in appointments, advancements, awards and grant funding[28]. Authors should ignore papers appearing in predatory outlets[40], even if those who published their work in such journals, unaware of the con, may feel some cognitive dissonance. However, countering their growth is challenging, not least because respectable publishing houses have launched many of their own OA spin-off journals, rendering the identification of predatory operations more ambiguous[41].

The well-meant Plan S and the crooked predatory marked are two sides of the same coin: in a market dominated by pay-to-publish, who will have an interest in guaranteeing rigor and quality? Not publishing companies, who will gain more by publishing more, not the researchers who may jump at the chance of easy publication and not the readers who, not realising they may be exposed to drivel, will enjoy free access to journals previously hidden by paywalls.

Fortunately, not all is contemptible; there are also good OA initiatives, including journals managed by Learned Societies, as well as new formats promoting thorough science, like Pre-Registrations also available in OA regime.

### Pre-registration

To counter publication biases and poor methodology, the format of Registered Reports was nearly launched a decade ago. Registered Reports is a format of publication whereby the proposed experiments are peer reviewed before the research is carried out and, if accepted, will be published independently of the results. The format was first adopted by Cortex in 2012[42] and, thanks to the unflinching determination of Chris Chambers, has spread to hundreds of other outlets[43]. This format guarantees quality and is less prone to the hurry imposed by quick and dirty reviewing style to accept all submissions for publication, as it aims at constructively assisting authors to better their study before embarking in data collection. Registered Reports offer a bulwark against the tide of substandard reports, at least until predatory outlets will annex this format as well.

The scale and severity of the problem is daunting. The scientific community should actively discourage the shortcuts of deceiving publishing, promoting a thoughtful and responsible dissemination, and embracing ethical reporting and sharing of data, putting an end to the current pandemic of unsound and immoral practices.

## ACKNOWLEDGEMENT

The author thanks Rob McIntosh who commented on an earlier version of this manuscript.

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# Long-term studies in cognitive training for older adults:
## a systematic review

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**ABSTRACT.** Studies show that aging is accompanied by losses in cognitive functions and that interventions can increase performance and/or support the maintenance of cognitive skills in the elderly. **Objective:** The objective of this study was to carry out a systematic review of long-term studies involving cognitive training (CT) in older adults without dementia and/or with mild cognitive impairment (MCI). **Methods:** A systematic review of controlled studies was published in scientific journals from 2000 onward, with duration ≥6 months, CT intervention, cognitively normal (CN) or MCI participants aged ≥60 years, and assessments using cognitive and/or neuropsychological tests. **Results:** A total of 32 studies were reviewed, comprising 10 on study protocols, 14 in CN older adults (no MCI and/or dementia), and 8 in older adults with MCI or at risk for dementia. **Conclusions:** The studies reported improvements in cognitive performance for some motor abilities, among older participants of CT with or without booster sessions, including multimodal interventions or otherwise.

**Keywords:** Aging; Aged; Cognition; Cognitive Aging; Time.

**ESTUDOS DE LONGA DURAÇÃO DE TREINO COGNITIVO PARA IDOSOS: UMA REVISÃO SISTEMÁTICA**

**RESUMO.** Estudos mostram que o envelhecimento é acompanhado por perdas nas funções cognitivas, e que as intervenções podem gerar um aumento no desempenho e/ou apoiar a manutenção de habilidades cognitivas em idosos. **Objetivo:** Realizar uma revisão sistemática de pesquisas com longa duração que ofereceram treino cognitivo (CT) em idosos sem demência e/ou com comprometimento cognitivo leve (MCI). **Métodos:** Revisão sistemática de estudos controlados, publicados em periódicos científicos a partir de 2000, com duração ≥6 meses, CT na intervenção, participantes ≥60 anos, saudáveis ou com MCI, avaliações por testes cognitivos e/ou neuropsicológicos. **Resultados:** Foram selecionados 32 estudos, sendo dez protocolos de pesquisa, 14 com idosos sem MCI e/ou sem demência e oito com idosos com MCI ou risco de demência. **Conclusões:** Foram relatados benefícios no desempenho cognitivo, incluindo habilidades motoras, de idosos que participaram de CT, com ou sem sessões de reforço, incluindo ou não intervenções multimodais.

**Palavras-chave:** Envelhecimento; Idoso; Cognição; Envelhecimento Cognitivo; Tempo.

## INTRODUCTION

According to the estimates of the United Nations 2019 Revision of World Population Prospects[1], 17.8% of people in the world will be above age 65 by 2060, up from 9.6% in 2021. In Brazil, this proportion will increase from 9.9 to 27%. During the normal cognitive aging process, the organism undergoes periods of stability and change. These changes partially stem from physiological and anatomical components. Most notable of the normal changes accompanying healthy aging are the aspects relating to the brain and cognitive functioning[2], which may affect more complex everyday tasks, such as driving, paying bills, and remembering dates and appointments[3].

This study was conducted by the Group of Cognitive and Behavioral Neurology, School of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on June 29, 2021; Received in its final form on October 25, 2021; Accepted on October 30, 2021.

Studies show that aging is accompanied by losses in cognitive functions and that interventions can promote performance gains and/or support the maintenance of cognitive abilities in healthy older persons[3,4]. According to the literature, the existing cognitive interventions, such as cognitive training (CT), have the potential for promoting health by optimizing cognitive and neural plasticity. These effects may be increased by combining CT with other types of interventions, such as physical activities and a balanced diet, with the aim of improving the performance of the individual and neural reorganization as a result of the intervention[5,6]. Both neural and cognitive plasticity are an inherent part of the life course of an individual. Although diminishing with age, plasticity supports the learning of mnemonic techniques, as well as the expansion and integration of knowledge related to cognitive functions[7].

The effects of CT can extend to other domains, such as health promotion[8,9], as well as functioning[10]. A plethora of cognitive modalities have been tested in both healthy and cognitively impaired elderly, displaying similar positive effects on cognitive performance and other variables, such as psychological well-being. According to Ngandu et al.[6], intervention might not be too late for presymptomatic and predementia disease stages and also for at-risk states, such as in mild cognitive impairment (MCI). For example, recent studies by Peng et al.[11], Valdés et al.[12], Lee et al.[13], and Djabelkhir et al.[14]. reported cognitive gains in older adults with MCI. The research by Lee et al.[13] indicated benefits even for mild dementia.

One of the first CT studies of the long-term type, i.e., lasting 6 consecutive months or longer, was the multicenter study conducted by Ball et al.[15], involving a large number of participants: 2,832 subjects aged 65–94 years. Participants received one of the following types of cognitive intervention: (a) verbal episodic memory training (group 1), (b) logical reasoning training (group 2), (c) processing speed training (group 3), or (d) control group without training (group 4). A total of 10 training sessions were given and 60% of the sample received 4 booster sessions after 11 months. The results showed that 87% of participants from group 3 improved performance on processing speed, 74% from group 2 improved logical reasoning, and 26% from group 1 improved memory. Booster sessions were effective for maintaining processing speed and logical reasoning, but not for episodic memory. The positive effects of training were not detected during the daily routine of participants, but persisted after 2 years, suggesting that the intervention effects can remain consistent over the long term.

Ngandu et al.[6], in a study involving a multidomain intervention of nutritional diet, physical exercise, CT, and vascular risk monitoring, reported this to be more effective and efficient, showing 20–150% of improvement in cognitive performance of participants. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) described the effects of this approach, showing that the intensity of the intervention, the target public, the type of approach, and the fact of being long-term training explained the beneficial effects for cognition observed in participants. These results reveal the importance of healthy dietary habits and regular physical exercise in conjunction with cognitive interventions.

Training studies differ not only in duration but also in strategies trained and methodology employed. Results reported in the literature varied widely regarding the strength of effects, generalization to untrained tasks, and long-term maintenance of improvements[16]. This heterogeneity justifies an analysis of the literature on long-term cognitive interventions with the aim of adding to the knowledge on CT and providing consistent, in-depth information on the cognitive benefits associated with long-term interventions and the strategies they employ. The objective of this study was to carry out a systematic review of long-term studies involving CT in older adults without dementia and/or with MCI.

## METHODS

This systematic review had its protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) in April 2021 (submitted in February 2021) under registration number CRD42021239130. The protocol can be assessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021239130.

Eligibility criteria were as follows: clinical trial studies with a 6-month duration or longer, intervention involving CT and a control group, cognitively normal (CN) or MCI participants aged ≥60 years, articles published in 2000 or later in scientific journals, and follow-up assessments of intervention effects using cognitive and/or neuropsychological tests. The criterion used for CT studies to be considered long term was to have a duration of 6 consecutive months or more.

Publications of master's dissertations, book chapters, doctoral theses, letters to the editor and case studies, studies whose samples included individuals aged <60 years or with dementia, studies performed at long-term care institutions, and studies failing to report the effects of intervention on cognitive performance were excluded.

The systematic review was conducted between February and April 2021. All manuscripts in Portuguese and English were revised for eligibility criteria. The Scielo, LILACS, and PubMed/MEDLINE scientific databases were searched using the following combinations of the key words: ((idoso OR idosos OR idosa OR idosas) OR (elder OR "older person" OR "older persons" OR "older people" OR "senior citizen" OR "senior citizens" OR elderly OR "aging people" OR "aging person" OR "aging persons")) AND ("treino cognitivo" OR "cognitive training") AND ("longa duração" OR "long term" OR longitudinal OR "follow up") AND (envelhecimento OR aging).

To guide the stages of identification, screening, and eligibility of studies, two pairs of reviewers working independently screened all records retrieved, following the steps of the Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17]. The initial identification of studies was performed by searching the abovementioned databases. In the screening stage, duplicate studies were excluded, and titles and abstracts were read for the first selection, according to the preestablished inclusion and exclusion criteria. In the eligibility stage, the remaining studies were read in full in order to be selected according to the same criteria. The remaining studies after this stage were the studies included in the review.

The following data were extracted from the articles: study title, authors' name, summary, results, methods, justification, objectives, and conclusion. Excel spreadsheets were used as support tools in this process.

The studies were assessed for quality according to Downs and Black's[18] checklist. This assessment tool consists of 27 questions, which are divided into 5 subscales: report or assessment of adequate information (10 items), external validity (3 items), internal validity of detailed measurements and result bias (7 items), confounding factors (6 items), and power (1 item). Each item that makes up the checklist assigns a score from 0 to 1, except for the item that assesses the description of confounding factors, which can assign up to 2 points, and the item that assesses the description of the study's power (27), which originally assigned from 0 to 5 points, but was modified to assign from 0 to 1 point, as in other studies[19-21] so that a score of 1 was given if the article presented power calculation and/or sample size calculation and a score of 0 if it did not present any of these calculations. Thus, the checklist has total scores ranging from 0 to 28 points. For a better understanding of the data obtained, the score was converted into a percentage for each domain, and a final average of the total score of all domains was calculated. Next, the quality of the articles was classified as follows: up to 0.39 was considered bad, 0.40–0.69 considered regular, 0.70–0.79 considered good, and 0.80 or above was considered excellent.

## RESULTS

The initial search led to the retrieval of 83 studies, of which 1 was subsequently excluded owing to duplication. Titles and abstracts of the remaining 82 studies were read and screened for relevance to the review topic. After applying inclusion and exclusion criteria, a total of 27 studies were excluded. Thus, 56 articles were read in full; of these, 24 studies that did not meet the eligibility criteria were excluded. The process of study selection for inclusion in the review is shown in Figure 1. The final 32 studies included in the review for analysis are listed in Tables 1–3.

### Publications of study protocols

Ten of the studies included were protocols, i.e., publications of study methods and planning, but not results[22-38]. Study protocols are regularly published before the intervention is carried out so that its originality and authorship are assured, thus enabling its application by other researchers in different research centers.

Eight of the study protocols[22-29] had innovative methods and objectives, which, in general, sought to investigate the effects of multiple domain interventions focusing on a range of aspects, such as preventing cognitive impairment, cognitive functions, physical fitness, activities of daily living (ADL), quality of life, gait speed, incidence of falls, and executive functions. For these studies, participants were categorized into CN older adults, elderly at risk for cognitive impairment, subjects with aging-related cognitive impairment, and older patients diagnosed with MCI. Interventions used a variety of resources, such as tablets, computers, physical training (PT), walking, health advice, software such as Fit Brains and Tonic and Phasic Alertness Training (TAPAT), electrostimulation, and vitamins.

Two other studies included in this review were publications of study protocols. Jobe et al.[31] presented the design of the long-term Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, based on a sample of 2,802 older adults. The participants were randomized into a control group, speed of processing training (SOPT) group, a reasoning training group, and a memory group. The intervention consisted of 10 sessions of 60–75 min over a period of 56 weeks, plus booster sessions for 11 months after the primary training. To determine the long-term effects, assessments were carried out after 1 and 2 years.

Similarly, Rebok et al.[10] applied booster sessions for 35 months after the primary intervention, with data collected 3, 5, and 10 years after the pre-intervention assessment. Due to the magnitude of the ACTIVE study, many studies recruited its data, of which 11 were selected for inclusion in this review.

The study by Kivipelto et al.[30] described the protocol of the FINGER study, with 1,200 older persons at risk for cognitive impairment. Participants were randomized into two groups. One group received CT combined with nutritional counseling, PT, social activity, and management of metabolic and vascular risk factors, for two 6-month periods, three times a week, totaling 72 sessions of 10–15 min each. The other group consisted of control and was given regular health advice. Long-term effects were to be measured by assessments planned 1 and 2 years after the intervention. One of the studies derived from the FINGER was also included in this review.

### Complete clinical trials

Of the 22 studies whose results were analyzed in this review, 14 involved samples comprising CN older adults, i.e., without MCI and/or early dementia[10,32-44], whereas 8 involved subjects with MCI or at risk for dementia[6,45-51].

Ten[10,37-44,51] of 22 studies drew on data from the ACTIVE study. Besides, a number of studies included employed multimodal interventions, also referred to as multifactorial, namely, FINGER, with nutritional interventions based on a specific diet, physical fitness training programs, and cognitive interventions, such as CT, and also with vascular risk monitoring[6,30]; AgeWell, which includes nutritional counseling, physical activity, CT, optimization of medication, management of vascular risk factors, social activity, and further specific interventions targeting grief and depression[33]; other studies whose interventions include combined CT and PT[22,23,28,32,34,35]; and a study with training of memory, reasoning, problem resolution strategies, visuospatial map reading skills, and handicraft making[34].

### Objectives

The objectives of the studies varied widely, in which those involving CN subjects tended to investigate the long-term effects of programs for SOPT, reasoning and/or episodic memory on everyday functioning and cognition[10,41,43], on the trajectory of cognitive aging[42], increase in cognitive function of older people[33], impact of CT on objective measures of physical functioning[38], on use of cognitive strategies[40,44], on initial recall and

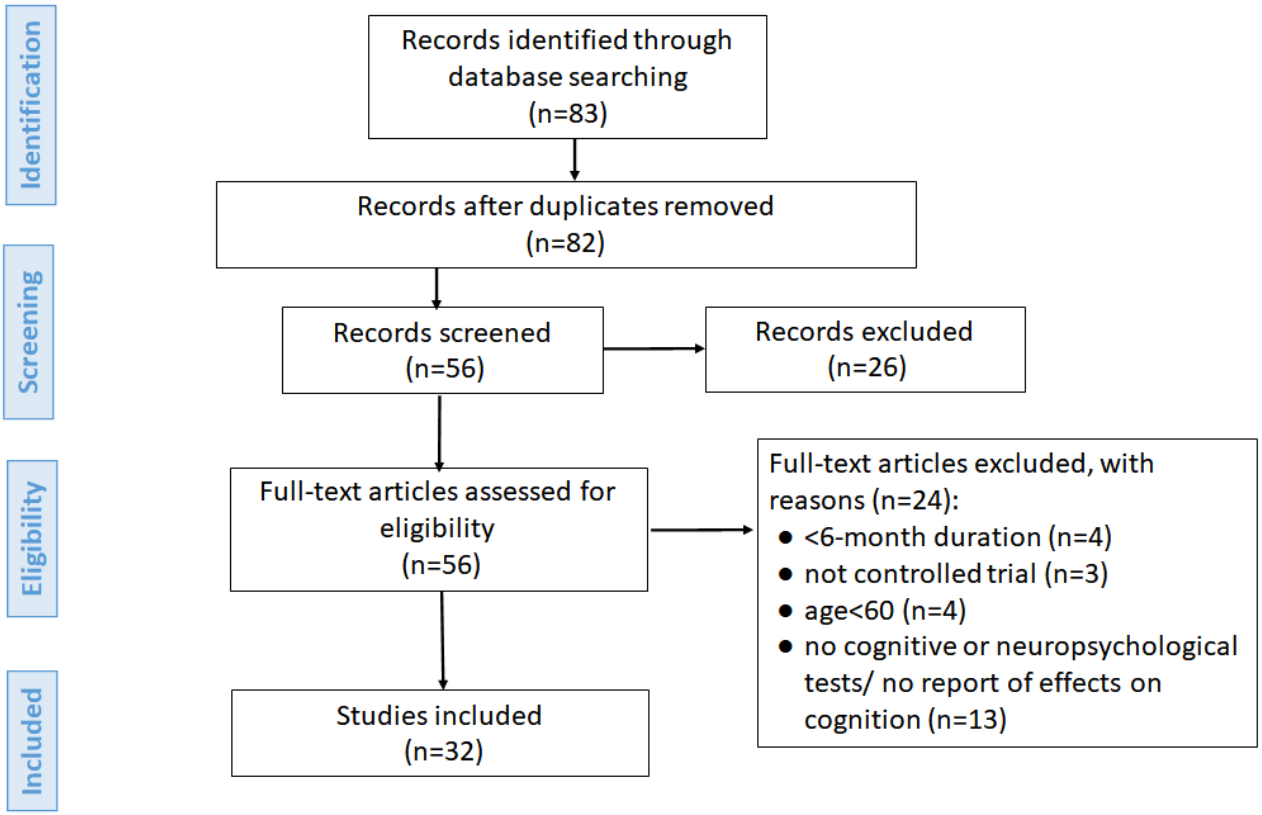


**Figure 1.** Flowchart showing study selection process.[17]

**Table 1.** Long-term studies with cognitively normal older adults.

| Authors | Sample | Objectives | Main intervention | Results found | Downs and Black |
|---|---|---|---|---|---|
| Willis et al.[41] | n=2,832 (mean age, 73.6 years) | To determine the effects of cognitive training on daily function and durability of training on cognitive abilities. | Ten-session training for memory (verbal episodic memory), reasoning (inductive reasoning), or speed of processing (visual search and identification); four-session booster training at 11 and 35 months after training in a random sample of those who completed training. | Reasoning training resulted in less functional decline in self-reported IADL. CT cognitive training improved cognitive abilities specific to the abilities trained that continued 5 years after initiation of intervention. | 24 |
| Gross and Rebok[40] | n=1,401 (mean age, 73.8 years) | To report long-term impact of memory training on strategy use and longitudinal associations between strategy clustering, memory performance, and everyday functioning. | Data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study (n=1,401) were used to describe strategy use in a community-dwelling sample of older adults. Strategy clustering scores on verbal list learning tasks of episodic memory were used to test the impact of memory training on strategy use and study longitudinal associations between strategy clustering, memory performance, and everyday functioning. | Memory training improved strategy use. Effects were maintained for up to 5 years. The strategies were positively associated with memory performance and everyday functioning. | 24 |
| Ball et al.[43] | n=2,802 (mean age, 73.6 years) | To examine the longitudinal impact of dosage (number of training sessions) on improvement and maintenance of cognitive abilities and everyday functions. | Participants were randomly assigned to one of four groups: 10-session group training for memory (verbal episodic memory; n=711), or reasoning (ability to solve problems that follow a serial pattern; n=705), or speed of processing (visual search and identification; n=712); or a no-contact control group (n=704). For the three treatment groups, four-session booster training was offered to a 60% random sample 11 months later. | Initial SOPT effects were maintained over 5 years and amplified by booster sessions. A single booster session counteracted 4.92 months of age-related processing speed decline. | 24 |
| Borella et al.[36] | n=36 (above 75 years of age) | To examine whether WM training can improve WM performance in old-old individuals and produce and maintain transfer effects on untrained tasks. | 2 weeks, 60 min per session, memory training (n=18), active control (n=18); assessments: pre and post-test; follow-up: after 8 months; tests: CWMS task, Dot Matrix, Forward and Backward Digit Span, Cattell, pattern comparison task, and Stroop Color task. | The WM training program produced benefits maintained over time even in old-old adults, confirming there is still room for plasticity in the basic mechanisms of cognition in advanced old age. | 22 |
| Gross et al.[37] | n=1,401 (mean age, 73.8 years) | To investigate the influence of memory training on initial recall and learning. | Each ACTIVE intervention was administered in 10 small-group training sessions, each lasting 60–75 min, offered over a course of 10 weeks. The first of 10 sessions provided didactic training on how memory works and how to maximize benefits of training. | Memory strategy training was associated with significant long-term gains in learning, stemming from both the highly significant effect of the training and from a slower decline, for up to 5 years, in memory span. | 24 |
| Jones et al.[42] | n=1,659 (mean age, 73.7 years) | To determine the influence of CT in the ACTIVE study on the pace of cognitive aging. | Briefly, older adults (aged 65–94) were randomly assigned to one of the three cognitive training or no contact control arms. Training lasted 5–6 weeks, and participants were assessed pre- and post-intervention, and at 1, 2, 3, 5, and 10 years after post-test. This analysis considers outcomes through 5 years, as the 10-year main results are currently under analysis. | Reasoning training attenuated aging-related training. Memory gains were maintained but about half of reasoning and speed gains were lost. All trained groups performed better than controls at 5 years. Performance differences at end of follow-up were equivalent to about 6, 4, and 8 years of aging for memory, reasoning, and speed training, respectively. | 24 |

Continue...

**Table 1.** Continuation.

| Authors | Sample | Objectives | Main intervention | Results found | Downs and Black |
|---|---|---|---|---|---|
| Kwok et al.[33] | n=223 (mean age, 75.4 years) | To examine the short- and long-term effects of a cognitive training (CT) program in enhancing cognitive function of older people with subjective memory complaints. | A single-blind randomized placebo-controlled trial was carried out in a sample of 223 older adults aged 65 years or above with subjective memory complaints in Hong Kong. They were randomly assigned to either receive CT (intervention group, n=111) or attend health-related educational lectures only (control group, n=112). Participants' cognitive abilities were assessed by the Chinese version of Mattis Dementia Rating Scale at baseline, immediately after the training, and 9 months after the training. | Cognitive training was effective in enhancing the overall cognitive functioning of less educated older adults with subjective memory complaints. The positive effect was durable for at least 9 months in conceptualization and memory. | 23 |
| Sisco et al.[39] | n=1,912 (mean age, 72.9 years) | To investigate how a multicomponent memory intervention affected memory for prose. | Participants were randomized into one of the three training arms (i.e., memory, reasoning, and speed of processing) or a no-contact control group; about half of the trained participants received additional booster training 1 and 3 years post intervention. | Multi-factorial memory training can improve verbatim recall for prose, but the effect does not last without continued intervention. | 24 |
| Gross et al.[44] | n=1,401 (mean age, 73.3 years) | To evaluate whether training can increase the use of MoL and whether MoL is associated with better memory maintained over time. | The authors analyzed skip patterns on response forms for the Auditory Verbal Learning Test (AVLT) in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE; n=1,401) trial using 5 years of longitudinal follow-up. | The use of MoL was associated with improved memory sustained over time. Changes in strategies resulted in differences in memory performance. | 25 |
| Linde et al.[35] | n=70 (mean age, 66.8 years) | To analyze the short- and long-term effects of PT, combined CT, and PT plus CT programs on age-sensitive fluid cognitive abilities. | 70 healthy senior citizens (age 60–75) were allocated to a physical, cognitive, combined physical plus cognitive, and waiting control group. The trial assessed information processing speed, short-term memory, spatial relations, concentration, reasoning, and cognitive speed. | Physical, cognitive, and combined physical plus cognitive activity can be seen as cognition-enrichment behaviors in healthy older adults that show different rather than equal intervention effects. | 21 |
| Rebok et al.[10] | n=2,832 (mean age,73.6 years) | To determine the effects of cognitive training on cognitive abilities and everyday function over 10 years. | Ten training sessions for memory, reasoning, or speed of processing; four sessions of booster training 11 and 35 months after initial training. | Ten training sessions for memory, reasoning, or speed of processing, four sessions of booster training 11 and 35 months after initial training tests; tests: RAVLT, HVLT, RBPR, Letter Series, Letter Sets, Word Series, UFOV, MDS-HC, EPT, OTDL, CRT, and TIADL. | 24 |
| Eggenberger et al.[32] | n=89 (mean age, 78.9 years) | To evaluate synergistic effects of multicomponent PT complemented with novel simultaneous CT on cognition in older adults. | Seniors, older than 70 years, without cognitive impairment, were randomly assigned to either: (1) virtual reality video game dancing (DANCE), (2) treadmill walking with simultaneous verbal memory training (MEMORY), or (3) treadmill walking (PHYS). Each program was complemented with strength and balance exercises. Two 1-h training sessions per week over 6 months were applied. | Particular executive functions benefit from simultaneous cognitive–physical training compared to exclusively physical multicomponent training. Cognitive–physical training programs may counteract widespread cognitive impairments in the elderly. | 22 |

Continue...

**Table 1.** Continuation.

| Authors | Sample | Objectives | Main intervention | Results found | Downs and Black |
|---|---|---|---|---|---|
| Li et al.[34] | n=270 (mean age, 69.8 years) | To examine the relationship between changes in spontaneous brain activity and cognitive performance that occur after CT. | Participants were trained for 1 h, twice a week, for 12 weeks. Cognition was assessed in all participants and magnetic resonance images were obtained at baseline and 1 year after training. To assess spontaneous fluctuations in brain activity, we acquired resting-state fMRI data. Two indices—functional entropy and time-domain entropy—were used to measure the effects of training. Functional entropy increases with aging and indicates disruptions in functional connectivity. Time-domain entropy decreases with aging and indicates structural alterations in the brain and blood-flow reduction. | Seventy participants completed the study: 26 in the multidomain cognitive training group (70.38±3.30 years), 27 in single-domain group (70.48±3.93 years), and 17 in a control group (68.59±3.24 years). Functional entropy increased significantly less in the multi-domain ($p=0.047$) and single-domain groups ($p=9.51\times10^{-4}$) compared with the control group. In the multi-domain group, this was true in the paracentral lobule ($p=0.004$, Bonferroni corrected $p<0.05$). Time-domain entropy also improved with training. Compared with controls, time-domain entropy in the multi-domain group decreased less in the inferior frontal gyrus pars opercularis ($p=3.59\times10^{-4}$), the medial part of superior frontal gyrus ($p=1.17\times10^{-5}$), and the thalamus ($p=4.72\times10^{-5}$), while that in the single-domain group decreased less in the cuneus ($p=2.58\times10^{-4}$, Bonferroni corrected $p<0.05$). | 24 |
| Ross et al.[38] | n=2,802 (mean age, 73.6 years) | To assess the impact of three CT programs on objective measures of physical functioning across 5 years. | Older adults randomized into a processing speed (n=702), reasoning (n=694), or memory (n=703) training intervention were compared to those randomized into a no-contact control condition (n=698). Intention-to-treat (ITT) and treatment-received (time-varying number of training sessions) analyses were conducted. | There were no transfer effects in the ITT analyses. Treatment-received models demonstrated that training sessions (i.e., higher dosage) across all intervention arms transferred to better maintained Digit Symbol Copy and Turn 360 performance relative to the control group. More reasoning training transferred to better grip strength. | 23 |

CN: cognitively normal controls; CT: cognitive training; ACTIVE: Advanced Cognitive Training for Independent and Vital Elderly; SOPT: speed of processing training; HVLT: Hopkins Verbal Learning Test; AVLT: Rey Auditory-Verbal Learning Test; RBPR: Rivermead Behavioral Paragraph Recall; EPT: everyday problems test; IADL: instrumental activities of daily living; OTDL: observed tasks of daily living; TIADL: timed instrumental activities of daily living; CRT: complex reaction time test; CES-D: Center for Epidemiological Studies–Depression scale; MMSE: Mini-Mental State Examination; SF-36: Short Form 36-Item; RBMT: Rivermead Behavioral Memory Test; PT: physical training; UFOV: useful field of view; CWMS: categorization working memory span; RAVLT: Rey Auditory-Verbal Learning Test; CMSS: Chinese Memory Symptoms Scale; CMMSE: Chinese version of Mini-Mental State Examination; WM: working memory; CDRS: Chinese version of Mattis Dementia Rating Scale; MoL: method of loci; LPS: LeistungsPrüfSystem; TMT-A: Trail-Making Test Part A; MDS-HC: Minimum Dataset – Home Care, TMT-B: Trail-Making Test Part B, PAL: paired-associates learning; WMS-R: Wechsler Memory Scale – Revised; WAIS-R: Wechsler Adult Intelligence Scale – Revised; DSST: Digit Symbol Substitution Test; PACES: Physical Activity Enjoyment Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status (Form A); CWST: Color Word Stroop Test; DSC: Digit Symbol Copy.

learning[37], on memory for prose[39], on performance of working memory (WM), and on untrained tasks[36]. Studies with interventions involving combined CT and PT investigated the long-term effects on cognition[32] and fluid cognitive abilities sensitive to age[35]. Finally, the study by Li et al.[34] examined the relationship between changes in brain activity and cognitive performance after a multimodal or multifactorial intervention.

The studies with samples comprising older adults with MCI focused on investigating the longitudinal effects of SOPT on processing speed[51] and examining longitudinal efficacy for cognitive performance of different

**Table 2.** Long-term studies with older adults with MCI or risk for dementia.

| Authors | Sample | Objectives | Main intervention | Results found | Downs and Black |
|---|---|---|---|---|---|
| Rozzini et al.[49] | n=59 (between 63 and 78 years of age) | To evaluate the efficacy of an NPT in patients with MCI treated with ChEIs, compared with patients MCI treated only with ChEIs, in a longitudinal, one year follow-up study. | ChEIs, ChEIs+NPT, control; assessments: pre-test; follow-up 3 months after intervention; tests: MMSE, category fluency and letter fluency, Raven's colored matrices, Rey's figure – delayed recall and copy, NPI-Q, GDS, BADL, and IADL. | Subjects treated with TNP+ChEIs showed improvements in episodic memory, abstract reasoning and behavioral disturbances, long-term NPT in ChEIs-treated MCI subjects induces additional cognitive and mood benefits. | 21 |
| Valdes et al.[51] | n=2,802 (mean age, 77.6 years) | To examine the longitudinal effects of SOPT among older adults with psychometrically defined MCI from the ACTIVE trial | SOPT (n=702), reasoning training (n=694), memory training (n=703), control (n=698); booster: Participants completed eight or more training sessions, four sessions before assessments at years 1 and 3, training and control groups; assessments: pre-test and post-test (2 months later); follow-up: 1, 2, 3, and 5 years after pre-test. | Immediate improvement in participants with MCI, particularly the non-amnestic subtype. Initial training gains were maintained, where all subtypes showed similar trajectories across 5 years, with no significant changes in performance. SOPT proved effective and promoted durable effects. | 24 |
| Rojas et al.[48] | n=46 (mean age, 76.5 years) | To examine the efficacy of a CIP in patients with MCI and to assess patients' condition at 1-year follow-up. | CT (n=24), control (n=22); assessments: pre-test; follow-up: 1 year; tests: MMSE, CDR, Signoret's memory battery, BNT, verbal fluency, WASI-II, TMT-A, WAIS-III, TMT-B, QoL questionnaire, NPI, and the IADL scale. | Persons with MCI can improve their performance on cognitive and functional measures, and effects could persist in the long term. CT in MCI may prevent cognitive decline or slow conversion to dementia. | 20 |
| Law et al.[50] | n=83 (mean age, 73.6 years) | The aim of this study was to compare the effects of a functional tasks exercise program to a cognitive training program in older adults with mild cognitive impairment. | Participants were randomized into either a functional task exercise group (n=43) or an active cognitive training group (n=40) for 10 weeks. All outcome measures were undertaken at baseline, post-intervention, and 6-month follow-up using Neurobehavioral Cognitive Status Examination, Trail Making Test, Chinese Version Verbal Learning Test, Category Verbal Learning Test, Lawton Instrumental Activities of Daily Living Scale, and Problems in Everyday Living Test. | The FcTSim promoted significant sustained improvements in general cognitive functions, executive function, and problem-solving ability, as well as promoting brain plasticity. | 22 |
| Ngandu et al.[6] | n=1,260 (mean age, 69.4 years) | To assess a 2-year multidomain intervention in elderly people from the general population at risk for cognitive problems. | Multi-domain intervention (n=631), control (n=629); assessments: pre-test, post-test; follow-up: 1, 2, and 7 years after intervention; tests: NTB, Zung scale, SPPB, and CAIDE. | Results suggested a multi-domain intervention could improve or maintain cognitive functioning in elderly people at risk for cognitive problems. | 25 |
| Bahar-Fuchs et al.[46] | n=44 (mean age, 74.6 years) | To evaluate the extent to which CCT benefits older adults with MCI and MrNPS and examine its effects on meta-cognitive and non-cognitive outcomes. | CCT (n=21), active control (n=23); assessments: pre and post-test; follow-up: 3 months; tests: NIA-AA, BADL, NPI-Q, and ANZCTR. | Home-based CCT with adaptive difficulty and personal tailoring appears superior to more generic CCT in relation to both cognitive and non-cognitive outcomes. | 23 |

Continue...

**Table 2.** Continuation.

| Authors | Sample | Objectives | Main intervention | Results found | Downs and Black |
|---|---|---|---|---|---|
| Zhao et al.[45] | n=93 (mean age, 70.1 years) | To explore the effects of a CrExp program on cognitive functioning in older adults with MCI. | CrExp (n=48), control (n=45); assessments: pre and post-test; follow-up: 6 months; tests: MoCA, CVAVLT, CVCVFT, DST, TMT-A, TMT-B, CVADL, and MSQ. | CrExp therapy has greater positive effects on cognitive functions and daily living ability than standard cognitive training. This unique therapy may serve as a cost-effective adjunct to standard interventions for older adults with mild cognitive impairment. | 22 |
| Belleville et al.[47] | n=145 (mean age, 72.2 years) | To assess the effect of memory training on the cognitive functioning of persons with MCI and its durability and to evaluate whether this effect generalizes to daily life and whether positive effects can be obtained from psychosocial intervention. | Memory training (n=49), psychosocial intervention (n=49), control (n=47); booster intervention: one session after assessment at 3 months; assessments: pre and post-test; follow-up: 3 and 6 months; tests: GAI, GDS, GWBS, MMQ, QAM, ADL-PI, Free and Cued Recall memory test, EPI, EPR, Inventaire d'Activities Physiques, and GSE. | CT group showed an improvement on delayed memory and use of strategy use in everyday life, maintained at follow-up. Participants in psychosocial intervention group did not show any significant improvement. | 24 |

NPT: neuropsychological training; MCI: mild cognitive impairment; ChEIs: cholinesterase inhibitors; MMSE: Mini-Mental State Examination; NPI-Q: Neuropsychiatric Inventory Questionnaire; GDS: Geriatric Depression Scale; BADL: Bristol Activities of Daily Living Scale; IADL: instrumental activities of daily living; SOPT: speed of processing training; ACTIVE: Advanced Cognitive Training for Independent and Vital Elderly; HVLT: Hopkins Verbal Learning Test; RAVLT: Rey Auditory-Verbal Learning Test; RBMT: Rivermead Behavioral Memory Test; UFOV: useful field of view; CIP: cognitive intervention program; CDR: clinical dementia rating; BNT: Boston Naming Test; WASI-II: Vocabulary from the Wechsler Abbreviated Scale of Intelligence – Block Design; TMT-A: Trail-Making Test A; WAIS-III: Wechsler Adult Intelligence Scale III; FcTSim: simulated functional tasks; TMT-B: Trail-Making Test B; CVAVLT: Chinese Version of the Auditory Verbal Learning Test; CVCVFT: Chinese Version of the Category Verbal Fluency Test; NTB: neuropsychological test battery; SPPB: Short Physical Performance Battery; CAIDE: Cardiovascular risk factors, aging and dementia; NIA-AA: National Institute on Aging – Alzheimer's Association; NPI-Q: Neuropsychiatric Inventory Questionnaire; ANZCTR: Australian-New-Zealand Clinical Trial Registry; CrExp: creative expression; MoCA: Montreal Cognitive Assessment; DST: Digit Span Test; CVADL: Chinese Version of Activities of Daily Living Scale; MSQ: Memory Satisfaction Questionnaire; GAI: Geriatric Anxiety Inventory; GWBS: General Well-Being Schedule; MMQ: Multifactorial Memory Questionnaire – Memory Strategies; QAM: Questionnaire d'Auto-Evaluation de la Mémoire; ADL-PI: Activities of Daily Living – Prevention Instrument questionnaire; EPI: Eysenck Personality Inventory; EPR: Echelle de Préférence de Routinisation; GSE: General Self-Efficacy Scale; MrNPS: Mood-related neuropsychiatric symptoms; CCT: computerized cognitive training.

types of intervention: a program using episodic memory coding strategies[48], a neuropsychological training (NPT) program in patients treated with cholinesterase inhibitors (ChEIs)[49], a creative expression therapy (CrExp)[45], CT plus psychosocial intervention[47], a computerized cognitive training (CCT) program[46], and a program of simulated functional tasks (FcTSim)[50].

With regard to the study in older adults with some cognitive impairment but no MCI diagnosis, the objective was to investigate the longitudinal effects on cognitive functions of a multidomain intervention, combined CT, diet, physical exercise, and cardiovascular risk monitoring[6].

### Main interventions with cognitively normal older adults

Of the 14 studies conducted in CN samples, 4 studies[10,38,41,42] analyzed data from the three intervention groups of the ACTIVE study[31]. Based on the protocol of this study, Kwok et al.[33] conducted a trial in 223 older people with subjective cognitive complaints who received an intervention of 12 sessions of 90 min given weekly, also entailing SOPT, besides memory and reasoning training.

Five studies involving CN elderly were specific interventions for training memory. Three studies analyzed data from memory, training, and control groups in the ACTIVE study, involving a total of 1,401 participants[37,40,44]. The studies of by Gross and Rebok[40] and Gross et al.[44] assessed the impact of the memory training program from the ACTIVE study on the use of strategies. In a specific learning intervention involving the memorizing of short stories, the study by Sisco et al.[39] assessed the impacts of the memory training program from the ACTIVE study in conjunction with the booster intervention, including a total of 1,902 participants[39]. Borella et al.[36] carried out WM training with 36 older adults who underwent a 2-week intervention of 60-min sessions.

**Table 3.** Publications of study protocols describing methods and planning.

| Authors | Sample characteristics | Objectives | Main intervention | Results | Downs and Black |
|---|---|---|---|---|---|
| Jobe et al.[31] | n=2,832 (mean age, 73.6 years) | To determine the effects of three different CIP on improvement in performance of cognitively based measures under laboratory or field conditions and on measures of cognitively demanding everyday functioning associated with independent living. | SOPT, reasoning training, memory training, control; booster intervention: Participants shall complete eight training sessions or more, 11 months after the end of the primary training, 4 sessions, 3 weeks; assessments: pre- and post-test; follow-up: 12 and 24 months after pre-test; tests: MMSE, RAVLT, HVLT, RBMT, TIADL, Related Word Lists, RBMT, RBPR, UFOV, Word Series, Letter series, Letter Sets, DSST, DSC, EPT, OTDL, CRT, MDS-HC, SF-36, Turn 360, Grip Strength, and CES-D. | Primary outcomes focus on measures of cognitively demanding everyday functioning, including financial management, food preparation, medication use, and driving. Secondary outcomes include health-related quality of life, mobility, and health-service utilization. | 24 |
| Kivipelto et al.[30] | n=1,200 (25–74 years) | To investigate to what extent a multidomain intervention can prevent/delay cognitive impairment in elderly with an elevated risk of MCI. | Nutritional guidance, PT, CT (2 6-month periods, 3 times/week, 10–15 min/session, 72 training sessions/period), social activity, intensive monitoring, and management of metabolic and vascular risk factors, control group (regular health advice). Assessments: pre-test, 1 year after pre-test and post-test; tests: mNTB, CWST, and TMT (A and B). | All 1,200 persons are enrolled and the intervention is ongoing as planned. Baseline clinical characteristics indicate that several vascular risk factors and unhealthy lifestyle-related factors are present, creating a window of opportunity for prevention. The intervention completed during 2014. | 25 |
| Lee et al.[25] | n=80 (age ≥60 years) | To determine whether combined therapies, sequential, or simultaneous are a feasible approach for training older individuals with MCI and whether they can induce superior results compared with a single intervention mode and to compare which approach is best for cognitive functions, physical fitness, ADL, and QoL. | CT, PT, sequential training, or dual-task training. Assessments: pre- and post-test; follow-up: 6 months; tests: MoCA, Stroop test, WAIS, WMS, 10-m Walk Test, BBT, TUG, CST, IPAQ, ActiGraph GX3, DAD, BI, IADL, QoLAD, CBI, GDS, and CIQ. | The results of this proposed study provide important information regarding the feasibility and intervention effects of combining physical exercise and cognitive training for older individuals with MCI. | 24 |
| Woods et al.[24] | n=360 (age ≥65 years) | To examine whether tDCS of frontal cortices enhances neurocognitive outcomes achieved from cognitive training in older adults experiencing age-related cognitive decline: the Augmenting Cognitive Training in Older Adults study (ACT). | CT+tDCS, CT+placebo, training control+tDCS, training control+placebo; assessments: Initial pre-training, after 12 weeks of CT/training control+stimulation/simulation; follow-up: 1 year after training; tests: NIH Toolbox Cognitive Function Battery, neuroimaging, SF-36, AUDIT-10, DAST-10, 10-m walk test, Beck Depression Inventory-II, State Trait Anxiety Inventory, Starkstein Apathy Scale, UCLA Loneliness Scale, Lubben Social Network Scale, Pittsburgh Sleep Quality Index, and Graded Chronic Pain Scale. | The findings from this study have the potential to significantly enhance efforts to ameliorate cognitive aging and slow dementia. | 25 |

Continue...

**Table 3.** Continuation.

| Authors | Sample characteristics | Objectives | Main intervention | Results | Downs and Black |
|---|---|---|---|---|---|
| Montero-Odasso et al.[23] | n=200 (age ≥60 years) | To ascertain whether combined AE and RT have better effect on cognition that a BAT intervention in older adults with MCI. | (1) AE and RT+CT+vitamin D, (2) AE and RT+CT+placebo D, (3) control AE and RT+CT+vitamin D, (4) Control AE and RT+CT+placebo D, (5) control BAT+CT+placebo D; assessments: pre-test and post-test (6 months after pre-test); follow-up: 1 year; tests: ADAS-Cog 13, ADAS-Cog plus, MRI, TMT-A, TMT-B, DSST, Digit Span forward & backward, and Category Fluency, MoCA, Color Word Interference Test, 6-MWT, SPPB, SF-36, IADL, CDR, GDS-30, and GAD-7. | The SYNERGIC Trial established the efficacy and feasibility of a multimodal intervention to improve cognitive performance and mobility outcomes in MCI. | 26 |
| Sipilä et al.[22] | n=314 (70–85 years old) | To determine whether a combination of PT and CT has greater effects on walking speed, dual-task cost in walking speed, fall incidence, and executive functions compared to PT alone. | (1) PT, (2) PT+CT; assessments: pre-test; follow-up: 6 and 12 months after; tests: Stroop Test, TMT-A, TMT-B, CERAD, and Letter Verbal Fluency Test. | When completed, this study will provide new knowledge on the effects of physical and cognitive training on the prevention of walking limitations and rate of falls in older people. The expected results will be of value in informing strategies designed to promote safe walking among older people and may have a significant health and socioeconomic impact. | 22 |
| Ten Brinke et al.[28] | n=379 (65–85 years old) | To examine the effect of a CCT program, alone and preceded by a brisk walk, on cognitive function and explore the underlying neural mechanism in community – dwelling older adults. | Eight weeks sessions, three times week for 1 h+3 three times 1-h session at home; study groups: (1) computerized (FBT), (2) exercise plus CCT (Ex-FBT), and (3) active control (BAT). Assessments: pre-test and post-intervention (8 weeks); follow-up: after 1 year; tests: MoCA, MMSE, IADL, FCI, RAVLT; Toolbox Cognition Battery, Stroop Color-Word Test, TMT-A, TMT-B, DSST, SPPB; 6-MWT, PASE, and Neuroimaging. | If results from this study show benefits for cognition at trial completion, CCT programs, alone or in combination with walking, might be a strategy to promote healthy cognitive aging in older adults. In addition, results from the 1-year follow-up measurement could provide important information regarding the long-term benefits of these CCT programs. | 22 |
| VanVleet et al.[29] | n=120 (age≥65 years) | To test the effectiveness of a longer computer-based version of the TAPAT for improving cognitive abilities, functional status, and QoL in individuals with cognitive decline. | TAPAT (versions 1 and 2) (n=60), active control (n=60); evaluations: pre-test, halfway through the intervention, post-test; follow-up: after 3 months; tests: TMT-B, DKEFS Verbal Fluency, Auditory Consonant Trigrams, WAIS Digit Span, Attention Blink Task, Category Change Task, Gradual Start Continuous Performance Task, Stop Signal Task, flanker task, Stroop cross-modal, WAIS IV Digit Span, WM task, Reinforcement Learning Task, WMS IV Logical Memory I and II immediate and late recall, measurement of walking behavior, self-efficacy assessment, Fall Effectiveness Scale, TUG, SF- 12, Cognitive Failure Questionnaire, Pittsburg Sleep Quality Index, MAAS, and Breath Counting Task. | The strengths of this protocol are that it tests an innovative, in-home administered treatment that targets a fundamental deficit in adults with age-related cognitive decline; employs highly sensitive computer-based assessments of cognition as well as functional abilities, and incorporates a large sample size in an RCT design. | 24 |

Continue...

**Table 3.** Continuation.

| Authors | Sample characteristics | Objectives | Main intervention | Results | Downs and Black |
|---|---|---|---|---|---|
| Zülke et al.[26] | n=1,152 (60–77 years) | To evaluate the effectiveness of a multi-component intervention in preventing or delaying cognitive decline in older adults at risk for dementia and to assess the effects of the intervention on mortality, nursing home placement, functioning in everyday activities, QoL, depressive symptoms, social inclusion, and cost-effectiveness of the intervention. | Compared to previous trials, AgeWell.de covers an even broader set of interventions suggested to be beneficial for the intended outcomes. The findings will add substantial knowledge on modifiable lifestyle factors to prevent or delay cognitive decline. (1) nutritional counseling, PT, CT, optimization of medication, management of vascular risk factors, social activity, and further interventions targeting grief and depression; (2) control; follow-up: 2 years; tests: TMT A and B, Word List Memorization – CERAD subtest, Verbal Fluency Test – Animals – CERAD subtest, Constructional Praxis – CERAD subtest, Reading the Mind in the Eyes Test – revised version, and MoCA. | Compared to previous trials, AgeWell.de covers an even broader set of interventions suggested to be beneficial for the intended outcomes. The findings will add substantial knowledge on modifiable lifestyle factors to prevent or delay cognitive decline. | 25 |
| Yoon et al.[27] | n=230 (mean age, 72.0 years) | To compare the effect of broad and directed (narrow) technology-based training on basic perceptual and cognitive abilities in older adults and on the performance of simulated tasks of daily living including driving and fraud avoidance. | Web-based brain game suite (Brain HQ) and strategy video game (Rise of Nations) or to directed training for IADL training using web-based programs for both driving and fraud avoidance training, active control; assessments: pre- and post-test; follow-up: 1 year after training; tests: ability tests of IADL (driving simulator test for hazard perception, and a financial fraud recognition test), UFOV, DSST, RAPM, Letter sets, HVLT, RAVLT, and UMCFAB. | The baseline results support that randomization was successful across the intervention conditions. | 23 |

CIP: cognitive intervention program; ACTIVE: Advanced Cognitive Training for Independent and Vital Elderly; SOPT: speed of processing training; MMSE: Mini-Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; HVLT: Hopkins Verbal Learning Test; RBMT: Rivermead Behavioral Memory Test; TIADL: timed instrumental activities of daily living; RBPR: Rivermead Behavioral Paragraph Recall; UFOV: useful field of view; DSST: Digit Symbol Substitution Test; DSC: Digit Symbols Copy; EPT: everyday problems test; OTDL: observed tasks of daily living; CRT: complex reaction time; MDHC: Minimum Dataset – Home Care; SF-36: Short Form 36-Item; CES-D: Center for Epidemiological Studies – Depression scale; PT: physical training; CT: cognitive training; mNTB: modified neuropsychological test battery; CWST: Color Word Stroop Test; TMT-A: Trail-Making Test A; TMT-B: Trail-Making Test B; ADLs: activities of daily living; MoCA: Montreal Cognitive Assessment; WAIS: Wechsler Adult Intelligence Scale; WM: working memory; WMS: Wechsler Memory Scale; BBT: Box and Block Test; TUG: Timed Up and Go; CST: 30-s Chair-Stand Test; IPAQ: International Physical Activity Questionnaires; DAD: Disability Assessment for Dementia; BI: Barthel Index; IADL: instrumental activities of daily living; QoLAD: quality of life in Alzheimer's disease instrument; CBI: caregiver burden inventory; GDS: Geriatric Depression Scale; CIQ: Community Integration Questionnaire; tDCS: transcranial Direct Current Stimulation; AUDIT-10: Alcohol Use Disorders Test; DAST-10: Drug Abuse Screening Test; AE: aerobic exercise; RT: progressive resistance training; BAT: balance and toning control; MRI: magnetic resonance imaging (Neuroimaging); 6-MWT: Six-Minute Walk Test; SPPB: Short Physical Performance Battery; CDR: clinical dementia rating; GAD-7: Generalized Anxiety Disorder 7; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; FCI: Functional Comorbidity Index; PASE: Physical Activity Scale for the Elderly; TAPAT: Tonic and Phasic Alertness Training; SF-12: Short-Form 12; MAAS: Mindful Attention Awareness Scale; RAPM: Raven's Advanced Progressive Matrices; UMCFAB: University of Miami Computer-Based Functional Assessment Battery.

The study by Ball et al.[43] analyzed the data from the primary SOPT program plus booster sessions of the ACTIVE study, in which 1,400 and 633 older adults participated, respectively, including control groups.

A further two studies in CN older adults applied interventions involving combined CT plus PT[32,35]. The study by Linde et al.[35], involving 70 senior citizens, applied an intervention comprising weekly 30- to 90-min sessions of PT, CT, and combined PT plus CT, given over a 16-week period. Eggenberger et al.[32] conducted an intervention with 89 older adults comprising 52 sessions for 1 h, given twice weekly over 26 weeks, consisting of a virtual reality (VR) videogame dancing and treadmill walking with and without simultaneous verbal memory training.

Finally, Li et al.[34] recruited 270 CN older persons and performed a CT intervention for 12 weeks, twice a week

with 1-h sessions, consisting of training of memory, reasoning, problem resolution strategies, visuospatial map reading skills, and production of handcraft.

### Main interventions with older adults with mild cognitive impairment or at risk for dementia

Seven of the eight studies with cognitively impaired individuals examined the effects of a variety of forms of CT in older adults with MCI[45-51] and one in participants at risk for dementia, but not diagnosed with MCI[6].

Among the investigations in samples of older subjects with MCI, the study by Valdes et al.[51] assessed the data of 1,298 participants of the SOPT and control groups of the ACTIVE study. Belleville et al.[47] carried out an 8-week intervention of eight 2-h sessions. A total of 145 older adults participated in memory training, psychosocial intervention, and a control group. A booster session of the same duration was performed 3 months after the intervention. In the study by Rojas et al.[48], 46 MCI participants were randomized and the intervention group participated in a 6-month intervention in sessions of 2 h, twice weekly, of CT and cognitive stimulation, including episodic memory training and executive control training techniques. Rozzini et al.[49] carried out an intervention with 59 participants and 20 sessions of 1 h, five times a week. The investigation groups were divided into a group receiving ChEIs only, a group receiving ChEIs plus NPT (software training memory, language, attention, abstract reasoning, and visuospatial abilities), and a control group. In their study, Bahar-Fuchs et al.[46] applied an intervention lasting 8–12 weeks with two sessions of 20–30 min/ day, three times a week. Notably, 68 participants were randomized into CCT and active control conditions. In the study by Law et al.[50], 83 older adults were randomized to receive 13 sessions of functional task exercises (FcTSim) with PT or to an active CT group for 10 weeks. In the study by Zhao et al.[45], an intervention was performed, comprising 25 sessions of 1 h each over 16 weeks with 93 participants, who were randomized into a CrExp group or a standard CT control group.

With regard to the study in older adults at risk for developing dementia[6], a multidomain intervention combining PT, diet, cardiovascular risk monitoring, and CT with the use of technology was performed. The authors carried out the intervention based on the protocol of the FINGER study[30].

### Risk of bias

Regarding the categories of the methodological quality checklist, according to the scores, no articles obtained less than 0.71 points and 23 reached more than 0.80, which corresponds to a high score, excellent quality in the studies analyzed, and low risk of bias. The total average of articles for all categories was 0.84 out of a total of 1.0, meeting the methodological quality requirements of Downs and Black[18]. When divided by domains, the scores achieved were as follows: report 0.84, external validity 0.77, internal validity 0.74, confusion 1.0, and power 0.75 (Table 4).

## DISCUSSION

The aim of this study was to carry out a systematic review of studies investigating the long-term effects of CT programs in older adults without dementia. A total of 32 studies were reviewed, comprising 14 in CN older adults, 8 in older adults with MCI and/or at risk of developing dementia, and 10 on study protocols.

### Cognitive training long-term studies with cognitively normal older adults

With regard to the CT long-term studies with CN older adults, and among the studies analyzing data from the

**Table 4.** Downs and Black's[18] checklist results for the present systematic review.

| Checklist of Downs and Black [18] | n | Mean | SD | Minimum | Median | Maximum |
|---|---|---|---|---|---|---|
| Report (converted) | 32 | 0.84 | 0.04 | 0.82 | 0.82 | 0.91 |
| External validity (converted) | 32 | 0.77 | 0.32 | 0.33 | 1.00 | 1.00 |
| Internal validity and result bias (converted) | 32 | 0.74 | 0.07 | 0.57 | 0.71 | 0.86 |
| Confounding factors (converted) | 32 | 1.00 | 0.00 | 1.00 | 1.00 | 1.00 |
| Power (converted) | 32 | 0.75 | 0.44 | 0.00 | 1.00 | 1.00 |
| Total (converted) | 32 | 0.84 | 0.05 | 0.71 | 0.86 | 0.93 |
| Total (original, no conversion) | 32 | 23.41 | 1.39 | 20.00 | 24.00 | 26.00 |

SD: standard deviation.

three intervention groups of the ACTIVE study, Willis et al.[41] and Rebok et al.[10]. found less decline in self-reported IADL, particularly in the reasoning training group[41]. Regarding this finding in the functionality of the elderly, Carvalho et al.[52] highlighted the importance of cognitive interventions, with an emphasis on memory training, to improve the performance on mnemonic tasks.

The results from the studies by Willis et al.[41] and Rebok et al.[10]. also showed improvements in trained cognitive abilities, with benefits sustained for 5 years after the start of the intervention in all three CT groups[41] and for 10 years in the reasoning training and SOPT groups.[10]. The study by Rebok et al.[10] also revealed a medium-to-large effect of the SOPT on processing speed after 10 years. This finding, which represents highly effective maintenance of gains of this type of CT over time, highlights the importance of performing longer follow-up of the effects of CT interventions. In previous year, the study by Ball et al.[43], also derived from the ACTIVE study, confirmed the maintenance of positive effects of SOPT for 5 years after the intervention, corroborating the results of the study by Willis et al.[41].

The study by Jones et al.[42], who drew data from the ACTIVE study, except those related to the booster intervention, showed that memory gains were maintained for 5 years, akin to Willis et al.[41] and Ball et al.[43], and that reasoning training significantly attenuated the aging-related limitations in this cognitive ability. The results of the study by Li et al.[34], included in this review, were consistent with this finding. The authors reported, based on neuroimaging analyses, that CT can promote plastic gains in intrinsic activity patterns, particularly through improvements in functional connectivity and in brain structure which, according to the researchers, are probably part of the neural mechanisms underlying the effects of CT. In other words, according to these findings, CT can slow the pace of cognitive aging.

The results of the study by Ross et al.[38], however, showed that more training sessions in all intervention groups of the ACTIVE study, i.e., SOPT, memory, and reasoning training, enhanced the performance on tests evaluating fine motor coordination (abilities such as drawing and painting) and gross motor coordination (running, jumping, and walking up and down the stairs), visuomotor coordination (observe, recognize, and use of visual information on shapes, figures, and objects), and also motor speed. However, these results suggested that greater training on reasoning increased hand-grip strength, closely associated with ADL. Effects on cognitive-motor abilities were also observed by Theill et al.[53], although in this case through simultaneous performance of PT and CT, as opposed to the use of CT alone by Ross et al.[38]. Theill et al.[53] found that simultaneous training can promote specific improvement in both cognitive performance and dual-task motor-cognitive performance, providing greater potential for performing ADLs.

In a study based on the ACTIVE protocol, Kwok et al.[33] showed an improvement in general cognitive functioning of low-educated individuals, with effects maintained for at least 9 months in the cognitive areas of conceptualization and memory. The authors proposed this finding might be explained by the ceiling effect, i.e., a tendency of the CT to promote greater gains among subjects with below normal cognition prior to the training and in individuals who received no simultaneous training. In contrast, the results of the study by Teixeira-Fabrício et al.[54] showed that a higher educational level can lead to greater use of strategies, higher self-efficacy for memory, and larger performance gain post-training. In addition, Casemiro et al.[55] emphasized that greater education can be directly associated with ease of learning. The researchers reported that high-educated individuals perform visual search tasks more effectively than subjects with a lower educational level.

The studies by Gross and Rebok[40] and Gross et al.[44]. assessed the impact of the memory training program from the ACTIVE study on the use of strategies. The results of the first of these two studies[40] indicated that memory training improved the levels of use of strategies and can assist older adults who deploy them in appropriate situations. The authors reported that the effects of training persisted for up to 5 years and that strategies are positively associated with memory performance and daily functioning. The results of the study by Gross et al.[44] suggested that the method of loci (MoL) (post-training) was used by up to 25% of older adults and immediately improved memory, with effects sustained throughout the follow-up period. These results corroborate the notion that a balance occurs between complexity and novelty in strategy selection by the elderly and that the memory training produces, by promoting changes in the strategies used, observable qualitative and quantitative differences in memory performance. Other studies assessing the effects of memory training on the use of strategies in CN older persons are also available in the literature. In contrast to the findings of Gross and Rebok[40] and Gross et al.[44], the results of the study by Yassuda et al.[16] suggested that the more intense use of memory strategies resulting from training does not necessarily guarantee better

performance. Carvalho et al.[52], however, showed that categorization strategy training led to greater use of the trained strategy and significantly improved the performance on the episodic memory task.

Another study by Gross et al.[37], also derived from the ACTIVE study, reported an association of memory training with significant long-term gains in learning, stemming from both the highly significant training effect and slower memory decline for up to 5 years. The study by Sisco et al.[9], which assessed the impacts of the memory training program from the ACTIVE study in conjunction with the booster intervention, suggested in their results that, when carried out in a multifactorial manner together with the booster intervention, the training can improve literal recall for stories.

Borella et al.[36] showed in their study that WM training produced benefits that were maintained over time. The authors suggested that these findings confirmed there is still room for plasticity in the basic mechanisms of cognition in old age, congruent with other studies addressing CT in CN older adults in which these subjects were able to attain a level of current performance closer to their maximum possible performance[56].

Ball et al.[43] reported that positive initial SOPT effects were amplified by booster sessions. According to these authors, a single booster session counteracted around 5 months of age-related processing speed decline. In line with this finding, the results of the study by Aramaki and Yassuda[57] showed that, besides stability in participants' cognitive performance between the two interventions, additional gains on episodic memory scales were observed after the booster intervention.

Linde et al.[35] revealed in the results of their study that the three types of activities carried out by the participants, i.e., PT, CT, and combined PT plus CT, can be seen as cognition-enrichment behaviors. Eggenberger et al.[32] reported that particular executive functions benefited from simultaneous CT and PT compared to exclusively physical multicomponent training, concluding that cognitive-physical training programs may counteract widespread cognitive impairments in the elderly. These findings are consistent with the recent study by McEwen et al.[58], who carried out an intervention of simultaneous aerobic exercise and memory training and found that the intervention promoted improvements in memory, attention, and reasoning abilities.

### Long-term studies on cognitive training in older adults with mild cognitive impairment or at risk for dementia

Of the eight studies involving cognitively impaired individuals, seven examined the longitudinal effects of a variety of forms of CT in older adults with MCI[45-51], while one was a multidomain intervention in elderly people at risk for dementia, but not diagnosed with MCI[6].

The study by Valdes et al.[51] revealed that all MCI groups showed an immediate improvement relative to the control group, with an emphasis on the non-amnestic MCI group, in which no significant changes were observed during the 5-year follow-up. Belleville et al.[47]. suggested in their results an improvement on the memory task and strategy use in everyday life of participants of the CT. Consistent with the findings of both studies[47,51], the study by Olchik[59], in which older persons with MCI performed memory training, reported that CT can benefit participants in terms of acquisition of strategies for coping with and overcoming cognitive impairment, and even reverse MCI, allowing these individuals to attain a similar level of performance to CN subjects. In addition, the authors believe this training modality represents a cost-effective viable educational intervention that can benefit older persons with MCI.

Rojas et al.[48] reported that CT in individuals with MCI can also represent a promising treatment option for optimizing performance, preventing cognitive decline, or delaying progression to dementia in this patient group. Brum et al.[60] noted that CT in older adults with MCI constitutes a non-pharmacological alternative for preventing cognitive and functional decline and for promoting improvement in cognitive performance.

In the study by Rozzini et al.[49], participants who received ChEIs plus NPT showed significant improvements in cognitive areas and in behavioral disturbances, confirming that a long-term NPT in ChEIs-treated MCI subjects induces additional cognitive and mood benefits. These results are in line with the findings of Olazarán et al.[61], who reported that patients with MCI, mild Alzheimer's disease (AD), or moderate AD treated with ChEIs and undergoing a long-term cognitive-motor intervention had greater mood and cognitive benefits compared to the control group.

Bahar-Fuchs et al.[46] showed in their study that unsupervised home-based CCT with individual tailoring can lead to cognitive and non-cognitive benefits in older adults with MCI. Consistent with these results, the study by Hill et al.[62] in older adults with MCI and dementia revealed the efficacy of CCT on global cognition, selected cognitive domains, and psychosocial functioning of individuals with MCI.

In the study by Law et al.[50], the results showed that the FcTSim promoted improvements in general cognitive functions, particularly executive function and problem-solving ability, thereby serving as a cost-effective way of promoting brain plasticity, even in patients with MCI. These findings are consistent with

the study by Liao et al.[63], who randomized older adults with MCI into either a VR-based PT with CT group or a combined PT and CT group without VR. Results showed that the VR group improved global cognition, while both groups improved executive function and verbal memory.

Zhao et al.[45] suggested in their study that the CrExp therapy promoted greater gains in general cognitive functioning, memory, executive functions, functional status, and everyday living ability among patients receiving the therapy compared to participants receiving standard CT. The authors reported that improvements were maintained at the 6-month follow-up and concluded that this therapy may serve as a cost-effective adjunct to standard interventions for older adults with MCI.

Law et al.[50] and Zhao et al.[45] showed that these interventions can serve as cost-effective strategies for older adults with MCI, satisfying the premises of the World Health Organization (WHO), which holds that CT should be provided and applied to both CN older adults and individuals with MCI as a preventive action for cognitive decline and development of dementia, irrespective of social class[64]. This is also guaranteed by the Active Aging policy, which highlights the necessity of incentive for care and development of cognitive abilities to maintain the autonomy of an individual[64].

With regard to the study in older adults at risk for developing dementia but not diagnosed with MCI[6], results showed that multidomain intervention can improve cognitive functioning in older adults at risk of cognitive decline[6].

To sum up, the studies reviewed reported a number of cognitive performance benefits, including a role in improving some motor abilities, among older adults without dementia who participated in CT programs with or without booster sessions and who received multimodal interventions or otherwise.

A total of 14 long-term studies were gathered in which cognitively healthy elderly people, without any type of cognitive impairment, were followed up. In view of this, it was possible to report several cognitive performance benefits. Furthermore, the results of these studies documented that such cognitive benefits lasted up to 5 years after starting the intervention. Eight long-term studies were also gathered in which elderly with MCI or at risk for dementia were followed up. Studies have indicated significant sustained improvements in general cognitive function, executive function, and problem-solving ability, in addition to an increase in brain plasticity. Furthermore, it has also been observed that computerized cognitive interventions at the MCI can prevent cognitive decline or slow conversion to dementia. Finally, 10 publications of protocols were analyzed, studies that will describe their methods and plans. Among them, one protocol has demonstrated the potential to significantly improve efforts to ameliorate cognitive decline, providing important information about the feasibility and intervention effects of a combination of exercise and CT for older adults with MCI.

It is important to highlight that the studies with methodology models included in this review were mostly interventions characterized as multicomponent cognitive stimulation and allow the replication of their methods to other research centers, to verify in a contemporary way to the original authors, if the models of proposed interventions can generate cognitive gains in healthy elderly and in elderly people with MCI.

Therefore, different types of CT programs appear to represent highly applicable cost-effective strategies for promoting health and quality of life in older age. There were a vast number of studies addressing the theme and a wide variety of objectives related to the specific subthemes, with consequent heterogeneity in study results. Generally, however, all findings showed positive effects on the cognition of participants.

The limitations of this study included the selection and inclusion of multimodal CT research; the comparison of CT studies whose participants were CN elderly with studies in which older adults with MCI participated; and the citing of cognitive improvements measured using cognitive screening tests as opposed to more specific tests, such as neuropsychological assessment scales.

As presented in this article, some of the studies employed original, innovative methods incorporating a long-term follow-up. Thus, the methodology of these studies should be replicated in different cultures, given some have been published without results, providing fertile ground for future studies. It is also suggested to carry out future systematic review studies of CT only with a focus on multimodal studies and with samples focused on CN elderly and older adults with MCI.

**Authors' contributions.** TBLS, JSB, MECB, GAS, MGZ, LCM, PPL, NPC, TNO, SMDB: conceptualization, investigation, methodology, visualization, writing – original draft, and writing – review & editing. TBLS, LCM, PPL, SMDB: funding acquisition. TBLS, TNO, SMDB: project administration, supervision, and writing – review & editing.

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Dement Neuropsychol 2022 June;16(2):153-161

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0019

# Falls in Parkinson's disease:
## the impact of disease progression, treatment, and motor complications

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**ABSTRACT.** The prevalence of Parkinson's disease (PD) tends to increase worldwide in the coming decades. Thus, the incidence of falls is likely to increase, with a relevant burden on the health care system. **Objective:** The objective of this study was to evaluate clinical factors and drug use associated with falls in PD patients. **Methods:** We conducted a cross-sectional study at the Movement Disorders outpatient clinic of a tertiary hospital in Northeast Brazil. We performed structured interviews to collect sociodemographic and clinical data. Functional capacity was assessed using the Schwab and England Activities of Daily Living Scale and the modified Hoehn and Yahr Staging Scale. We divided the study sample into non-fallers (no falls) and fallers (≥1 fall), and non-recurrent (≤1 fall) and recurrent fallers (>1 fall). **Results:** The study population comprised 327 PD patients (48% women), with a mean age of 70 years. The mean disease duration was 9.9±6.9 years. The most prevalent comorbidities were depression (47.2%), hypertension (44.0%), and type 2 *diabetes mellitus* (21.5%). The logistic regression analysis revealed that hallucinations, amantadine, and catechol-*O*-methyltransferase inhibitors (entacapone) were independently associated with falls in PD patients. Also, hallucinations, dyskinesia, and the use of amantadine were independently associated with recurrent falls. **Conclusions:** Health care providers play an essential role in fall prevention in PD patients, particularly by identifying older adults experiencing dyskinesia and visual hallucinations. Prospective studies should investigate the use of amantadine as a risk factor for falls in PD patients.

**Keywords:** Accidental Falls; Parkinson Disease; Gait.

**QUEDAS NA DOENÇA DE PARKINSON: IMPACTO DA PROGRESSÃO DA DOENÇA, DO TRATAMENTO E DAS COMPLICAÇÕES MOTORAS**

**RESUMO.** Estima-se aumento na prevalência da doença de Parkinson (DP) em todo o mundo nas próximas décadas. Dessa forma, espera-se também aumento na incidência de quedas e seu impacto no sistema de saúde. **Objetivo:** O objetivo deste estudo foi avaliar fatores clínicos e medicamentos associados a quedas em pacientes com DP. **Métodos:** Trata-se de um estudo observacional transversal, realizado no ambulatório de Distúrbios do Movimento de hospital terciário no Brasil. Os dados sociodemográficos e clínicos foram coletados por meio de entrevista estruturada. A capacidade funcional foi avaliada pela Escala de Atividades de Vida Diária de Schwab e England e o estadiamento por Hoehn e Yahr modificado. A amostra foi dividida em não caidores (0 quedas) e caidores (≥1 queda) e não caidores recorrentes (≤1 queda) e caidores recorrentes (>1 queda). A informação sobre o número de quedas nos últimos seis meses foi confirmada com familiares e cuidadores. **Resultados:** A população do estudo foi de 327 pacientes (48% mulheres), com idade média de 70 anos e duração média da doença de 9,9±6,9 anos. As comorbidades mais prevalentes foram depressão (47,2%), hipertensão (44%) e *diabetes mellitus* tipo 2 (21,5%). A análise de regressão logística revelou que alucinações visuais, uso de amantadina e uso de entacapona foram independentemente associadas a quedas. Alucinações visuais, discinesia e uso de amantadina foram independentemente associados a quedas recorrentes neste estudo. **Conclusões:** Os profissionais de saúde desempenham um papel importante na prevenção de quedas em pacientes com DP, principalmente idosos que apresentam discinesia e alucinações visuais. Estudos prospectivos da amantadina devem ser realizados para investigar sua associação com quedas em pacientes com DP.

**Palavras-chave:** Acidentes por Quedas; Doença de Parkinson; Marcha.

This study was conducted by the Walter Cantídio University Hospital, Universidade Federal do Ceará, Fortaleza, CE, Brazil.

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**Disclosure:** The authors report no conflict of interest.

**Funding:** none.

Received on February 16, 2021; Received in its final form on August 10, 2021; Accepted on October 09, 2021.

## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder[1]. It is a complex disease that causes motor and non-motor symptoms and impairs functionality[2]. People with PD require regular medical and multiprofessional evaluations for function adjustments, rehabilitation, and management of complications. The annual risk of falls in PD ranges from 45 to 68%[3]. Notably, some parkinsonian factors could predict fall risk, including orthostatic hypotension, freezing of gait, disease severity, and postural instability[4]. Recurrent falls are an issue in the life of PD patients and suggest disease progression[3]. The definition of recurrent falls comprises more than one fall in a certain period[5] and allows discriminating people who happened to fall from those with an increased intrinsic risk for falls[3].

Underlying factors associated with recurrent falls in PD patients are different from those of the general population[5]. Risk factors for falls may be intrinsic or extrinsic. Intrinsic factors include physiological changes related to age, balance and gait alterations, visual and hearing impairment, and the presence of comorbidities. Extrinsic factors include environmental risks, such as insufficient lighting and slippery floor, risk behaviors, and behaviors related to activities of daily living[6].

The prevalence of PD tends to increase worldwide in the coming decades[1]. Thus, the incidence of falls is likely to increase with a relevant burden on the health care system, considering their consequences. Falls may result in deaths, decreased mobility, and lower quality of life[7]. It is a complex issue, with a long way for effective prevention and treatment[5]. Previous studies have found an association between the use of certain drugs and increased risk of falls in older people[8-10]. The most effective prevention programs have multidimensional strategies to reduce falls, including careful regular review of medication use[11]. Neurological consultations of PD patients have often focused on prescribing antiparkinsonian drugs and addressing motor symptoms[12]. However, it is necessary to actively address factors associated with fall risk during a routine neurological consultation to prevent future falls. In this sense, neurologists should be aware of fall risk and review the medications prescribed to their patients. Many studies focus on falls in older people. However, few studies have addressed falls in PD, focusing on medications associated with increased risk of falls. Thus, the purpose of this study was to characterize the clinical features of PD patients and assess variables related to the occurrence of falls and recurrent falls in the previous 6 months.

## METHODS

### Study design and participants

We conducted a cross-sectional study to evaluate consecutive PD patients who attended the Movement Disorders outpatient clinic of Hospital Universitário Walter Cantidio (HUWC), Fortaleza (Ceará), Northeast Brazil. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cross-sectional studies. Participants were recruited from January 2018 to August 2019. Diagnosis of PD was confirmed when they fulfilled the clinical diagnostic criteria by the Movement Disorders Society and the U.K. Parkinson's Disease Society Brain Bank. We excluded the patients with severe PD, according to the modified Hoehn and Yahr (HY) Scale for PD Staging (HY-5).

### Clinical evaluation

We evaluated the patients during regular face-to-face consultations. Our team comprised two neurology residents, one internal medicine resident, one geriatrics resident, two neurologists, and one geriatrician previously trained to evaluate PD patients. Potential confounders were minimized by the previous training to address these patients. We used a structured questionnaire to collect sociodemographic and clinical information, including age, sex, disease duration, family history of PD, marital status, history of hypertension, diabetes, cardiac insufficiency, peripheral arterial disease, cancer, chronic obstructive pulmonary disease[13], chronic kidney disease, orthostatic hypotension, stroke[14], dementia, mild neurocognitive disorder (15), epilepsy, hip fracture, depression, bipolar affective disorder[15], osteoporosis, osteoarthritis, and urgent urinary incontinence.

We also collected information on antiparkinsonian drug treatments, including L-DOPA (L-DOPA/carbidopa, L-DOPA/benserazide, and sustained-release formulation of L-DOPA), catechol-*O*-methyltransferase (COMT) inhibitors (entacapone), monoamine oxidase B (MAO-B) inhibitors (rasagiline), amantadine, and dopamine agonists (pramipexole). To compare different doses of antiparkinsonian medications, we adopted the levodopa equivalent dose (LED) according to a systematic review by Tomlinson et al.[16].

Moreover, we collected information on the number of drugs used by each participant. We used the Schwab and England Activities of Daily Living (SE ADL) Scale to assess the ability to perform ADL and the modified HY scale for PD staging[17]. We evaluated all patients during the "on" phase. We collected any information on complications of antiparkinsonian treatments,

including visual hallucinations, dyskinesias, and motor fluctuations, by consulting patients, family, caregivers, and clinical records. In case of difficulties obtaining information with the patients (e.g., cognitive impairment), we collected the data by interviewing their family or caregivers. The interview was followed by a physical examination, in which clinical changes not perceived by the patients or their family could be recognized.

### Assessment of falls

A fall was defined as an event that results in a person coming to rest unintentionally on the floor or another lower level without any cause (e.g., violent behavior, assaults, or car or bike accidents) or precipitant (syncope or epilepsy)[18]. A faller was defined as the patient who had at least one fall and a non-faller who did not have any fall in the past 6 months. A non-recurrent faller was defined as the individual who had none or one fall. A recurrent faller was defined as an individual who had two or more falls[3]. We evaluated the number of falls in the past 6 months before the medical evaluation.

### Statistical analysis

We calculated the mean, standard deviation, and median for each continuous variable. We compared non-fallers (0 falls) and fallers (≥1 fall), as well as non-recurrent (≤1 fall) and recurrent fallers (>1 fall). We used the Shapiro-Wilk test to assess the normality distribution of data. We compared the demographic and clinical characteristics between the groups using the Mann-Whitney U test for continuous variables and the $X^2$ test or Fisher's exact test for categorical variables. We constructed two separate multivariate logistic regression models using a forward stepwise procedure to assess the relationship between the study variables (fallers vs. non-fallers and non-recurrent fallers vs. recurrent fallers). Fallers and recurrent fallers were considered as dichotomous-dependent variables (yes or no) in the regression models.

After conducting a univariate analysis including the variables of interest (Tables 1 and 2, and Figure 1), we included those with $p<0.05$ in the multivariate regression analysis (Tables 3 and 4). For the multivariate regression analyses, we used binary logistic regression analysis with a forward stepwise method. A detailed description of these analyses with the interactions of the models and the inputs and outputs of variables are available in Supplementary Materials 1 and 2. We used the variance inflation factor to verify multicollinearity in the independent variables. Statistical analyses were performed using the JAMOVI statistics package (version 0.9).

### Ethics

The local ethics committee approved the study (registration number: 91075318.1.0000.5045). All participants gave their written informed consent before the collection of data. We conducted all procedures by following the ethical standards of the human experimentation committee and the principles of the Declaration of Helsinki.

## RESULTS

We included 327 patients in the analysis (48% women). The mean age was 70 years old, and the mean disease duration was 9.9±6.9 years. Over half of them (201; 62.2%) were married. Notably, 61 (19.1%) participants had a family history of PD. The most common clinical manifestations associated with PD were sleep disorders (67.1%), motor fluctuations (58.4%), urinary incontinence (36.7%), and orthostatic hypotension (28.4%). The most prevalent comorbidities were depression (47.2%), hypertension (44%), and type 2 *diabetes mellitus* (21.5%). Sociodemographic variables were not significantly associated with fallers (Table 1). Figure 1 illustrates the frequency of medication use among fallers and recurrent fallers.

The participants were sorted into two groups: fallers and non-fallers in the first analysis and recurrent fallers and non-fallers in the second analysis. In the logistic regression models, we included the clinical symptoms that were substantially related to the occurrence of falls in the previous 6 months: motor fluctuations (odds ratio [OR]=1.66, p=0.027), dyskinesia (OR=2.99, p<0.001), hallucinations (OR=2.79, p<0.001), hypertension (OR=0.62, p=0.034), urinary incontinence (OR=1.73, p=0.018), and walking aids (OR=1.78, p=0.044). Regarding the scale variables, the significant ones were HY stage (p=0.002), SE ADL score (p=0.007), and disease duration (p<0.001).

Table 1 and Figure 1 show the variables significantly associated with falls in the univariate analysis. The following clinical symptoms were shown to be categorical variables substantially related to recurrent falls: dyskinesia (OR=4.53, p<0.001), hallucinations (OR=2.87, p<0.001), mild cognitive impairment (OR=2.71, p=0.017), motor fluctuations (OR=2.08, p=0.003), walking aids (OR=1.97, p=0.019), dementia (OR=1.83, p=0.037), and urinary incontinence (OR=1.69, p=0.028). Regarding the scale variables, the significant ones were HY stage (p<0.001), SE ADL score (p=0.007), and disease duration (p<0.001). Table 3 and Figure 1 show the variables significantly associated with recurrent fallers in the univariate analysis. These variables were included in the logistic regression models (Table 4).

**Table 1.** Sociodemographic and clinical characteristics of fallers and non-fallers among patients with Parkinson's disease.

| | Fallers | Non-fallers | p-value | OR (95%CI) |
|---|---|---|---|---|
| Age (years) | 70 (60–78) | 71 (60–78) | 0.761[a] | – |
| Male sex, n (%) | 86 (57.0) | 84 (47.7) | 0.096[b] | 1.45 (0.94–2.24) |
| Family history of PD, n (%) | 32 (22.1) | 29 (16.7) | 0.222[b] | 1.42 (0.81–2.48) |
| Sleep complaints, n (%) | 104 (69.3) | 114 (65.1) | 0.423[b] | 1.21 (0.76–1.93) |
| Motor fluctuations, n (%) | 95 (65.1) | 92 (52.9) | **0.027**[b] | **1.66 (1.06–2.61)** |
| Dyskinesia, n (%) | 75 (51.0) | 45 (25.9) | **<0.001**[b] | **2.99 (1.87–4.77)** |
| Hallucinations, n (%) | 49 (34.3) | 26 (15.8) | **<0.001**[b] | **2.79 (1.62–4.80)** |
| Hypertension, n (%) | 57 (37.7) | 87 (49.4) | **0.034**[b] | **0.62 (0.40–0.97)** |
| Type 2 DM, n (%) | 30 (19.9) | 40 (23.0) | 0.495[b] | 0.83 (0.49–1.42) |
| Congestive heart failure, n (%) | 2 (1.3) | 6 (3.4) | 0.294[b] | 0.38 (0.08–1.90) |
| Coronary artery disease, n (%) | 7 (4.6) | 11 (6.3) | 0.515[b] | 0.72 (0.27–1.92) |
| Peripheral artery disease, n (%) | 0 (0.0) | 2 (1.1) | 0.501[c] | 0.23 (0.01–4.81) |
| Chronic venous insufficiency, n (%) | 3 (2.0) | 4 (2.3) | >0.999[c] | 0.87 (0.19–3.96) |
| Active cancer, n (%) | 3 (2.0) | 3 (1.8) | >0.999[c] | 1.14 (0.23–5.71) |
| Previous cancer, n (%) | 3.5 (5) | 3.4 (6) | >0.999[c] | 0.94 (0.28–3.14) |
| COPD, n (%) | 2 (1.3) | 3 (1.7) | >0.999[c] | 0.77 (0.13–4.67) |
| Chronic kidney disease, n (%) | 2 (1.3) | 3 (1.7) | >0.999[c] | 0.77 (0.13–4.68) |
| Orthostatic hypotension, n (%) | 33 (28.9) | 33 (28.0) | 0.868[b] | 1.05 (0.59–1.86) |
| Previous stroke, n (%) | 11 (7.3) | 7 (4.1) | 0.204[b] | 1.87 (0.70–4.94) |
| Dementia, n (%) | 32 (21.3) | 27 (15.4) | 0.169[b] | 1.49 (0.84–2.62) |
| Mild cognitive impairment, n (%) | 15 (10.3) | 9 (5.4) | 0.109[b] | 2.00 (0.85–4.71) |
| Epilepsy, n (%) | 3 (2) | 5 (2.8) | 0.731[c] | 0.71 (0.17–3.01) |
| Hip fracture, n (%) | 3 (2) | 4 (2.3) | >0.999[c] | 0.88 (0.19–3.99) |
| Depression, n (%) | 79 (52.7) | 75 (42.6) | 0.070[d] | 1.50 (0.97–2.32) |
| Bipolar disorder, n (%) | 1 (0.7) | 2 (1.1) | >0.999[b] | 0.58 (0.05–6.46) |
| Osteoporosis, n (%) | 15 (10.3) | 21 (13.1) | 0.452[b] | 0.76 (0.38–1.54) |
| Osteoarthritis, n (%) | 28 (19.9) | 27 (17.4) | 0.590[b] | 1.17 (0.65–2.11) |
| Urinary incontinence, n (%) | 65 (43.6) | 54 (30.9) | **0.018**[b] | **1.73 (1.10–2.74)** |
| Walking aids, n (%) | 35 (25) | 26 (15.8) | **0.044**[b] | **1.78 (1.01–3.14)** |
| Motor physical therapy, n (%) | 22 (16.3) | 20 (12.3) | 0.331[b] | 1.38 (0.72–2.66) |
| Hoehn and Yahr stage | 3 (2–4) | 2.64±1.15 (2.25) | **0.002**[a] | – |
| SE ADL score | 80 (50–90) | 80 (50–90) | **0.007**[a] | – |
| Disease duration (years) | 10 (6–17) | 2.25 (2–3) | **<0.001**[a] | – |

Data expressed as percentages and medians (25th–75th). [a]Mann-Whitney U test; [b]Pearson's $X^2$ test; [c]Fisher's exact test. PD: Parkinson's disease; SE ADL: Schwab and England Activities of Daily Living scale; DM: *diabetes mellitus*; COPD: chronic obstructive pulmonary disease; SNRIs: serotonin–norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; OR: *Odds Ratio*; 95%CI: 95% confidence interval. Bold values denote a statistically significant difference.

**Table 2.** Sociodemographic and clinical characteristics of occasional and recurrent fallers among patients with Parkinson's disease.

| | Falls | | | |
|---|---|---|---|---|
| | **>1** | **≤1** | **p-value** | **OR (95%CI)** |
| Age (years) | 70 (63–76) | 70 (60–78) | 0.728[a] | – |
| Male gender, n (%) | 64 (55.2) | 106 (50.2) | 0.393[b] | 1.22 (0.77–1.92) |
| Family history of PD, n (%) | 22 (19.8) | 39 (18.8) | 0.817[b] | 1.07 (0.60–1.92) |
| Sleep complaints, n (%) | 81 (70.4) | 137 (65.2) | 0.340[b] | 1.27 (0.78–2.07) |
| Motor fluctuations, n (%) | 78 (69.6) | 109 (52.4) | **0.003**[b] | **2.08 (1.28–3.39)** |
| Dyskinesia, n (%) | 68 (60.2) | 52 (25.0) | **<0.001**[b] | **4.53 (2.78–7.40)** |
| Hallucinations, n (%) | 41 (37.3) | 34 (17.2) | **<0.001**[b] | **2.87 (1.68–4.89)** |
| Hypertension, n (%) | 46 (39.7) | 98 (46.4) | 0.237[b] | 0.76 (0.48–1.20) |
| Type 2 DM, n (%) | 22 (19.0) | 48 (23.0) | 0.401[b] | 0.79 (0.45–1.38) |
| Congestive heart failure, n (%) | 2 (1.7) | 6 (2.9) | 0.717[c] | 0.60 (0.12–3.00) |
| Coronary artery disease, n (%) | 4 (3.4) | 14 (6.7) | 0.223[b] | 0.50 (0.16–1.56) |
| Peripheral artery disease, n (%) | 0 (0.0) | 2 (1.0) | 0.539[c] | 0.35 (0.02–.745) |
| Chronic venous insufficiency, n (%) | 3 (2.6) | 4 (1.9) | 0.703[c] | 1.36 (0.30–6.19) |
| Active cancer, n (%) | 2 (1.7) | 4 (1.9) | >0.999[c] | 0.89 (0.16–4.91) |
| Previous cancer, n (%) | 4 (3.5) | 7 (3.5) | >0.999[c] | 1.00 (0.29–3.51) |
| COPD, n (%) | 3 (2.6) | 2 (1.0) | 0.352[c] | 2.76 (0.45–16.7) |
| Chronic kidney disease, n (%) | 2 (1.7) | 3 (1.4) | >0.999[c] | 1.20 (0.20–7.31) |
| Orthostatic hypotension, n (%) | 26 (29.5) | 40 (27.8) | 0.772[b] | 1.09 (0.61–1.96) |
| Previous stroke, n (%) | 9 (7.8) | 9 (4.4) | 0.204[b] | 1.84 (0.71–4.78) |
| Dementia, n (%) | 28 (24.1) | 31 (14.8) | **0.037**[b] | **1.83 (1.03–3.23)** |
| Mild cognitive impairment, n (%) | 14 (12.5) | 10 (5.0) | **0.017**[b] | **2.71 (1.16–6.33)** |
| Epilepsy, n (%) | 2 (1.8) | 6 (2.9) | 0.717[c] | 0.61 (0.12–3.06) |
| Hip fracture, n (%) | 3 (2.6) | 4 (1.9) | 0.700 c | 1.39 (0.31–6.33) |
| Hearing impairment, n (%) | 12 (10.5) | 14 (6.8) | 0.247[b] | 1.61 (0.72–3.60) |
| Visual impairment, n (%) | 10 (8.8) | 9 (4.4) | 0.108[b] | 2.11 (0.83–5.37) |
| Depression, n (%) | 62 (53.4) | 92 (43.8) | 0.095[b] | 1.47 (0.93–2.32) |
| Bipolar disorder, n (%) | 1 (0.9) | 2 (0.9) | >0.999[c] | 0.91 (0.08–10.13) |
| Osteoporosis, n (%) | 11 (9.8) | 25 (13.0) | 0.414[b] | 0.73 (0.35–1.55) |
| Osteoarthritis, n (%) | 21 (19.3) | 34 (18.2) | 0.817[b] | 1.07 (0.59–1.96) |
| Urinary incontinence, n (%) | 51 (44.7) | 68 (32.4) | **0.028**[b] | **1.69 (1.06–2.70)** |
| Walking aids, n (%) | 29 (27.4) | 32 (16.1) | **0.019**[b] | **1.97 (1.11–3.48)** |
| Motor physical therapy, n (%) | 14 (13.3) | 28 (14.6) | 0.768[b] | 0.90 (0.45–1.80) |
| Hoehn and Yahr stage | 3.0 (2.5–4.0) | 2.3 (2.0–3.0) | **<0.001**[a] | – |
| SE ADL score | 75 (50–90) | 80 (60–90) | **0.007**[a] | – |
| Disease duration (years) | 10.00 (6.00–17.00) | 7.00 (4.00–11.00) | **<0.001**[a] | – |

Data expressed as percentages and medians (25th–75th). [a]Mann-Whitney U test; [b]Pearson's $X^2$ test; [c]Fisher's exact test. PD: Parkinson's disease; SE ADL: Schwab and England Activities of Daily Living scale; DM: *diabetes mellitus*; COPD: chronic obstructive pulmonary disease; SNRIs: serotonin–norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; OR: *Odds Ratio*; 95%CI: confidence interval. Bold values denote a statistically significant difference.

**Table 3.** Multivariate logistic regression model.

| | OR (95%CI) | p-value |
|---|---|---|
| Amantadine use | 2.81 (1.63–4.85) | <0.001 |
| Hallucinations | 2.49 (1.35–4.61) | 0.004 |
| COMT inhibitor/entacapone use | 2.03 (1.10–3.72) | 0.023 |

Dependent variable: fall in the past 6 months (yes or no). OR: *Odds Ratio*; 95%CI: confidence interval; COMT: catechol-*O*-methyltransferase.

**Table 4.** Multivariate logistic regression model.

| | OR (95%CI) | p-value |
|---|---|---|
| Hallucinations | 3.19 (1.71–5.94) | <0.001 |
| Amantadine use | 3.13 (1.60–6.12) | 0.001 |
| Dyskinesia | 2.20 (1.14–4.23) | 0.019 |

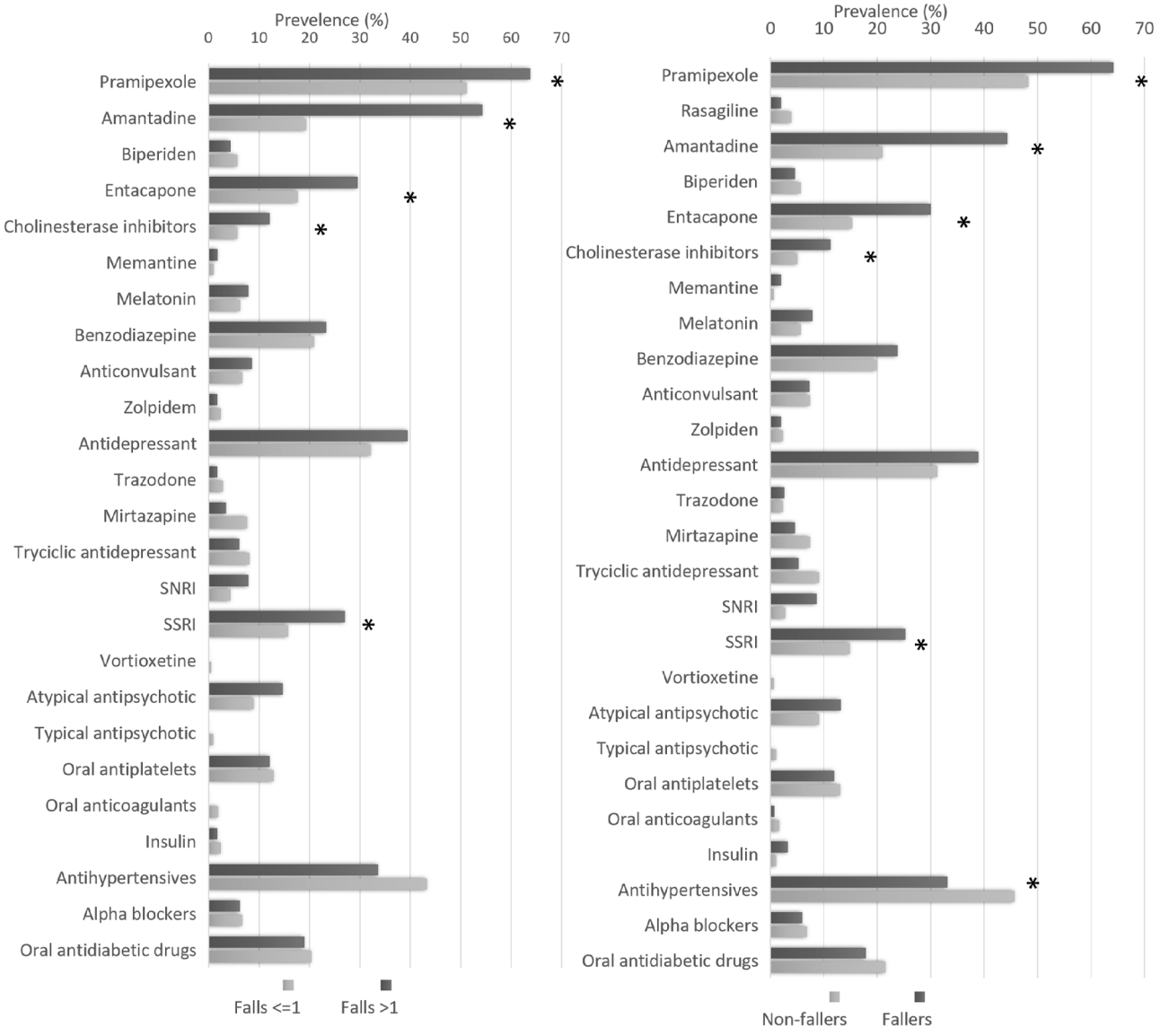
Dependent variable: fallers (yes or no). OR: *Odds Ratio*; 95%CI: 95% confidence interval.

## DISCUSSION

We showed that amantadine use, visual hallucinations, and entacapone use were significantly associated with falls. In the multivariate analysis, we found an association of recurrent falls with hallucinations, amantadine use, and dyskinesias. Amantadine use was the independent variable and most strongly associated with falls, and hallucinations were most strongly associated with recurrent falls. Fallers and recurrent fallers are likely to have more severe symptoms and present dyskinesias, requiring more antiparkinsonian drugs[9,19]. Moreover, they were likely to have more motor fluctuations and receive entacapone to improve these symptoms[20]. Also, patients with advanced PD have more hallucinations that are associated with cognitive decline[21].

Dyskinesia encompasses abnormal and involuntary movements, and its treatment is often challenging[16]. In a systematic review, Manson et al.[22]. concluded that dyskinesia in PD ranges from 40% to 50% within 5 years of treatment, and this rate may increase to 50–75% within 10 years of treatment.[22] Most patients have mild dyskinesia without functional impairment. This symptom may be improved with adjustments in dopaminergic drug treatment, reflecting a more cautious use of levodopa[23], once amantadine's side effects include blurred vision, dizziness, hallucinations, confusion, urinary disturbances, constipation, orthostatic hypotension, peripheral edema, and dry mouth[23], which could partially account for the increased fall risk. Also, amantadine is a drug frequently used for the treatment of dyskinesia. In this study, we found an association of amantadine use with falls and recurrent falls. Amantadine potentially causes anticholinergic effects[24], and its anti-dyskinetic effects are transient. Thomas et al.[25] reported that amantadine reduced dyskinesia, but from 3 to 8 months of treatment. Amantadine elimination is through renal clearance, and toxicity is more common in elderly patients with renal dysfunction. Thus, it is necessary to measure nitrogenous bases before prescribing this medication[24]. Individualized risk-to-benefit assessment should form a part of the decision on maintaining this drug treatment for dyskinesia in PD patients.

Dyskinesia was associated with recurrent falls in our study. In a 1-year prospective study, Rudziñska et al.[26] compared 106 PD patients against 55 age-matched controls. They reported a rate of fall of 54% in PD patients compared with 18% in controls. In another study, 3.6% of falls in PD patients were due to severe dyskinesia[26]. In a 6-month prospective study conducted with 64 PD patients without dementia or severe comorbidities, Lamont et al.[27] indicated that a prevalence of 54% experienced near falls or falls. The authors found that dyskinesia, defined as the occurrence of scores ≥1 in the Unified Parkinson's Disease Rating Scale item-32, was the strongest predictor of future or near falls[27]. Involuntary movements that interfere with gait can explain the link between dyskinesia and repeated falls. Indeed,




*Statistical difference.

**Figure 1.** Frequency between fallers and medication use.

gait is impaired in patients with severe dyskinesia and advanced PD[23].

Visual hallucinations are frequent in PD, and their prevalence ranges from 30 to 50% in cross-sectional studies[28]. A hypocholinergic status may be involved in the pathophysiology of visual hallucinations[29] once cholinergic deficit causes impaired attention and visual hallucinations[30]. Hallucinations were significantly associated with falls and recurrent falls in our study, supporting the hypothesis that acetylcholine reduction is related to hallucinations, which in turn are associated with impaired attention and increased risk of fall[29].

The cholinergic system of subcortical regions in the striatum, thalamus, and cerebellum plays a substantial role in mobility. Executive function is essential for cognition and the cognitive control of gait and balance[31]. Cholinergic activity in the thalamus, originating from the pedunculopontine nucleus (PPN), is essential for gait regulation and is implicated in gait impairment in PD. Some studies have evidenced cholinergic dysfunction by using positron emission tomography in PD patients, experiencing falls compared to non-fallers[32].

Hallucinations in PD probably involve a cholinergic neuronal loss and a loss of dopaminergic neurons.

Cholinergic dysfunction causes attention deficits and impairment in executive functions. Hence, gait and balance may no longer be compensated by attentional control, thus increasing the risk of falls[33].

In this study, we also found an association between COMT inhibitors and falls. In a case–control study conducted in U.S. veterans with hip fractures, French et al.[34] showed that the association between antiparkinsonian drug use and falls was four times higher in cases compared with controls. However, it is unlikely to determine whether this association is due to the disease or the medicines used to treat it.

Considering that the main side effects of COMT inhibitors are nausea, diarrhea, vomiting, and postural hypotension[35], the increased risk of falls due to drug use may be due to these distress symptoms. Patients expressing discomfort due to these symptoms were 2–5 times more likely to fall. However, long-term studies are needed to confirm the use of COMT inhibitors as a predictor of falls[36].

In a case-control study that included patients with parkinsonism and PD, Vestegaard et al.[37] evaluated the association between the incidence of fracture and antiparkinsonian drug use. Participants who experienced fractures (n=124,655) were matched for age and sex with three randomly assigned controls (n=373,962). The authors found a dose-dependent increase in the risk of fracture related to levodopa use, either alone or combined with carbidopa and/or a COMT inhibitor.

This study has some strengths and limitations. As strength, we highlighted the detailed information collected on the drugs prescribed, showing prescription practices in routine consultations. As a limitation, we did not use a specific instrument to assess dyskinesia and its severity. It is critical to enhance dyskinesia diagnosis accuracy by educating patients and their families and utilize diaries or video recordings to track their frequency and severity. Also, we did not have data on locomotor function (balance and gait).

Individualized clinical assessment and review of drug prescribing in PD are practices that must be incorporated into neurological consultations. Health care providers play a relevant role in fall prevention in PD patients, particularly by identifying older adults experiencing dyskinesia and visual hallucinations. Also, patients taking amantadine and entacapone should be carefully assessed for fall risk. Prospective studies should investigate the possible role of these medications as risk factors for falls in PD patients.

## ACKNOWLEDGMENTS

The authors thank Samuel Ranieri Oliveira Veras (Division of Neurology, Hospital Universitário Walter Cantidio, Fortaleza, Ceará) for providing care to PD patients and medical students and also thank Isabelle de Sousa Pereira (UFC), Lara Sobreira Pires de Carvalho, Ilzane Maria de Oliveira Morais, and Bianca Fernandes Távora Arruda (Universidade de Fortaleza, UNIFOR) for their help with cross-checking of data. The authors also thank all patients who agreed to participate in this study. Samuel Brito de Almeida benefits from the scholarship of the UFC doctoral programme in Medical Science by FUNCAP. Pedro Braga-Neto received funding from the Brazilian National Council for Scientific and Technological Development (CNPq) as research grant funding (Productivity scholarship).

**Authors' contributions.** DPL: contributed to the study conception and design, data collection, statistical analysis, and interpretation of data and participated in drafting this manuscript and revising it for important intellectual content. SBA and JCB: contributed to the study design and participated in revising this manuscript for important intellectual content. AHSC: participated in revising this manuscript for important intellectual content. JRGL: contributed to interpretation of data and participated in drafting this manuscript. MSA, PGBR, and ISP: contributed to data collection. ABVJ contributed to statistical analysis and interpretation of data. MASN and JSRF: participated in revising the draft for important intellectual content. PBN: contributed to the study conception and design, interpretation of data, and revising this manuscript for important intellectual content. All authors reviewed and approved the final version of this manuscript.

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Dement Neuropsychol 2022 June;16(2):162-170

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0071

# Do boys with MAOA_LPR*2R allele present cognitive and learning impairments?

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**ABSTRACT.** Monoamine oxidase A (*MAOA*) polymorphisms have been associated with antisocial disorders. Less attention has been paid to the cognitive functioning of individuals with different *MAOA* alleles. No study has described the cognitive phenotype associated with the less frequent, low enzyme activity allele, MAOA_LPR*2R. **Objective:** We describe the cognitive correlates of boys having MAOA_LPR*2R allele, ascertained in a sample of school children with normal intelligence, not referred for behavioral disorders. **Methods:** Participants were eight boys, attending from the second to fifth grades in state-run schools. They were identified among 712 children with typical general cognitive ability, genotyped for MAOA_LPR polymorphism. Participants were assessed with general intelligence, mathematics and spelling achievement, and verbal and visuospatial working memory tests. Neuropsychological performance was compared to published standards, using 1 SD below the mean as a cutoff value for low performance. **Results:** Intelligence of boys with MAOA_LPR*2R allele varied from above average (N=2) to low average in the other children. Five out of eight boys with the MAOA_LPR*2R allele had low mathematics achievement, and three presented additional difficulties with spelling. Four out of eight children had low short-term and working memory performance. **Discussion:** This is the first study describing cognitive correlates and school performance in boys having the MAOA_LPR*2R allele. Having this allele, and therefore, probably low MAO-A activity, does not necessarily imply low intelligence or low school performance. However, learning difficulties, particularly in math, and low working memory performance were observed in boys having this allele. This suggests a role of *MAOA* in learning difficulties.

**Keywords:** Monoamine Oxidase; Working Memory; Intelligence; Learning Disabilities; Dyscalculia; Neuropsychology.

**MENINOS COM O ALELO MAOA_LPR*2R APRESENTAM PREJUÍZOS COGNITIVOS E DE APRENDIZAGEM?**

**RESUMO.** Polimorfismos da monoaminoxidase A (MAOA) são associados a transtornos antissociais. Menos atenção tem sido dada ao funcionamento cognitivo de indivíduos com diferentes alelos de MAOA. Nenhum estudo descreveu o fenótipo cognitivo associado ao alelo menos frequente, de baixa atividade enzimática, MAOA_LPR*2R. **Objetivo:** Descrevemos os correlatos cognitivos de meninos com o alelo MAOA_LPR*2R, identificados em uma amostra de escolares com inteligência normal, não encaminhados por transtornos de comportamento. **Métodos:** Oito meninos com o alelo MAOA_LPR*2R foram identificados entre 712 crianças genotipadas, com inteligência típica, que cursavam do 2º ao 5º ano em escolas públicas. Foram avaliados:

This study was conducted by the group of Developmental Neuropsychology Laboratory, Department of Psychology, and the group of Laboratory of Human and Medical Genetics, Department of Genetics, Ecology and Evolution, both from Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil. This study was conducted also in partnership with Neurocog Laboratory, Department of Psychology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** MRSC is supported by a CNPq fellowship (312068/2015-8 and 312405/2018-9). GMP, EOS, AHBC, and CAJ are supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). This research was supported by grants from Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and the CAPES-DAAD Program (PROBRAL). The authors thank the Program for Technological Development in Tools for Health-PDTIS/FIOCRUZ for use of its facilities.

Received on July 14, 2021; Received in its fnal form on October 04, 2021; Accepted in final form on October 09, 2021.

inteligência, desempenho em matemática e ortografia, memória de trabalho verbal e visuoespacial. O desempenho foi comparado a normas publicadas, utilizando-se 1 desvio padrão (DP) abaixo da média como ponto de corte para desempenho rebaixado. **Resultados:** A inteligência dos meninos com alelo MAOA_LPR*2R variou de acima da média (N=2) a médio-inferior nas demais crianças. Cinco dos oito meninos com alelo MAOA_LPR*2R apresentaram desempenho rebaixado em matemática e três apresentaram dificuldades adicionais em ortografia. Quatro dos oito meninos apresentaram baixo desempenho de memória de curto prazo e de trabalho. **Discussão:** Este é o primeiro estudo a descrever os correlatos cognitivos e o desempenho escolar em meninos com alelo MAOA_LPR*2R. Ter esse alelo não significa necessariamente baixa inteligência ou baixo desempenho escolar. No entanto, dificuldades de aprendizagem, principalmente em matemática, e desempenho rebaixado da memória de trabalho foram observados em mais da metade dos meninos com esse alelo. Isso sugere um papel do MAOA nas dificuldades de aprendizagem.

**Palavras-chave:** Monoaminoxidase; Memória de Trabalho; Inteligência; Deficiências da Aprendizagem; Discalculia; Neuropsicologia.

## INTRODUCTION

Monoamine oxidase A (MAO-A) is a mitochondrial enzyme involved in several different metabolic pathways, processing endogenous as well as exogenous metabolites[1]. MAO-A is one of the enzymes that catalyzes neurotransmitters in the central nervous system, including dopamine, serotonin, and norepinephrine[2]. MAO-A contributes to the regulation of the half-life of these neurotransmitters and, consequently, contributes to the regulation of their availability in the synaptic cleft. The *MAOA* gene is ubiquitously expressed, but its behavioral effects vary according to the brain region and the expression levels of other partners in the catecholamine availability regulation, such as catechol-*O*-methyltransferase (COMT) or MAO-B[1].

The first clearcut evidence for an MAO-A contribution for behavioral phenotypes emerged, when a pathogenic variant in the *MAOA* gene was identified in 14 individuals of a Dutch family[3]. Men in this family presented nonsyndromic, mild intellectual disability or borderline intelligence. Eight of the affected men in this family were examined. All presented stereotyped hand movements described as "wringing, plucking, and fiddling." In addition, their behavior was characterized by shyness, aggressive outbursts, stabbing, and fighting. Arson was reported for two of them. They also presented abnormal sexual behavior, characterized by exhibitionism, voyeurism, grasping, or holding of female relatives, and rape or rape attempts[4]. Females in this family were reportedly unaffected. Subsequently, evidence for the role of MAO-A in aggression and antisocial behaviors was found in many studies[5-8].

Polymorphisms in *MAOA* have been associated with several neuropsychiatric disorders such as mood disorders and attention deficit and hyperactivity disorder (ADHD)[9-11]. Additionally, *MAOA* polymorphisms have been associated with autism[7,12]. The most investigated polymorphism is a variable number of tandem repeats (VNTR) located in the *MAOA* gene promoter region and identified as MAOA_LPR (also known as MAOA-uVNTR). The monomer of the repetitive element is 30 bp long. MAOA_LPR has two frequent alleles (i.e., MAOA_LPR*3R and MAOA_LPR*4R) and three less common ones (i.e., MAOA_LPR*2R, MAOA_LPR*3.5R, and MAOA_LPR*5R). This is a regulatory polymorphism. The MAOA_LPR*3.5R and MAOA_LPR*4R alleles have been associated with a higher gene transcription and enzyme activity and are referred to as MAOA-H. Meanwhile, MAOA_LPR*3R and MAOA_LPR*5R present low enzymatic activity and are referred to as MAOA-L alleles[13]. It has been described that the MAOA_LPR*2R allele presents 25–30% of the transcriptional activity when compared to the MAOA_LPR*4R allele[6]. Consequently, MAOA_LPR*2R would also be a low activity allele. A synthesis of the studies describing MAOA_LPR*2R effects is presented in Table 1. *MAOA* polymorphisms have been consistently associated with disruptive and antisocial behavioral disorders. Most studies have focused on the behavioral aspects, with considerably less studies investigating cognitive aspects. Less attention has also been given to the less common alleles such as MAOA_LPR*2R. In this study, the cognitive correlates of the MAOA_LPR*2R allele are investigated.

Epigenetic studies comparing the degree of methylation of *MAOA* gene promoter between participants presenting antisocial behavior and normal controls also provided evidence that low *MAOA* activity (aka, high promoter methylation levels) is associated with antisocial personality[14,15]. A complex interaction with alleles in other genes has been described. For example, low activity alleles in both *MAOA* and *COMT* have been associated with higher adrenocorticotropic responses and cortical levels[16,17]. Stressful interactions in early life are a risk factor for antisocial disorders in male individuals with low *MAOA* activity, but not in females[5]. Such gene–gene and gene–environment effects help understanding the individual variation in the responses to stressful life experiences. For example, gene–environment interaction involving low activity alleles in *COMT* and *MAOA* genes

**Table 1.** Studies investigating the association between MAOA*2R and behavior disorders (PubMed search using MAOA, MAOA AND working memory, MAOA 2R, MAOA AND intelligence, MAOA 2-repeat allele).

| References | n | Sex | Population/cohort | Phenotypes | Findings and conclusions |
|---|---|---|---|---|---|
| Guo et al.[6] | 2,524 | Both sexes | National Longitudinal Study of Adolescent Health (Add Health) | Delinquent behavior | Boys with the MAOA_LPR*2R allele had twice the chance of presenting delinquent and violent behaviors when compared with participants with other alleles. The same effect is observed in girls but with less intensity. |
| Åslund et al.[19] | 1,825 | Both sexes | Survey of Adolescent Life in Vestmanland 2006 (SALVe-2006) | Delinquent behavior | MAOA_LPR genotype (one short variant for boys and one or two long variants for girls) showed a significant effect on delinquency when controlled for maltreatment. |
| Roettger et al.[22] | 6,001 | Males | National Longitudinal Study of Adolescent Health (Add Health) | Delinquent behavior | The relationship between delinquency and the MAOA_ LPR*2R allele decreases in participants who were close to their biological or adoptive father, but not in those close to their mother. |
| Beaver et al.[23] | 2,574 | Males | National Longitudinal Study of Adolescent Health (Add Health) | Violent behaviors | African Americans carrying the MAOA_LPR*2R allele were more likely to engage in violent behaviors such as shooting or stabbing someone when compared to other MAOA_LPR genotypes. |
| Beaver et al.[24] | 167/174 | Males | National Longitudinal Study of Adolescent Health (Add Health) | Anti-social phenotypes | African Americans with MAOA_LPR*2R allele had higher scores on an antisocial phenotype scale. Individuals with the MAOA_LPR*2R allele were also significantly more likely to be arrested, when compared to individuals with other alleles. There were no data for Caucasians. |
| Daw and Guo[25] | 2,167 | Both sexes | National Longitudinal Study of Adolescent Health (Add Health) | Contraceptive use | Females carrying the MAOA_LPR*2R allele have higher odds of having unprotected sex. The authors did not find this association in males. |
| Stetler et al.[26] | 89 | Male | Imprisoned population | Violent behaviors | Violent crime charges were significantly more frequent in carriers of MAOA_LPR*2R or MAOA_LPR*3R alleles. |
| Barnett et al.[27] | 6,000 | Both sexes | Avon Longitudinal Study of Parents and Children (ALSPAC) | Cognitive function | MAOA_LPR alone did not show a significant effect on cognitive function. The authors found an association between MAOA_LPR and COMT Val158Met genotypes with better working memory. |
| Belsky and Beaver[28] | 1,586 | Both sexes | National Longitudinal Study of Adolescent Health (Add Health) | Self-regulation and adolescence parenting | Under different environmental conditions, MAOA_LPR could be one moderator of parenting and self-regulation in boys. |
| Rommelse et al.[29] | 545 | Both sexes | Dutch part of the International Multicenter ADHD Genetics (IMAGE) cohort | ADHD and neuropsychological functioning | One of the haplotypes was associated with poorer motor control in boys and with better visuospatial working memory in girls. |
| Chien et al.[30] | 1,074 | Male | In custody population | Heroin dependence | MAOA_LPR polymorphism does not appear to be involved in heroin dependence. |
| Ko et al.[31] | 50 | Males | ADHD and non-ADHD population | ADHD | ADHD carriers of rs1137070 T allele had higher activation of pars opercularis when compared with carriers of C allele. |

and academic pressure has been reported[18]. *MAOA* maps to the short arm of the X-chromosome and, therefore, males are hemizygous, while females are homozygous or heterozygous. Consequently, allele/genotype effects vary depending according to sex. For example, the presence of low activity *MAOA* alleles in males has been associated with higher susceptibility to environmental stressors. On the contrary, higher sensitivity to environmental stressful influences has been associated with the presence of high activity *MAOA* alleles in females[19-21].

Considering MAO-A relevance in the regulation of the half-life of neurotransmitters such as serotonin, norepinephrine, and dopamine, a large number of studies have been conducted, investigating the association of *MAOA* genotypes and different behavioral traits. Due to their higher frequencies, most studies consider only the MAOA_LPR*3R and MAOA_LPR*4R genotypes; sometimes, MAOA_LPR*3.5R is added to the MAOA_LPR*4R genotype. In comparison, the effects of MAOA_LPR*2R are less understood and investigated. Most known effects are related to antisocial behaviors and delinquency. These effects are usually associated with specific environmental conditions that can increase or decrease the genotype effects. Closeness to a father could moderate the MAOA_LPR*2R effect for delinquency over time[22]. Effects of maltreatment and other adverse conditions may also be mediated by MAOA_LPR*2R. Boys, who underwent maltreatment in childhood and who were hemizygous for the MAOA_LPR*2R allele, were more likely to commit infractions in adolescents or adulthood[19].

Although several studies have shown the relationship between MAOA_LPR*2R and antisocial behaviors when associated with other environmental conditions, there is evidence for this effect without any apparent environmental influence. In a sample composed of Caucasian and African American men, the group carrying the MAOA_LPR*2R allele had higher chances of stabbing or shooting someone at least once in life, when compared with individuals having any other *MAOA* allele[23]. As MAOA*2R presents a higher frequency among African Americans and to correct for the economical risk factors associated, skin color was included in the analytic models. A possible source of bias in such studies is the low frequency of the MAOA_LPR*2R allele in Caucasian populations[24], and large samples are required for the investigation of MAOA_LPR*2R effects in such populations. In addition to antisocial behavior, the MAOA*2R allele is also associated with impulsive behaviors. It has been shown that females carrying this allele had higher odds of having unprotected sex[25].

Most studies on the effects of MAOA_LPR*2R allele were conducted in samples of individuals presenting antisocial behaviors[8,19,22,24-26]. There are no studies investigating the neuropsychological profile of children from the general population. In the present study, we review the literature and describe the neuropsychological characteristics observed in school boys having the MAOA_LPR*2R genotype. PubMed searches were done using the terms MAOA, MAOA AND working memory, MAOA 2R, MAOA AND intelligence, and MAOA 2-repeat allele. The search results are presented in Table 1.

In general, cognitive-behavioral characteristics associated with the MAOA_LPR*2R have been less explored than those with the more frequent phenotypes (Table 1). With the exception of one study[27-29], the literature on phenotypes associated with the MAOA_LPR*2R genotype has explored the maladaptive behavioral more than the cognitive traits. In this study, we assessed cognitive abilities (i.e., intelligence, working memory, and numerical-arithmetic abilities) of eight male school children with the MAOA_LPR*2R genotype, who had normal intelligence and who were identified from a larger population sample. The hypothesis explored is that individuals with the MAOA_LPR*2R genotype may present difficulties with school achievement and working memory.

## METHODS

### Ethics in research

The selected participants are from two research projects with population data. Both projects were submitted and approved by the local ethics research board and complied with the Helsinki research principles for human beings (Project 1: "Developmental dyscalculia in school-age children: population screening and characterization of cognitive and genetic-molecular aspects" — COEP-UFMG: ETIC 42/08; Project 2: "Endophenotypes of learning difficulties in mathematics" — COEP-UFMG: CAAE 15070013.1.0000.5149). All children were authorized by their parents, through a written informed consent. Children's participation was also conditioned to their oral consent. The evaluation was conducted in a separate quiet room that had been arranged by the school.

### Participants

Data were obtained from two research projects in which 712 children with intelligence above the 15th percentile (PR), aged between 7 and 11 years, were neuropsychologically assessed at their state-run schools and genotyped for the MAOA_LPR polymorphism. Children were attending state-run schools. Eight boys were hemizygotes for MAOA_LPR*2R. The children having the MAOA_LPR*2R allele attended the second (n=3), third (n=3), and fifth (n=2) grades. Neuropsychological data from the boys with MAOA_LPR*2R were compared with those of the published test norms (Table 2).

### Assessment

Children were assessed at their schools. The instruments were applied by specially trained psychology undergraduate and graduate students. The Raven's Coloured

**Table 2.** Neuropsychological instruments.

| Construct | Instrument | References |
|---|---|---|
| General cognitive abilities (Intelligence) | Raven's Coloured Progressive Matrices (CPM) | Angelini et al.[32] |
| School achievement | TDE – Arithmetic subtest and Spelling subtest | Oliveira-Ferreira et al.[33], and Gomides et al.[34] |
| Verbal and visuospatial short-term and working memory | WISC-III Digits (Verbal Short Term and Working Memory) and Corsi Blocks | Figueiredo and Nascimento[35], and Galera and Souza[36] |
| Numerical and arithmetic abilities | Arabic number dictation, Addition, Subtraction, Multiplication | Gomides et al.[34] |

WISC-III: Wechsler Intelligence Scale for Children III. With exception of Raven's CPM, normative data were obtained from reference 33.

Progressive Matrices (CPM), Arabic Number Dictation, and TDE Spelling subtest were applied in groups of an average of six children. The TDE — Arithmetic subtest; WISC-III Digits and Corsi Blocks; and Addition, Subtraction, and Multiplication tasks were applied in individual sessions. The description and references of the instruments used in the neuropsychological assessment are presented in Table 2.

### Genotyping

Genomic DNA extraction was conducted using a proteinase K/salting out adapted method[37,38]. The protocol is available under request. DNA quantity and purity were assessed using spectrophotometry in a Nanodrop spectrophotometer. The MAOA_LPR was genotyped by fragment analysis in a capillary electrophoresis sequencer. PCR primer sequences were obtained from the literature[39]: MAOA-LPR forward: 5'-FAM CCCAGGCTGCTCCAGAAACATG-3' and MAOA-LPR reverse: 5'-GTTCGGGACCTGGGCAGTTGT-3'. The PCR consisted of 50 ng of total DNA, 10 pmol of each primer, 2 µg of Taq DNA polymerase, 5 µL of 5× buffer (Phoneutria Biotechnology, Belo Horizonte, Brazil), 2 µL of DMSO 100%, 20 mM dNTP, and Milli-Q water to a total volume of 25 µL. PCR cycling was composed of a 5 min initial denaturation step at 94°C, followed by 25 cycles of 94°C for 30 s, 56°C for 20 s, and 72°C for 30 s, and the last extension step of 5 min at 72°C. Amplicons were analyzed in an ABI 3730 capillary sequencer (Thermo Fisher Scientific), using the GeneScan™ 1200 LIZ® Size Standard. Genotypes were obtained in the Applied Biosystems® Sizing Analysis module Peak Scanner Software, version 3.0, available online in the Thermo Fisher Cloud. According to the fragment sizes, alleles were classified as 2-repeat (MAOA*2R), 183 bp; 3-repeat (MAOA*3R), 213 bp; 3.5-repeat (MAOA*3.5R), 229 bp; 4-repeat (MAOA*4R), 243 bp; and 5-repeat (MAOA*5R), 373 bp.

### Statistical analysis

Data were qualitatively analyzed, comparing z-scores in the neuropsychological tests for the MAOA*2R individuals with those of the published norms (Table 2) (40). The z-scores for Raven's CPM, Digit span, and Corsi Blocks were standardized by age. z-scores for TDE, simple addition, subtraction and multiplication, and transcoding were standardized by grade (Figure 1). Scores lower than 1 SD below the mean were characterized as low performance.

## RESULTS

### Neuropsychological assessment results

Allelic and genotype frequencies are shown in Supplementary Table 1. The qualitative results of the neuropsychological assessments are presented in Table 3. Quantitative neuropsychological results for children with MAOA_LPR*2R are presented in Figure 1 and Supplementary Table 2, and their results are shown in Supplementary Figure S1. The neuropsychological performance among boys with the MAOA_LPR*2R genotype was variable, with a completely normal neuropsychological examination in two out of eight boys. The most frequent findings were abnormally low performance in verbal and/or visuospatial working memory (VSWM) (4/8), math learning difficulty (5/8), and spelling difficulties (3/8). Low performance in working memory and school achievement tests become salient when data for all children with MAOA_LPR*2R are compared in the same figure (Figure 1 and Supplementary Figure S1).

## DISCUSSION

The aim of this study was to describe the results of a neuropsychological assessment of eight healthy, school-age boys with MAOA_LPR*2R genotype. A variable neuropsychological profile was observed in boys with

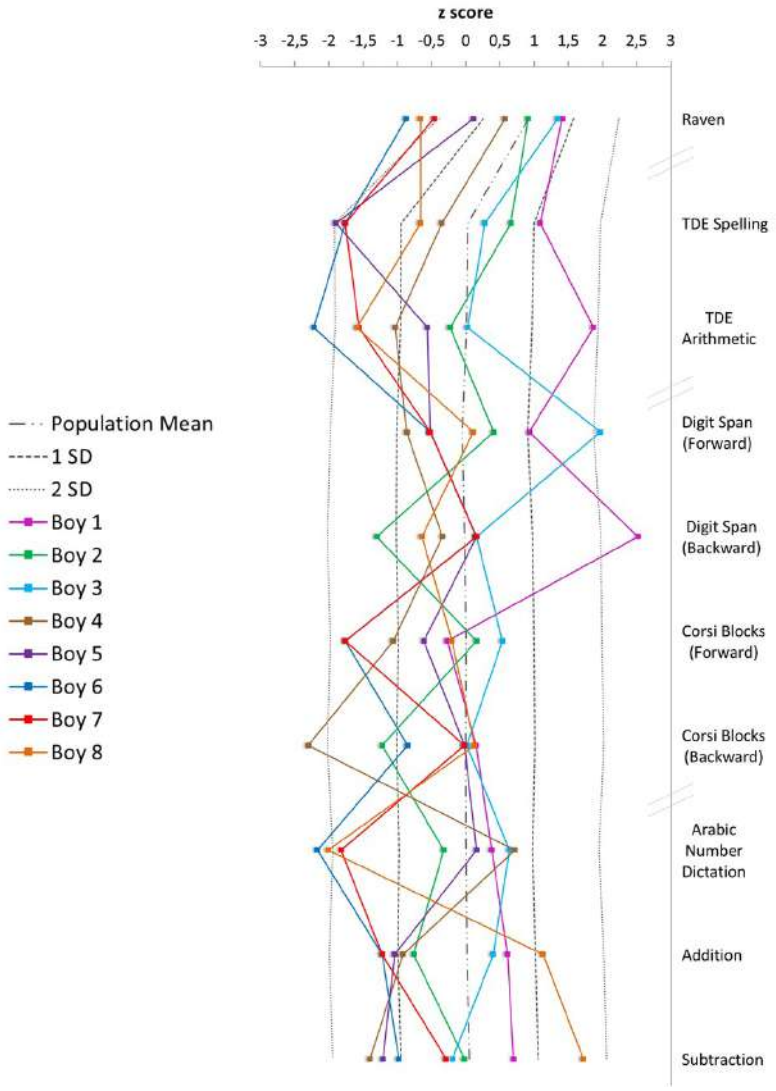


**Figure 1.** Quantitative results of the neuropsychological assessment for each boy having the MAOA_LPR*2R allele.

normal intelligence. One of the children evaluated had a typical performance for his age in all tasks. However, a tendency toward difficulties in visuospatial and verbal short-term and working memory was observed. Furthermore, most children had difficulties in school performance, especially in arithmetic. A smaller number presented difficulties in spelling. In the following sections, results related to intelligence, working memory, and school achievement are discussed.

General intelligence in the participants was normal, compared to the population standards. This was expected as an intelligence above the PR15 was used as an inclusion criterion. Two boys with MAOA_LPR*2R genotype scored 1.3 SD above the intelligence mean. The intelligence of the other children was situated in the low normal range. Intelligence is a neuropsychological function with high heritability[41]. An association between *MAOA* and IQ has been found in several studies[42], usually in connection with behavioral disorders. A study evaluated the predictive effect of *MAOA* on the intelligence of children with ADHD, in which approximately 40% of the sample had comorbidities with conduct disorder and oppositional defiant disorder. The results indicated that MAOA predicts the IQ of these children, while COMT Val158Met independently does not. An interaction was also found between COMT *Val158Met* genes and MAOA_LPR*2R and MAOA_LPR*4R polymorphisms with effect only on the performance IQ of the children in the sample[43]. Healthy women with the homozygous MAOA_LPR*4R allele had a higher intelligence than those who carry the homozygous MAOA_LPR*3R allele[42].

Four of eight children were impaired in working memory tasks. Impairments in VSWM were more

**Table 3.** Qualitative neuropsychological results for the boys having the MAOA_LPR*2R allele.

| Initials | Grade/age | Neuropsychological results |
|---|---|---|
| Boy 1 | 5th grade/10 years | Superior normal intelligence (1.4 SD above mean). Verbal working memory (2.5 SD above mean) and arithmetic achievement superior (1.8 SD above mean) for age. Typical for age performance in visuospatial short and working memory tasks; spelling achievement. |
| Boy 2 | 3rd grade/8 years | Normal intelligence. Typical for age performance in verbal and visuospatial short-term memory; arithmetic; and spelling achievement. Low performance on visuospatial and verbal working memory tasks. |
| Boy 3 | 3rd grade/7 years | Superior normal intelligence (1.3 SD above mean). Typical for age performance in verbal and visuospatial short-term and working memory; arithmetic; and spelling achievement. |
| Boy 4 | 3rd grade/ 9 years old | Normal intelligence. Typical for age performance on verbal short-term and working memory, and spelling achievement. Low performance in visuospatial short-term and working memory, and arithmetic achievement. |
| Boy 5 | 2nd grade/7 years | Normal intelligence. Typical for age performance in verbal and visuospatial short-term and working memory; and in spelling tasks. Low achievement in spelling and arithmetic tasks. |
| Boy 6 | 2nd grade/7 years | Normal intelligence. Typical for age performance in verbal and visuospatial short memory; visuospatial working memory. Low performance in a visuospatial short-term memory task, arithmetic, and spelling achievement. |
| Boy 7 | 2nd grade/7 years | Normal intelligence. Typical for age performance in verbal and visuospatial working memory, verbal working memory. Low performance in visuospatial short memory, spelling, and arithmetic achievement. |
| Boy 8 | 5th grade/11 years | Normal intelligence. Typical for age performance in verbal and visuospatial short-term and working memory, and spelling achievement. Low achievement in arithmetic. |

frequent than impairments in verbal working memory. Working memory deficits have been observed in individuals with disruptive behavioral disorders[44-46]. The literature suggests associations between *MAOA* polymorphisms and both verbal and VSWM. An association between verbal working memory mechanisms and the activation levels in *pars opercularis* was observed in adult individuals with ADHD. These individuals exhibited higher levels in the *pars opercularis* compared to controls when performing an N-back task. An SNP in *MAOA* (rs1137070) was described as a moderator of *pars opercularis* activation in these individuals. The effect of *MAOA* on *pars opercularis* activation was only significant in the carriers of the rs1137070 T/T genotype[22]. Evidence also indicates that MAOA is implicated in the neurobiological regulation of VSWM activity. VSWM deficits are a correlate of maladaptive behaviors[47]. Carriers of the allele A for the SNP rs6609257 exhibited higher cortical activity in the frontal, parietal, and occipital regions associated with working memory[47]. Alleles associated with higher *MAOA* activity modulate responses of the ventrolateral prefrontal cortex to VSWM tasks[48].

Of the eight participants, five performed below 1 SD on the math achievement test. To the best of our knowledge, no previous investigation has addressed the impact of MAOA_LPR polymorphisms on school achievement. Disruptive behavioral disorders are not considered learning disorders. However, disruptive behavioral disorders are consistently associated with low achievement and school dropout[49]. As low school performance, especially in mathematics, was detected in individuals with MAOA_LPR*2R, it is possible to suggest that polymorphisms in MAOA_LPR*2R may also be associated with school underachievement in children with normal intelligence. A search on PubMed using "math achievement OR mathematics AND MAOA" in March 2021 yielded no results. This could be a venue for new research, as the results presented here suggest an association between the MAOA_LPR*2R allele and math achievement. The association between MAOA polymorphisms and mathematics achievement may be mediated by working memory mechanisms and could, eventually, be also moderated by COMT Val158Met polymorphisms[50].

This study has some limitations. It is an exploratory study with a small sample size and we did not assess behavioral constructs. However, this is the first study investigating the cognitive correlates of a relatively infrequent *MAOA*-related genotype with potential neuropsychiatric and educational implications. This study fills in the gap of information on the effects of the MAOA_LPR*2R allele in children not selected due to antisocial behavior or intellectual disability.

An interesting finding in the present study is the phenotypic variability observed among the boys having the MAOA_LPR*2R allele, ranging from high performance in all tests to low performance in working

memory tasks and learning difficulties associated with low but normal intelligence. This finding suggests that the effects of MAOA_LPR*2R are modulated by a multifactorial context, which includes possible environmental as well as genetic background effects. The findings reported here reinforce the concept that genetic polymorphisms affect behavior and school achievement in children with normal intelligence. At the population level, school achievement is a multifactorial characteristic. Although our results suggest an association between this polymorphism and school achievement, it is necessary to be parsimonious regarding its effects. The genetic architecture of behavioral traits is highly polygenic; MAOA_LPR*2R polymorphism is one risk factor contributing to the phenotype in these children. However, the finding that five out of eight boys having the MAOA_LPR*2R presented learning difficulties and low working memory performance suggested that in some individuals, this genotype may have a major effect. On the contrary, the finding that three out of eight boys having normal or even high intelligence and school achievement indicates that having a MAOA_LPR*2R allele should not be considered as the sole cause of learning difficulties and should not be taken as a marker of school problems.

**Authors' contributions.** All authors contributed to data collection and analysis. EOS, AHBC, VGH, MRSC: wrote the manuscript, which was reviewed by all the authors.

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https://doi.org/10.1590/1980-5764-DN-2021-0027

# Retest effects in a diverse sample: sociodemographic predictors and possible correction approaches

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**ABSTRACT.** Repeated cognitive assessment in longitudinal studies favors the occurrence of retest effects, usually increasing the scores obtained at the follow-up assessments when compared to baseline. Therefore, retest effects can compromise the evaluation of cognitive decline in older adults. **Objectives:** We aimed to verify the occurrence of the retest effect and the impact of sociodemographic characteristics on the follow-up scores in a sample of 5,592 participants with a diverse sociodemographic profile, who were assessed twice during 4 years of follow-up. **Methods:** We tested two possible approaches to correct the retest effect and calculated the Reliable Change Index. **Results:** We observed increased scores at the follow-up assessment after 4 years, but the results indicate a modest occurrence of retest effects. The regression difference correction successfully generated follow-up corrected scores, while the mean difference did not provide effective corrections. Sociodemographic characteristics had a minor impact on the retest. **Conclusions:** We recommend the regression difference correction for retest effects. The absence of this methodological approach might lead to biased results using longitudinal cognitive scores.

**Keywords:** Reproducibility of Results; Aged; Longitudinal Studies; Psychometrics.

**EFEITO DE RETESTE EM UMA AMOSTRA DIVERSA: PREDITORES SOCIODEMOGRÁFICOS E POSSÍVEIS ABORDAGENS PARA A CORREÇÃO**

**RESUMO.** Avaliações cognitivas repetidas em estudos longitudinais favorecem a ocorrência de efeitos de retestagem ou de prática, geralmente aumentando os escores obtidos nas avaliações de acompanhamento quando comparados aos da primeira avaliação. Sendo assim, os efeitos do retestagem podem comprometer a verificação do declínio cognitivo em idosos.

This study was conducted by the Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (FINEP [Financiadora de Estudos e Projetos] and CNPq, National Research Council) (grants 01 06 0010.00 to RS, 01 06 0212.00 to BA, 01 06 0300.00 to ES, 01 06 0278.00 to MG, 01 06 0115.00 to SP, and 01 06 0071.00 to RJ). S.M.B. and R.H.G. are research fellows of the National Research Council (CNPq, grant numbers 300159/99-4 and 301807/2016-7, respectively). P.C. receives support from CNPq Brazil (research productivity fellow).

Received on March 05, 2021; Accepted in final form on October 13, 2021.

**Objetivos:** Objetivamos verificar a ocorrência do efeito de prática e o impacto das características sociodemográficas nos escores de seguimento em uma amostra de 5.592 participantes com perfil sociodemográfico diverso, avaliada duas vezes durante quatro anos de seguimento. **Métodos:** Testamos duas abordagens possíveis para corrigir o efeito de prática e calculamos o índice de mudança confiável. **Resultados:** Observamos escores sutilmente maiores na avaliação de seguimento após quatro anos, o que sugere a ocorrência de efeitos de retestagem. A correção pela diferença da regressão gerou escores corrigidos de acompanhamento satisfatórios, enquanto a correção pela diferença média não forneceu correções eficazes. As características sociodemográficas tiveram impacto mínimo no efeito de prática. **Conclusões:** Recomendamos a forma de correção pela diferença da regressão para efeitos de retestagem. A ausência dessa abordagem metodológica, quando utilizamos escores cognitivos longitudinais, pode levar a resultados enviesados.

**Palavras-chave:** Reprodutibilidade dos Testes; Idoso; Estudos Longitudinais; Psicometria.

## INTRODUCTION

Longitudinal cognitive studies should consider the occurrence of practice or retest effects with repeated neuropsychological assessments. Repeated assessments with the same tests increase the occurrence of retest effects, usually increasing the score obtained at the follow-up assessment when compared to the first evaluation. Previous studies have shown that the second assessment shows the largest retest effects[1]. After three or more repeated cognitive assessments, there is a plateau in the retest effects[2,3]. Therefore, from the third assessment onward, the cognitive scores became more reliable due to the more stable retest effect[1,4,5]. The increase in the second assessment score might be due to several causes, including increased comfort in being tested, reduced anxiety at the follow-up visits for knowing what to expect, learning the test paradigm more than the items themselves, or even remembering test items. Besides, regression to the mean could be present since subjects with very low scores on the first assessment might increase their performance in subsequent evaluations[2,6]. These possible explanations can lead to increased cognitive scores at the second visit or they might even have caused slightly reduced performance at the first visit.

Retest effects produce unique repercussions in aging studies, compromising the expected observation of cognitive decline in older adults[7]. This phenomenon occurs because the average score gains in the presence of retest are often higher than the real cognitive change that happens during the follow-up period[2].

It is also known that frequent assessments may obscure the real cognitive decline[5] and that cognitive tests have distinct practice effects[1,8,9]. Previous studies have suggested the use of parallel tests to reduce the retest effects[7]. However, this solution depends on well-matched equivalent test forms to avoid measurement errors that can be erroneously interpreted as cognitive improvement or decline[10].

Literature diverges about whether sociodemographic characteristics are related to the retest effects. Effects were reported to be higher in younger participants (18–53 years old compared to 54–97 years old)[4], while other studies found that age and other sociodemographic variables (e.g., sex, education, and race/ethnicity) were not related to retest effects[8,11]. Although education was not previously related to retest effects, we hypothesized that individuals with low education are more prone to underperform in their first assessment due to unfamiliarity with testing situations.

Therefore, we assume that, if not considered in the analyses, retest effects can lead to biased cognitive results in longitudinal studies. Therefore, the aims of this study were to (1) verify the occurrence of retest effects in a longitudinal study, (2) verify whether sociodemographic characteristics are related to this effect, and (3) address how to take retest effects into account when using a data set with two visits.

## METHODS

### Participants

The ELSA-Brasil sample is composed of 15,105 active or retired employees from public institutions from six large Brazilian cities (e.g., Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo, and Vitória), of both sexes, aged between 35 and 74 years at baseline (2008–2010)[12,13]. The ELSA-Brasil is a longitudinal study investigating the incidence and evolution of chronic diseases, especially cardiovascular diseases and diabetes, among middle-aged and older adults. The exclusion criteria of this study were the presence of clinically observed severe cognitive or communication impairment, intention to quit work at the institution shortly for reasons not related to retirement, and, if retired, living outside the corresponding metropolitan area. Women currently or recently pregnant were rescheduled so that the first interview could take place at least 4 months after delivery. All participants were Brazilian-Portuguese speakers.

The baseline assessment in the study included sociodemographic information, clinical history, cognitive and mental health evaluation, lifestyle factors, occupational

history, and family history of major diseases. Cognitive function was reassessed only in participants aged 55 years or older (7,066 eligible participants) at the second visit (2012–2014), after 4-year interval. The local institutional review board approved the study that was conducted following the ethical rules for human experimentation stated in the Declaration of Helsinki, and all participants signed an informed consent.

For this study, participants were excluded if they reported diagnoses of neurological diseases at the baseline (e.g., stroke, concussion, brain tumor, multiple sclerosis, Parkinson's disease, dementia, and epilepsy), if they were using any medication with psychoactive effects (e.g., benzodiazepines, neuroleptics, antiparkinsonian agents, anticonvulsants, sedating antihistamines, lithium, α-adrenergic agonists, and tricyclic antidepressants), and those who had psychiatric symptoms based on mental health evaluation (Figure 1). We also excluded participants with missing cognitive test scores at baseline or follow-up evaluations. Among 7,066 eligible participants who were 55 years old at the second visit, 5,592 were considered the final sample (Figure 1).

### Neuropsychological assessment

Baseline assessment used the standardized memory tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[14] validated for the Brazilian population[15] to assess learning, delayed word recall, and recognition (CERAD Word List Test [WLT]). The recognition score is the number of corrected classified words that belonged to the list (0–10 points) with penalization for including distractors (the number of correctly identified words minus false-positive errors — distractors words identified as part of the list). The baseline assessment also included the semantic verbal fluency (SVF) and phonemic verbal fluency (PVF) tests (animals and letter F, respectively)[16,17] and the Trail Making Test B (TMT-B)[18]. All tests were performed using the Brazilian-Portuguese version. Follow-up assessment used the same cognitive measures, except in the case of the verbal fluency tasks. Letter A replaced the PVF of letter F, and the SVF of animals was replaced by vegetables in order to reduce learning effects. However, we used previously test equated scores[19]. Equated scores aim to guarantee that the distinct versions of the verbal fluency tests measure the construct with the same difficulty level, by transforming one test score into the same metric and range of values from another test. Trained examiners administered the tests in a fixed order during one single session, and all psychometric environment requirements were met (a quiet, lighted, and free of distractors environment)[20].

### Statistical analysis

We evaluated the retest effects using three approaches to clarify if there is a real increase in cognitive performance, and we tested distinct possibilities to correct retest scores to be used in clinical studies. Two approaches were inspired on the study by Racine et al.[21] The comparative approach was no retest correction, using the raw cognitive scores at follow-up. The first approach was the mean difference correction[21]. This approach first subtracts the observed baseline score from the follow-up score and then the mean of the difference of the sample is considered the retest effect. Then, the mean retest effect was subtracted from the follow-up value to obtain the mean difference corrected score for follow-up. The second approach was the predicted difference correction[21]. This regression-based approach first uses the baseline score to predict a retest score (follow-up).

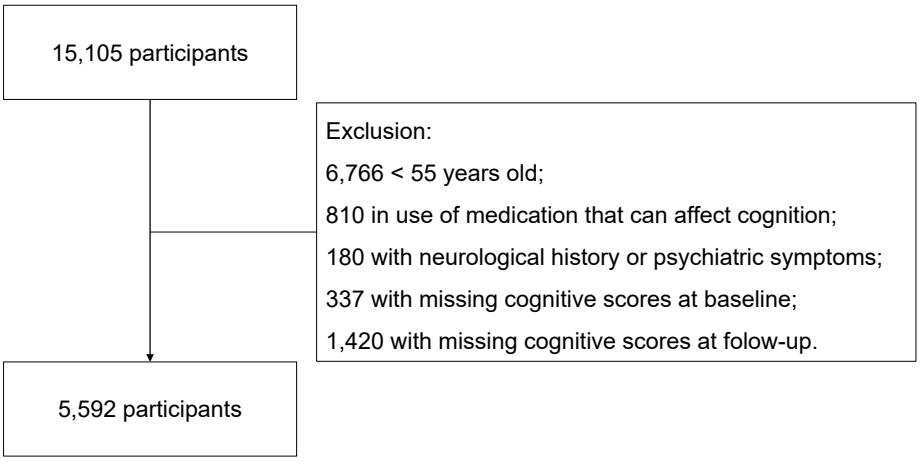


**Figure 1.** Sample selection flowchart.

Then, the regression predicted retest score is subtracted from the observed score at follow-up to obtain the retest effect. Finally, the retest effect was added to the observed baseline score at baseline to obtain the predicted difference corrected score for follow-up. All assumptions required to perform the linear regression models were met. Considering that the regular method for these corrections is to use a control sample to first extract the retest effect and subsequently apply the correction to the entire sample, we used a subsample of participants that previously built a robust normative data, based on the absence of risk factors and objective cognitive decline (for the complete description, see Bertola et al.)[22]. Briefly, this robust subsample of the ELSA-Brasil was composed of 3,888 participants who, after exclusion criteria (e.g., baseline and follow-up self-reported stroke, use of psychoactive medications, missing cognitive scores, and Reliable Change Index [RCI]>-1.96), were considered not having possible cognitive decline after 4-year interval. This subsample offers the mean retest effect at the second approach, so it could be subtracted from the follow-up value for the entire sample. Similarly, this subsample provided the regression coefficients needed to predict the retest score (follow-up) for the entire sample.

We calculated the within-subject t-test to compare the baseline score with no correction, mean predicted difference correction, and predicted difference correction.

The third approach is an RCI[23]. Considering that there are distinct options to compute the RCI, we decided to use the Crawford and Howell's method once their mathematical expression corrects for practice and regression to the mean in the predicted score and individualizes error term based on the initial test score[24]. Basically, the individual's predicted retest score is subtracted from their actual retest score and then divided by a standard error (the complete formula is published and can be accessed from Hinton-Bayre)[23]. This approach extracted the correlation value, baseline and follow-up mean, standard deviation, and variance values from the same robust normative subsample. The regression coefficient to obtain the predicted score was derived using a weighted least square model to account for heteroscedasticity. This approach does not produce a corrected score, but rather indicates if the observed change in scores from baseline to the follow-up visit is a meaningful score change or a change that might be attributable to retest effect and/or the test reliability. RCI score between -1.64 and 1.64 suggests cognitive stability, score below -1.64 suggests cognitive decline, and score above 1.64 suggests cognitive improvement with a 90% confidence interval.

### Retest effects and sociodemographic characteristics

To verify if sociodemographic characteristics can distinctly affect the occurrence of retest effects, we performed linear regression analysis for each task retest effect from the predicted difference correction method. Age, education, and sex were added as predictors of the retest effect.

## RESULTS

Table 1 shows the characteristics of the sample (n=5,592). Overall, 12% of our participants had only elementary school levels (up to 10 years of schooling), 56% were white, and 55% were women. The raw mean cognitive scores on baseline and follow-up revealed a small increase after the 4-year interval (Tables 2), with exception of PVF task, revealing retest effects after within-subject t-test (Table 3). The approaches of mean difference correction and the predicted difference correction showed scores slightly lower than the baseline ones (Tables 2 and 3).

**Table 1.** Descriptive characteristics of the sample (n=5,592).

| | Baseline | |
|---|---|---|
| | **M (SD)** | **Min–Max** |
| Age | 58.56 (5.78) | 50–75 |
| | **n** | **%** |
| Age (years) | | |
| <65 | 4640 | 83.0 |
| ≥65 | 952 | 17.0 |
| Sex | | |
| Female | 3,091 | 55.28 |
| Education | | |
| Elementary | 659 | 11.78 |
| High school | 1,682 | 30.08 |
| College or more | 3,251 | 58.14 |
| Race | | |
| White | 3,115 | 56.5 |
| Black | 1,413 | 25.63 |
| Brown | 764 | 13.86 |
| Asian | 169 | 3.07 |
| Other | 52 | 0.94 |

M: mean; SD: standard deviation.

**Table 2.** Mean and standard deviation for each cognitive test, considering no correction, mean difference correction, predicted difference correction, and Reliable Change Index (n=5,592).

| | Baseline | Follow-up | | | RCI |
|---|---|---|---|---|---|
| | | No correction | Mean difference correction | Predicted difference correction | |
| | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) |
| WLT Learning | 20.94 (3.85) | 21.11 (3.98) | 20.73 (3.98) | 20.73 (4.95) | -0.20 (0.45) |
| WLT Recall | 6.83 (1.97) | 6.96 (2.04) | 6.72 (2.03) | 6.72 (2.53) | -0.27 (0.42) |
| WLT Recognition | 9.52 (0.89) | 9.62 (0.80) | 9.50 (0.80) | 9.50 (1.17) | 0.52 (0.78) |
| SVF | 18.25 (5.09) | 18.75 (4.97) | 18.10 (4.97) | 18.10 (6.64) | -0.10 (0.61) |
| PVF | 12.49 (4.40) | 12.11 (4.41) | 12.29 (4.41) | 12.31 (5.62) | -0.00 (0.48) |
| TMT-B | 133.56 (88.48) | 129.47 (85.62) | 135.33 (85.62) | 134.65 (100.61) | 0.48 (0.58) |

RCI: Reliable Change Index; WLT Learning: Word Learning Test – Learning trial; WLT Recall: Word Learning Test – Recall Trial; WLT Recognition: Word Learning Test – Recognition Trial; SVF: semantic verbal fluency; PVF: phonemic verbal fluency; TMT-B: Trail Making Test Part B; M: mean; SD: standard deviation. Note: Higher score indicates better performance for WLT Learning, WLT Recall, WLT Recognition, SVF, and PVF, while TMT-B is measured in second, with less time indicating better performance.

**Table 3.** Within-subject t-test comparing the baseline score with follow-up no correction, mean difference correction, and predicted difference correction.

| | No correction | Mean difference | Predicted difference |
|---|---|---|---|
| WLT Learning | B<F (t=-3.51, p<0.001, d=0.05) | B>F (t=4.70, p<0.001, d=0.06) | B>F (t=5.11, p<0.001, d=0.08) |
| WLT Recall | B<F (t=-5.35, p<0.001, d=0.07) | B>F (t=4.75, p<0.001, d=0.06) | B>F (t=5.10, p<0.001, d=0.08) |
| WLT Recognition | B<F (t=-7.82, p<0.001, d=0.10) | B>F (t=1.68, p<0.05, d=0.02) | B>F (t=2.63, p<0.01, d=0.03) |
| SVF | B < F (t=-7.22, p<0.001, d=0.09) | B>F (t=2.12, p<0.01, d=0.02) | B>F (t=2.51, p<0.01, d=0.04) |
| PVF | B>F (t=6.85, p<0.001, d=0.09) | B>F (t=3.55, p<0.001, d=0.05) | B>F (t=3.76, p<0.001, d=0.06) |
| TMT-B | B>F (t=4.09, p<0.001, d=0.05) | B<F (t=-1.76, p<0.05, d=0.02) | B<F (t=-1.20, p<0.11, d=0.02) |

WLT Learning: Word Learning Test – Learning trial; WLT Recall: Word Learning Test – Recall Trial; WLT Recognition: Word Learning Test – Recognition Trial; SVF: semantic verbal fluency; PVF: phonemic verbal fluency; TMT-B: Trail Making Test Part B; B: baseline; F: follow-up.

The RCI analysis (Supplementary Table 1) suggests that the majority of the sample did not have an actual change in the cognitive performance after considering the effect for practice and regression to the mean in the predicted score and individualized error term based on the initial test score. The majority of participants (95–99%) obtained RCI scores between -1.64 and 1.64.

Education, age, and sex demonstrated to be significant predictors of retest effects for most of the cognitive scores. However, the models revealed small explained variance and small effect sizes (Table 4), indicating a minor impact of sociodemographic characteristics on the retest effects. Being older, having lower education, and being male were indicatives of marginally larger effect sizes at follow-up, but these results should be interpreted carefully. Sex was not a predictor for PVF and TMT-B.

Figure 2 illustrates the retest effects as a function of age (<65 years or ≥65 years) and education group (elementary or high school [HS]+college or more), the most consistent predictors. Retest effects were more prevalent among older participants (≥65 years) with lower education (E), but younger participants (<65 years) with lower educational attainment (E) also revealed pronounced retest effects. The WLT Recognition trial (Figure 2C) was the only score with minimal or absence of retest effects and maintenance of ceiling effects, except for the participants with lower education attainment.

Considering that the educational group division resulted in uneven sample sizes, we performed additional comparisons of the retest effect among further educational groups (Supplementary Table 2). Retest effect reduced when educational attainment increase

**Table 4.** Linear regression of sociodemographic predictors of retest effect (n=5,592).

| | | Constant | Age | Education | Sex | Model | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | F-test | p-value | $R^2$ |
| WLT Learning | Coef. | 1.40 | -0.07 | 0.58 | 0.55 | 97.85 | <0.001 | 0.05 |
| | 95%CI | 0.48–2.32 | -0.09 to -0.06 | 0.48–0.68 | 0.38–0.71 | | | |
| | Eta-squared | | 0.02 | 0.02 | 0.01 | | | |
| WLT Recall | Coef. | 0.39 | -0.03 | 0.26 | 0.30 | 8.173 | <0.001 | 0.04 |
| | 95%CI | -0.07–0.85 | -0.04 to -0.02 | 0.21–0.31 | 0.22–0.38 | | | |
| | Eta-squared | | 0.01 | 0.02 | 0.01 | | | |
| WLT Recognition | Coef. | **0.09*** | -0.01 | 0.07 | 0.10 | 34.27 | <0.001 | 0.02 |
| | 95%CI | -0.11–0.31 | -0.01–0.01 | 0.05–0.09 | 0.07–0.14 | | | |
| | Eta-squared | | 0.00 | 0.01 | 0.00 | | | |
| SVF | Coef. | -2.93 | -0.05 | 0.85 | 1.67 | 135.75 | <0.001 | 0.07 |
| | 95%CI | -4.19 to -1.67 | -0.06 to -0.03 | 0.71–0.98 | 1.44–1.89 | | | |
| | Eta-squared | | 0.00 | 0.03 | 0.04 | | | |
| PVF | Coef. | -2.74 | -0.02 | 1.10 | **0.10*** | 126.22 | <0.001 | 0.06 |
| | 95%CI | -3.78 to -1.69 | -0.04 to -0.01 | 1.00–1.22 | -0.09–0.28 | | | |
| | Eta-squared | | 0.00 | 0.06 | 0.00 | | | |
| TMT-B | Coef. | -35.54 | 1.02 | -5.58 | **-2.91*** | 23.81 | <0.001 | 0.01 |
| | 95%CI | -55.50 to -15.60 | 0.72; 1.33 | -7.74 to -3.42 | -6.46–0.62 | | | |
| | Eta-squared | | 0.01 | 0.00 | 0.00 | | | |

F: ; *Nonsignificant. WLT Learning: Word Learning Test – Learning trial; WLT Recall: Word Learning Test – Recall Trial; WLT Recognition: Word Learning Test – Recognition Trial; SVF: semantic verbal fluency; PVF: phonemic verbal fluency; TMT-B: Trail Making Test Part B; 95%CI: 95% confidence interval; Coef.: coefficient.

in participants younger than 65 years, except for the WLT Recognition trial. For participants aged 65 years or older, retest effect is similar to participants with elementary and HS levels, suggesting that the retest effect only reduces after a higher educational level (college or more). When educational level was kept constant and participants were compared across age, younger and older participants with elementary level did not differ in their retest effect, except for the TMT-B. Participants with HS and college levels differed, among the age groups, in WLT Learning, WLT Recall, and TMT-B.

We also performed analysis comparing the retest effect of participants with the lowest level of education (<5 years of schooling) with participants who completed the elementary school (8 years), HS (11 years), and college or more (15-16 years) (Supplementary Table 3). This additional analysis aimed to clarify the impact of the second assessment, considering that very low educated subjects underwent fewer situations of performance assessment during life. Younger participants (<65 years old) with less than 5 years of education had higher levels of retest effect only when compared with participants with HS or more (except for WLT Recognition and TMT-B). Older participants (65 years or older) with less than 5 years of education have higher levels of retest effect when compared to participants with college or more (except for WLT Recognition).

## DISCUSSION

Retest effects are common in longitudinal studies with recurrent cognitive assessments and a source of bias when not taken into account to verify cognitive change across time. We aimed to verify the occurrence of retest effects, possible approaches to correct for it, and the sociodemographic predictors of its occurrence. We found

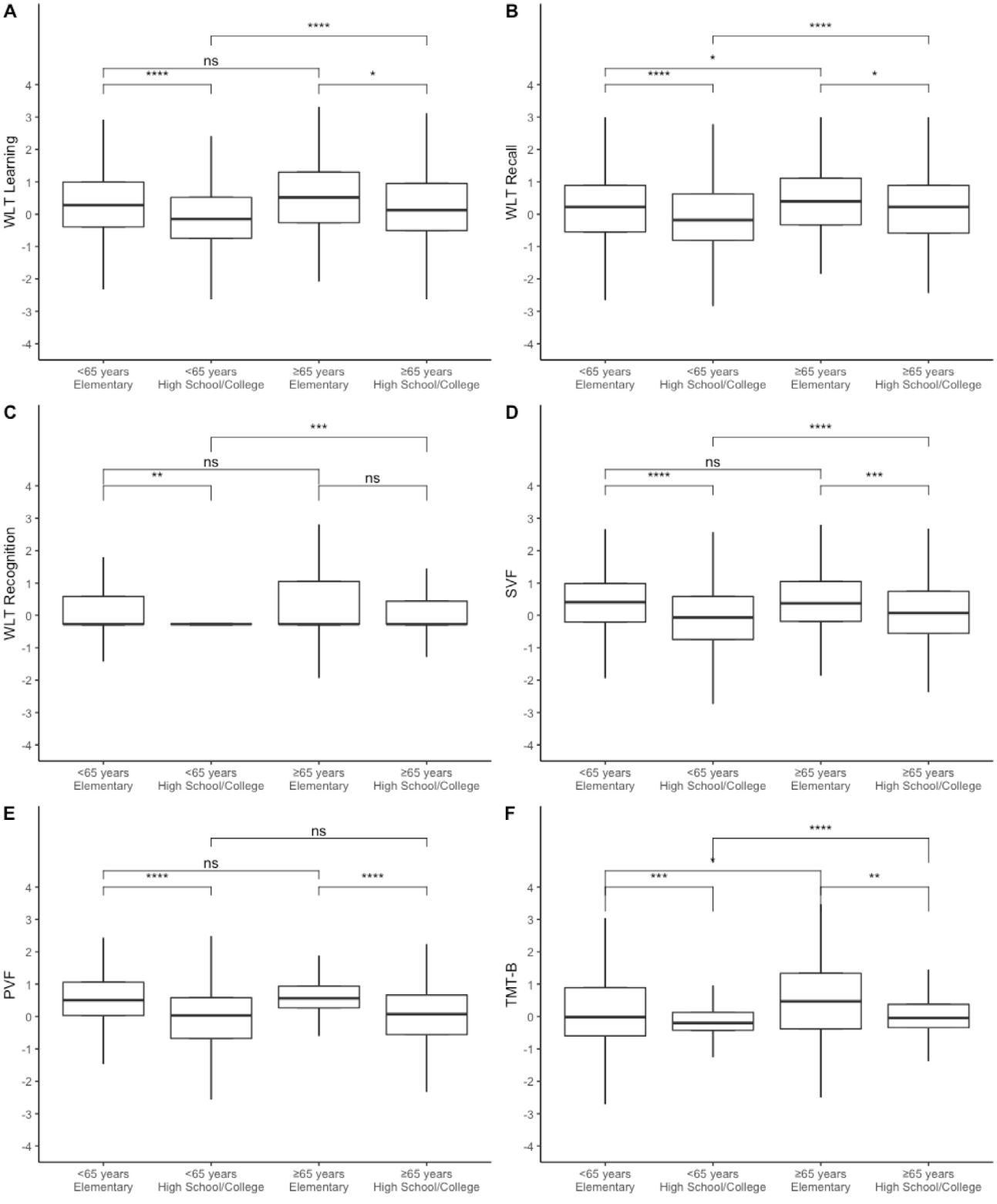


**Figure 2.** Retest effects boxplot by age (<65 years and 65 years or older) and education (elementary or high school and college or more) and groups comparisons (corrected for multiple comparisons). (A) WLT Learning: Word Learning Test – Learning trial. (B) WLT Recall: Word Learning Test – Recall Trial. (C) WLT Recognition: Word Learning Test – Recognition Trial. (D) SVF: semantic verbal fluency. (E) PVF: phonemic verbal fluency. (F) TMT-B: Trail Making Test Part B. Whiskers represent the standard deviation. ns: p>0.05, *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001.

that modest retest effects occurred in the tests used at the ELSA-Brasil study (except on PVF), with some tests revealing higher effect and others revealing lower effect, especially those with the limitation of showing ceiling effects (WLT Recognition). Our results revealed smaller retest effects than usually observed in numerous studies that observed marked by improvement in test scores on the second assessment[1,2,4-8,25,26].

Although most cited studies have a smaller follow-up interval than the ELSA-Brasil (4 years), the longitudinal increase has been reported even after a 7-year interval[27]. Additionally, a 3-year interval was associated with a mean increase of 0.30 standard deviation in scores due to retest effects[26], a similar mean value found by our study with 4-year interval.

Our results suggest that age, education, and sex might be the potential predictors of the retest effects. However, the small effect sizes indicated that the influence of sociodemographic variables might be minimal. Gross et al.[8] found no sociodemographic predictors in a sample of older adults, while Salthouse[4] found that young adults revealed a higher effect. This last study compared adults aged 18–53 years with older adults aged 54–97 years that might had a true cognitive decline commonly seen in advanced ages. Middle-aged adults and young older adults might not demonstrate meaningful differences in retest effects, once age effect is not always shown. Nevertheless, we found that older adults aged 55–64 years with lower educational levels revealed higher retest effects than their more educated counterparts. Also, we found that among participants with HS or college education, adults aged 65 years or older revealed higher retest effects than their younger counterparts (aged 55–64 years).

Educational experience usually exposes the subject to recurrent schooling assessments. Higher educational levels increase the performance and knowledge about evaluation procedures, and this might contribute to less anxiety in the face of a first formal cognitive assessment. Subjects with lower education might face assessments with more anxiety symptoms for not being used to have their performance evaluated[28]. This experience might be similar to previous controlled exposures that reduce retests effects[7].

Considering that this effect might be more prominent in lower educated subjects and that these subjects are at higher risk for presenting cognitive decline or dementia[29], longitudinal studies from low- and middle-income countries should be extremely aware of follow-up scores correction. These subjects are a considerable proportion of older adults in these countries[30], and higher practice effects might cover a true cognitive decline.

Once the correction of follow-up scores is needed, there are two main options to avoid biased cognitive scores: the mean difference and the predicted difference corrections. Nonetheless, considering the possible impact of sociodemographic predictors on this effect in this sample, we recommend that further studies choose the predicted difference correction. This approach allows the inclusion of relevant predictors in the regression analysis to improve the correction of retest effects for each research question asked and additionally account for the effect of regression to the mean[21,31].

The RCI results also highlighted that the majority of the participants did not increase their cognitive performance after 4 years. Most of the small differences in scores from baseline to follow-up might be due to test reliability and practice effect susceptibility. The RCI did not revealed higher proportion of lower educated (elementary level) participants with significant decreased or increased scores on the second assessment when compared to HS and college education, except for the TMT-B (20% revealed an improvement). Stein and colleagues studied the CERAD battery and found that the RCI analysis revealed that changes in the test battery after 3 years can be interpreted with uncertainty due to possible measurement errors, practice effects, and even normal age-related cognitive decline[32]. The RCI is a limited approach that only allows for the comparison of two evaluation at a time and is not suitable for longitudinal studies with multiple cognitive assessments, in which regression approaches are more recommended[33].

Previous to baseline or in-between waves exposure to external cognitive assessment might increase or decrease the retest effects. The absence of this information in the ELSA-Brasil questionnaire is a limitation to our comprehension of additional factors that might affect the retest effects. Given that we only have available data for two waves, we could not apply a model-based correction[21]. Further studies with this approach are recommended, including the interaction terms with time when future follow-up data become available. There are other approaches (e.g., indicator of the first cognitive visit, number of prior testing occasions, and square root of the number of prior testing occasions) to account for practice effects in the face of multiple follow-ups, and how the effects are specified can lead to considerable differences in estimated rates of cognitive change[34].

Our study has some limitations. We do not have information if the participant has been exposed to other out-of-the study cognitive assessment previously to the baseline assessment. We could not control for other sources that might have contributed to the increase

in follow-up scores. However, it is highly unlikely that participants were exposed to a cognitive assessment or rehabilitation outside the ELSA-Brasil during the study period. The absence of a test validity assessment on the battery also contributes to our limited interpretation of why the low educated participants revealed a higher practice effect. However, considering the sample selection, it is unlikely that the participants were not sufficiently engaged to perform the cognitive battery to consider the scores unreliable. Finally, the tests have reliability studies inside the ELSA-Brasil study and validity studies in other Brazilian samples, and thus the complete absence of bias cannot be guaranteed.

Our study addressed and contributed to the understanding of predictors of retest effects using a diverse socioeconomic sample. Moreover, we identified and recommended the best retest correction for an extensive data set with the potential to explore factors associated with cognitive decline in a low- to middle-income country. Future studies with the ELSA-Brasil data set will contribute to increasing the knowledge about protective and risk factors for health and pathological aging, through unbiased cognitive change scores.

**Authors' contributions.** LB: conceptualization, data curation, formal analysis, visualization, and writing – original draft preparation. IMB, SMB, ABM, RG, MCV, and PAL: funding acquisition, investigation, project administration, resources, and writing – review & editing. ARB and PC: writing – review & editing. CKS: conceptualization, supervision, validation, and writing – original draft preparation.

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Dement Neuropsychol 2022 June;16(2):181-186

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0043

# 12-item version of Boston Naming Test: usefulness in the diagnosis of primary progressive aphasia, frontotemporal dementia, and Alzheimer's disease

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**ABSTRACT.** The 12-item version of the Boston Naming Test (BNT) was adapted to Argentina for the detection of dementia due to Alzheimer's disease (AD), with scores similar to the original 60-item version (sensitivity and specificity of 85 and 94%, respectively) without demographic influence (age and educational level). To date, no publications on the use of abbreviated BNT in other degenerative pathologies with language impairment have been reported. **Objective:** The objective of this study was to evaluate the usefulness of 12-item BNT in primary progressive aphasia (PPA), the behavioral variant of frontotemporal dementia (FTDbv), and AD. **Methods**: Notably, 47 patients with probable AD (NIA-AA 2011) — clinical dementia rating (CDR) 0.5–1, 55 with FTDbv, 17 with PPA, and 46 controls were evaluated and matched for age and education. Exclusion criteria were as follows: alcoholism, other previous neurological or psychiatric illnesses, and education <4 years. All were assessed with a full neuropsychological battery and a 12-item version of BNT. **Results:** Median scores of 12-item BNT were as follows: PPA: 3.87 (SD=2.99), AD: 6.13 (SD=3.03); FTDbv: 8.41 (SD=2.53); and controls: 10.22 (SD=1.82). Receiver Operating Characteristic (ROC) curves were plotted. **Conclusions:** The 12-item version of BNT can be useful, simple, and fast to identify and differentiate PPA, FTDbv, and AD from controls while retaining the discriminative ability of the original version.

**Keywords:** Aphasia; Anomia; Language Tests; Dementia.

**TESTE DE NOMEAÇÃO DE BOSTON DE 12 ITENS: UTILIDADE NO DIAGNÓSTICO DE AFASIA PROGRESSIVA PRIMÁRIA, DEMÊNCIA FRONTOTEMPORAL E DOENÇA DE ALZHEIMER**

**RESUMO.** A versão de 12 itens do Teste de Nomeação de Boston (TNB) foi adaptada para a Argentina para a detecção de demência por doença de Alzheimer (DA), com escores semelhantes à versão original de 60 itens (sensibilidade e especificidade de 85 e 94%, respectivamente) sem influência demográfica (idade e escolaridade). Até o momento, não foram relatadas publicações sobre o uso do TNB abreviado em outras patologias degenerativas com comprometimento da linguagem. **Objetivo:** avaliar a utilidade do TNB de 12 itens na afasia progressiva primária (APP), na variante comportamental da demência frontotemporal (DFT) e na doença de Alzheimer (DA). **Métodos:** 47 prováveis DA (NIA-AA 2011) — CDR 0,5–1, 55 DFT, 17 APP e 46 controles foram avaliados e pareados por idade e escolaridade. Critérios de exclusão: alcoolismo, outras doenças neurológicas ou psiquiátricas prévias e escolaridade <4 anos. Todos foram avaliados com uma bateria neuropsicológica completa e versão de 12 itens do TNB. **Resultados:** medianas das pontuações de 12 itens TNB: APP: 3,87 (DP=2,99), DA: 6,13 (DP=3,03); DFT: 8,41 (DP=2,53) e Controles: 10,22 (DP=1,82). As curvas ROC foram traçadas. **Conclusões:** O TNB de 12 itens pode ser útil, simples e rápido para identificar e diferenciar APP, DFT e DA nos controles, mantendo a capacidade discriminativa da versão original.

**Palavras-chave:** Afasia; Anomia; Testes de Linguagem; Demência.

## INTRODUCTION

Aphasia is an acquired language disorder caused by brain damage. It can affect production, understanding, or both. Acute onset cerebrovascular accident is usually the most common cause of aphasia, affecting at least one-third of people, with considerable sequelae until spontaneous recovery of language[1].

Certain dementias usually manifest with aphasic forms and should be taken

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on April 28, 2021; Received in its final form on October 05, 2021; Accepted on October 16, 2021.

into account as a differential diagnosis, although their symptoms and evolution are different.

The two main dementias in which language disorders probably represent an early presenting feature are Alzheimer's type dementia and primary progressive aphasia (PPA) as the second major form of frontotemporal degeneration. In Alzheimer's disease (AD), cognitive impairment extends beyond language and typically affects episodic (i.e., anterograde or day to day) memory. In PPA, the gradual deterioration of language skills is contrasted with the relatively preserved nonverbal skills and daily activities. Progressively, more communication difficulties and greater cognitive impairment appear[2,3]. Occasionally, the behavioral variant of frontotemporal dementia (FTDbv) can begin with a language disorder and is presented simultaneously with executive or behavioral disorders.

The type of aphasia in AD usually depends on the stage of the disease. In the early stages, there may be slight word-finding difficulties, with occasional semantic paraphasia (e.g., semantic substitutions such as saying "aunt" instead of "sister"), but the speech is still fluent and grammatically correct like an anomic aphasia. With disease progression, patients present with transcortical sensory aphasia, in which there is evident anomia and comprehension is severely impaired. In the moderate to severe stages, there is a reduced lexical production, and in the most severe stages, echolalia and verbal stereotypies may be evident[2,3].

The PPAs are classified as fluent, nonfluent, or logopenic variant[4,5]. In the fluent variant, speech remains fluent, with normal prosody, good articulation, and grammatically correct; it still becomes circumlocution progressively and lacks content. Language impairment is associated with a deficit of semantic memory and is, therefore, often referred to as semantic dementia, as it associates aphasia with early comprehensive compromise with later associative agnosia and behavioral disturbances. In the nonfluent-agrammatic variant, speech is forced, hesitant, and choppy, with phonemic paraphasias (e.g., "prinoceros" instead of "rhinoceros"). In the logopenic variant, speech is characterized by logopenia (fluctuation of verbal fluency), anomias, and noticeable disturbances in the repetition of words and phrases[6,7].

Localized atrophy in the frontotemporal lobes in FTDbv often involves language-related brain networks, suggesting that FTDbv may lead to language dysfunction, especially when processing verbal associations, searching the verbal lexicon, or planning propositional utterances is required.

Therefore, word-finding difficulty or anomia is one of the basic disorders observed in aphasias, as well as a clear marker of cortical profile in dementia syndromes and an early neuropsychological sign of AD[6-8].

The most widely used way to assess naming is the Boston Naming Test (BNT), which consists of 60 object figures, to be named in increasing order of difficulty. Currently, it is an essential test for the study of semantic memory in dementia assessment protocols. In Buenos Aires, a 60-slide version of the BNT was developed, adapted, and standardized for the adult population[9].

The BNT is of great help in the diagnosis of dementias, but its length has led to the development of shortened versions that maintain the original objectives and criteria[10]. Several abbreviated forms have been proposed. The only Argentine version, which includes the administration of 12 slides instead of 60, was adapted by Serrano et al., in 2001, maintaining the sensitivity and specificity of 85 and 94%, respectively, similar to the version applied to AD[10].

There are no publications in the literature on the usefulness of the abbreviated Argentine version of the BNT in non-Alzheimer's degenerative pathologies with language involvement. The aim of this study was to evaluate the sensitivity and specificity of the abbreviated version of the BNT in the differential diagnosis of degenerative pathologies with aphasic predominance: PPA, FTDbv, and AD.

## METHODS

### Type of study

Diagnostic test validation study: It is a observational, analytical, retrospective, cross-sectional, and case-control study.

### Participants

The sample consists of adult subjects, who consulted for cognitive disorders during the period of 2014–2017 in the neurology service of the César Milstein Hospital. The inclusion criteria were to have ≥4 years of schooling and no history of alcoholism and other neurological diseases, such as stroke, severe cerebrovascular disease by neuroimaging, Parkinson's disease, severe traumatic brain injuries (with loss of consciousness, contusions, or hematomas), multiple sclerosis, primary epilepsy, neuromuscular diseases, or previous psychiatric diseases (e.g., major depression, bipolar, and schizophrenia).

### Instrument

The 12-item BNT is a brief naming test. It consists of the following figures: helicopter, octopus, mask, volcano, harmonica, stilt, domino, cactus, hammock, pyramid, muzzle, and palette.

### Methodology

The sample was evaluated by means of the 12-item BNT and a complete cognitive evaluation that included the following tests: Signoret Verbal Memory Test, Boston Naming Test (BNT), Spanish version, Verbal Fluency Test, Trail making test A and B, Digit span, Clock Test, Clinical dementia rating (CDR) test, and The Lawton Instrumental Activities of Daily Living Scale. The neuropsychological protocol and the abbreviated version of the BNT were administered on different days and by two different evaluators, who were blinded to the results obtained by each one of them.

Subjects were evaluated with a neurological and neuroimaging examination (e.g., magnetic resonance imaging [MRI] or computed tomography [CT]) according to the neurology service's protocol for the study of cognitive disorders.

Subsequently, the participants were classified by the type of pathology into the following groups: probable AD according to the criteria of NINCDS-ADRDA[11] (very mild stage: CDR 0.5–1), behavioral variant of FTDbv according to the criteria of Rascovsky et al.[12], and PPA according to the criteria of Gorno-Tempini et al.[13] Highly functional patients were selected (≥6) according to the Lawton Instrumental Activities of Daily Living (score ranges from 0=low function to 8=high function). A control group of subjects without cognitive complaints and with a normal cognitive evaluation (usually corresponding to relatives, close friends, or caregivers of the patients) was also selected.

### Statistical analysis

Demographic differences between the different groups were evaluated using an analysis of variance (ANOVA) test and Student's t-test, as appropriate. Performance on the abbreviated BNT was assessed between the different groups by means of an ANOVA. To analyze the correlation of the test with age and education, the Spearman correlation coefficient was used, and Receiver Operating Characteristic (ROC) curves were drawn to analyze the discriminative capacity of the test in each of the subgroups. A significance level of 5% was used to reject the null hypothesis. The statistical analysis was processed using the statistical package SPSS version 25 (IBM corporation).

### Ethical analysis

To guarantee the ethical aspects of the research, the entire project was carried out by following the current National and International Standards including the recommendations of the Declaration of Helsinki of the AMM of 1964 and subsequent amendments; the Belmont Report: "respect for people, charities and Justice"; CIOMS Guidelines: "ethical principles that should govern the execution of research in human beings"; and Law 3,301 in accordance with Basic Health Law No. 153 and Resolution 1480/2011 of the National Ministry of Health.

This study was approved by the Institutional Ethics Committee under the supervision of the Central Committee of the city of Buenos Aires.

## RESULTS

A total of 165 adult subjects were selected and classified by the type of pathology into 4 groups: 47 patients with probable AD (NINCDS-ADRDA, 1984)[11] — CDR 0.5–1, 55 with FTDbv[12], 17 with PPA[13], and 46 were controls (subjects without cognitive impairment with normal cognitive study).

### Demographic comparison by subgroups

The ANOVA test (ANOVA with the Bonferroni correction for multiple comparisons) was used to compare the variables of age and years of schooling between the four subgroups, and no statistically significant differences were found ($p>0.05$) (Table 1).

**Table 1.** The 12-item version of the BNT: demographic comparison by subgroups.

| | AD (n=46) | FTDbv (n=55) | PPA (n=17) | Control (n=47) |
|---|---|---|---|---|
| Age | 68.3 (SD=5.41) | 68.5 (SD=8.30) | 71.7 (SD=8.06) | 70.2 (SD=7.61) |
| Gender (%male) | 34.8 | 43.6 | 23.5 | 34 |
| Years of schooling | 92,609 (SD=3.56) | 106,909 (SD=4.31) | 95,294 (SD=3.20) | 9,766 (SD=3.59) |
| 12-Item version of the BNT median score | 6.13 (SD=3.03) | 8.41 (SD=2.53) | 3.87 (SD=2.99) | 10.22 (SD=1.82) |

BNT: Boston Naming Test; SD: standard deviation.

### Performance of the reduced version of Boston Naming Test

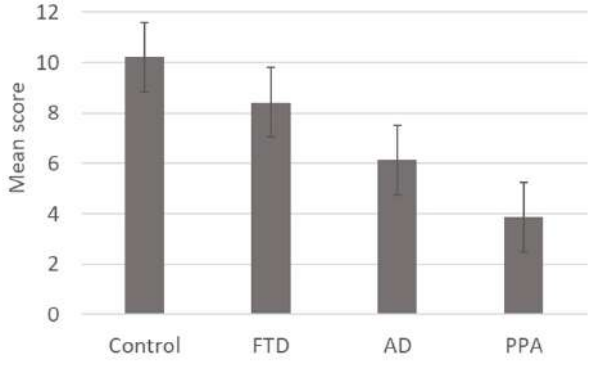
For the comparison of performance between the subgroups (ANOVA with the Bonferroni correction for multiple comparisons), the difference in performance between all the subgroups was significant ($p<0.05$), in which worse performance is observed in those patients with a diagnosis of PPA, followed by those with a diagnosis of AD (Figure 1).

### Discriminative capacity of the test

The correlation of the test with age and education was analyzed, and the Spearman correlation coefficient was used.

The ROC curves for the reduced version of BNT were drawn for PPA vs. controls, for AD vs. controls, and FTDbv vs. controls. The ROC curves are presented in Figure 2, and the area under the ROC curve was of 0.951 (95%CI [0.892–1]) for PPA, 0.895 (95%CI [0.825–0.965]) for AD, and 0.721 (95%CI [0.610–0.832]) for FTDbv.

Thereupon, sensitivity, specificity, and the predictive values (+) and (–) were calculated. The Youden index was applied to establish an optimal cutoff point for pathology discrimination using the abbreviated version of BNT. The sensitivity and specificity of the test were optimized for the population sample by using a cutoff point of 8 (any score of ≤7 was considered as an abnormal result). With this cutoff point, a better balance between sensitivity and specificity was achieved. The sensitivity of the test to detect PPA was 86.7% for PPA, 82.1% for AD, and 41.5% for FTDbv. Specificity was defined as the percentage of controls that scored at or above the cutoff score of 8. The reduced version of BNT had a specificity of 87.8%.




BNT: Boston Naming Test. FTD: Frontotemporal dementia. AD: Alzheimer's disease. PPA: Primary progressive aphasia.

**Figure 1.** Performance of the 12-item BNT by subgroups.

## DISCUSSION

Screening tests for dementia should be widely explored in Latin America[14]. The vast majority of those that exist are intended for the diagnosis of Alzheimer's dementia. Atypical presentations or non-Alzheimer's dementia with aphasic manifestations can offer a great diagnostic challenge. Therefore, validations and adaptations of short batteries for both AD and other types of dementia are of great importance.

Aphasia is often present in several dementias, and its finding is synonymous with pathology[5]. Aphasia arises from disruption of the structural integrity and interconnectivity of the extensive network of the language system. Anomia, at least in spontaneous speech and simple picture naming tasks, could be due to extralinguistic deficits or impairment of the underlying semantic/conceptual system. Extralinguistic impairments may include inattention to the task, forgetting the target word, or being distracted by related competing responses[15].

All variants of PPA have been shown to have decreased connectivity between inferior frontal gyrus (IFG) and medial temporal gyrus (MTG). The semantic variant generally shows an additional loss of connectivity between the anterior temporal lobe (ATL) and other linguistic regions. In general, the intensity of connectivity in IFG-MTG regions in PPA is correlated with repetition and grammar tasks, whereas MTG-ATL connectivity is associated with picture naming and single-word comprehension.

Altered connectivity in PPA may reflect not only irreversible loss of cortical components due to atrophy but also dysfunction of the remaining neurons.

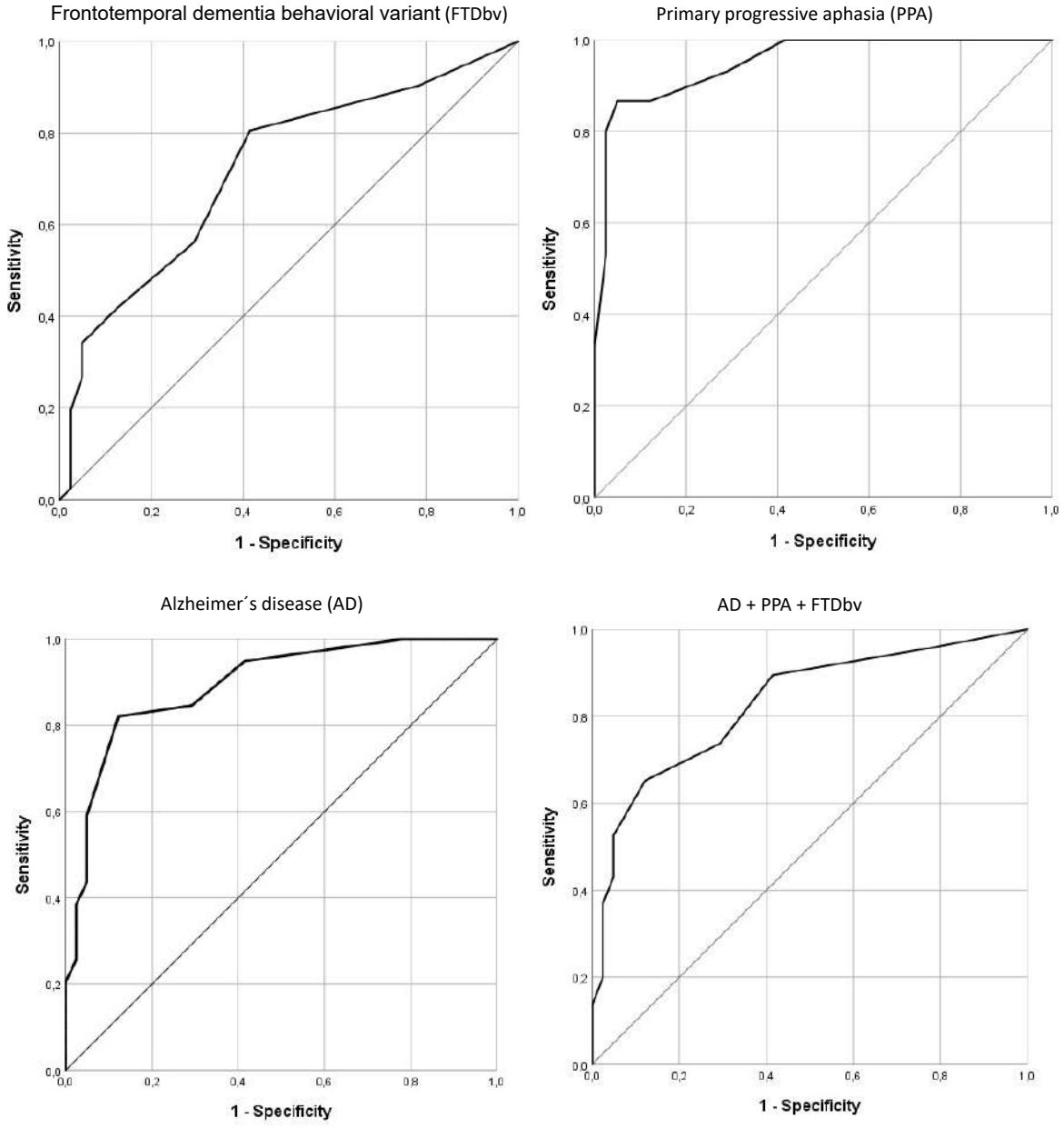
It is necessary, then, to be able to assess naming, one of the key elements since its alteration is synonymous with aphasia, mainly in PPA, where aphasia is the central diagnosis and in other entities where aphasic disorder is part of the diagnosis (FTDbv and AD)[16].

Our findings indicate that the abbreviated version of BNT is a simple and fast battery and may be useful to differentiate normal aging from language dysfunction. Specifically, the results suggest that it could be a valid tool to identify PPA, FTDbv, and AD from healthy subjects.

As expected, the best diagnostic performance was observed in patients with PPA; nevertheless, the test showed an excellent performance in patients with Alzheimer's type dementia followed by acceptable results in FTDbv.

The abbreviated version of the BNT, as we described in the initial publication when administered to Alzheimer's subjects, has no demographic influence[10].

Language dysfunction is a central element in dementia and is not limited to the classic subvariants, has the




BNT: Boston Naming Test.

**Figure 2.** Receiver Operating Characteristic curves of 12-item BNT by subgroups.

ability to assess and identify from an early stage, can help an accurate diagnosis of a specific type of disorder, can improve the understanding of these, can modify the prognosis, and can change the direction of treatment[17].

**Authors' contributions.** HGG and MGS: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, supervision, validation, visualization, writing – original draft, and writing – review & editing. CMTR: writing – review & editing. CMS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, and writing – review & editing.

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Dement Neuropsychol 2022 June;16(2):187-193

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0029

# Changes in personality traits in patients with Alzheimer's Disease

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**ABSTRACT.** Changes in personality traits in patients with Alzheimer's disease (AD) are extremely common throughout the course of the pathology, and these behavioral changes present themselves as challenges in clinical management and as a significant cause of caregivers' burden. **Objective:** Using a personality inventory based on the five-factor model of personality, this study aimed to assesses the change in these factors by comparing the premorbid and current personality of individuals recently diagnosed with AD. **Methods:** A total of 30 AD patients were recruited, and their respective family members responded to the personality inventory at home through a hosted site. The patients were also divided into two groups according to the Clinical Dementia Rating (CDR): mild dementia (CDR 1) and moderate dementia (CDR 2). **Results:** Among all patients, there was a significant increase in neuroticism factor levels and a significant decrease in the extraversion, conscientiousness, openness, and socialization factors. When comparing the groups, only the extraversion factor showed a difference, with CDR 1 group accusing a higher change in scores. Higher scores in the factor neuroticism in the premorbid personality correlated with the current severity of the disease. **Conclusions:** This research draws the attention of family members and health professionals to changes in personality traits or behavior of relatives or patients, because it can reflect an underlying neurodegenerative process.

**Keywords:** Alzheimer Disease; Personality Inventory; Mental Status and Dementia Tests; Neuroticism; Extraversion, Psychological.

**MUDANÇAS NOS TRAÇOS DE PERSONALIDADE EM PACIENTES COM DOENÇA DE ALZHEIMER**

**RESUMO.** Mudanças em traços de personalidade em pacientes com doença de Alzheimer (DA) são extremamente comuns ao longo do curso da referida patologia, e essas alterações comportamentais apresentam-se como desafios no manejo clínico e como causa significativa de esgotamento dos cuidadores. **Objetivo:** Por meio de um inventário de personalidade baseado nos cinco fatores de personalidade, este estudo avalia a mudança nos escores desses fatores comparando a personalidade pré-mórbida e a atual dos indivíduos com DA. **Métodos:** O total de 30 pacientes com DA foi recrutado, e seus familiares responderam ao inventário de personalidade. Os pacientes também foram divididos em dois grupos conforme a avaliação clínica da demência: demência leve (CDR1) e demência moderada (CDR2). **Resultados:** Em todos os pacientes, houve aumento significativo nos escores do fator neuroticismo e decréscimos significativos nos fatores extroversão, realização, abertura e socialização. Quando feita a comparação entre grupos, apenas o fator extroversão apresentou diferença, com o grupo CDR 1 mostrando maiores mudanças nos escores. Os níveis do fator neuroticismo da personalidade pré-mórbida correlacionaram-se com a gravidade da doença no momento do diagnóstico. **Conclusões:** Este estudo procura esclarecer aos familiares e profissionais de saúde que mudanças em traços de personalidade de seus parentes ou pacientes podem refletir processos neurodegenerativos subjacentes.

**Palavras-chave:** Doença de Alzheimer; Inventário de Personalidade; Testes de Estado Mental e Demência; Neuroticismo; Extroversão Psicológica.

## INTRODUCTION

Personality traits are generally consistent in adulthood and old age, although small changes in personality occur throughout life [1]. However, progressive changes are not typical and can mean underlying neurological disease, such as Alzheimer's disease (AD)[2]. Thus, it is common for close relatives to observe

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on June 04, 2021. Accepted in final form on October 30, 2021.

significant changes in the personality of individuals who develop dementia[3].

In the seminal case described by Alois Alzheimer, Auguste D's husband observed significant behavioral disorders, including paranoia, crying, aggression, and other unpredictable behaviors. As described in this first case, changes in behavior and personality remain the most challenging clinical symptoms in the treatment of dementia[4,5]. In this context, clinical research has studied the influence of AD dementia syndrome on changing personality traits[6-8].

One means of assessing personality change has been through retrospective studies in which an experienced informant, usually the spouse or child, assesses the premorbid and current personality of the person with dementia[9,10]. These reports from informants play a critical role in clinical assessments and are an important source of information to characterize the current state of the patient and the changes that have occurred over time[11,12]. In this sense, to compare the changes that occurred between the premorbid and current personality, the assessment of characteristics based on the five-factor model of personality is widely used (also known as the Big Five)[10]. This model anchors personality to the following factors: neuroticism (the tendency to experience negative emotions such as fear and sadness), extroversion (tendency to be outgoing, social, and energetic), openness (tendency to prefer new and diverse experiences and have intellectual curiosity), socialization (tendency to being cooperative, kind, and confident), and conscientiousness (tendency to be organized, persistent, and careful). Narrower traits, called facets, are part of each of the five dimensions. For example, neuroticism includes facets that reflect anxiety, angry hostility, depression, self-awareness, impulsiveness, and vulnerability[13-15].

As designed in this research, other studies have investigated the change in each of the five characteristics over the course of AD[15] and have shown associations between changes in the factors' scores with cognitive decline. Similar patterns were observed in individuals diagnosed with mild cognitive impairment (MCI) but to a lesser extent[16-18]. Indeed, the personality dimensions or factors shape, throughout an individual's life, contexts of reactions to stress, engagement in physical, cognitive, and social activities, and situations that are related to AD[19].

Thus, the objective of this study was to advance knowledge regarding the changes in personality factors that occur in individuals diagnosed with AD, reported by close relatives, with the hypothesis of an increase in the levels of the neuroticism factor and a decrease in the levels of openness, extraversion, conscientiousness, and socialization.

## METHODS

### Sample and procedures

A total of 30 individuals with cognitive complaints were attended by a neurologist and diagnosed with dementia due to AD based on Mckhann's criteria[15] at an outpatient clinic. They were recruited for the study with family consensus. Mini-Mental Status Examination (MMSE)[20] and Clinical Dementia Rating (CDR) scale[21] were applied to patients, and also the age and level of education data were collected.

After medical consultation, spouse or children who lived with the patient for at least 15 consecutive years responded to the Personality Factorial Battery (PFB)[10], a psychometric instrument based on the model of the five major personality factors validated for the Brazilian population with excellent internal consistency and test–retest reliability[22].

The battery comprises 126 items in a seven-point Likert format for family members to judge how much each statement applies to the participants, and it was responded in patients' home through a hosted site on Internet. Family members responded to statements about patients' personalities and characteristics in two times: thinking about 10 years ago when participants were asymptomatic (t1) and thinking about the present when the patients received the diagnostic AD (t2). Patients were also separated into two groups: mild dementia (CDR 1) and moderate dementia (CDR 2).

Patients were excluded from the research if they had CDR 3, had moderate-to-advanced cerebrovascular disease[23], or were not using psychotropic medications in a stable manner for at least 3 months. Individuals with a positive polymerase chain reaction (PCR) test for COVID-19 in the past 14 days or with flu-like symptoms on the day of the medical appointment were also excluded. In addition, patients who were analphabets or without Internet access were excluded.

The study was approved by the Research Ethics Committee of the Institute of Human Sciences of the Universidade de Brasília.

### Data analysis

The *Statistical Package for the Social Sciences* (SPSS) software, 21st version, was used to analyze database. The means and standard deviations for the personality factors' scores were calculated in t1 and t2, and paired t-tests for one sample were performed to verify the

differences in means, assuming a significance level equal to 5%. Scores for all factors and subfactors were reported in relation to the normative sample of the PFB.

Comparative analyses through multivariate analysis of variance (MANOVA) and two-sample t-test were performed to evaluate the existence of significant differences of the means between group scores.

Linear regression was used to access possible confounders of age and schooling between the groups. Correlations through the groups were conducted by Pearson's coefficient.

## RESULTS

As shown in Table 1, the study included 30 patients with AD, 18 of whom were women. The mean age was 71.9 years (SD=7.4), and the mean MMSE was 22.1 (SD=3.1) and 14.5 (SD=2.5) in the mild dementia group and the moderate dementia group, respectively.

Regarding the education of patients, 9.7% had completed higher education, 9.7% had incomplete higher education, 22.6% had completed high school, 12.9% had completed elementary school, and 45.2% had incomplete elementary schooling, and the groups were homogeneous in terms of age [t(30)=-0.29; p=0.78] and level of education [t(30)=1.30; p=0.20].

In the paired t-test analysis of the 30 patients, significant differences were verified between the premorbid state and the current state in all the factors (Table 2). Regarding the subfactors, kindness[t(30)=-5.37; p<0.001], dynamism [t(30)=-8.48; p<0.001], social interactions [t(30)=-6.80; p<0.001], competence [t(30)=-9.53; p<0.001], and endeavor/commitment [t(30)=-4.75; p<0.001] showed higher levels of changes. In contrast, there was no significant difference between the scores of the subfactors trust in people before and after [t(30)=-1.49; p=0.14], arrogance before and after [t(30)=-1.64; p=0.11], vulnerability before and after [t(30)=0.44; p=0.66], and search for novelty before and after [t(30)=-1.70; p=0.090].

In the MANOVA analysis (Table 3), both groups showed significant changes in the five factors across t1 and t2, with an increase in the neuroticism scores and a decrease in the other four factors.

When comparing the two groups, only the factor extraversion showed a significant change in the scores across t1 and t2 (Figure 1).

When considering just the CDR, higher scores in neuroticism in t1 correlated with more numbers of patients with moderate dementia in t2 (Figure 2).

## DISCUSSION

The present study investigated the influence of AD on the change in personality traits of outpatients with this pathology. The results obtained revealed a significant increase in the scores of neuroticism and a significant decrease in the level factors, such as extraversion, conscientiousness, openness, and socialization, when the factors were compared between the premorbid and current personality[24,25].

The data found are consistent with most studies similarly outlined in the literature. They have shown remarkable patterns of personality change and huge differences when comparing AD patients with normal aging[17].

Functional neuroimaging studies correlate personality factors with structural dimensions and degrees of large networks activation. As an example, low levels in conscientiousness correlated with an increase in cerebral white matter lesions and in a reduced volume of the dorsolateral prefrontal cortex[13,18]. In turn, it is important to remember that characteristics of conscientiousness or neuroticism are factors related to circumstances like smoking, physical inactivity, obesity, and depressive symptoms, which are established risk factors for dementia[26,27].

**Table 1.** Clinical Dementia Rating, Mini-Mental Status Examination, gender, and age scores of the patients.

| Female | | | Total | | |
|---|---|---|---|---|---|
| Participants | Mean | | Participants | Mean | |
| | Age Mean (SD) | MMSE Mean (SD) | | Age Mean (SD) | MMSE Mean (SD) |
| 8 | 75.9 (5) | 20.6 (2) | **16** | 70.9 (8.6) | 22.1 (3.1) |
| 10 | 74.1 (5.4) | 13.8 (1.8) | **14** | 73 (5.8) | 14.5 (2.5) |
| 18 | 74.9 (5.1) | 16.8 (3.9) | **30** | 71.9 (7.4) | 18.5 (4.7) |

MMSE: Mini-Mental Status Examination; SD: standard deviation.

**Table 2.** Comparison between premorbid and current personality factors.

| Personality facets | 10 years ago | Currently | p-value | R | D |
|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | | | |
| Socialization | 5.55 (1.02) | 4.59 (1.17) | <0.001 | 0.40 | -0.87 |
| Kindness | 5.77 (1.44) | 4.20 (1.52) | <0.001 | -0.47 | -1.06 |
| Pro-sociability | 5.85 (0.90) | 5.25 (1.23) | 0.001 | -0.27 | -0.56 |
| Trust in people | 4.90 (1.35) | 4.52 (1.48) | 0.14* | -0.13 | -0.27 |
| Extraversion | 4.66 (1.06) | 3.21 (0.96) | <0.001 | 0.58 | -1.43 |
| Communication | 4.56 (1.33) | 3.50 (1.18) | 0.001 | -0.39 | -0.84 |
| Dynamism | 5.34 (1.35) | 2.93 (1.24) | <0.001 | -0.68 | -1.86 |
| Social interactions | 4.93 (1.42) | 2.92 (1.06) | <0.001 | -0.63 | -1.62 |
| Arrogance | 3.96 (1.29) | 3.45 (1.29) | 0.11* | -0.19 | -0.39 |
| Conscientiousness | 5.26 (1.09) | 3.03 (1.17) | <0.001 | 0.70 | -1.97 |
| Competence | 5.63 (1.23) | 2.72 (1.47) | <0.001 | -0.73 | -2.15 |
| Reflection/Prudence | 4.63 (1.38) | 3.60 (1.17) | <0.001 | -0.37 | -0.80 |
| Endeavor/Commitment | 5.07 (1.31) | 3.16 (1.47) | <0.001 | -0.56 | -1.37 |
| Neuroticism | 3.52 (1.05) | 4.39 (1.02) | 0.001 | 0.84 | 0.39 |
| Emotional instability | 3.65 (1.80) | 4.64 (1.62) | 0.006 | 0.28 | 0.59 |
| Passivity | 3.63 (1.34) | 4.78 (1.20) | 0.001 | 0.41 | 0.90 |
| Depression | 2.85 (1.36) | 4.34 (1.55) | <0.001 | 0.45 | 1.02 |
| Vulnerability | 3.93 (1.11) | 4.02 (1.08) | 0.66* | 0.04 | 0.08 |
| Openness | 3.69 (0.83) | 3.18 (0.70) | 0.002 | 0.31 | -0.66 |
| Openness to new ideas | 3.74 (1.15) | 3.12 (1.12) | 0.006 | 0.55 | -0.26 |
| Liberalism | 3.56 (1.05) | 3.17 (0.96) | 0.011 | 0.39 | -0.19 |
| Search for novelty | 3.61 (1.03) | 3.31 (1.09) | 0.09* | 0.29 | -0.14 |

*p<0.05; SD: standard deviation.

**Table 3.** Comparative analysis between the groups.

| Analysis | Neuroticism | | Extroversion | | Socialization | | Conscientiousness | | Openness | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F | p-value | F | p-value | F | p-value | F | p-value | F | p-value |
| MANOVA | | | | | | | | | | |
| Time | 12.559 | 0.001 | 36.006 | 0.000 | 19.416 | 0.000 | 74.705 | 0.000 | 11.455 | 0.002 |
| CDR×time | 0.336 | 0.567 | 6.217 | 0.019 | 0.436 | 0.515 | 3.861 | 0.059 | 2.368 | 0.135 |
| Paired comparison between subjects | | | | | | | | | | |
| CDR | | 0.009 | | 0.644 | | 0.378 | | 0.775 | | 0.880 |

F: statistical value; CDR: Clinical Dementia Rating; MANOVA: multivariate analysis of variance.

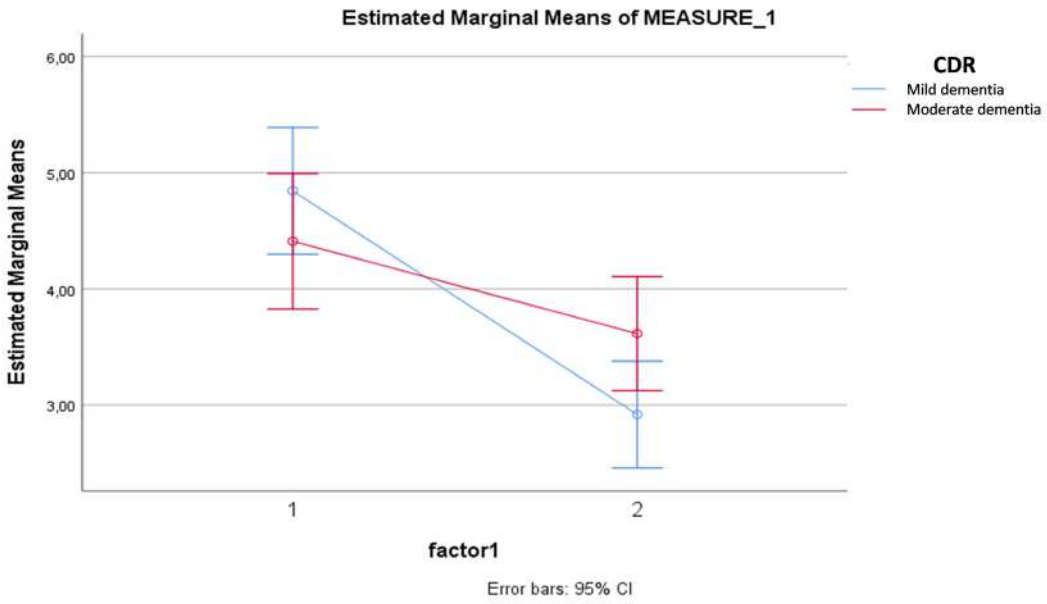


**Figure 1.** Difference in the extroversion factor scores between the groups.

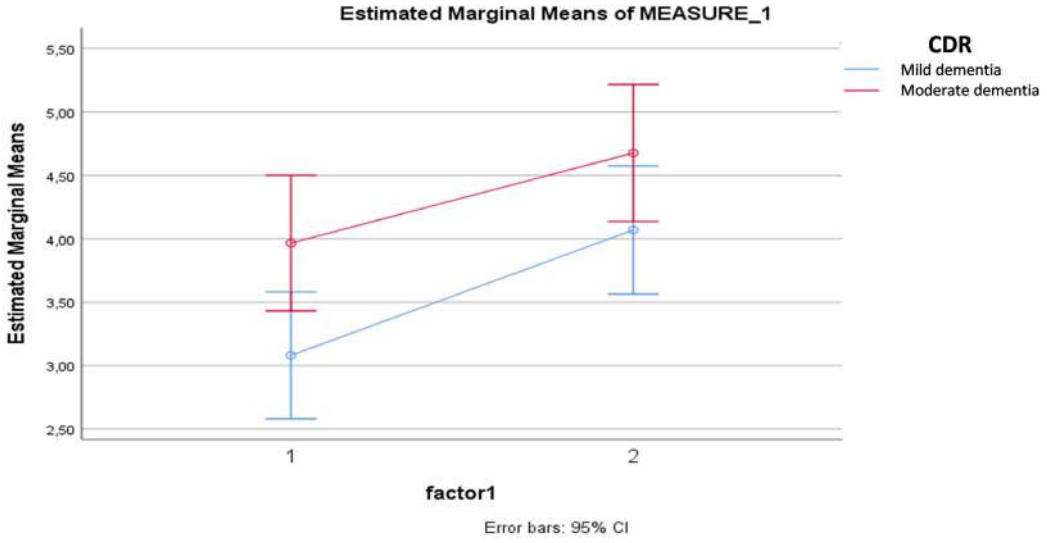


**Figure 2.** Difference in the neuroticism factor scores between the groups.

In this sense, personality traits can also have an impact on the concept of individuals' cognitive reserve due to poorly adaptive behaviors or activities related to intellectual curiosity, creativity, interest in places, and social ties. This concept links the resilience with individual behaviors of AD pathologies that can be protective or disruptive. In the other way, incipient AD pathology can degenerate important cerebral areas and provide deleterious effects, such as the behavioral and psychological symptoms of dementia. For these reasons, studies on neuroimaging and clinical personality assessment help elucidate this intricate relationship between personality and cerebral structure and function[17,28].

Maheen et al.[29], in a meta-analysis with 592 patients, where personality changes were reported retrospectively from the informant perspective, found a replicable evidence for large changes in personality among individuals with AD, particularly decrease in extraversion and conscientiousness and increase in neuroticism. Seeking for responses or even more questions, Terraciano and Sutin[17] reviewed prospective studies and found elevated scores in neuroticism and decreased scores in conscientiousness as independent risk factors for dementia.

Future research should continue to examine whether different patterns of personality changes across etiologies of dementia and prospective assessments of personality using both self-report and informant report are needed to interpret this mental trajectory built by personality and cognition[30].

In the context of this study, family members of patients with mild dementia noticed a greater decrease in extroversion compared with family members of patients with moderate AD. This fact may suggest that in mild AD, changes in behaviors related to communication, dynamism, and social interactions are perceived in a more intense way by family members. There was also a correlation between higher levels of premorbid neuroticism, which favors characteristics such as emotional instability and vulnerability, with a greater severity of the disease[17,18].

Some important limitations in this study include a small sample, data collection based on information from third parties, and the absence of a control group and retrospective design that makes it difficult to establish causalities. For this purpose, prospective studies are needed to be done, including individuals with MCI and other types of dementia. However, in conclusion, it is a research design that brings clinical information regarding personality changes in the course of dementia processes. The early identification of these changes can assist clinicians in choosing tailored interventions to mitigate the psychological distress of their patients together with preventive coping strategies to avoid harmful behaviors.

## ACKNOWLEDGMENT

The authors thank professors Wânia Cristina de Souza and Valéria Santoro Bahia for their orientations and comments.

**Authors' contributions:** VSB: conception, planning, data interpretation, and writing– review. WCS: conception, analysis, planning, data interpretation, and writing – review. JCN, RVSB, and WAS: analysis, data interpretation, and writing – review. KERS: data analysis and writing – review. KFL: conception, planning, data collection, analysis, data interpretation, and writing.

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Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0088

# Effects of concert music on cognitive, physiological, and psychological parameters in the elderly with dementia:
## a quasi-experimental study

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**ABSTRACT.** Non-pharmacological interventions, such as the use of music, have been shown to be important potential means of controlling adverse symptoms and signs resulting from chronic diseases already present in elderly patients with dementia. **Objectives:** The objective of this study was to analyze the effects of concert music on cognitive and physiological parameters, and behavioral and psychological symptoms in institutionalized elderly people with dementia. **Methods:** A descriptive-exploratory, quantitative, quasi-experimental study was conducted with 14 elderly people. They were allocated in intervention group (IG) (n=7) with eight sessions of music listening, once a week, for 2 months, and control group (CG) (n=7) with the same procedure but without listening to the music. All participants were assessed by Neuropsychiatric Inventory Questionnaire (NPI-Q) and Addenbrooke's Cognitive Examination – Revised (ACE-R) before and after the intervention. Blood pressure (BP) data were obtained; heart rate (HR) and coherence were obtained through Cardioemotion during sessions. The data were analyzed using Fisher's exact test and Student's *t*-test. **Results:** There was a predominance of female participants, who were widowed and diagnosed with Alzheimer's disease (AD) in both groups. A statistically significant reduction was found in the mean of apathy reduction (p=0.038) and the total mean of NPI-Q severity (p=0.033) (paired Student's *t*-test) in IG. No significant differences were found in mean level of the pre- and post-analysis variables in CG. **Conclusions:** Concert music had a positive effect on the behavior of institutionalized elderly. Stimuli and possibilities of improving the current behavioral conditions are observed.

**Keywords:** Aged; Dementia; Music; Alzheimer Disease.

**EFEITOS DA MÚSICA DE CONCERTO SOBRE A COGNIÇÃO, PARÂMETROS FISIOLÓGICOS E PSICOLÓGICOS EM IDOSOS COM DEMÊNCIA: ESTUDO QUASE EXPERIMENTAL**

**RESUMO.** Intervenções não farmacológicas, como o uso da música, têm-se mostrado importantes meios potenciais de controlar os sintomas e sinais adversos decorrentes das enfermidades crônicas já instaladas em idosos com demência. **Objetivos:** Analisar o efeito da música de concerto sobre a cognição, parâmetros fisiológicos e sintomas comportamentais e psicológicos em idosos com demência institucionalizados. **Métodos:** Estudo descritivo-exploratório, quantitativo, quase experimental, realizado com 14 idosos. Eles foram alocados em: Grupo Intervenção (GI) (n=7), com oito sessões de audição musical, uma vez por semana, durante dois meses; e Grupo Controle (GC) (n=7), com o mesmo procedimento, porém sem a audição da música. Todos os participantes foram avaliados pelo Neuropsychiatric Inventory Questionnaire (NPI-Q) e Addenbrooke's Cognitive Examination – Revised (ACE-R) antes e depois do período da intervenção. Foram obtidos dados de pressão arterial, frequência e coerência cardíaca por meio do *cardioemotion* durante as sessões. Os dados foram analisados pelos testes Exato de Fischer e *t* de Student. **Resultados:** Em ambos os grupos houve predominância de participantes do sexo feminino, estado civil de viuvez e com diagnóstico de Alzheimer. Foi encontrada redução estatisticamente significativa na média do desgaste na apatia (p=0,038) e média total do NPI-Q gravidade (p=0,033) (teste *t* de Student pareado) no GI. Para o GC, não foram encontradas diferenças significativas no nível médio das variáveis na pré e pós-análise. **Conclusões:** A música de concerto teve efeitos positivos no comportamento dos idosos institucionalizados. Nota-se que, em geral, ela trouxe estímulos e possibilidades de melhoria das condições comportamentais atuais.

**Palavras-chave:** Idoso; Demência; Música; Doença de Alzheimer.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** This research had the financial support of research from CAPES. Process: 88882.426462/2019-01.

Received on September 01, 2021; Received in its final form on October 29, 2021; Accepted on November 04, 2021.

## INTRODUCTION

Concurrently with population aging, the prevalence of dementia syndromes also increases. Many studies reported rates between 4.2 and 7.2% (≥65 years), with age having a direct influence with average of 1.2% in the 65–69 age group and 39.9% in the 90–94 age group[1]. Dementia (major neurocognitive disorder) is a clinical syndrome that leads to deterioration of cognitive domains, behavioral changes, and functional loss[2].

Alzheimer's disease (AD) is the most common cause of dementia, followed by vascular dementia (VD) and the coexistence of both characterize mixed dementia (MD), among others. AD is a progressive and degenerative neurological disease that compromises behavioral and cognitive processes, leading to reduction of memory functions and visuospatial skills and independence and autonomy loss[3].

Common dementia framework is the presence of behavioral and psychological symptoms. The terminology Behavioral and Psychological Symptoms of Dementia (BPSD) determines the set of signs and symptoms associated with disturbances of perception, mood, behavior, and thought content, such as delirium, hallucination, agitation or aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability or emotional lability, loss of motor function, nocturnal behavior, appetite, and dietary changes. These signs and symptoms are an important factor to patient suffering and distress of caregivers[3].

As a consequence of supporting people with dementia, it has been increasing the number of elderlies on Long-Term Institutions for the Elderly (LTIE) as an alternative in providing essential care for maintaining life and being capable of providing quality of life[4]. These environments offer care assistance but generally almost do not offer stimuli to the elderly.

Therefore, pharmacological treatment consists of psychotropic drugs (e.g., antipsychotics, antidepressants, anticonvulsants, mood stabilizers, cholinesterase inhibitors, and memantine), which are the main options for the treatment of BPSD currently available[5], but which sometimes are less effective for the control of the disease[6], being of great relevance to search for alternative therapeutic measures to the already established medications. As a result, there has been an increase in research on non-pharmacological interventions to reduce the symptom burden for people with AD and their caregivers[7]. Among the interventions, there is the use of music to minimize symptoms related to dementia syndromes, as well as an improvement in quality of life[8].

In general, an intervention using music can promote cognitive stimulation[9]. This is possible because musical memory networks are separated from traditional memory networks and are spared until the final stage of disease, activating a wide net in the brain, instead of only one "music area"[9]. In addition to decreasing the process of cognitive impairment, music intervention can stimulate motor skills, improve quality of life, and reduce problematic behavior associated with dementia[10].

Music presents well-established psychological effects, including induction and mood and emotional changes. Some music types, such as meditative or concert music, reduce neurohormone markers of stress. In addition, music has heart rate (HR) and blood pressure (BP) effects. Relaxing music is capable of decreasing HR and BP, while fast rhythm music increases the signs[11].

There is evidence that concert music interferes in some aspects of physiological variables due to a balance between sympathetic and parasympathetic system, in favor of parasympathetic system, through the possible involvement of limbic brain areas that would modulate hypothalamic-pituitary functions. These changes have an impact on induction and mood and emotional changes and can lower stress levels, providing relaxation[11].

It is a recent academic-scientific investigation process, at a national and international level, related to music interventions being used as therapy in healthcare institutions, such as LTIE. As a result, it is believed that this study contributes to the advancement of gerontological intervention practices, based on clinical evidence, which will clarify important issues and is not yet sufficiently resolved in relation to cognitive stimulus, satisfaction, and well-being with the use of music in institutionalized elderly people with dementia. Thus, the general objective of this study was to analyze concert music effects on cognitive and physiological parameters, and psychological and behavioral symptoms in institutionalized elderly people with dementia.

## METHODS

It is a descriptive-exploratory, quantitative, quasi-experimental study developed from September to December 2018. It is understood that the quasi-experimental design was chosen because the sample was intentional and not probabilistic, in which the intervention group (IG) belonged to an LTIE (A) and the control group (CG) represented the residents of another LTIE (B). The CG was listed in this study for the possibility of comparing two similar groups, which were not randomized; however, similarities between them were guaranteed in demographic and health variables, except for outcome

variable to the possibility of testing a cause-and-effect relation.

This study was realized in two private LTIE in the state of São Paulo. Both have elderly profile similarities: people with cognitive, behavioral, physical, and mental limitations, associated with neurological diseases and common diseases in old age, diagnosed by geriatricians associated with the institutions.

Therefore, elderly people aged above 60 years were included, LTIE A and LTIE B residents, with clinical diagnosis of dementia (varied etiologies), responsive to verbal commands. Exclusion criteria were as follows: other serious psychiatric disorders diagnosis, such as bipolar affective disorder, schizophrenia, and other psychoses, and having uncorrected possessing deficit that would make it impossible to hear music.

Notably, 14 elderly people participated in this research. Of a total of 42 individuals, 28 were excluded for not responding to verbal commands necessary for cognitive assessment. At LTIE A, 24 individuals were residents and 7 were assessed. At LTIE B, 18 individuals were residents and 7 were assessed (Figure 1).

The IG experienced one musical listening session of 20 min/week, consisting of concert music, for 2 months. The eight sessions always took place in the same appointments quiet room and at the same time (in the afternoon), in the institution itself, individually, realized by gerontologists. A headphone was placed in the auditory pavilion of the elderly, which was connected to a notebook for the complete emission of the music in a random sequence, in a 70-dB frequency. The songs were selected by a music therapists partner of the research group Laboratory of Evaluation and Intervention in Gerontology (LEIG), with the aim of causing relaxation, improving mood, and well-being, namely, Nocturne Opus 9 no. 2 by Frederic Chopin; Adagio in G minor (best live version) by Tomaso Albinoni; and Serenade for Winds (K. 361, 3rd movement) by Wolfgang Amadeus Mozart. The criteria for selecting the songs were as follows: bars with a sense of continuity; harmony and repeated melodies with slower pace respecting the speed of cognitive processing of the elderly; and songs that rescued the collective unconscious and the lost sound identity (possibly hearing throughout life) and that were stimuli to maintain the attention of the elderly. In the CG, the participants went through the same process as the IG (headphone use), however without music, and were evaluated by the intervention protocol, and in the same way, they maintained their day-to-day activities at the institution.

The research protocol contained the systolic blood pressure (SBP) and diastolic blood pressure (DBP) verification before and after each musical hearing (was considered for analyzing the average of all sessions for each group). The HR and cardiac coherence (CC) were collected during the sessions and their values were obtained

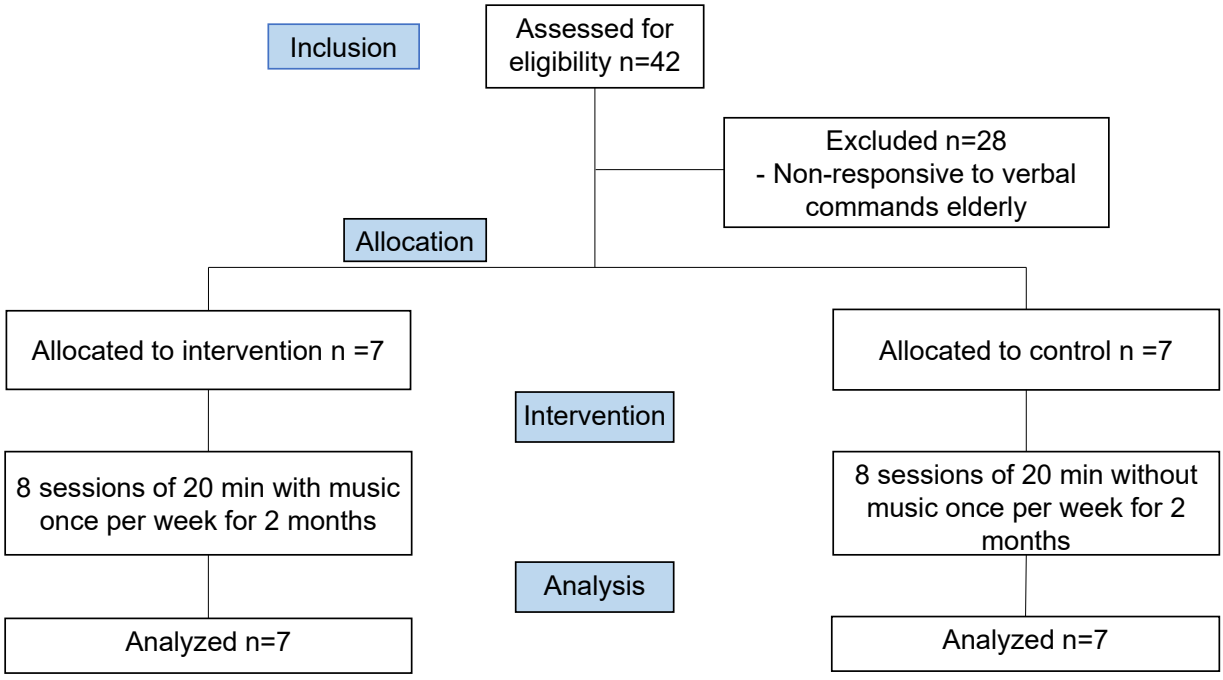


**Figure 1.** Participant allocation flowchart. São Carlos, SP, Brazil.

at the end of each session (for analysis, the data from the first and last sessions were considered), through biofeedback cardiovascular (Cardioemotion). The evaluation takes place by recording the time intervals, elapsed between each heartbeat, by an external sensor coupled to the second finger, followed by mathematical treatment of the data by the software[12].

The nurses responsible for the two institutions (blind to intervention) were instructed to characterize the participants with demographic and health information and 1 month before and after the intervention, with the Neuropsychiatric Inventory Questionnaire (NPI-Q), a self-administered instrument, validated for evaluating the behavioral state of dementia patients during the last month[13]. This instrument assesses the severity (1–3) and the distress of caregivers (0–5) for 12 symptoms, namely, delirium, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, loss of motor function, nocturnal behavior, and dietary changes. The total NPI-Q score is obtained from the sum of the two subscales.

Addenbrooke's Cognitive Examination-Revised (ACE-R) was used to assess cognition, also before and after the intervention period, by trained researchers from the research group. ACE-R evaluates six cognitive domains separately, namely, orientation, attention, memory, verbal fluency, speech, and visuospatial skill. The maximum score is 100 points, and the sum of all is equivalent to the individual's total score in the ACE-R. Among this total, 30 relative points of the Mini-Mental State Examination (MMSE)[14] are included.

The data were stored and processed in specific software for statistical analysis. The Shapiro-Wilk test was performed to assess data adherence to normality. The presence/absence of differences for continuous sociodemographic variables, at baseline, was verified using the independent samples Student's *t*-test, and comparison of categorical variables using Fisher's exact test. The presence/absence of differences between CG and IG of the outcome variables, before and after the intervention, was verified using Student's *t*-test for paired samples. The level of significance adopted for all tests was $p \leq 0.05$ (5%).

The Research Ethics Committee of the Federal University of São Carlos approved this study, under opinion no. 1.981.699, in accordance with the provisions of Resolution no. 466/2012 of the National Health Council (NHC) and Resolution no. 510/2016, which defines the guidelines and regulatory standards that rule human being's research. In addition, the informed consent form (ICF) was presented to the legal guardians of the participants and their consent was respected.

## RESULTS

In both groups, there was the predominance of widowed female participants diagnosed with AD. No statistically significant differences were identified between CG and IG in terms of demographic characteristics, with the exception of drugs, in which CG makes use of a greater number of medicines when compared to the IG (p=0.031). Table 1 shows the demographic variables of patients in each of the evaluated groups.

Table 2 shows the comparative data for the variables of severity and distress in NPI-Q, in addition to HR, SBP, DBP, CC, and ACE-R. It is worth to note the significant decrease in apathy reduction ($t$=2.646; p=0.038) and in the total mean of NPI-Q severity ($t$=2.760; p=0.033). Although not statistically significant, it is observed that some of the NPI-Q variables improved when compared to the moments before and after for IG, with lower averages in the post-analysis, such as the severity of depression and apathy, among others. For the CG, no significant differences were found in the mean level of the variables in the pre- and post-analysis, with the majority of the means remaining the same.

## DISCUSSION

The elderly who participated in this study are long-lived, with an average age above 80 years, corroborating with other studies in this area, which evaluated institutionalized elderly people with dementia[15,16]. In addition, it is known that dementia is quite common in the elderly population, with a prevalence that doubles approximately every 5 years, starting at 65 years old[17]. There is also a predominance of women, which reflects on a feminization of old age, in which the elderly population majority, worldwide, is composed of women, due to a higher average of life expectancy when compared with men[18]. However, even if it seems positive, the high percentage of women in this study is associated with the high prevalence of dementia, in addition to the issue of widowhood and lack of support. The most prevalent type of dementia in the sample was AD, which is the most common, with an estimated number of 50 million people living with this disease in the world nowadays[19].

This study shows that intervention with concert music has a positive impact on the behavioral symptoms of institutionalized elderly people with dementia and on the distress caused by them to the caregivers involved, mainly in the apathy symptom. Apathetic behavior is one of the neuropsychiatry symptoms most frequently reported in the elderly with dementia because it causes suffering for caregivers[3,20]. A study in China, with 77 institutionalized elderly people with dementia, evaluated

**Table 1.** Sociodemographic and health data of the intervention group and control group (n=14). São Carlos, SP, 2021.

| Sociodemographic and health data | | IG (n=7) | CG (n=7) | p-value |
|---|---|---|---|---|
| Gender [n(%)] | Male | 0 (0.0) | 2 (28.6) | 0.462* |
| | Female | 7 (100.0) | 5 (71.4) | |
| Age [average (±SD)] | | 86.14 (±4.63) | 81.29 (±7.99) | 0.190** |
| Marital status [n(%)] | Married | 1 (14.3) | 0 (0.0) | 0.378* |
| | Divorced/separated | 0 (0.0) | 1 (14.3) | |
| | Widowed | 5 (71.4) | 6 (85.7) | |
| | Single | 1 (14.3) | 0 (0.0) | |
| Education (years) [average (±SD)] | | 8.86 (±5.04) | 6.86 (±5.42) | 0.489** |
| Comorbidities (n) | | 2.57 (±0.97) | 2.57 (±1.39) | 1.000** |
| Medicines (n) | | 2.43 (±0.97) | 5.43 (±3.10) | **0.031**** |
| Institutionalization time (months) | | 13.57 (±10.76) | 6.71 (±5.93) | 0.166** |
| Etiology of dementia [n(%)] | Alzheimer's disease | 7 (100.0) | 3 (42.9) | 0.061* |
| | Mixed dementia | 0 (0.0) | 2 (28.6) | |
| | Others | 0 (0.0) | 2 (28.6) | |

IG: intervention group; CG: control group; n: number; SD: standard deviation; bold: statistically significant; *Fisher's exact test; **Student's *t*-test.

the effect of a 12 week music therapy intervention on apathy. The IG received a musical intervention program, which included listening to nostalgic songs and playing instruments, e.g., xylophone. After 12 weeks of study, the apathy of patients undergoing the intervention showed a significant improvement, verified by Apathy Evaluation Scale (the pre- and post-intervention score difference, $z=4.516$, $p<0.001$), while the CG did not show a significant change in relation to this neuropsychiatric symptom. The cognitive function, evaluated by MMSE, was stable in the IG ($t=1.720$, $p>0.05$) but decreased in the CG ($t=-1.973$, $p<0.05$)[21].

Concurrent with other studies, the result of this study suggested beneficial effects of the music intervention on the dementia symptoms and occupation disturbance, as measured by NPI[15,16,22]. In a study carried out in Spain with 42 institutionalized elderly with mild-to-moderate AD, who underwent music therapy for 6 weeks, a significant improvement was found in memory, orientation, depression, and anxiety (Hospital Anxiety and Depression Scale [HADS]) in patients with mild-to-moderate dementia; anxiety (NPI scale) in patients with mild dementia; and delirium, hallucinations, agitation, irritability, and language disorder in patients with moderate dementia. The effect on cognitive measures (MMSE) was noticeable after four music therapy sessions for all individuals[23].

In another research conducted in Taiwan[24], the authors selected concert music (Sonata by Mozart KV448 and Canon by Pachelbel), for the elderly to listen with headphones for 30 min daily in the morning and before bed, respectively, for 6 months. They found no behavioral alterations related to the intervention, but they found small cognition changes when examining the subcategories of cognitive tests (Cognitive Abilities Screening Instrument [CASI] and MMSE), contradicting the findings of this study, which did not obtain statistical differences in the cognitive domains of ACE-R.

In a study conducted in Australia, 99 institutionalized elderly participated in an experiment performed with a personalized playlist. The authors investigated the influence of depression, anxiety, apathy, and cognitive loss in the affective music response. Facial expressions were analyzed, and the behavioral responses were continuously observed. The results showed people with low depression, but high apathy levels demonstrated a greater behavioral evidence of pleasure during music listening. They concluded that music interventions are positive for people with dementia, but they need to consider the background and mental health symptoms of those involved[25].

In a systematic review[26], the authors suggested that the environments of long-term institutions contribute to the reduction of cognitive scores and that music is the path to improve patients' quality of life. The concert

**Table 2.** Comparison of the pre- and post-intervention group (n=7) and the pre- and post-control group (n=7) for the outcome variables. São Carlos, SP, 2021.

| | IG (n=7) | | | CG (n=7) | | |
|---|---|---|---|---|---|---|
| | **Pre-average (±SD)** | **Post-average (±SD)** | ***t* (p-value)** | **Pre-average (±SD)** | **Post-average (±SD)** | ***t* (p-value)** |
| Delirium severity | 1.57 (±0.97) | 1.71 (±1.11) | -1.000 (0.356) | 2.14 (±1.46) | 2.14 (±1.46) | NR |
| Delirium distress | 1.43 (±0.97) | 1.29 (±0.95) | 1.000 (0.356) | 3.57 (±2.44) | 3.14 (±2.41) | 1.000 (0.356) |
| Hallucination severity | 1.43 (±0.78) | 1.29 (±0.75) | 1.000 (0.356) | 1.14 (±1.46) | 1.14 (±1.46) | NR |
| Hallucination distress | 1.57 (±0.97) | 1.71 (±1.11) | -1.000 (0.356) | 1.71 (±2.36) | 1.71 (±2.36) | NR |
| Agitation severity | 0.29 (±0.48) | 0.29 (±0.48) | NR | 0.71 (±1.25) | 0.71 (±1.25) | NR |
| Agitation distress | 0.29 (±0.75) | 0.14 (±0.37) | 1.000 (0.356) | 1.00 (±1.91) | 1.00 (±1.91) | NR |
| Depression severity | 1.29 (±1.25) | 0.86 (±0.90) | 2.121 (0.078) | 1.14 (±1.46) | 1.14 (±1.46) | NR |
| Depression distress | 1.43 (±1.51) | 0.86 (±0.90) | 1.922 (0.103) | 1.71 (±2.36) | 1.71 (±2.36) | NR |
| Anxiety severity | 0.71 (±0.95) | 0.57 (±0.78) | 1.000 (0.356) | 2.14 (±1.46) | 2.14 (±1.46) | NR |
| Anxiety distress | 0.71 (±1.11) | 0.43 (±0.78) | 1.549 (0.172) | 3.57 (±2.44) | 3.57 (±2.44) | NR |
| Motor disorder severity | 1.00 (±1.29) | 0.57 (±0.97) | 1.000 (0.356) | 0.43 (±1.13) | 0.43 (±1.13) | NR |
| Motor disorder distress | 1.29 (±1.70) | 0.29 (±0.75) | 1.732 (0.134) | 0.71 (±1.89) | 0.71 (±1.89) | NR |
| Nocturnal behavior severity | 0.86 (±1.21) | 0.43 (±0.53) | 1.441 (0.200) | 0.43 (±1.13) | 0.43 (±1.13) | NR |
| Nocturnal behavior distress | 0.71 (±1.25) | 0.14 (±0.37) | 1.333 (0.231) | 0.71 (±1.89) | 0.71 (±1.89) | NR |
| Appetite severity | 0 | 0 | NR | 0 | 0 | NR |
| Appetite distress | 0 | 0 | NR | 0 | 0 | NR |
| Euphoria severity | 0.57 (±0.78) | 0.43 (±0.53) | 1.000 (0.356) | 1.29 (±1.60) | 0.86 (±1.46) | 1.000 (0.356) |
| Euphoria distress | 0 | 0 | NR | 1.86 (±2.41) | 1.14 (±2.03) | 1.000 (0.356) |
| Apathy severity | 1.29 (±0.95) | 0.86 (±1.06) | 1.441 (0.200) | 0.86 (±1.21) | 1.00 (±1.29) | -1.000 (0.356) |
| Apathy distress | 1.43 (±1.39) | 0.43 (±0.79) | **2.646 (0.038)*** | 1.57 (±2.14) | 1.71 (±2.21) | -1.000 (0.356) |
| Disinhibition severity | 0 | 0 | NR | 0 | 0 | NR |
| Disinhibition distress | 0 | 0 | NR | 0 | 0 | NR |
| Irritability severity | 0.29 (±0.75) | 0.29 (0.75) | NR | 1.29 (±1.60) | 1.14 (±1.46) | 1.000 (0.356) |
| Irritability distress | 0.43 (±1.13) | 0.43 (±1.13) | NR | 2.14 (±2.67) | 1.71 (±2.36) | 1.000 (0.356) |
| NPI total severity | 9.29 (±5.09) | 7.29 (±4.23) | **2.760 (0.033)*** | 11.57 (±6.13) | 11.14 (±6.56) | 0.701 (0.510) |
| NPI total distress | 9.29 (±8.73) | 5.71 (±6.18) | 2.09 (0.081) | 18.57 (±9.84) | 17.14 (±11.29) | 0.892 (0.407) |
| HR | 71.14 (±5.61) | 74.14 (±11.24) | -0.632 (0.540) | 75.14 (±8.70) | 73.71 (±12.93) | 0.242 (0.813) |
| SBP average | 121.57 (±6.52) | 119.71 (±9.30) | 0.432 (0.673) | 126.43 (±6.90) | 125.71 (±6.72) | 0.196 (0.848) |
| DBP average | 72.71 (±6.44) | 70.29 (±6.77) | 0.687 (0.505) | 71.43 (±8.99) | 68.57 (±7.48) | 0.646 (0.530) |
| % coherence | 24.57 (±8.16) | 25.71 (±9.46) | -0.242 (0.813) | 24.29 (±11.52) | 24.43 (±8.05) | -0.027 (0.979) |
| MMSE | 13.00 (±5.35) | 13.29 (±4.19) | -0.111 (0.913) | 14.00 (±6.75) | 13.29 (±7.52) | 0.187 (0.855) |
| ACE-R | 37.29 (±13.42) | 37.57 (±9.79) | -0.045 (0.964) | 39.14 (±23.19) | 36.29 (±21.89) | 0.237 (0.817) |
| Attention/orientation | 6.57 (±3.69) | 6.57 (±3.10) | NA | 7.29 (±4.07) | 7.57 (±4.99) | -0.117 (0.909) |
| Memory | 4.43 (±4.57) | 4.43 (±3.10) | NA | 8.57 (±5.38) | 7.29 (±5.49) | 0.442 (0.666) |
| Verbal Fluency | 1.86 (±2.19) | 1.57 (±2.44) | 0.230 (0.822) | 3.43 (±2.69) | 2.71 (±3.03) | 0.465 (0.650) |
| Speech | 16.00 (±4.12) | 16.57 (±4.23) | -0.256 (0.802) | 12.71 (±7.74) | 12.29 (±8.67) | 0.098 (0.924) |
| Visuospatial skill | 8.43 (±1.71) | 8.43 (±1.39) | NA | 7.14 (±5.01) | 6.57 (±3.59) | 0.245 (0.811) |

*p<0.05 paired Student's *t*-test; NR: not rated; bold: statistically significant.

music choice is still less used in research found in dementia literature context. Listening to music can work as a relaxation technique and, therefore, can have a long-term impact on the patients (symptom reduction), while active music therapy can set to involve the participants through social interaction and provide other benefits[7]. The findings suggest that musical techniques can be used in several ways to improve behavior and cognition[7]. Receptive music therapy can reduce restlessness, behavioral problems, and anxiety in the elderly with dementia and seems to be more effective than interactive music therapy in the treatment of dementia symptoms[6].

Regarding the physiological parameters, no statistically significant differences were found, which may infer that the elderly remains stable, and hearing the concert music did not cause discomfort or altered physiological functions. A study conducted in Japan evaluated the effects of music therapy on the autonomic nervous system on plasma levels of cytokines and catecholamines in elderly with cerebrovascular disease and dementia, and in heart failure events. Notably, 87 elderly were evaluated in 10 sessions of 45 min with Japanese popular music. One study suggested that music therapy increased parasympathetic activities and decreased heart failure by reducing the plasma level of cytokines and catecholamines, providing well-being[27].

Similar to other studies, this research is seeking a variety of promising discoveries related to dementia treatment. Pharmacological interventions are available but have limited capacity to treat many aspects of the syndrome[10]. Although most elderly people had the same diagnosis of dementia (AD), those in the CG used more medication ($p<0.05$) than the elderly in the IG, and it was not possible at this time to identify the class of drug used by each one, which did not allow for more in-depth analysis in these aspects.

The presence of BPSD is related to a greater cognitive impairment and the disease progression, although worsening the elderly life conditions and increasing the caregiver's distress, as it requires a longer time of dedication and constant supervision by the professional[20].

A limitation of this study is the reduced number of participants due to the difficulty of finding older adults with dementia who still respond to stimuli in the institutional environment, and the non-randomized sample may also have contributed to the lack of further findings. It is important to highlight that this study was not composed of music therapy sessions, but sessions using music, making up an elaborate intervention. In addition, the use of the NPI-Q by the nurse may have been insensitive, as this professional does not spend all the time with the patients due to shift changes; thus, the use of specific scales is suggested in future studies, such as the Apathy Scale and the Geriatric Depression Scale, applied directly to elderly participants.

Despite the limitations pointed out, the results showed that the intervention with concert music for institutionalized elderly people was effective in improving NIP severity symptoms and reducing stress on the professional in the apathy symptom in the IG. This study showed that stimuli and possibility to improve current behavioral conditions can be achieved and emphasizes the importance of continuing studies in this area. The result of well-designed interventions in the sociodemographic context can improve health care, safe, humanized, low cost, and easy-to-implement care. In addition, the relevance of identifying neuropsychiatric symptoms in the elderly with dementia diagnosis is perceived, so that health professionals can consider them in planning individualized care, as well as assisting caregivers for continuity of care with quality.

**Authors' contributions.** LAR contributed to the design and interpretation of data, writing and critical review of this article, and approval of the final content; BFS and CEG contributed to the data design, writing of this article, and approval of the final content; ACMG contributed to the research design, elaboration of the protocol, conception, analysis, and interpretation of data, writing and critical review of this article, and approval of the final content. All authors approved the final version of this article.

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Dement Neuropsychol 2022 June;16(2):202-212

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0022

# Use of multisensory stimulation in institutionalized older adults with moderate or severe dementia

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**ABSTRACT.** The Multisensory Stimulation Program can help manage behavioral and psychological symptoms of dementia. **Objective:** The objective of this study was to investigate the effects of the Multisensory Stimulation Program on behavioral, mood, and biomedical parameters of older adults with moderate and severe dementia compared to a control group not submitted to this program. **Methods:** This study is an interventional, parallel, open-label, quasi-experimental clinical trial, which is quantitative and qualitative in nature and is also an exploratory type. The sample was divided for convenience into intervention group (IG) and control group (GC) that did not participate in the Multisensory Stimulation Program. Data analysis included descriptive statistics, nonparametric tests (two-tailed alpha value of 0.1 was applied), and thematic content analysis. **Results:** The sample consisted of 20 older adults (IG=10 and GC=10), with a mean age of 83 years, an average of 3 years of education, and moderate or severe dementia. Reduction in intervention group behavioral changes ($p=0.059$) and numerical improvement in intervention group cognition were observed. A decrease in heart rate ($p<0.05$) and diastolic blood pressure ($p<0.05$) was observed before and immediately after the session in the intervention group. The caregivers described engaged behavior in intervention group, while they reported apathetic behavior in control group. Session records described verbal and nonverbal communication and sustained attention for more than 3 min regarding the sensory resource explored. **Conclusions:** The Multisensory Stimulation Program could be a new look at the health care practices performed in the nursing homes that consider the older adults' sensory preferences and may help with dementia behavior management.

**Keywords:** Dementia; Complementary Therapies; Behavior; Health of Institutionalized Elderly.

**USO DA ESTIMULAÇÃO MULTISSENSORIAL EM IDOSOS INSTITUCIONALIZADOS COM DEMÊNCIA MODERADA OU GRAVE**

**RESUMO.** Um programa de estimulação multissensorial pode auxiliar no manejo dos sintomas comportamentais e psicológicos da demência. **Objetivo:** Investigar os efeitos do programa de estimulação multissensorial sobre o comportamento, o humor e parâmetros biomédicos de idosos com demência moderada e grave, quando comparados a um grupo controle não submetido a esse programa. **Métodos:** Estudo de intervenção quase experimental, paralelo, mascaramento aberto, de natureza quantitativa e qualitativa, do tipo exploratório. Amostra foi dividida igualmente por conveniência entre grupo de intervenção (GI) e grupo controle (GC), que não participou do programa de estimulação multissensorial. estatística descritiva, testes não paramétricos (valor alfa bicaudal de 10% aplicado) e análise temática de conteúdo. **Resultados:** Amostra composta de 20 idosos (GI=10 e GC=10), com média de idade de 83 anos, média de três anos de escolaridade e demência moderada ou grave. Houve redução de alterações comportamentais ($p=0.059$) e melhora numérica no desempenho da cognição de Grupo de Intervenção. Observou-se diminuição da frequência cardíaca ($p<0.05$) e da pressão arterial diastólica ($p<0.05$) antes e imediatamente depois da sessão no grupo de intervenção. Os cuidadores descreveram comportamento engajado no grupo de intervenção, enquanto relataram comportamento apático no grupo controle. Os registros da sessão descreveram ações de interação verbal e não verbal e atenção sustentada por mais de três min diante do recurso sensorial explorado. **Conclusões:** O programa de estimulação multissensorial poderia ser um novo olhar sobre as práticas de saúde realizadas em instituições de longa permanência de idosos que considerem as preferências sensoriais do idoso, e pode auxiliar no manejo do comportamento demencial.

**Palavras-chave:** Demência; Terapias Complementares; Comportamento; Saúde do Idoso Institucionalizado.

This study was conducted by the Bioengineering Interunits Program (EESC/FMRP/IQSC-USP), São Carlos SP, Brazil.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** This work was supported by the Bioengineering Interunits Program (EESC/FMRP/IQSC-USP), Brazilian agency CNPq and FAEPA/HCFMRP.

Received on May 12, 2021; Received in its final form on October 21, 2021; Accepted on November 09, 2021.

## INTRODUCTION

Dementia is characterized by a significant cognitive decline in the performance of cognitive abilities; such deficits interfere with functional capacity[1]. Symptoms may vary according to the etiological subtype and stage (i.e., mild, moderate, or severe). The severe stage has a more significant impact on the functional capacity to perform daily activities and results in the loss of sensitive functions, such as hearing and vision[2-4].

It was estimated that there were about 43.8 million people with dementia in the world in 2016[5]. The incidence of dementia doubles every 6.3 years with increasing age[6], with an estimated economic cost of 818 billion dollars per year globally[2]. Brazil had about 1.6 million cases with the second-highest prevalence by standardized age (1,037 cases per 100,000 inhabitants) in 2016[5].

In the severe stage of dementia, pharmacological measures have limited efficacy, complex management, and side effects[7]. Nonpharmacological interventions can effectively manage behavioral and psychological symptoms, especially in institutional contexts8, and present lower risks than drug treatment[9].

The Multisensory Stimulation Program (MSSP) is a nonpharmacological approach in environments that offer sensory experiences. It stimulates the primary senses (e.g., sight, hearing, smell, touch, taste, and vestibular) provided through controlled interventions[10].

This approach is nondirective. There is no standardization of task sequences without focusing on short-term memory but on momentary experiences[11]. The stimulation usually takes place in a room designed with equipment, such as fiber-optic cables, water columns, aroma diffusers, ambient music, objects with textures, among others[12].

The MSSP can bring the following benefits to institutionalized older adults with moderate to severe dementia: favor sensory processing abilities and reduce sensory overload[13]; promote improvement in aggressive behavior[14]; increase self-esteem up to 1 week after the last session[15]; have immediate positive effects on mood, behavior, and anxiety[16-18]; and improve communication during morning care between professionals and institutionalized older adults[19]; after the end of the intervention, it can decrease blood pressure (BP)[15], reduce heart rate (HR) [15,16-20], and increase oxygen saturation[14,16].

No adverse effects were reported in older adults with dementia due to MSSP use. However, moderate investments are needed for its implementation in institutional environments, either in resources, time, or training of caregivers. More research on MSSP with higher methodological quality is also recommended, such as a control group (CG), consistent outcome measures, and generalization of results to other environments[21,22].

There is limited evidence of the benefits of pharmacological interventions on behavioral changes of the older adults with dementia, and physical restrictions are contraindicated[21]. There is also a lack of nonpharmacological intervention programs aimed at this population. Generally, groups of activities with cognitive and motor emphasis are offered to residents, not including the older adults with dementia.

Considering that scientific productions on the subject are incipient, and further studies are recommended, given the scarcity of stimuli in the institutional environment, this study emphasized the relevance of using the MSSP in behavioral changes and parametric biomedical services for institutionalized older adults with moderate and severe dementia. The study methods used a mixed and quantitative approach together with a qualitative approach.

The hypothesis of this study was whether the use of MSSP produces effects in reducing behavioral changes, promoting neutral mood, and producing changes in biometric parameters (e.g., BP and HR). The objective of this study was to investigate the effects of MSSP on behavioral, mood, and biomedical parameters of older adults with moderate and severe dementia compared to a CG not submitted to this program.

## METHODS

### Methodological and ethical issues

This study is an interventional, parallel, open-label, quasi-experimental clinical trial, of mixed nature (quantitative and qualitative), and exploratory type.

This study was approved by the Research Ethics Committee of the Hospital das Clínicas of the Medical School of Ribeirão Preto under opinion no. 11,134/2016. The project was registered in the Brazilian Registry of Clinical Trials (ReBEC): RBR-459x9d. The management of the nursing home approved the collection of information, the installation of the multisensory room, and the performance of interventions. The written informed consent was obtained in the beginning of the study by formal caregivers (e.g., nursing staff). Older adults with dementia were informed about the purpose of this study and verbally agreed to participate.

### Participants

A survey of institutionalized older adults diagnosed with dementia was carried out based on the medical records of the nursing home in the Brazilian city of Ribeirão Preto.

Inclusion criteria were as follows: being over 65 years old; having a medical diagnosis of dementia, such as Alzheimer's dementia, unspecified dementia, or mixed dementia (Alzheimer's plus vascular/other subtypes); being institutionalized in a nursing home; achieving scores below the cutoff score (<26 points for people with more than 8 years of education, <18 points for 1–7 years of education, and <13 points for illiterate people) according to the Brazilian version of the Mini-Mental State Examination (MMSE) to identify the cognitive status[23]; and having dementia at stage 2 (moderate) or 3 (severe) according to the clinical dementia rating (CDR) to determine the stage of dementia[24].

The exclusion criteria were as follows: having aphasia of expression or understanding, being confined to bed, and having severe visual impairment or hearing loss that is not corrected by visual and auditory resources.

Formal caregivers (e.g., nursing staff) were invited to fill out standardized instruments and questionnaires about information of the older adults. The inclusion criteria were to work for at least 3 months at the institution before starting the research. The caregivers were selected for convenience: the head nurse suggested which nursing staff was responsible for the primary daily care for each older adult chosen in this study. Due to this type of selection, it was not possible to have blind conditions about the study groups. The family members were not invited because they did not live with the residents in this institution and were sometimes absent.

## Study procedures

### Sample characterization

It included medical record research (e.g., type of dementia and health comorbidities), questionnaire with sociodemographic aspects (e.g., age, sex, education level, and time living in the institution), and the Katz index to evaluate the functional capacity[25] (primary daily life activity dependency: mild: 0–1, moderate: 2–4, and severe: 5–6).

Pre-intervention period: Both groups were evaluated with the following standardized instruments before starting the intervention period: Cornell Scale for Depression in Dementia (CSDD) to quantify depressive symptoms[26] and Neuropsychiatric Inventory (NPI) to quantify behavioral changes in the older adults[27,28]. The higher the score obtained, the worse will be the changes in mood and behavior.

A semi-structured checklist was used to collect the perceptions of formal caregivers during the intervention program. Caregivers were asked to select which alternatives were most prevalent in that month regarding behavior (disruptive to engaged), mood (normal to irritable), and level of interaction with the institutional environment and communication with the caregiver (none/very much). There was also an open field to describe notes regarding the behavior and interaction of the older adults.

### Intervention period

A total of 20 older adults were selected and divided for convenience into intervention group (IG) and CG.

The convenience sample was justified due to the use of the entire sample available during the research period. There were a small number of older adults diagnosed with dementia at the institution, i.e., only 36 of 105 residents. From this small number, participants were excluded due to death and other exclusion criteria. There was no other institution with a multisensory environment in the city. The use of this institution's sensory room was reserved for its residents.

(A) IG: Notably, 10 older adults received individual care in a multisensory room, twice a week, for 30 min, during 3 months, totaling 24 sessions. Two researchers participated in the session, of whom one performing the interventions and the other one, as an observer, recording the reactions and data of the intervention. The IG participants continued to attend the activities promoted by the institution's health care team.

A semi-structured script for observation adapted and modified from the preliminary version of the Snoezelen Assessment Scale[29] was used during the sessions to describe the subjects' reactions to the stimuli presented during the sensory stimulation intervention and to record the sensory resource used and time spent in it. The therapist measured the systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR right after the older adult arrived at the environment and the end of the session, using an automatic digital BP monitor.

(B) CG: CG was formed with 10 older adults who did not participate in the MSSP but continued to participate in activities promoted by the institution's health care team.

Post-intervention period: Both groups were reevaluated with instruments of the pre-intervention period after the end of the therapeutic program (3 months).

## Session structure

The MSSP consisted of a set of sessions based on the multisensory stimulation concept[11,30]. The therapist's approach is nondirective. In the first session, therapist invites the participant to explore the spaces, introducing each resource one at a time, and observes the participant's reactions (verbal and nonverbal).

Positive responses allow the therapist to again show the most preferred stimuli in future sessions. Adverse reactions, i.e., repulsion to specific resources, can be avoided. Verbal or nonverbal positive reinforcements can be prepared from the participant's responses to the stimuli as a form of positive feedback, favoring a sense of effectiveness for making such a choice[30].

In the following sessions, the therapist can prepare the environment in advance with some resources that obtained favorable responses, based on observing the participant's reactions, allowing the preparation of a sensory diet (personalized program)[31] and prioritizing the most interesting stimuli. Based on the therapist's observations, some more excitatory sensory stimuli could be offered for those with more apathetic and depressed behavior, and more relaxing stimuli could be offered for those with more agitated, anxious, or irritable behavior.

The participant must be able to have accessible handling, easy exploration, and visual recognition of the resources, which integrates the primary senses[31-33]. The therapist could use fewer verbal commands, allowing the participant to explore the materials and encourage decision-making[30].

The participants can spend as much time as they want in the space/resource, even if they wish to stay there for the entire session. The session ended at 30 min or when the older adult showed signs of tiredness or restlessness that were not mitigated by the stimuli.

Three environments were created at the institution based on friendly design principles for people with dementia. Some principles such as being a safe, familiar, and visually accessible environment; favoring engagement in daily activities; and optimizing good stimulation[32].

The spatial order was sensory garden (e.g., plants with different aromas) (Figure 1), vintage room (e.g., decorative elements from the 1940s to 1960s) (Figure 2), transition corridor (e.g., beaded curtain and pictures with different textures) (Figure 3), and finally, the lights room (e.g., colorful lights, music, and olfactory elements) (Figure 4). The places were similar to a domestic space, facilitating the transition of the older adult between physical spaces[33]. Examples of low-cost sensory resources were illustrated in Figures 1–4, of which many were handcrafted or purchased at stationery, party, and craft stores.

The following is an example of a session used in this study based on these references[11,30,31,33].

"The session started in the garden. The participant handled the dream filter and commented on what she saw in that space (flowers, drawing on the wall) for about

**Figure 1.** The sensory garden had aromatic plants, wind bell, and textures in painting on the wall.

**Figure 2.** The vintage room had decoration features from the 1940s to 1960s, a photo album, flavored sachets and topiaries, tactile pillows, feather fan, stuffed animal, thermal bag and hand massager, ambient music, and a tambourine.

5 min. The therapist asked if she wanted to stay there or move to the vintage room. In the vintage room, she sang the ambient music for a few minutes; then she stopped singing when she saw a stuffed toy on a chair. She hugged and caressed the toy, asked questions about it, exclaimed that it is so cute (...). After some minutes,

**Figure 3.** The transition corridor (between the vintage room and the lights room) had a beaded curtain and pictures with different textures on the wall.

**Figure 4.** The lights room had optical fiber light, LED lights on the roof, overhead projector, aroma diffuser, and ambient music.

she spontaneously described what she saw in a painting on the wall (...). In the lights room, she pointed with her index finger to the video of birds in nature, flexed her back, and yelled, "it is looking at me!" – with a surprised facial expression and laughing a lot. She talked to the therapist about the videos for some time (...). When the time ended (30 min), she was informed that they should go back to the living room."

### Data analysis

Statistical analysis was performed using the Minitab version 19 software. The Ryan-Joiner test was used to determine whether or not the data followed a normal distribution. Variance coefficient and skewness (asymmetry) values were also observed. The Bonett's and Levene's tests were calculated to assume variance equality between variables (by groups and between groups). The Grubbs' test was used to detect outliers. A two-tailed alpha value of 0.1 was applied. The Mann–Whitney nonparametric U-test was used to verify whether there were statistical differences between groups (independent variables). The Wilcoxon signed-rank nonparametric test was used to verify the before and after measures by group (dependent variables).

Thematic content analysis was used for qualitative analysis of the data from the observation records of the sessions carried out by the following three chronological steps[34,35].

#### Pre-analysis

Organization of observation records for each session to facilitate and systematize initial ideas.

#### Material exploration

Exhaustive reading, classification, and categorization of themes and creation of thematic units that appeared more frequently in the records. The thematic units were built from the actions observed by the participants in the multisensory environment, based on the following themes: behavior, mood, interaction, and cognition.

#### Treatment of results

Analysis of thematic units, allowing the authors to propose inferences and interpret the data obtained according to their theoretical framework and the objectives foreseen in the research[34,35].

## RESULTS

### Characterization of the participants

There were 105 residents in the nursing home. The residents were excluded from this study due to the following exclusion criteria: 69 older adults without a dementia diagnosis and 16 with dementia, but 5 were confined to the bed, 4 with aphasia expression, 3 with mild dementia, 2 were visually impaired, and 2 died before the sensory room was completed.

The sample consisted of 20 older adults with a mean age of 83 years, with 17 women and 3 men with an average of 3 years of education, diagnosed with moderate or severe dementia and institutionalized in the nursing home for about 4 years, partially dependent on self-care (Table 1). Most of the older adults presented socioeconomic vulnerability, weakened family ties, and came from rural areas.

**Table 1.** Characterization of the intervention group and control group regarding age, sex, education level, time in the institution (in years), types, and stages of dementia, comorbidities, and functionality.

| Categories | | IG | CG | Total |
|---|---|---|---|---|
| | | n=10 | n=10 | n=20 |
| Age | Mean | 84.4 | 80.7 | 82.7 |
| | SD | 6.8 | 8.5 | 7.7 |
| Sex | Female | 10 | 7 | 17 |
| | Male | 0 | 3 | 3 |
| Education level | 0 years | 4 | 1 | 5 |
| | 1–4 years | 5 | 8 | 13 |
| | Over 8 years | 1 | 1 | 2 |
| Time in the institution | Up to 1 year | 3 | 2 | 5 |
| | 1–4 years | 4 | 4 | 8 |
| | Over 4 years | 3 | 4 | 7 |
| Types of dementia | NS | 6 | 8 | 14 |
| | Mixed | 3 | 1 | 4 |
| | Alzheimer | 1 | 1 | 2 |
| Stages of dementia | Moderate | 4 | 2 | 6 |
| | Severe | 6 | 8 | 14 |
| Comorbidities | Depression | 3 | 0 | 3 |
| | Parkinson | 1 | 1 | 2 |
| | Prior stroke | 1 | 1 | 2 |
| | COPD | 1 | 2 | 3 |
| Dependence on BADL | 0–1 | 1 | 3 | 4 |
| | 2–4 | 7 | 3 | 10 |
| | 5–6 | 2 | 4 | 6 |

IG: intervention group; CG: control group; SD: standard deviation; NS: not specified; COPD: chronic obstructive pulmonary disease; BADL: basic activities of daily living.

Notably, 11 formal female caregivers were consulted, including 7 nursing technicians, 2 nursing assistants, and 2 caregivers (training course).

## Effects on behavior, mood, and cognition in the institutional environment

The MSSP decreased the behavioral changes (p=0.059) of the IG during the intervention period. There was no statistically significant difference when the groups were compared to each other (Table 2).

Both groups showed a numerical improvement in mood symptoms, with no statistically significant difference between the pre- and post-intervention measurements and in relation to the groups compared to each other (Table 2).

The IG showed a numerical improvement in cognitive capacity, while the CG had a numerical worsening. There was no statistically significant difference between the pre- and post-intervention measurements and when the groups were compared to each other (Table 2).

The caregivers had the perception that the IG had more engaged behavior (nondisruptive, collaborative, and interactive behavior) in the institutional environment over 3 months. The caregivers reported that the IG seemed to interact better with the institutional environment upon returning from the multisensory environment after the sessions. For example, these

**Table 2.** Effects on behavior, changes in mood, and cognitive capacity of both groups in the pre- and post-intervention period.

| | | IG | | CG | |
|---|---|---|---|---|---|
| Behavior (NPI) | Score: (0–144 points) | Pre | Post | Pre | Post |
| | Mean | 43.3 | 28 | 32.5 | 29.8 |
| | Median | 41.5 | 18.5 | 28 | 25.5 |
| | Standard deviation | 25.9 | 31 | 20.1 | 17.9 |
| | Pre and post by groups* | p=0.059 | | p=0.918 | |
| | Between groups* | p=0.161 | | | |
| Mood (CSDD) | Score: (0–38 points) | Pre | Post | Pre | Post |
| | Mean | 11.1 | 9.4 | 10.3 | 8 |
| | Median | 9.5 | 9.5 | 11 | 7 |
| | Standard deviation | 7.1 | 6.1 | 4.2 | 4 |
| | Pre and post by groups | p=0.406 | | p=0.235 | |
| | Between groups | p=0.97 | | | |
| Cognition (MMSE test) | Score: (0–30 points) | Pre | Post | Pre | Post |
| | Mean | 11.1 | 12.2 | 6.8 | 5.8 |
| | Median | 11.5 | 14 | 7.5 | 4.5 |
| | Standard deviation | 3.2 | 3.8 | 4.6 | 5.4 |
| | Pre and post by groups | p=0.153 | | p=0.441 | |
| | Between groups | p=0.109 | | | |

IG: intervention group; CG: control group; NPI: Neuropsychiatric Inventory; CSDD: Cornell Scale for Depression in Dementia; MMSE: Mini-Mental State Examination. *Two-tailed alpha value of 0.1 ($p<0.1$).

participants showed a happy facial expression, gaze directed to the physical environment around them, were more communicative with caregivers, and had better interaction among the residents. The caregivers described that the CG had less engaged behavior and more apathetic behavior in the institutional environment over 3 months. For example, these participants reduced their conversations with caregivers, and they worsened the quality of dialogues (e.g., negative verbalizations, shouting, and increased vocal volume). In some cases, adverse reactions occurred during self-care (e.g., moaning, nodding, and closed facial expressions).

### Effects on behavioral, mood, cognitive, and biomedical parameters in the multisensory environment

The session records described beneficial effects in the IG during the session in the multisensory environment. A summary of the central thematic units of content analysis was described (Table 3).

A higher frequency of engaged behavior and decreased apathy was observed during the session. Participants showed the signs of relaxation or excitement according to the types of stimuli offered. The communication was described by verbal and nonverbal actions, directed at the therapist, stuffed animal, or ambient music. A neutral mood with a sense of well-being and volition was reported. A favoring of cognitive abilities was observed, such as sustaining attention for more than 3 min, long-term memory, and sensory perception.

The SBP, DBP, and HR indicated decreased measurements at the end of the session. A significant difference was found in the pre- and post-intervention measurements of DBP ($p<0.05$) and HR ($p<0.05$) attested by the Wilcoxon signed-rank nonparametric test. There was a numerical improvement in the SBP measurements but no significant difference (Table 4).

## DISCUSSION

This study found the positive effects of MSSP in older adults with moderate and severe dementia on behavioral, interactive, and biomedical parameters in the

**Table 3.** Intervention group behaviors, mood, and interaction observed in the multisensory environment.

| | Thematic units | Observed actions |
|---|---|---|
| **Behavior** | Decrease in apathy | Greater resources exploration, whether requested by a therapist or on their initiative. |
| | Relaxation response | Naps, slow movements, and relaxed posture. |
| | Excitatory response | Body and dance movements, smiles, and waves of laughter. |
| Mood | Euthymic mood | Feeling of well-being. |
| | Adverse effects on mood. | They were not observed. |
| | Labile or irritable mood | It was rare, softened with the course of the session. |
| | Promotion of volition | As the participants knew the environment, they requested more materials of their preferences. Resource exploration and decision-making initiatives without therapist's interference. |
| Interaction | Verbal communication | Verbalization of preferences and interests. |
| | Nonverbal communication | Reactions and facial expression, body language, eye contact, and sensory exploration of objects. |
| | Stuffed animals | When entering the room, visual search for the object, change in the timbre of the voice and serene facial expression, and presence of hugs and caresses to the thing. |
| | Ambient music | Recognition of sounds, closing of the eyes, singing pieces of music, dance movements, clapping and foot tapping along with the musical rhythm, and storytelling of life. |
| Cognition | Cognitive abilities | Stimulation of long-term memory and sensory perception. Sustained attention for more than 3 min in specific resources of the participant's interest, especially tactile and visual ones, which were usually offered in the foreground. |

**Table 4.** Effects on biomedical parameters of intervention group in the pre- and post-session period at multisensory environments.

| Biomedical parameters | | Pre | Post |
|---|---|---|---|
| SBP (mmHg) | Mean | 12.85 | 12.65 |
| | Median | 13 | 12.55 |
| | Standard deviation | 2.05 | 1.79 |
| | Pre and post | p=0.177 | |
| DBP (mmHg) | Mean | 7.62 | 7.18 |
| | Median | 7 | 6.8 |
| | Standard deviation | 2.04 | 1.84 |
| | Pre and post | p<0.01 | |
| HR (bpm) | Mean | 80.76 | 78.72 |
| | Median | 80 | 80 |
| | Standard deviation | 12.48 | 11.99 |
| | Pre and post | p<0.01* | |

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate. *Two-tailed alpha value of 0.1 (p<0.1).

multisensory and institutional environment compared to a CG not submitted to the interventions of this program.

The MSSP can affect the behavior of older adults with dementia in nursing homes based on the reduction of behavioral changes, such as reduced agitation and apathetic behavior[16,18,30]. Positive emotions increase the interaction with the environment, redirecting to engaged behavior[36].

The IG's engaged behavior observed by caregivers and described in the session records may be related to the therapeutic process within the multisensory environment that allowed the possibility of choices, favoring an engaged, interactive, and collaborative behavior. Given the participants' stage of dementia, the interventions demonstrated a rich potential to stimulate cognitive and social abilities.

The enhancement of the stimulus in multisensory environments can also assist in a balanced sensory processing[37], by controlling the number of competing stimuli and the intensity of the stimulation, combining sensory preferences and individual needs[13].

The nursing home surveyed had few opportunities for the older adult with severe dementia to receive a personalized and continuous approach. A program more focused on the needs of the most committed older adults, even if performed collectively or in small groups, would be more appropriate.

In this study, the quantitative improvement in mood symptoms in both groups could be related to the interfering variables since both groups had drug changes in this period, being more present in the CG, according to the medical record and caregivers' reports.

Positive interaction reactions were described in this study. Such data draw attention to the importance of favoring an enriched routine in nursing homes through a more significant offer of structured and meaningful activities to the older adults with dementia. Other studies have found an improvement in communication and interaction with the environment after multisensory interventions[14,38].

Another interesting fact in this study was the interaction between the older adults and stuffed animals. This resource could help older adults with moderate or severe dementia express unmet needs[39] and can be a behavioral change strategy[40].

More humanized actions within the nursing home should consider the identification of elements that influence the interaction. It should also consider which barriers can be mitigated through the design of environments to achieve higher levels of social inclusion[41]. Optimizing the physical environment is essential to facilitate participation in daily activities and help the older adult feel at home[42].

The effects of MSSP on the cognitive status of older adults with moderate or severe dementia have been poorly studied[22]; Baker et al.[43] found no change in the average cognitive performance.

The IG's numerical improvement of cognitive performance and sustained attention described during the sessions (Table 3) may also be related to the person-centered therapeutic process developed in a multisensory approach, having structured sessions with targeted stimuli composed of attractive stimuli elements that arouse the older adults' curiosity. The worsening in GC's cognitive performance may be related to the progression of dementia associated with the few stimuli offered in the institutional environment to the population of this study.

Studies that have analyzed the relaxing effect of MSSP on biomedical parameters have not provided conclusive data on its effectiveness[14,15,20]. In this study, there were methodological differences regarding these studies. One possibility for the variation in BP and HR may be related to the less agitated state of the participants or to the fact that they are more adapted to the environment throughout the session. Interference factors must be considered, such as variability between subjects. The MSSP offered relaxing or exciting stimuli according to the degree of interest of the older adults in the resources offered. Thus, part of the sessions showed an increase in the measures described.

Some factors that could be considered interference variables were as follows: changing medications, dynamics of the institution (changing the older adults' rooms and changing institutional routine), and high turnover of the nursing staff. The CG had more participants with medication changes (replacing, increasing, or changing the dosage), hospital admissions, and complications (agitation, confusion, or irritability, requiring tranquilizers on this day) compared to the IG.

There were difficulties in recruiting eligible older adults. The sample size may have influenced the ability to determine statistical significance in the quantitative variables. Larger samples, identification and optimum monitoring of interfering variables, and long-term longitudinal studies are suggested for future research.

There was a lack of information in the institution regarding factors that interfered with the behavior of older adults with dementia. Institutions with a staff-to-resident ratio balance would better observe the older adults' routine, better care management, and more reliable and qualified research interlocutors.

Regarding biomedical data measurements, relaxing or exciting sessions should be analyzed separately since, in theory, they would have different measurement trends, causing statistical interference in the data. These measurements could also be compared with a CG to serve as a standard reference to these variables.

This study identified a higher quality of observations regarding the reactions and behaviors generated during the interventions using a mixed approach (quantitative and qualitative), differing from the studies already carried out with only the quantitative approach.

The low cost of implementing a multisensory room with the characteristics described here, covering older adults with low education and with moderate and severe stages of dementia, is a viable possibility to be reproduced in other institutions.

Finally, it proposes a new look at the health care practices performed in nursing homes that consider the individuality of the older adults with dementia and their sensory preferences and interests, stimulating their participation in collective contexts and supporting their demands.

## ACKNOWLEDGMENTS

The authors thank Laurie Marangon, Lilian Carvalho Silva, Maria Letícia de Callis Izar, Rafaela Paulo, and Rebecca Maris de Sousa for data collection and Mauricio Perez for supporting the statistical data. The authors thank the Brazilian funding agency CNPq for the scholarship awarded to Bento M. Machado.

**Authors' contributions.** BMM: conceptualization, methodology, literature search, data collection, formal analysis, and writing – review & editing. CSSC: conceptualization, methodology, funding acquisition, supervision, and writing – review & editing.

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Dement Neuropsychol 2022 June;16(2):213-219

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0056

# Non-motor symptoms fluctuations in patients with Parkinson's disease at the Clinical Hospital of Salvador, Bahia

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**ABSTRACT.** Motor fluctuations in Parkinson's disease (PD) are a frequent long-term complication. Knowledge is limited on the prevalence and incidence of non-motor symptoms (NMS) fluctuations, especially in Brazil. **Objective:** The objective of this study was to verify the frequency of NMS fluctuations and its relationship with other aspects of PD in patients followed at an outpatient movement disorders clinic. **Methods:** This is a cross-sectional study in which patients were evaluated for the presence of both types of fluctuations using the Wearing Off Questionnaire (WOQ-19). **Results:** A total of 37 patients (11 women and 26 men) were participated in this study, and the frequency of NMS fluctuations was 54.1% (90.9% in women and 38.5% in men). Anxiety was the most frequent non-motor fluctuation (35.1%). The highest percentage of NMS fluctuations (70%) was found in the group in which disease duration was more than 6 years. Most patients with motor fluctuations also had NMS fluctuations (66.7%). No patient presented with isolated NMS fluctuations. **Conclusions:** This study showed that, in the study population, approximately half of the patients had NMS fluctuations, with a higher frequency among women. A higher frequency was present in patients with earlier age of diagnosis, longer duration, and greater severity of disease. These findings point to the importance of recognizing the fluctuations of NMS in the study population, since these may not be spontaneously mentioned by the patient, who is remaining unnoticed, undiagnosed, and not treated by the neurologist, representing a significant aggravating factor in the patient's quality of life.

**Keywords:** Parkinson Disease; Symptom Assessment.

**FLUTUAÇÕES DE SINTOMAS NÃO MOTORES EM PACIENTES COM DOENÇA DE PARKINSON NO HOSPITAL DAS CLÍNICAS DE SALVADOR, BAHIA**

**RESUMO.** A flutuação dos sintomas na doença de Parkinson é uma complicação frequente em longo prazo. Pouco é conhecido sobre a prevalência e a incidência de flutuações de sintomas não motores (SNM), principalmente na população brasileira. **Objetivo:** Verificar a frequência das flutuações dos SNM e sua relação com outros aspectos da doença de Parkinson em pacientes acompanhados em ambulatório de movimentos anormais do Hospital das Clínicas de Salvador, Bahia. **Métodos:** Trata-se de um estudo de corte transversal, no qual os pacientes foram avaliados quanto à presença de flutuações utilizando-se o Wearing-Off Questionnaire (WOQ-19). **Resultados:** O total de 37 pacientes (11 mulheres e 26 homens) participou do estudo. A frequência de flutuações dos SNM foi de 54,1% (90,9% no sexo feminino e 38,5% no sexo masculino). Ansiedade foi a flutuação não motora mais frequente (35,1%). O maior percentual de flutuações dos SNM (70%) encontrou-se no grupo cujo tempo de doença estava acima de seis anos. A maioria dos pacientes com flutuações motoras teve também flutuações dos SNM (66,7%). Nenhum paciente apresentou apenas flutuação de SNM. **Conclusões:** O presente estudo mostrou que, na população estudada, aproximadamente metade dos pacientes apresentaram flutuações dos SNM, sendo essa frequência maior no sexo feminino. Estes achados apontam para a importância do reconhecimento das flutuações dos SNM na população estudada, já que elas podem não ser espontaneamente citadas pelo paciente, passando despercebidas, não sendo diagnosticadas nem tratadas pelo neurologista e constituindo-se em agravante não desprezível na qualidade de vida dos pacientes.

**Palavras-chave:** Doença de Parkinson; Avaliação de Sintomas.

This study was conducted by the Outpatient Clinic of Movement Disorders, Edgar Santos Professor University Hospital, Salvador, BA, Brazil.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on June 09, 2021; Received in its final form on October 23, 2021; Accepted on November 12, 2021.

## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide[1]. Although the disease is widely known for its motor symptoms (MS), the involvement of structures outside the basal nuclei circuit is quite significant, and the resulting changes form a set of symptoms called non-MS (NMS). Psychiatric-behavioral disorders, autonomic dysfunctions, and sensory symptoms are among the most common non-motor manifestations[2]. These changes may precede the onset of MS and continue to progress after the diagnosis of PD, following the patients throughout their lifetime[3].

Treatment with dopamine replacement is very effective during the first year of the disease, significantly decreasing the appearance of MS[4]. However, with the progress of dopaminergic neuronal degeneration and long-term treatment, complications begin to emerge, one of them being the shortening duration of the medication effect. As a result, parkinsonian symptoms, once suppressed by therapy, start to manifest in different levels before the next dose is taken. This phenomenon is also known as end-of-dose deterioration or wearing-off[2]. The appearance of fluctuations in symptoms is so common that, in their absence, a reassessment of the diagnosis of PD should be performed.

Motor fluctuations are extensively studied. However, concerning non-motor fluctuations, although already described, there are still many gaps in the literature regarding their incidence and prevalence in the population with PD, as well as the impact on the quality of life of these patients. Nevertheless, its presence significantly impairs patients' quality of life and can be as harmful as or even worse than motor fluctuations[4]. Consistent studies have shown that NMS, such as depression, anxiety, sleep disorders, and fatigue, were primarily responsible for the worst quality of life scores. In these studies, the motor component played a minor role in worsening the patient's quality of life, showing the importance of giving attention to NMS and its fluctuations[5,6].

There are very few population-based studies that describe the prevalence of PD in the Brazilian population. In one of these studies, a prevalence of 3.3% was found in individuals aged above 64 years[7]. This study did not address the aspects related to fluctuations of NMS. Therefore, studies carried out on Brazilian PD population are strongly relevant, especially on such a poorly explored theme as non-motor fluctuations.

The goal of this study was to verify the frequency of non-motor fluctuations and their relationship with other epidemiological and clinical aspects of PD in a sample of patients from the outpatient clinic of movement disorders of the Edgar Santos Professor University Hospital (HUPES). Data obtained have the potential to contribute to a better understanding of the characteristics of non-motor fluctuations in patients with PD followed at the mentioned outpatient clinic.

## METHODS

This study is a cross-sectional study, in which data from individuals who were diagnosed with PD and followed up at an outpatient clinic in the city of Salvador (Bahia) were collected during the period from June to October 2018. It was a convenience sample, which was composed of all the interviews performed during this period.

To be included in the research, individuals had to have a diagnosis of PD given by a neurologist who specialized in movement disorders (according to the Queen Square Brain Bank criteria)[8], the absence of dementia of any other etiologies (except dementia in PD) supported by laboratory and imaging tests, 18 years of age or older, and to agree to participate in this study. Individuals with parkinsonism associated with other neurodegenerative diseases or secondary parkinsonism, and individuals with impaired hearing or visual deficit were excluded from this study.

Initially, 90 patients who attended the movement disorders outpatient clinic were screened. Of these, 28 patients were excluded because they had a diagnosis of parkinsonism associated with other neurodegenerative diseases or secondary parkinsonism. Of the 62 remaining patients with PD, data were collected from 37 of them, when they attended the routine appointment. The other 25 patients with PD did not participate in this study for several reasons: refusal to participate, not attending the routine appointment, impossibility of interviewing them on routine appointment day due to the limited number of researchers and/or attendance room, severe auditory or visual deficits, or dementia of other etiologies other than dementia in PD.

Demographic data were obtained in the interview through a standardized questionnaire, complemented by the patient's medical record. Clinical and functional data were obtained through the application of the Unified Parkinson's Disease Scale (UPDRS) Part III[9] and the Hoehn and Yahr Scale (H&Y)[10]. Data related to NMS and NMS fluctuations were obtained from the application of the Non-Motor Symptom Assessment Scale (NMAS) for PD[11] and the Wearing Off Questionnaire (WOQ-19)[12], respectively. All the scales were filled by the researcher during the interview to the individual and by clinical examination and observation.

The presence of fluctuations in symptoms was determined by the WOQ-19, which consists of 19 items, 9 of them addressing MS and 10 addressing NMS. For each item, the patients were questioned about the presence of the symptom and its improvement after the next dose of dopaminergic treatment. The positive response to the last question, of any symptom, identified the patient as belonging to the group with general fluctuation of symptoms (WOQ-19 total score of ≥1)[12]. Patients were considered to have MS fluctuations when a cutoff score of ≥1 for MS of the WOQ-19 was reached (WOQ-19 M≥1). Likewise, patients were considered to have NMS fluctuations when a cutoff score of ≥1 for NMS of the WOQ-19 was reached (WOQ-19 NM≥1). The WOQ-19 has not yet been formally validated in Brazil, and, therefore, its items were freely translated by the research team to the Portuguese language.

### Statistical analysis plan

For the elaboration of the database and descriptive analysis, the software Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 17.0, for Windows was used. The results were presented using tables. Categorical variables were expressed as frequencies and percentages — n (%). Continuous variables with normal distribution were expressed as means and standard deviations, and those with non-normal distribution were expressed in median and interquartile range. The normality of the numerical variables was verified through descriptive statistics, graphical analysis, and the Kolmogorov-Smirnov test.

When comparing categorical variables, the $\chi^2$ test was used. When the distribution had an "n" in each category containing less than five individuals, Fischer's exact test was used. For the comparison between categorical variables (two groups: absence and presence of NMS fluctuations) and numerical variables, the independent sample Student's *t*-test was used when the variables had a normal distribution, and the Mann-Whitney U test was used for those with an asymmetrical distribution.

### Ethical considerations

The survey subjects had no research costs. All patients were signed the informed consent form prior to data collection.

This work composes an arm of a larger research, previously approved by the Research Ethics Committee (CEP) of the HUPES Complex, with an approval issued on May 18, 2018, and CAAE number 82741418.6.0000.0049.

## RESULTS

This study consisted of 37 patients (11 women and 6 men). Demographic and clinical characteristics are shown in Table 1.

According to the cutoff point of the WOQ-19 total score, 30 (81.5%) patients were identified with general fluctuation of symptoms (Table 2). The frequency of NMS fluctuations in the sample was 54.1%. The frequency of NMS fluctuations was 90.9% in women and 38.5% in men. Anxiety was the most frequent NMS fluctuation (35.1%) diagnosed in the whole sample, and also the most frequent non-motor fluctuation (63.3%) in women. In men, anxiety (23.1%) and mood changes (23.1%) were among the most frequent NMS fluctuations. In both, there were no panic attacks diagnosed as a non-motor fluctuation.

Table 3 shows the comparison of the frequency of NMS fluctuation between groups divided by the median age at diagnosis and the duration of the disease. The association between the younger age of the diagnosis and the presence of NMS fluctuation stands out, and this association was possible to notice by assessing the age of the diagnosis in both categorical (below 54 years old) and numerical ways. For the variable disease duration, an association is observed between longer disease

**Table 1.** Demographic and clinical characteristics of the sample.

| General features | | |
|---|---|---|
| Age in years mean (SD) | | 62.08 (7.41) |
| Age of onset in years mean (SD) | | 54.46 (8.51) |
| Duration of disease in years mean (SD) | | 7.62 (5.10) |
| Part III UPDRS mean (SD) | | 44.59 (16.28) |
| Hoehn & Yahr* mean (SD) | | 3.0 (3.0–2.0) |
| Gender n (%) | Male | 26 (70.3%) |
| Color n (%) | White | 5 (13.51%) |
| | Brown | 21 (56.8%) |
| | Black | 11 (29.7%) |
| Scholarity n (%) | Illiterate | 5 (13.5%) |
| | Elementary school (complete or incomplete) | 14 (37.8%) |
| | High school (complete or incomplete) | 15 (40.5%) |
| | College (complete or incomplete or postgraduate) | 3 (8.1%) |

SD: standard deviation; UPDRS: Unified Parkinson's Disease Assessment Scale; *median (interquartile range).

duration and presence of NMS fluctuation (both in the numerical and categorical variables).

The frequency of NMS fluctuation was analyzed according to the severity of the disease, as verified by the H&Y, and the result is shown in Figure 1. The frequency of patients with non-motor fluctuations was higher in stages 3 and 4 (64.7 and 66.7%, respectively).

The frequency of NMS fluctuations was compared with the frequency of MS fluctuations. The results are shown in Table 4. No patient presented only NMS fluctuation. Notably, 30 (81.1%) patients had MS fluctuations and, among them, 20 (66.7%) patients also had NMS fluctuations.

## DISCUSSION

Fluctuations in NMS are a long-term complication of PD and, in some patients, can be considered as debilitating as fluctuations in MS[13]. In this study, 54.1% of patients presented fluctuations in NMS. Due to the absence of standardized tools for research on fluctuations, the literature data on the prevalence of fluctuations vary widely according to the methodology used and the population studied.

Very broad frequencies, ranging from 19[14] to 100%[13], have already been described in the previous studies. These studies did not use the WOQ-19 to assess the fluctuations of NMS, which could explain the

**Table 2.** Frequency of non-motor symptoms fluctuations according to the Wearing Off Questionnaire.

| Symptoms, n (%) | All (37) | Women (11) | Men (26) | p-value |
|---|---|---|---|---|
| Anxiety | 13 (35.1%) | 7 (63.3%) | 6 (23.1%) | 0.035 § |
| Experiencing sweating | 6 (16.2%) | 4 (36.4%) | 2 (7.7%) | 0.051‖ |
| Mood changes | 9 (24.3%) | 3 (27.3%) | 6 (23.1%) | 0.672‖ |
| Numbness | 9 (24.3%) | 4 (36.4%) | 5 (19.2%) | 0.267§ |
| Experiencing panic attacks | 0 | 0 | 0 | — |
| Cloudy mind/dullness thinking | 5 (13.5%) | 4 (36.4%) | 1 (3.8%) | 0.021‖ |
| Abdominal discomfort | 2 (5.4%) | 1 (9.1%) | 1 (3.8%) | 0.512‖ |
| Experiencing hot and cold | 4 (10.8%) | 3 (27.3%) | 1 (3.8%) | 0.070‖ |
| Pain | 8 (21.6%) | 4 (36.4%) | 4 (15.4%) | 0.404‖ |
| WOQ-19 total score ≥1* | 30 (81.5%) | 10 (90.9%) | 20 (76.9%) | 0.649‖ |
| WOQ-19 NM ≥1+ | 20 (54.1%) | 10 (90.9%) | 10 (38.5%) | 0.004‖ |

*Frequency of general fluctuation of symptoms; +frequency of NMS fluctuations; §$\chi^2$ test; ‖Fischer's exact test. NMS: non-motor symptoms.

**Table 3.** Comparison of the frequency of non-motor symptoms fluctuation between groups divided by the median age at diagnosis and disease duration.

| | Median | NMS fluctuations n (%) | | | p-value |
|---|---|---|---|---|---|
| | | WOQ-19 NM <1* | WOQ-19 NM ≥1+ | Total | |
| Diagnostic age | <54 years | 4 (23.5%) | 15 (78.9%) | 19 (51.4%) | |
| | ≥54 years | 13 (76.5%) | 5 (27.8%) | 18 (48.6%) | 0.003§ |
| | Total | 17 (100%) | 20 (100%) | 37 (100%) | |
| Diagnostic age | | 58.8±6.9 | 49.7±8.4 | | 0.001‖ |
| Diagnostic age (numeric variable) | | 63.5±7.2 | 59.8±7.9 | | 0.140‖ |
| Disease duration | ≤6 years | 14 (82.4%) | 6 (30%) | 20 (54.1%) | 0.003§ |
| | >6 years | 3 (17.6%) | 14 (70%) | 17 (45.9%) | |
| Disease duration (numeric variable) | | 4 (2–5.5) | 9.5 (6.0–14.5) | | 0.001¶ |
| Total | | 17 (100%) | 20 (100%) | 37 (100%) | |

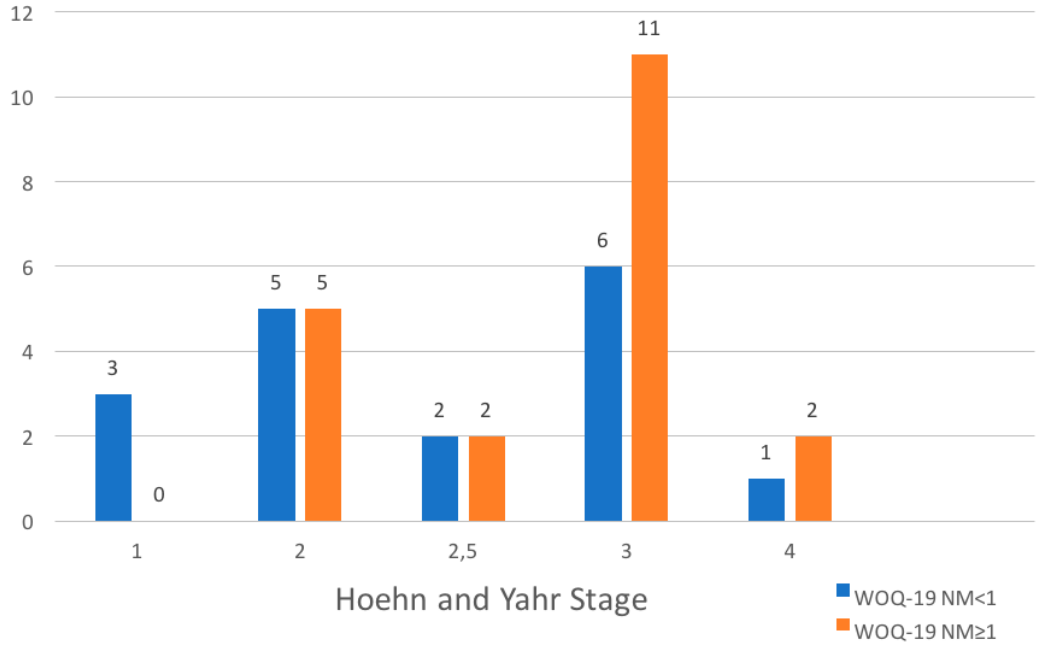
*Absence of NMS fluctuations; +presence of NMS fluctuations; §Fischer's exact test; ‖independent sample Student's *t*-test; ¶Mann-Whitney U test. NMS: non-motor symptoms.

marked difference found. More recent studies, using WOQ-19, showed frequencies ranging from 38.3 to 49.4%[15-17] in the study populations, closer to those found in this study. WOQ-19 is recommended by the Movement Disorders Society as a useful tool for screening the fluctuations[18].

The cohort of Picillo et al.[15] followed 47 patients for 4 years from the diagnosis of PD and pointed out the female sex as the major risk factor for the development of NMS fluctuations, regardless of the age of onset, levodopa dose, and MS and NMS at the time of diagnosis. This study showed a concordant result: the frequency of fluctuation of the NMS among women was 90.9%, which was more than double the frequency found in men (38.5%).

Among the NMS, anxiety (35.1%) was found to be associated with the highest frequency of fluctuation. It was also the most common non-motor fluctuation in women and men, along with mood changes in men. Van Der Velden et al., in a systematic review, calculated the weighted average of the frequency of anxiety from eight studies and reported it as being 35.4%. The neuropsychiatric category has been identified as the most common NMS fluctuations[19,20], with anxiety being the most frequent one, in general[13,15] and in both sex[15], with a greater impact on quality of life[20]. The proposed explanation for mood-related fluctuations lies in the same pathophysiological basis of motor fluctuations: the degeneration of dopaminergic neurons was involved in the regulation of mood through the mesocortical and mesolimbic pathways[20].

Among the patients diagnosed with NMS fluctuations, 14 (70%) of them were in the group whose diagnosis of PD had been given before the age of 54 years. Several studies indicate that the earliest age of onset of PD is associated with more frequent development of fluctuations in




WOQ-19 NM<1: absence of NMS fluctuations; WOQ-19 NM≥1: presence of NMS fluctuations.

**Figure 1.** Comparison of the frequency of non-motor symptoms fluctuation and disease severity (H&Y).

**Table 4.** Frequency of motor symptoms and non-motor symptoms fluctuations.

| Symptoms fluctuations | WOQ-19 NM<1[+] | WOQ-19 NM≥1[‖] | Total | p-value |
|---|---|---|---|---|
| n (%) | 17 (45.9%) | 20 (54.1%) | | |
| WOQ-19 M<1* | 7 (100%) | 0 | 7 (18.9%) | 0.002 |
| WOQ-19 M≥1[§] | 10 (33.3%) | 20 (66.7%) | 30 (81.1%) | |

*Absence of MS fluctuations; [+]absence of NMS fluctuations; [§]presence of MS fluctuations; [‖]presence of NMS fluctuations. MS: motor symptoms; NMS: non-motor symptoms.

symptoms[4,21-23]. One possible explanation is that younger people have greater brain plasticity, which may facilitate maladaptive neuroplasticity responses caused by both progressive degeneration of dopaminergic neurons and non-physiological dopamine pulsatility[24]. The degeneration of the neurons is progressive and, therefore, worsens over the years, being associated with a higher prevalence of the therapeutic complications[25]. Therefore, a higher frequency of fluctuation in patients with longer disease duration has also been found in studies[4,14,21]. In this study, the result was not different, since the majority (70%) of patients with NMS fluctuations were in the group with the longest disease duration (>6 years).

The frequency of patients with non-motor fluctuations was higher in the moderate and severe stages of the disease (64.7 and 66.7%, respectively). Studies have shown significantly higher scores on H&Y stages in patients with non-motor fluctuations[21], as well as patients with mixed fluctuations with more severe MS, accessed by the H&Y scale[16]. The discomfort caused by NMS fluctuations was also correlated with disease severity[13].

The presence of fluctuations in NMS is strongly associated with fluctuations in MS. In the L. Brun et al.'s[14] cohort with 303 patients, only 14% of patients presented fluctuations only in NMS, and in the study by M. Seki et al., this number was even lower (7%)[16]. The result of this research showed that, in the study sample, no patient (0%) presented only fluctuation of NMS. Among those with MS fluctuations, 66.7% also had fluctuation of NMS, a very close result compared to that reported in the study by Rodríguez-Violante M et al., where the calculated frequency from the published data revealed that 66.1% of patients presented fluctuations of NMS among those who had motor fluctuations[17]. In the latter study mentioned, patients with NMS fluctuations had the worst quality of life scores compared to those with mixed or MS fluctuations only, suggesting that NMS fluctuations have a greater impact on patient's quality of life than MS fluctuations.

This study has some limitations. Although recommended by the Movement Disorders Society, the use of WOQ-19 was one of the limitations, because it is still a very superficial tool for evaluating fluctuations, assessing just the presence of them, without measuring frequency and severity of symptoms. With the increasing recognition of the importance and impact of NMS fluctuations, new and more appropriate tools are expected to be tested and validated, and finally be available for use in clinical practice. In addition to this limitation, a small sample size, selected for convenience, in a hospital-based study, which is not representative of all PD populations, does not allow the results to be extrapolated and validated externally beyond the study population.

This study showed that, in the study population, approximately half of the patients presented NMS fluctuations, being this frequency much greater in the female sex. A higher frequency was present in patients with earlier age of diagnosis, longer duration, and greater severity of disease. The symptoms that fluctuated most were those of the neuropsychiatric category, especially anxiety. It is extremely important to recognize fluctuations of this category, since, for example, the recognition of anxiety as fluctuation will result in treatment with dopaminergic replacement, and not with antidepressants. Finally, there were no patients with fluctuations only in the NMS.

These findings point to the importance of recognizing fluctuations in patients with PD in the study population, since these may not be spontaneously mentioned by the patient, who is remaining unnoticed, undiagnosed, and not treated by the neurologist, representing a not insignificant aggravating factor in the patient's quality of life.

**Authors' contributions.** RBGK: conceptualization, funding acquisition, methodology, project administration, resources, supervision, writing – review & editing. JOF: methodology, supervision, writing – review & editing. KSB: data curation, investigation, writing – original draft. LDR: data curation, investigation. TGR: data curation, investigation.

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Dement Neuropsychol 2022 June;16(2):220-227

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0006

# Applicability of an immersive virtual reality system for assessing route learning in older adults

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**ABSTRACT.** Spatial orientation is defined as the ability to find one's way around an environment, follow familiar routes, recognize places, and learn new routes. Spatial disorientation is one of the early symptoms of Alzheimer's disease (AD), and traditional cognitive evaluation lacks ecological validity. Therefore, new assessment methods are needed for the early identification of this cognitive impairment. **Objective:** This study aimed to compare the applicability and stability of an immersive virtual reality (VR) system developed to assess route learning between older adults with and without mild cognitive impairment (MCI). **Methods:** The study sample included 43 older adults: 22 without MCI and 23 with MCI. Applicability was assessed based on the recording of adverse events and the sense of presence reported through questionnaires. The Mann–Whitney U test was applied to compare the applicability of the Spatial Orientation in Immersive Virtual Environment Test (SOIVET)-Route task between older adults with and without MCI. Both short- and long-term stabilities of the task were evaluated using the intraclass correlation coefficient (ICC). **Results:** The mean age of participants was 71.4 years (SD=5.5). A minimum number of adverse events (mean=1.46; SD=2.11) and high levels of presence (mean=138.04; SD=14.80) were reported, and there was no difference between groups with and without MCI. A good to excellent correlation was found for short-term stability (CCI 0.78) and a reasonable correlation was found for long-term stability (CCI 0.58). **Conclusions:** The VR system was applicable for older adults and showed a good to excellent correlation for short-term stability.

**Keywords:** Orientation, Spatial; Aged; Virtual Reality; Technology; Validation Study.

**APLICABILIDADE DE UM SISTEMA DE REALIDADE VIRTUAL IMERSIVO PARA AVALIAÇÃO DA APRENDIZAGEM DE ROTAS EM IDOSOS**

**RESUMO.** Orientação espacial é a capacidade de encontrar um caminho em um ambiente, seguir rotas familiares, reconhecer lugares e aprender novas rotas. A desorientação espacial é um dos primeiros sintomas da doença de Alzheimer, e a avaliação cognitiva tradicional carece de validade ecológica. Diante disso, novos métodos de avaliação são necessários para a identificação precoce desse comprometimento cognitivo. **Objetivo:** Este estudo teve como objetivo comparar a aplicabilidade e a estabilidade de um sistema de realidade virtual imersivo desenvolvido para avaliar a aprendizagem de rotas entre idosos com e sem comprometimento cognitivo leve (CCL). **Métodos:** Participaram do estudo 43 idosos: 22 sem CCL e 23 com CCL. A aplicabilidade foi avaliada por meio do registro de eventos adversos e pela sensação de presença relatados. O teste de Mann-Whitney foi aplicado para comparar a aplicabilidade da tarefa SOIVET-*Route* entre idosos com e sem CCL. A estabilidade da tarefa em curto e longo prazo foi avaliada pelo coeficiente de correlação intraclasse (ICC). **Resultados:** A idade média dos participantes foi de 71,4 anos (desvio padrão — DP=5,5). Em relação à aplicabilidade, encontramos mínimo relato de sintomas adversos (média=1,46; DP=2,11) e altos níveis de sensação de presença (média 138,04; DP=14,80), e não houve diferença entre os grupos com e sem CCL. Ao analisarmos a estabilidade, encontramos de boa a excelente correlação em curto prazo (CCI=0,78) e uma correlação razoável em longo prazo (CCI=0,58). **Conclusões:** O sistema de realidade virtual foi aplicável em idosos e mostrou boa correlação na estabilidade de curto prazo.

**Palavras-chave:** Orientação Espacial; Idoso; Realidade Virtual; Tecnologia; Estudo de Validação.

This study was conducted by the Physiotherapy, Speech Therapy and Occupational Therapy Department, Faculdade de Medicina, Universidade de São Paulo – São Paulo, SP, Brazil.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** This work was carried out with the support of the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) – Brazil, through a grant to the first author. This study was financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil* (CAPES) – Finance Code 001, through a grant to the second author. This research was conducted with support from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP), process nos. 16/04984-3 and 14/22348-1, through scholarships granted to the third and last authors, respectively.

Received on November 01, 2021; Accepted in final form on November 19, 2021.

## INTRODUCTION

Topographical orientation, or spatial orientation, is the ability to find one's way around an environment, follow familiar routes, recognize places, and learn new routes, and it is an essential skill for a person's autonomy[1,2]. The main spatial orientation strategies are egocentric and allocentric[3].

Along with these strategies, the individual needs to remember a series of motion directions at decision points to walk on a path at a greater distance than can be viewed in a single time, in other words, the direction of the destination[1,4]. A sense of direction leads to learning a new route, where the subject, within the environment itself, incorporates information through repeated visualizations of the environment and continuous changes in the egocentric orientation, being able to, when walking this path again, go from your origin to your destination[1].

Spatial disorientation is a common finding in Alzheimer's disease (AD), even in its early stages and, since the neurodegenerative process of AD precedes the clinical signs for diagnosis, it is believed that the detection of spatial disorientation in patients with mild cognitive impairment (MCI) is a predictor of higher risk of conversion of these patients[5]. Thus, the assessment of spatial orientation associated with other clinical assessments in patients with MCI can be a cognitive marker of AD[6,7].

There is no consensus on the best way to assess spatial orientation, and the traditionally used pen and paper tests are not sufficiently sensitive and ecological to detect spatial disorientation[6]. An assessment is considered ecological when it investigates the patient's skills and difficulties as close as possible to their reality, exposing them to their daily life problems[8]. Non-ecological assessments do not adequately evaluate the impairment of spatial orientation experienced by the patient in the real world[9].

New computerized methods have been developed to assess spatial orientation[10,11]. The use of virtual reality (VR) allows the patient to interact in environments like real ones through projection in three-dimensional (3D) scenarios and the use of one's sensory channels to interact with the visual and auditory stimuli of virtual systems[6,12,13]. The sense of presence and immersion experienced by the patient in an immersive virtual environment is greater, and the individual can interact with its elements, favoring their behavior as if they were acting in the real world[14,15]. Thus, immersive VR could simulate more realistic environments when compared to paper and pencil assessments and, therefore, more accurately reproduce the difficulties of spatial orientation and identify more subtle deficits[15,16].

With the lack of a reference standard to assess spatial orientation and the advantages of evaluating this cognitive domain through ecological tasks, our research group developed a system called Spatial Orientation in Immersive Virtual Environment Test (SOIVET)[7,17]. This system contains a task called Route (SOIVET-Route), which focuses on route learning.

In 2021, Costa et al.[18] analyzed the concurrent validity of the SOIVET-Route, concluding that it is a valid tool for assessing the spatial orientation of older adults, but its applicability and stability have not yet been analyzed. Therefore, this study aimed to compare the applicability of the SOIVET-Route in older adults with and without MCI. Besides, we assessed the short- and long-term stability of its assessments.

## METHODS

### Study sample

This study was conducted by following the guidelines and regulatory standards for research involving human beings (resolution 466/12 of the National Health Council), consubstantiated opinion no. 2.580.187, with the Certificate of Presentation for Ethical Appreciation (CAAE) no. 84904018.6.0000.0065, approved by the Ethics and Research Committee of the Faculdade de Medicina, Universidade de São Paulo.

Data collection started in February 2019 and ended in March 2020 involving the participation of 45 older adults: 22 were elderly residents in the community without objective evidence of cognitive impairment verified through a screening test – the Addenbrooke's Cognitive Examination – Revised (ACE-R)[19] and 23 elderly individuals with a diagnosis of MCI referred from the Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo.

Eligibility criteria included age ≥60 years; absence of a history of vertigo and/or labyrinthopathy; normal or corrected visual and auditory acuity; written informed consent form (ICF) for participation in the study; a score of >82 on the ACE-R for the control group; and a diagnosis of MCI according to Petersen's criteria[20] for the MCI group. Participants with incapacity to understand the instructions and interact with the tasks were excluded. In addition, participants who presented any limiting adverse events during the experience with the immersive system were excluded. Finally, older adults who abandoned the study before completing all its stages were excluded (dropouts).

## Data collection

The project was presented to the participants who met the eligibility criteria of the study. After agreeing to participate and signing the ICF, the participants were assessed in two different moments with an interval of 7–14 days between the sessions.

In the first moment, data collection started with the application of the ACE-R. Later, the sociodemographic characterization, motion sickness screening, and technology use profile questionnaires were applied.

After completing the questionnaires, the participants were guided to perform the tasks. Finally, immediately after completing the VR task, the Witmer and Singer Presence Questionnaire[21] and the questionnaire to identify adverse symptoms were applied.

In the second moment, only the task in a virtual environment was reapplied.

## Research procedures

### Sample characterization, cognitive screening, and motion sickness screening

A sociodemographic questionnaire and a questionnaire describing familiarization with the use of technology, both developed by the study authors, were applied to characterize the sample[7]. Scoring on the technology use profile questionnaire varies from 0 to 40 points; with the higher the score, the greater the familiarity of participants with technology.

The ACE-R was applied for cognitive screening. Individuals with ACE-R score of >82 were included in the group of older adults without cognitive impairment. This score is considered a cutoff value for older adults with cognitive impairment without dementia[22].

The absence of a history of vertigo and labyrinthopathy was assessed through self-report. Participants were also assessed using a motion sickness screening questionnaire, prepared by the study authors, with scores ranging from 0 to 6 points, with the higher the score, the greater the discomfort prior to task performance.

### SOIVET-Route task

The task performed is an adaptation of the Route subitem of the Rivermead Behavioral Memory Test (RBMT)[23]. The test can be conducted in a wide variety of locations and does not establish a minimum or maximum distance between them.

In this study, we used the main entrance of the Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo (ICHC-FMUSP) as a reference for the development of the task in a virtual environment, using similar dimensions to simulate the virtual environment task as realistically as possible, and it occurred in the following four stages:

- The avatar took the route together with the participant stopping at five different places with time to observe the surroundings. The stop points were the reception, a newsstand outside the building, a cafeteria, a table, and the entrance to the study center in this order (Figure 1).
- After completing the route with the avatar, the participants were invited to retrace the route alone stopping at the same places (immediate recall task).
- After 20 min, the individual was asked to recreate the route once again (late recall task).
- The participants were invited to return to the data collection place between 7 and 14 days to perform the abovementioned items 1–3 (Figure 2).

The system was developed using the Oculus Rift® head-mounted display and its controller.

The system automatically extracts the number of locations visited in the correct (correct) or incorrect (errors) sequence. The score, which can vary from 0 to 5 points, is assigned according to the participant's performance and the number of correct answers (places visited in the correct sequence).

### Assessment of the system applicability in older adults with and without mild cognitive impairment

Applicability was evaluated based on the report of adverse symptoms triggered by the task, such as general discomfort, headache, nausea, pallor, vomiting, sweating, and fatigue. The occurrence of these symptoms was assessed through a self-report questionnaire in which the higher the score, the lower the tolerability of the task performed, with a maximum score of 64 points[7].

The sense of presence was assessed using the Witmer and Singer Presence Questionnaire[21]. This questionnaire aims to measure the degree that individuals experience immersion in an environment, depending on the attentional resources existing in the environment to be explored. The questionnaire comprises 22 items, totaling 154 points. In the end, the higher the score, the greater the sense of presence and immersion, that is, the task applicability.

### Assessment of short- and long-term stability

Stability is the degree to which similar results are obtained at two different times, and for that, two correlations were made between the participant's performance in the SOIVET-Route task at two different times: correlation between immediate recall and late recall (short-term stability) and correlation between the first and second test days (long-term stability).

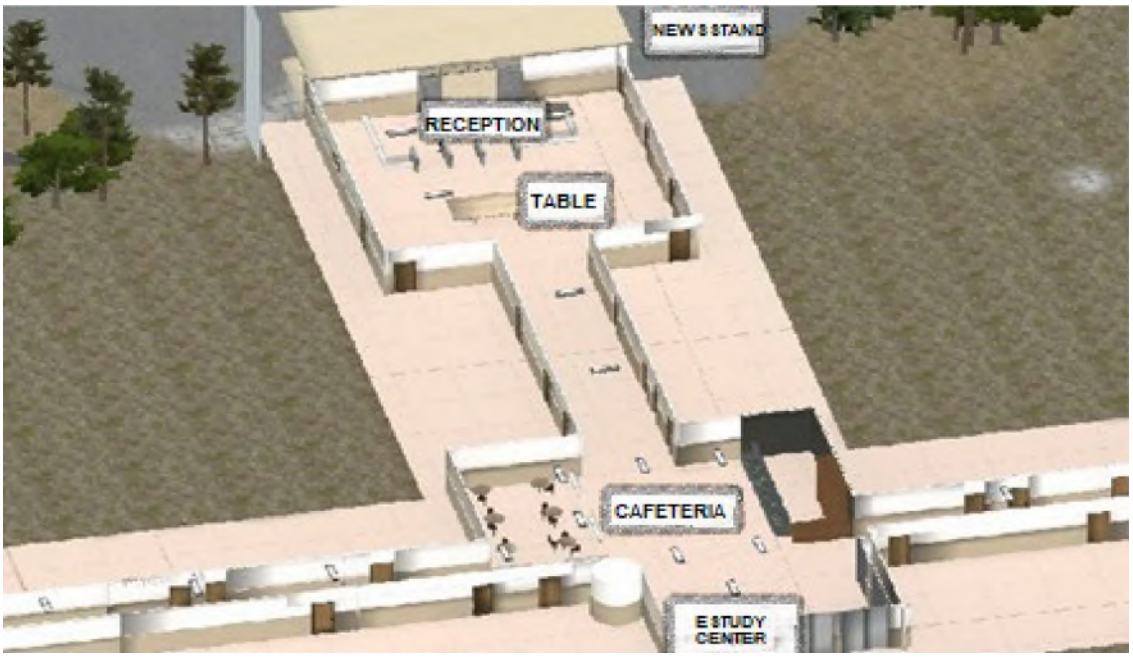


**Figure 1.** Route in the real and virtual tasks (aerial view of the virtual task).

### Statistical analysis

The collected data were processed using the SPSS version 20.0 software. The participants' clinical and sociodemographic characteristics were expressed as mean, standard deviation (SD), and 95% confidence interval (95%CI) for the numerical variables, whereas the categorical variables were expressed as absolute and relative frequencies.

Short- and long-term stabilities were analyzed using the intraclass correlation coefficient (ICC) between the first and second evaluation days and between the immediate and late recall evaluations performed on the same day using the following analysis criteria: ICC<0.4: poor, 0.4–6: reasonable, 0.6–0.75: good, and 0.75–1.0: excellent. We adopted an alpha of 0.05 as statistical significance[24].

The Mann-Whitney U test was applied to compare the applicability measures of the SOIVET-Route task between older adults with and without MCI. Hedge's g test was used to calculate the effect size considering the following results: large ≥0.8, medium 0.8–0.2, and small <0.2[25].

## RESULTS

The mean age of participants was 71.4 years (SD=5.5), and there was a predominance of females (n=28; 62%). Most participants had completed their higher education (n=29; 65%) and reported having some comorbidity (n=33; 75%). The most common comorbidities were systemic arterial hypertension, diabetes mellitus, and osteoporosis.

Among the 45 older adults who participated in the study, 23 (51%) met MCI diagnostic criteria and the other participants presented no complaints or evidence of having cognitive impairment, which verified through higher scores on the ACE-R, with a statistically significant difference in relation to those with MCI (p<0.001) (Table 1).

### Assessment of applicability

The elderly participants reported a small number of adverse events (mean=1.46; SD=2.11), with mild dizziness and nausea as the most frequent, and high levels of sense of presence and immersion (mean=138.04; SD=14.80). There was no difference between groups with and without MCI (Table 2).

However, 17% of participants were unable to complete the task due to complaints of nausea and severe dizziness: 5 (23%) elderly people without MCI and 4 (17%) with MCI. These participants were not included in the analyses, keeping 45 elderly graduating.

There was no correlation between the participants' scores in the questionnaires of adverse symptoms or sense of presence with age, gender, education, screening for motion sickness, and technology usage profile.

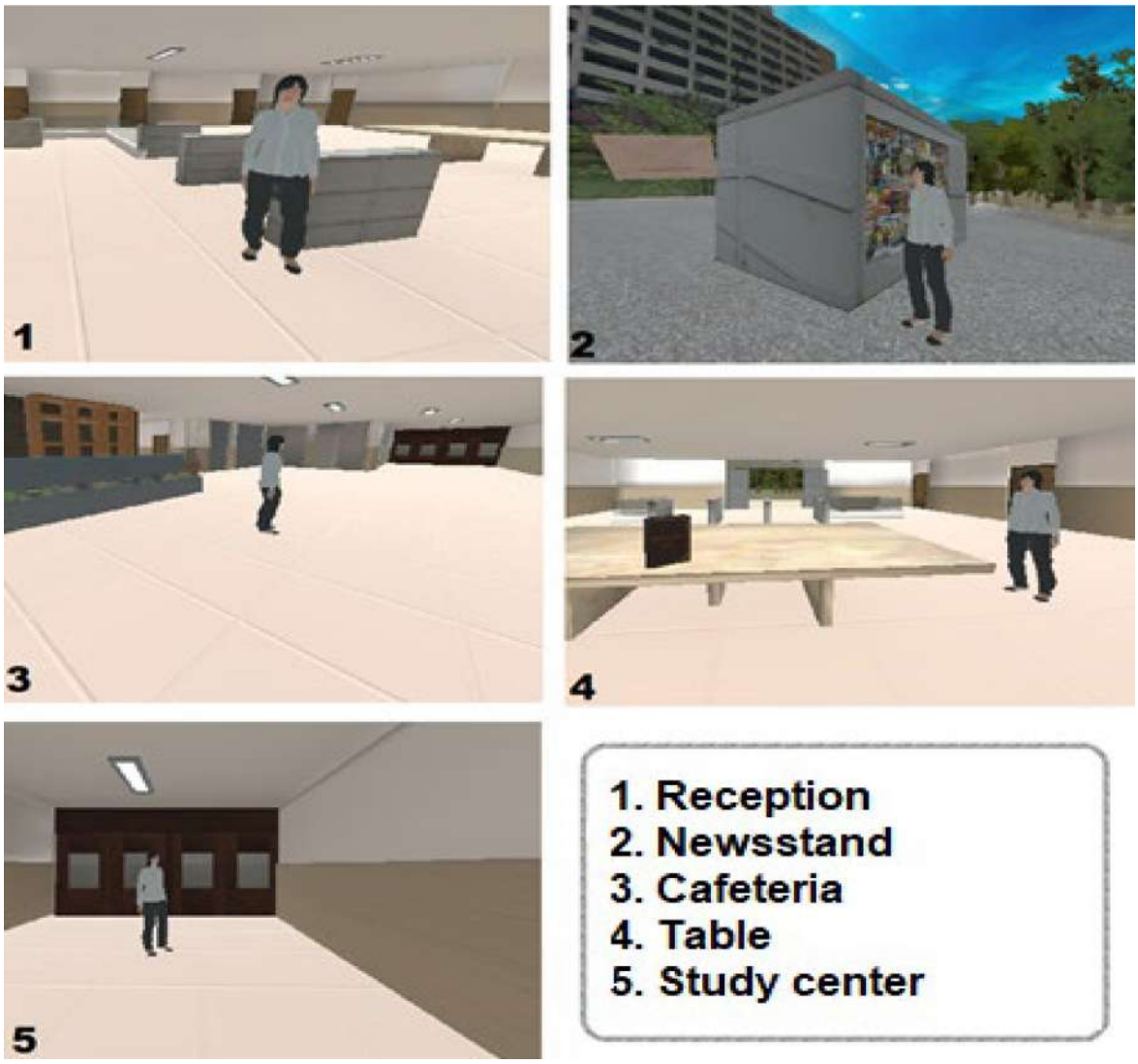


**Figure 2.** Reproduction of the real environment in virtual reality.

### Assessment of short- and long-term stability

Assessment of short- and long-term stability showed an excellent correlation for short-term stability (immediate and late recall, performed with an interval of 20 min) with effect size of 80% power, but poor to reasonable correlation for long-term stability (performed with an interval of 7–14 days) (Table 3).

## DISCUSSION

This study analyzed the applicability of the SOIV-ET-Route task and its respective stability in older adults with and without MCI.

For a VR assessment to be applicable in the elderly population, a low rate of adverse symptoms is necessary[15,26]. In this study, the elderly participants had good tolerability to perform the task, and there were minimal reports of adverse symptoms among those who managed to complete the assessment. There was no difference between groups and the incidence of dropouts because tolerability was 17%, which is considered low compared with the rates of 30–80% found in the literature[27]. There was also no correlation between the scores of the adverse symptoms' questionnaire and age, gender, education level, or familiarity with technology. This indicates that these factors did not influence the

**Table 1.** Characterization of the total elderly sample and comparison between older adults with and without mild cognitive impairment.

| | | Total sample (n=45) | Elderly people without MCI (n=22) | Elderly people with MCI (n=23) | p-value |
|---|---|---|---|---|---|
| Age (years) | | 71.4±5.5 | 71.0±5.7 | 71.8±5.4 | 0.53[a] |
| Gender, n (%) | Female | 28 (62) | 14 (64) | 14 (61) | 1.00[c] |
| | Male | 17 (37) | 8 (36) | 9 (39) | |
| Education, n (%) | First grade completed | 2 (4) | 2 (9) | 0 (0) | 0.005[c] |
| | Second grade completed | 12 (27) | 2 (9) | 10 (43) | |
| | Higher education | 29 (65) | 18 (82) | 11 (48) | |
| | Graduate course | 2 (4) | 0 (0) | 2 (9) | |
| ACE-R | | 90.5±6.3 | 94.9±2.8 | 86.3±5.8 | <0.001[b] |
| Motion sickness screening | | 0.55±1.13 | 0.40±1.18 | 0.69±1.10 | 0.08[a] |
| Familiarity with the technology | | 17.8±8.4 | 20.4±8.3 | 15.3±8.0 | 0.034[a] |
| Comorbidities, n (%) | Yes | 33 (75) | 17 (77) | 16 (73) | 1.00[c] |
| | No | 12 (25) | 5 (23) | 6 (27) | |

Numerical values represented by average±standard deviation and absolute number (%). [a]p-value referring to the Mann-Whitney U test; [b]p-value referring to the Student's *t*-test for independent samples; [c]p-value referring to Fisher's exact test. MCI: mild cognitive impairment; ACE-R: Addenbrooke's Cognitive Examination – Revised.

**Table 2.** Tolerability and sense of presence of the SOIVET-Route in the total sample of older adults and comparison between older adults with and without mild cognitive impairment.

| | Total sample (n=45) | Elderly people without MCI (n=22) | Elderly people with MCI (n=23) | p-value | Hedge's g |
|---|---|---|---|---|---|
| Cybersickness | 1.46±2.11 | 1.13±1.93 | 1.78±2.27 | 0.29 | 0.30 |
| Sense of presence and immersion | 138.04±14.80 | 137.81±14.62 | 138.26±15.30 | 0.73 | 0.03 |

Numerical values represented by average±standard deviation; p-value referring to the Mann-Whitney U test; effect size (Hedge's g): large ≥0.8, medium 0.8–0.2, small <0.2. MCI: mild cognitive impairment; D1: day 1; D2: day 2.

**Table 3.** Intraclass correlation coefficients between the first and second assessment days and between immediate and late recall performed on the same day of the SOIVET-Route task.

| | | ICC D1×D2 | | ICC Immediate×late |
|---|---|---|---|---|
| Total sample (n=45) | Immediate recall (virtual) | 0.58[b] | D1 | 0.78[b] |
| | Late recall (virtual) | 0.37[a] | D2 | 0.81[b] |
| Elderly people without MCI (n=22) | Immediate recall (virtual) | 0.28 | D1 | 0.60[b] |
| | Late recall (virtual) | 0.03 | D2 | 0.73[b] |
| Elderly people with MCI (n=23) | Immediate recall (virtual) | 0.63[b] | D1 | 0.80[b] |
| | Late recall (virtual) | 0.44 | D2 | 0.85[b] |

ICC<0.4: poor; 0.4–0.6: reasonable; 0.6–0.75: good; 0.75–1.0: excellent; effect size with 80% power: ICC≥0.5. ICC: intraclass correlation coefficient; MCI: mild cognitive impairment; D1: day 1; D2: day 2; [a]p<0.05; [b]p≤0.01.

applicability of immersive VR in the elderly population. Nevertheless, the immersive system needs to be accurate in capturing the patient's movements and the lowest latency possible in relation to the image displacement so that there is no sensory conflict and occurrence of possible adverse events[15,27]. These findings corroborate the study conducted by Kim et al.[15], who used the Oculus Rift® to assess elderly people with and without Parkinson's disease and obtained the results similar to this research. The studies that identified higher incidence rates of adverse events used immersive VR devices with lower visual processing speed, which induced delays between movement and simulation, increasing the occurrence of possible adverse symptoms.

The sense of presence experienced by the patients was another important aspect of the applicability of immersive VR. The greater the sense of presence in a VR task, the more the individuals experience actions and emotions similar to real-life situations, making it more environmentally friendly[7,28]. In this study, the high sense of presence scores were verified, and there was no statistically significant difference between the groups, suggesting that the SOIVET-Route task can be an ecological task despite having fewer sensory cues compared with the same task performed in a real environment.

Regarding the short- and long-term stability of the SOIVET-Route task, the analysis showed a good to excellent correlation in short-term stability (immediate and late recall, performed with a 20-min interval) and a poor to reasonable correlation in long-term stability (between the first and second test days, performed with an interval of 7–14 days). Bearing in mind that the system itself provides the orientation regarding the proposed activity during the task and registers the score, no performance bias from the evaluators is expected. This difference in short- and long-term stability could be explained by improved performance as a result of practice, as the participants were repeatedly exposed to the task, especially in the group of elderly people with MCI.

Among the studies that have investigated spatial orientation in elderly people through VR[10,29-34], only Pouya et al.[32] addressed test stability. Pouya et al.[32] obtained strong correlations in their analyses, but the participants repeated the VR assessment after 6 and 12 months of the first assessment, which may have prevented a possible learning effect and/or memorization of the task because of the long gap between exposures.

To better generalize the results, considering that the elderly performed better as they were repeatedly exposed to the task, it would be interesting to have more time for them to become familiarized with the system before recording their performance. A variation in the location of the five stop points during the route—in case there was a need to reapply the task at shorter intervals—would be interesting to avoid possible route memorization.

Finally, transposition of the immersive VR task to a tablet with a rotation sensor could be an alternative for the elderly people who presented adverse symptoms in immersion. However, the task would most likely have a lower sense of presence compared with immersive VR, but it would still be advantageous for elderly people with greater sensitivity to motion sickness.

The VR system developed to assess the route learning was applicable for older adults with and without MCI. The assessments showed good short-term stability. These results encourage the use of innovative tasks and immersive virtual environments for the assessment of cognition in older adults.

**Authors' contributions.** MDS, JMG, RQMC and JEP: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft and writing – review & editing; LAPV and SMDB: methodology and writing – review & editing; EGM: conceptualization, project administration and software; RDL: resources.

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Dement Neuropsychol 2022 June;16(2):228-236

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0090

# Effect of providing purple sweet potato water extract on tumor necrosis factor-α levels, protein 53 expression, glial fibrillary acidic protein expression, brain-derived neurotrophic factor levels, and spatial working memory in rats with d-galactose induction

Ketut Widyastuti[1], Tjokorda Gde Bagus Mahadewa[2], Dewa Ngurah Suprapta[3], Anak Agung Raka Sudewi[1]

**ABSTRACT.** Alzheimer's dementia (AD) is a neurodegenerative disease. The mechanism of oxidative stress in AD is due to amyloid beta (Aβ) protein that aggregates to form plaques, which further triggers chronic inflammation and neuronal apoptosis. Purple sweet potato extract with the main content of anthocyanins is a potential antioxidant with a direct target on the amyloid cascade hypothesis. **Objective:** The research objective was to determine the role of purple sweet potato water extract as an antioxidant and anti-inflammatory in preventing apoptosis in order to provide a neuroprotective effect in d-galactose-induced rats. **Methods:** A total of 100 male Wistar rats with randomized posttest-only control group design that met the eligibility criteria were included in this study. The treatment group was given 200 mg/kg BW/day of purple sweet potato water extract on days 1–70. d-galactose induction was administered in the treatment and control groups on days 15–70. **Results:** The independent t-test showed that the mean tumor necrosis factor-α (TNF-α) levels in the treatment group (735.36±139.74) was significantly lower than that in the control group (896.77±152.52). The p53 and glial fibrillary acidic protein (GFAP) expressions of astrocyte cells in the treatment group were significantly lower than that in the control group. The brain-derived neurotrophic factor (BDNF) levels in the treatment group (498.13±121.47) were higher than that in the control (391.93±140.28), and there was a significant increase in spatial working memory in the treatment group (72.01±10.22) than the control (59.77±11.87). **Conclusions:** The neuroprotective effect of purple sweet potato extract is due to d-galactose induction resulting from decrease in TNF-α levels, p53 expression, and GFAP expression and increase in BDNF levels and spatial working memory.

**Keywords:** Galactose; Tumor Necrosis Factor-alpha; Genes, p53; Glial Fibrillary Acidic Protein; Brain-Derived Neurotrophic Factor; Spatial Memory.

**EFEITO DO EXTRATO DE ÁGUA DE BATATA DOCE ROXO NO FATOR DE NECROSE TUMORAL NÍVEIS ALFA, NA EXPRESSÃO DA PROTEÍNA 53, NA EXPRESSÃO DE PROTEÍNA ÁCIDA FIBRILAR GLIAL, NOS NÍVEIS DE FATOR NEUROTRÓFICO CEREBRAL E NA MEMÓRIA ESPACIAL EM RATOS COM INDUÇÃO DE D-GALACTOSE**

**RESUMO.** A doença de Alzheimer (DA) é uma doença neurodegenerativa. O mecanismo de estresse oxidativo na DA ocorre devido à proteína beta amilóide que se agrega para formar placas que desencadeiam inflamação crônica e apoptose neuronal. O extrato de batata-doce roxa composto principalmente por antocianinas é um potencial antioxidante com

This study was conducted by the Group of Cognitive and Behavioral Neurology, School of Medicine, Udayana University, Bali, Indonesia.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on September 05, 2021; Received in its final form on November 11, 2021; Accepted on November 28, 2021.

efeito direto sobre a hipótese da cascata amilóide. **Objetivo:** O objetivo da pesquisa foi determinar o papel do extrato aquoso de batata-doce roxa como antioxidante e anti-inflamatório na prevenção da apoptose, para proporcionar um efeito neuroprotetor em ratos induzidos por D-galactose. **Métodos:** Grupo controle randomizado pós-teste com 100 ratos Wistar machos que preencheram os critérios de elegibilidade. O grupo de tratamento recebeu 200mg/kg de peso corporal/dia de extrato aquoso de batata-doce roxa nos dias 1-70. A indução de D-galactose foi testada nos grupos de tratamento e controle nos dias 15-70. **Resultados:** O teste t independente mostrou que a média dos níveis de TNF-α no grupo de tratamento (735,36±139,74) foi significativamente menor do que no grupo controle (896,77±152,52). A expressão de p53 e a expressão de GFAP de células de astrócitos foram significativamente menores no grupo de tratamento do que no grupo controle. Os níveis de BDNF no grupo de tratamento (498,13±121,47) foram maiores que no grupo controle (391,93±140,28) e houve um aumento significativo da memória de trabalho espacial no grupo de tratamento (72,01±10,22) em relação ao controle (59,77±11,87). **Conclusões:** O efeito neuroprotetor do extrato de batata-doce roxa é devido à indução de D-galactose pela diminuição dos níveis de TNF-α, expressão de p53 e expressão de GFAP, aumentando assim os níveis de BDNF e memória espacial.

**Palavras-chave:** Galactose; Fator de Necrose Tumoral alfa; Genes p53; Proteína Glial Fibrilar Ácida; Fator Neurotrófico Derivado do Encéfalo; Memória Espacial.

## INTRODUCTION

Increasing life expectancy causes an increase in the number of elderly people and problems related to the aging process. Dementia is a neurodegenerative disease that causes cognitive and behavioral disorders, affecting the elderly in their social and work activities. People with dementia experience dependence on their daily activities and become a burden to their family, community, and government. Efforts are needed to maintain the cognitive abilities of the elderly so that their quality of life remains good[1].

The most common cause is Alzheimer's dementia (AD), characterized by progressive memory decline in the early phase and several cognitive domains and behavioral changes in the late stage[2]. The main neuropathological signs in AD are senile plaque deposition of extracellular Aβ peptides and formation of intracellular neurofibrillary tangles (NFTs) or hyperphosphorylation of tau proteins. In addition, AD is accompanied by chronic neuroinflammation and oxidative stress with synaptic dysfunction and neurodegeneration in various brain areas, including the cortex and hippocampus[3].

Several previous studies have shown that D-galactose induction to rats causes excessive production of advanced glycation end products (AGEs) and reactive oxygen species (ROS), resulting in cognitive decline. Rats injected with D-galactose showed several features of brain aging, including decreased hippocampal neurogenesis, impaired synaptic plasticity, loss of cholinergic neurons in the basal forebrain, and accumulation of Aβ plaque. Increased accumulation of Aβ senile plaque in the rat brain due to D-galactose injection was associated with an increase in the β-secretase enzyme. Plaque Aβ42, being the most aggressive and neurotoxic form of Aβ plaque, is produced from the breakdown of amyloid precursor protein (APP) by the β-secretase enzyme[4].

The D-galactose model can be used to study the neurological disorders related to aging, including AD. The D-galactose induction stimulates the effects of aging through the formation of ROS, thereby causing mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis in neurons[5]. The improvements due to D-galactose induction result in an increase in β-secretase enzyme that causes the proteolytic breakdown of APP and increases Aβ42 plaque, which is the most neurotoxic plaque. D-galactose-induced brain aging is dose-dependent, starting from 100 to 500 mg/kg/day for 6–8 weeks[6]. The preelemination study on 20 Wistar rats injected with D-galactose at a dose of 100 mg/kg BW for 8 weeks showed that the mean locomotor activity and spatial memory scores in the intraperitoneal injection group were lower than that in the oral group ($p<0.05$)[7].

Neurodegenerative cases including AD started treatment after symptoms began to manifest, even though significant neuron loss had occurred at this stage. AD management with potential therapeutic targets is more effective in preventing dementia in order to increase neurotrophic factors associated with neurotransmission, synaptic plasticity, and elimination of Aβ from the brain[8]. The use of natural ingredients is an interesting option to develop. More and more evidence suggests that flavonoid compounds are effective in preventing the onset and slowing the progression of AD with a direct target of APP metabolism in the amyloid cascade hypothesis. Anthocyanins, a flavonoid compound, have been widely studied to have antioxidant, anti-inflammatory, and antiapoptotic effects[9]. Purple sweet potato extract rich in anthocyanins can modulate protein aggregation and autophagy to improve the disruption of protein homeostasis. These changes correlated with a decrease in apoptosis neurons in the hippocampus and a significant increase in brain-derived neurotrophic factor (BDNF) levels[10].

Purple sweet potato has a high anthocyanin content and is quite easy to cultivate in tropical climates in Indonesia, including Bali. Further studies are needed to evaluate the benefits of this purple sweet potato extract. To date, no research has been conducted on the effect of purple sweet potato water extract, cultivated in Bali, on dementia rat models with D-galactose induction. Therefore, this research aimed to determine whether purple sweet potato extract has a neuroprotective effect on brain damage caused by oxidative stress, inflammatory processes, and neuronal apoptosis in AD associated with tumor necrosis factor-α (TNF-α) levels, p53 expression, glial fibrillary acidic protein (GFAP) expression, BDNF levels, and spatial working memory.

## METHODS

This study used an experimental animal model with randomized posttest-only control group design.

### Ethical license

This research was approved by the ethics commission of research, Faculty of Medicine, Udayana University (no. 387/UN 14.2.2VII.14/LP/2020).

### Time and place of research

The research was conducted from February to July 2020 at the Integrated Biomedical Laboratory of the Faculty of Medicine, Udayana University, and the Molecular Immunology Laboratory of the Faculty of Veterinary Medicine, Udayana University.

### Research samples

The study samples were taken from affordable populations that met the inclusion and exclusion criteria. Inclusion criteria were male Wistar rats, age 12–14 weeks and weighing 200–300 g. Exclusion criteria were as follows: (a) sick mouse and (b) hyperactive Wistar rat (such as those biting his friend). Exclusion criteria were (a) death of mice during the study period and (b) damage to the sample tissue.

### Research variable

The independent variable is a water extract of purple sweet potato. The dependent variables were TNF-α levels, p53 expression, GFAP expression, BDNF levels, and spatial working memory. The control variables were gender, body weight, age, food, and environmental conditions.

### Research procedure

This study used dementia-induced mice with d-galactose. The analysis of water extract of purple sweet potato was carried out at the Laboratory of Agricultural Product Technology, Udayana University. The TNF-α and BDNF levels were examined using ELISA method. The expressions of p53 and GFAP were detected using immunohistochemical techniques. The spatial working memory was assessed using the Y-maze test.

### Data analysis

- A descriptive analysis was performed on the basic characteristics of the subjects in the two groups (i.e., treatment group and control group), representing mean with standard deviation or median with minimum–maximum as a measure of concentration.
- The data normality test used Shapiro-Wilk test on a sample size of <50. A p>0.05 indicates a normally distributed data.
- Homogeneity test with the Levene test was used to determine data variance.
- Parametric independent t-test was used to find the differences between control and treatment groups on normally and homogeneously distributed data.
- Path analysis was performed to determine the role of purple sweet potato water extract on TNF-α levels, BDNF levels, p53 expression, GFAP expression, and spatial working memory based on its contribution path.
- Test results were assessed using 95 confidence interval (95%CI) and p-value at a significance limit of 0.05.

## RESULTS

### Effect of purple sweet potato water extract on tumor necrosis factor-α levels

The results of the independent t-test analysis in Table 1 show that the water extract of purple sweet potato caused the mean TNF-α level in the treatment group to be significantly lower than the control group after D-galactose induction (p<0.05).

### Effect of water extract of purple sweet potato on p53 expression

The p53 expression averaged 6.68±1.76% in the treatment group and9.97±2.09% in the control group (Table 1). These results indicated that the water extract of purple sweet potato caused the expression of p53 in the brain tissue of the treatment group to be significantly lower than that in the control group (p<0.001)

The expression of p53 in neuron cells examined using immunohistochemistry is presented in Figure 1.

### Effect of water extract of purple sweet potato on glial fibrillary acidic protein expression

The GFAP expression was 25.29±13.57% in the treatment group and 33.92±4.23% in the control group (Table 1). These results indicated that the water extract of purple sweet potato caused the GFAP expression of astrocyte cells in the treatment group to be significantly lower than that in the control group ($p<0.001$). The GFAP expression of astrocyte cells examined using immunohistochemistry is presented in Figure 2.

### Effect of purple sweet potato water extract on brain-derived neurotrophic factor levels

BDNF levels averaged 498.13±121.47 pg/mg in the treatment group and 391.93±140.28 pg/mg in the control group (Table 1). These results indicated that the water extract of purple sweet potato caused the mean BDNF levels in the treatment group to be significantly higher than that in the control group after D-galactose induction ($p=0.029$).

### Effect of purple sweet potato water extract on spatial working memory

Based on the results of the independent t-test analysis in Table 2, it can be seen that the baseline spatial working memory before the study (pretest) in the control and treatment groups was not significantly different ($p=0.257$). After 70 days of observation (posttest), there was a significant difference in spatial working memory in both the groups ($p=0.004$). The comparative analysis in Table 2 also shows a decrease in spatial memory between the control group before and after the observation from 67.14±12.34 to 59.77±11.87%. These results indicated that injection of D-galactose at

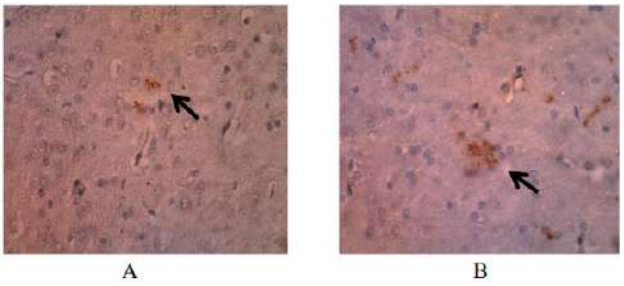


**Figure 1.** Expression of p53 rat brain on day 70 using immunohistochemical methods (magnification 400×). Astrocyte cells expressing p53 appear brownish (arrow). (A) The treatment group with three neuron cells that express p53. (B) The control group with 12 neuron cells that express p53.

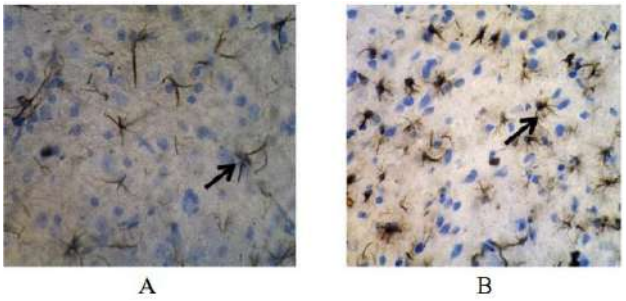


**Figure 2.** Expression of glial fibrillary acidic proteinin rat brain on day 70 using immunohistochemical method (magnification 400×). Astrocyte cells expressing glial fibrillary acidic proteinappear brownish (arrow). (A) Expression of glial fibrillary acidic proteinin the treatment group with 15 astrocyte cells expressing glial fibrillary acidic protein. (B) The control group with 39 astrocyte cells that express glial fibrillary acidic protein.

**Table 1.** Differences in tumor necrosis factor-α levels, p53 expression, glial fibrillary acidic protein expression, and brain-derived neurotrophic factor of brain tissue in both groups after observation.

| | Levels of brain tissue (pg/mg) | | | | | 95%CI (min–max) | p-value* |
|---|---|---|---|---|---|---|---|
| | Groups | n | Mean±SD | Range (min–max) | Mean differences | | |
| TNF-α levels | Control | 50 | 896.77±152.52 | 665.53–1248.68 | 161.4 | 55.79–267.02 | 0.004† |
| | Treatment | 50 | 735.36±139.74 | 436.39–966.57 | | | |
| p53 expression | Control | 50 | 9.97±2.09 | 5.29–13.83 | 3.28 | 1.88–4.68 | <0.001† |
| | Treatment | 50 | 6.68±1.76 | 4.36–9.28 | | | |
| GFAP | Control | 50 | 33.92±4.23 | 24.70–39.43 | 8.63 | 5.79–11.46 | <0.001† |
| | Treatment | 50 | 25.29±13.57 | 20.09–30.65 | | | |
| BDNF | Control | 50 | 391.93±140.28 | 128.02–583.64 | 106.20 | 11.46–200.94 | 0.029† |
| | Treatment | 50 | 498.13±121.47 | 321.90–845.79 | | | |

95%CI: 95% confidence interval, TNF-α: tumor necrosis factor-α, GFAP: glial fibrillary acidic protein, BDNF: brain-derived neurotrophic factor. *Student's t-test; †significant.

a dose of 200 mg/kg BW for 8 weeks caused a decrease in spatial working memory due to the symptoms in dementia mice model. Although purple sweet potato water extract was provided for 70 days, there was an increase in spatial working memory from 61.98±12.93 to 72.01±10.22%.

### Pathway analysis of the role of purple sweet potato water extract on p53 expression, tumor necrosis factor-α levels, glial fibrillary acidic protein expression, brain-derived neurotrophic factor levels, and spatial working memory

The role of purple sweet potato water extract on p53 expression, TNF-α levels, GFAP expression, BDNF levels, and spatial working memory based on the contribution pathway for each variable is presented simultaneously in the path analysis shown in Figure 3. Evaluation of model suitability (goodness of fit) describes how well or fit a series of variable observations to the model. Based on the goodness-of-fit index, this model is declared fit with root mean square error of approximation (RMSEA)<0.08.

This model explains the effect of purple sweet potato water extract on memory enhancement. The results of this pathway analysis show that purple sweet potato extract suppresses oxidative stress and inflammation, as indicated by its negative effect on the three biomarkers, namely, p53 expression, TNF-α levels, and GFAP expression. The suppression of oxidative stress and inflammatory biomarkers has a direct or an indirect effect on increasing spatial working memory by increasing BDNF levels. The effect of one variable on other variables in this study is shown in Table 3.

## DISCUSSION

The purple sweet potato water extract affected memory enhancement through its direct effect on suppression of oxidative stress and inflammatory pathways, such as p53 expression, TNF-α levels, and GFAP expression. The highly significant direct effect ($p<0.05$) was through the suppression of the GFAP activation pathway by 75.1%. Overall, from the total effect, it appears that purple sweet potato water extract has a significant

**Table 2.** Differences of spatial working memory in both the groups before (pretest) and after (posttest) observation.

| Memory spatial | | | | | | 95%CI (min–max) | p-value* |
|---|---|---|---|---|---|---|---|
| Groups | | n | Mean±SD | Range (min–max) | Mean differences | | |
| Pretest | Control | 50 | 67.14±12.34 | 40–81.82 | 85.16 | -3.96 to 14.29 | 0.257 |
| | Treatment | 50 | 61.98±12.93 | 37.5–83.33 | | | |
| Posttest | Control | 50 | 33.92±4.23 | 24.70–39.43 | 12.24 | 4.24 to 20.24 | 0.004† |

95%CI: 95% confidence interval. *Student's t-test; †Significant.

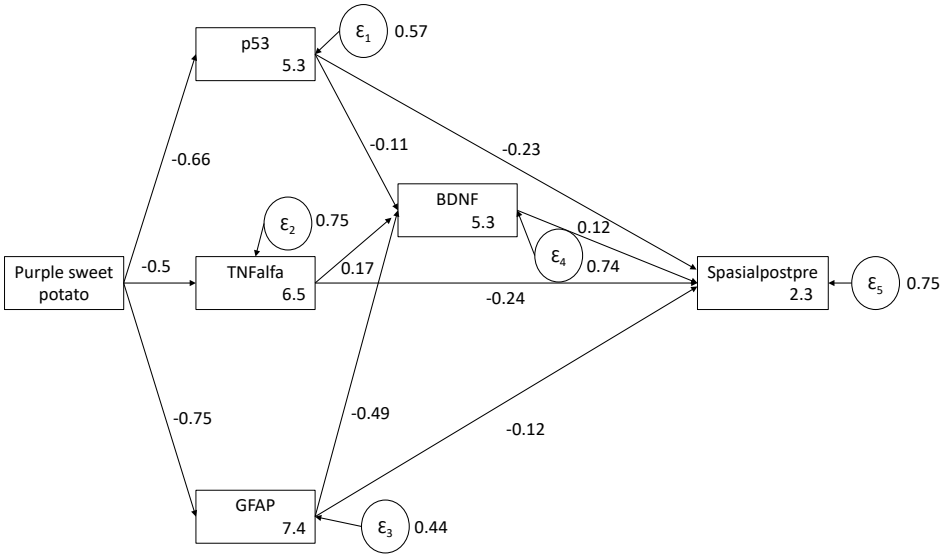


**Figure 3.** Goodness-of-fit model showing the role of purple sweet potato water extract on p53 expression, tumor necrosis factor-α levels, glial fibrillary acidic protein expression, brain-derived neurotrophic factor levels, and spatial working memory based on path analysis.

**Table 3.** Direct effect, indirect effect, and the total effect of one variable on other variable.

| | Effect | | | | | |
|---|---|---|---|---|---|---|
| | Direct | | Indirect | | Total | |
| | β | p-value* | β | p-value* | β | p-value* |
| Purple potato on p53 | -0.659 | <0.001† | – | – | -0.659 | <0.001† |
| Purple potato on TNF-α | -0.495 | <0.001† | – | – | -0.495 | <0.001† |
| Purple potato on GFAP | -0.754 | <0.001† | – | – | -0.754 | <0.001† |
| Purple potato on BDNF | – | – | 0.355 | 0.013† | 0.355 | 0.013† |
| Purple potato on memory | – | – | 0.400 | 0.004† | 0.400 | 0.004† |
| P53 on BDNF | -0.113 | 0.522 | – | – | -0.113 | 0.522 |
| P53 on memory | -0.232 | 0.188 | -0.013 | 0.645 | -0.246 | 0.171 |
| TNF-α on BDNF | 0.173 | 0.295 | – | – | 0.173 | 0.295 |
| TNF-α on memory | -0.235 | 0.158 | 0.020 | 0.573 | -0.215 | 0.202 |
| GFAP on memory | -0.488 | 0.003† | – | – | -0.488 | 0.003† |
| GFAP on BDNF | -0.117 | 0.556 | -0.058 | 0.516 | -0.175 | 0.334 |
| BDNF on memory | 0.119 | 0.501 | – | – | 0.119 | 0.501 |

TNF-α: tumor necrosis factor-α, GFAP: glial fibrillary acidic protein, BDNF: brain-derived neurotrophic factor. *Student's t-test; †significant; β=standardized coefficient.

indirect effect on improving memory. The results of this study indicate that purple sweet potato extract has the ability to suppress oxidative stress and inflammation and therefore inhibits apoptosis and triggers neurogenesis, thereby causing improvement in spatial memory.

The increase in memory is not solely through the BDNF pathway. There is a direct effect due to the suppression of the inflammatory process itself, and if inflammation is suppressed, there is a direct effect on memory improvement. Although there is an increasing understanding of the pathogenesis of AD, accurate evidence on the mechanism of the disease is still lacking. The focus therapy so far has largely targeted the excitotoxicity and cholinergic hypotheses, but recently there is an increasing evidence of the importance of non-neuronal cells such as astrocytes. This opens new research avenues to better understand disease pathology with the molecular target of astrocytes for drug development. Astrocytes have a role in protecting neurons in physiological conditions, and astrocyte dysfunction triggers neuronal degeneration, which interferes with synapse delivery and causes cognitive impairment that occurs in AD. Astrocytes become reactive due to the deposition of amyloid plaque, resulting in decreased glutamate uptake due to reduced transporter expression, changes in energy metabolism, disruption of K and Ca ion homeostasis, and the release of cytokines and inflammatory mediators[11].

Reactive astrocytes show changes in astrocyte function characterized by an increased expression of a number of astrocyte structural proteins, such as GFAP and vimentin. Morphological changes in reactive astrocytes such as hypertrophy and proliferation of processes are important in the formation of astrocyte scar around the lesion tissue. Continuous astrocyte reactivity is triggered by a positive feedback cycle between microglia and astrocytes in a prolonged brain disorder that disrupts neuronal function and leads to chronic neuroinflammation. The etiology of neurodegenerative diseases is largely unknown; however, there are a number of contributing factors including oxidative stress, calcium excitotoxicity, neuroinflammation, and disruption of protein homeostasis, leading to neuronal apoptosis in the brain. Anthocyanin polyphenol compounds present in purple sweet potato extract are able to modulate many of the pathways underlying neurodegenerative diseases so that their development is promising as multitarget drug ligands (MTDLs) for the prevention and treatment of neurodegenerative diseases. The neuroprotective effect of anthocyanins is inseparable from the evidence showing its ability to cross the blood–brain barrier[10].

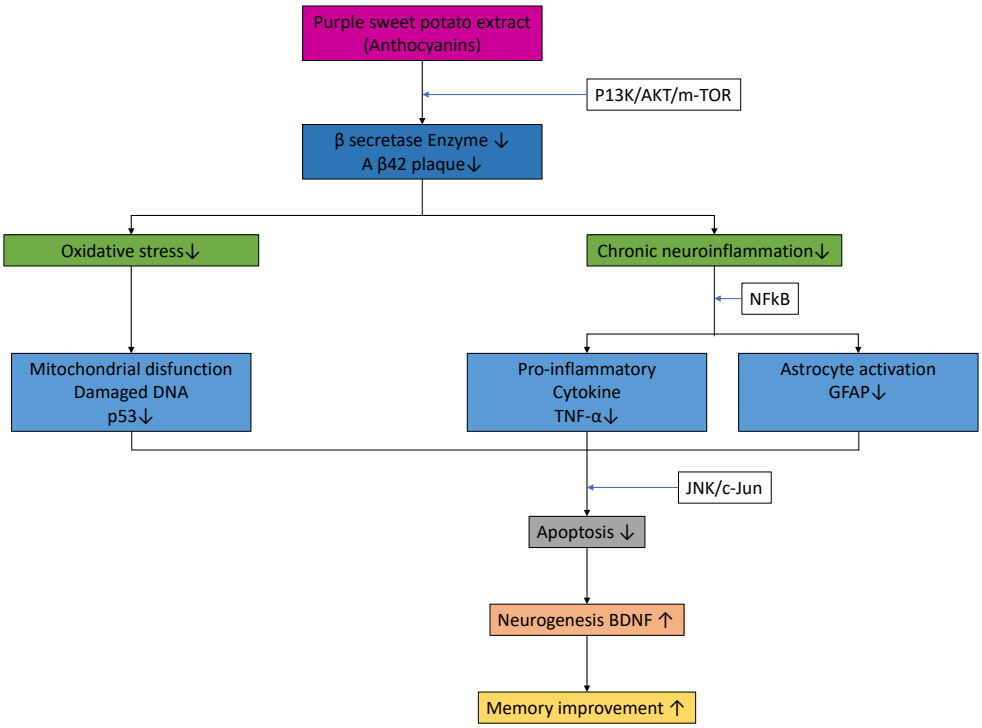


**Figure 4.** Schematic illustration of the mechanism of anthocyanin gives the effect of neuroprotective through decreased expression of p53, the levels of tumor necrosis factor-α, the expression of glial fibrillary acidic protein and increased brain-derived neurotrophic factor and spatial working memory.

Purple sweet potato water extract with the main content of anthocyanins has been shown to have a direct effect in suppressing oxidative stress and inflammation, thereby triggering apoptosis and causing neuroprotective effects, such as an increase in neurogenesis and improvement of spatial working memory. These results support previous research by Wurzelmann et al.[12] who demonstrated the neuroprotective role of anthocyanins on the mechanisms of oxidative stress and inflammation in dementia mice model. Based on the results of the research and discussion, an illustration scheme was made. The anthocyanin mechanism provides a neuroprotective effect by decreasing p53 expression, TNF-α levels, and GFAP expression and increasing BDNF and spatial working memory (Figure 4).

Anthocyanins have been shown to act as antioxidants that directly bind ROS, and reactive nitrogen species (RNS) were assessed directly by their high oxygen radical absorption capacity (ORAC) and indirectly by increasing intrinsic antioxidant defenses through increasing levels and activity of antioxidant enzymes such as catalase, SOD, and GSH through activation of the transcription factor Nrf2. In this study, it was proven that anthocyanins have antioxidant activity by suppressing DNA damage and apoptosis, which is judged by low p53 expression. Normal p53 bound with the mouse double minute 2 (MDM2) triggers ubiquitination so that p53 levels are low and do not cause apoptotic effects. If there is DNA damage, p53 functions to prevent replication in damaged cells by stopping the cell cycle in the G1 phase (interphase) so that the cells have time to repair themselves. However, the failure of repairing cells or extensive damage will trigger apoptosis. Apoptosis is triggered by p53 through the intrinsic pathway when DNA damage is triggered by oxidative stress, ATM/ATR, and CHK2 proteins are released so that p53 does not bind to MDM2 and p53 accumulates. Increased p53 will inhibit the activity of antiapoptotic protein (Bcl-2) and stimulate pro-apoptotic BH3-only proteins such as Bim, PUMA, NOXA to activate Bax and Bak proteins to form oligomers on the mitochondrial surface of a channel called MOMP (mitochondrial outer membrane permeability), which triggers the apoptotic cascade. This channel causes the release of cytochrome c to the cytoplasm, which combines with APAF-1 and caspase 9 to form the apoptosis. The apoptosis breaks down procaspase 3 into active caspase 3, which stimulates apoptosis. This study also proved the anti-inflammatory ability of anthocyanins based on TNF-α levels and GFAP expression. The inflammatory process in

dementia is triggered by the presence of Aβ protein that forms Aβ plaque. Toxic plaque triggers oxidative stress on the astrocytes and microglia around the plaque so that the microglia is activated and the astrocytes become reactive. Plaque Aβ induces activation of the microglia via TLR and RAGE signals, resulting in activation of Erk1/2, Akt, p38, and MAPK in order to activate transcription factor NFκB and triggering the release of pro-inflammatory mediators such as TNF-α, interleukin (IL)-1B, and IL-6. Inflammatory mediators in neurons cause increased amyloid production. This communication between neurons and glia further strengthens neurotoxicity, especially in the cholinergic neurons in the basal forebrain, which are the targets of AD. As a ligand, TNF-α will bind to the receptor. TNFR-1 triggers trimerization to bind to TRADD and FADD adapter proteins to form DISC so that procaspase 8 proteolysis becomes active caspase 8, which triggers apoptosis directly by activating caspases 3, 6, and 7. Astrocytes have the main function of protecting neurons and repairing tissue after injury/stress by forming scar glia (astrogliosis), which serves to resist the spread of inflammation and repair damage to the blood–brain barrier. Astrocytes near the amyloid plaque become reactive after oxidative stress. Reactive astrocytes are characterized by hypertrophy in the astrocyte process, leading to the release of the structural protein GFAP. In this study, neuroprotective effects of anthocyanin were obtained indirectly through the BDNF pathway. BDNF is a neurotrophic factor that plays an important role in synaptic plasticity and neuronal cell survival. BDNF binds to the tyrosine kinase B (TrkB) receptor to activate the PI3K/Akt pro-survival pathway. The activated PI3K produces phosphatidylinositol that will react with phosphatidylinositol-dependent kinase (PDK) and serine/threonine and form phosphorylated Akt. The Akt will activate the antiapoptotic gene and inhibit the transcription factors that trigger apoptosis and activate mammalian target of rapamycin (mTOR) which will activate and phosphorylate apoptosis genes, such as *MCL-1*. It also phosphorylates MDM2, thereby inhibiting p53 activation and phosphorylating CREB on Ser 133 residues to recruit CREB-binding protein that regulates antiapoptotic Bcl-2 regulation and will inhibit the Forkhead box O3 (FOXO3), which activates Bim and NOXA. However, in this study, it was found that although the neuroprotective effect of anthocyanins was not solely through the BDNF pathway, there was a direct effect due to the suppression of the inflammatory process itself, and if inflammation was suppressed, there was a direct effect on memory improvement. This is probably due to anthocyanins exhibiting a direct neuroprotective effect by preventing protein aggregation and stimulating autophagy, thereby suppressing inflammation. Protein aggregation plays an important role in neuronal death by inhibiting the oligomerization of amyloid proteins into toxic fibrils and plaques. Anthocyanin cyanidin-3-*O*-pure glucopyranoside have been shown to directly inhibit the oligomerization of Aβ peptides[13]. Likewise, malvidin and cyanidin-3-*O*-glucopyranoside were reported to have the potential to inhibit the oligomerization of Aβ into toxic fibrils[14]. This finding was further corroborated by other studies showing that pure anthocyanins and anthocyanidins prevent Aβ oligomerization directly in neuron cells, thereby preventing the formation of protein aggregates in AD[15]. Although the mechanism by which anthocyanins inhibit aggregate formation is not currently known, the ability of these compounds to inhibit the formation of toxic oligomers holds promise for therapeutic success. Recent studies also report the ability of anthocyanin-rich extracts to modulate autophagy to clear toxic protein aggregates from the intracellular space to prevent neuronal death. Anthocyanins significantly increase autophagosomes turnover and increase the activation of mTOR, one of the regulators of the autophagy pathway[16]. Similarly, a more recent study showed that extracts from purple sweet potato significantly increased autophagy markers in the hippocampus of rats fed a high-fat diet and showed that this process was dependent on protein kinase (AMPK) activation[17]. This change correlates with a decrease in neuronal apoptosis in the hippocampus and a significant increase in BDNF[16]. Overall, these results suggest that anthocyanins and anthocyanin-rich extracts can modulate processes such as protein aggregation and autophagy to correct the disruption of protein homeostasis in AD, although further data are needed to confirm this hypothesis.

The results of this study strengthen the theory of inflammation and oxidative stress as factors that play an important role in the pathogenesis of dementia and have succeeded in proving the neuroprotective effect of purple sweet potato water extract. This is shown from the invention: (1) TNF-α levels in mice with induction of D-galactose given purple sweet potato water extract were lower than those not given purple sweet potato water extract. (2) The expression of p53 in mice with induction of D-galactose given purple sweet potato water extract was lower than those that were not given purple sweet potato extract. (3) The expression of GFAP in mice with D-galactose induction given purple sweet potato water extract was lower than those not

given purple sweet potato water extract. (4) BDNF levels in mice with induction of D-galactose given purple sweet potato water extract were higher than those not given purple sweet potato water extract. (5) Spatial working memory in mice with induction of D-galactose given purple sweet potato water extract increased compared to those not given purple sweet potato water extract.

**Authors' contributions.** KW, TGBM, DNS, and AARS: conceptualization, methodology, and writing – review & editing. TGBM, DNS, and AARS: validation, investigation, resources, supervision, and funding acquisition. KW: software, formal analysis, data curation, writing – original draft preparation, visualization, and project administration. All authors have read and agreed to the published version of the manuscript.

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Dement Neuropsychol 2022 June;16(2):237-243

Original Article

https://doi.org/10.1590/1980-5764-DN-2021-0083

# Fatigue in Brazilian patients with Parkinson's disease

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**ABSTRACT.** Fatigue is a non-motor symptom of high prevalence in Parkinson's disease (PD); however, it is still unknown and neglected by health professionals. **Objective:** This study aimed to demonstrate the prevalence of fatigue in patients with PD after excluding confounding factors, as well as its correlation with clinical and demographic data, and to find its negative impact on the quality of life of these patients. **Methods:** A cross-sectional study was carried out with 237 randomly selected patients. According to inclusion and exclusion criteria, we selected 53 patients, who were then submitted to the Fatigue Severity Scale. Clinical and demographic data were also analyzed, comparing them between patients with and without fatigue. **Results:** We identified fatigue in 21 (39.62%) patients. Patients with and without fatigue had similar mean scores on the UPDRS-III (p=0.36), equivalent daily dose of levodopa (p=0.94), mean disease duration (p=0.43), and mean age (p<0.99). Fatigued patients had worse quality of life scores (PDQ-39) (p=0.00). We did not observe a correlation between fatigue, duration of illness (r=0.11; p=0.43), age (r=0.00; p=0.99), and UPDRS-III (r=0.20; p=0.16). **Conclusions:** Fatigue is a highly prevalent and independent symptom of PD. There is no correlation between age, mean duration of disease, motor impairment, and its presence. It has a negative impact on quality of life.

**Keywords:** Depression; Disorders of Excessive Somnolence; Fatigue; Parkinson Disease.

**FADIGA EM PACIENTES BRASILEIROS COM DOENÇA DE PARKINSON**

**RESUMO.** A fadiga é um sintoma não motor de elevada prevalência na doença de Parkinson, no entanto ela ainda é desconhecida e negligenciada por profissionais de saúde. **Objetivo:** Demonstrar a prevalência de fadiga em pacientes com doença de Parkinson após a exclusão de fatores de confusão, bem como sua correlação com dados clínicos e demográficos, comprovando seu impacto negativo na qualidade de vida desses pacientes. **Métodos:** Foi realizado um estudo transversal com 237 pacientes selecionados aleatoriamente. De acordo com critérios de inclusão e exclusão, escolhemos 53 pacientes, que foram então submetidos à Escala de Gravidade de Fadiga. Analisaram-se também dados clínicos e demográficos, comparando-os entre os pacientes com e sem fadiga. **Resultados:** Identificamos fadiga em 21 pacientes (39,62%). Pacientes com e sem fadiga apresentaram pontuação média semelhante na Escala Unificada de Avaliação para Doença de Parkinson (UPDRS-III) (p=0,36), dose diária equivalente de levodopa (p=0,94), tempo médio de duração da doença (p=0,43) e idade média (p<0,99). Pacientes fatigados apresentaram piores índices de qualidade de vida (*Parkinson's Disease Questionnaire* — PDQ-39) (p=0,00). Não observamos correlação entre fadiga, tempo de doença (r=0,11; p=0,43), idade (r=0,00; p=0,99) e UPDRS-III (r=0,20; p=0,16). **Conclusões:** A fadiga é um sintoma de alta prevalência e independente na doença de Parkinson. Não há correlação entre idade, tempo médio de duração da doença, comprometimento motor e sua presença. Possui impacto negativo na qualidade de vida.

**Palavras-chave:** Depressão; Distúrbios do Sono por Sonolência Excessiva; Fadiga; Doença de Parkinson.

## INTRODUCTION

Fatigue is one of the most common and disabling non-motor symptoms, which can affect up to half of patients with Parkinson's disease (PD)[1]. The case definition and diagnostic criteria for identifying PD-related fatigue were published in 2016[2]. Fatigue is a term widely used in clinical practice, and it can be a normal response to exercise or stress, or it can be a sign of some diseases, like PD. In this sense, fatigue can be considered physiological or pathological. In healthy individuals, fatigue is a physiological reaction to intense and prolonged activity, being predictable and

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** none.

Received on November 12, 2021; Received in its final form on December 06, 2021; Accepted on December 29, 2021.

transient and can be relieved with rest without compromising daily activities. In patients with pathological fatigue, the characterization is distinct, with fatigue involving feelings of tiredness at rest, a lack of energy that compromises daily activities, or even loss of vigour[3].

Identifying other non-motor symptoms that act as confounding factors, such as apathy, depression, and excessive daytime sleepiness (EDS), as well as excluding clinical and fatigue-related medications should be the first step in evaluating these patients[4]. This approach was not common in previous studies and should be standardized after the publication of these most recent recommendations[2,4]. Knowledge about the pathophysiology of fatigue is scarce, and its diagnosis in clinical practice is made through validated clinical scales[4]. Unfortunately, there is not enough evidence to apply pharmacological and non-pharmacological therapies; therefore, studies on fatigue are of great importance[4,5].

In this study, we aimed to identify fatigue as a primary non-motor symptom after excluding confounding factors, as well as to identify fatigue as an independent non-motor symptom by observing its prevalence in PD patients, its relationship with clinical and demographic characteristics, and the impact of this symptom in the quality of life.

## METHODS

This is an analytical, cross-sectional observational study carried out in the Movement Disorders Sector of Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil. The study was approved by the ethics committee of the coordinating center (CAAE number 67871316.9.0000.5259), and all patients signed an informed consent form.

Outpatients of both genders, aged between 50 and 85 years and with a confirmed diagnosis of PD, were randomly selected during a routinely scheduled medical appointment, according to the diagnostic criteria of the Movement Disorders Society[6], and who could be using any antiparkinsonian drugs. Patients under the age of 50 years (early-onset PD) may present a cognitive and psychiatric profile that are different from those who aged over 50 years, which could somehow make the study less homogeneous[7]. All patients were examined by the same neurologist, who was also responsible for applying all study scales. The exclusion criteria adopted were as follows: dementia, visual or hearing impairment (inability to apply the clinical scales), clinical conditions related to fatigue, such as untreated hypothyroidism, anemia, lung disease, heart disease, nephropathy or liver disease, decompensated diabetes mellitus, previous head injury, autoimmune disease, previous stroke and chronic infectious diseases; modified Hoehn-Yahr Scale (HYS) ≥4[8], fatigue-related medications such as hypnotics, beta-blockers, benzodiazepines, muscle relaxants, and antihistamines[4]; depressive symptoms, defined by a score >19 on the Beck-II Depression Inventory (BDI-II)[9]; EDS, defined by a score >10 on the Epworth Sleepiness Scale (ESS)[10]; and apathy, defined by a score ≥14 on the Apathy Scale (AE)[11]. The cutoff points used in the scales in question were defined in previous studies, all validated for application in patients with PD and for the Portuguese language. A noteworthy consideration is that BDI-II scores between 14 and 19 are indicative of mild depressive symptoms, but in this study, we prefer a cutoff score of 19 based on previous studies that have assessed the accuracy of this scale in diagnosing major depression in patients with PD. The BDI-II is a screening test and fatigue is related to major depression, not mild depressive symptoms, thus justifying the choice of the cutoff point[9].

Demographic and clinical characteristics including sex, age, disease duration, medications in use, levodopa equivalent daily dose (LEDD), and HYS were recorded. The LEDD was calculated using a conversion factor previously described in the literature[12]. Scales validated for patients with PD were used to identify apathy (AE), depression (BDI-II), ESS, and dementia (Mini-Mental State Examination [MMSE], as a cognitive screening test, and *DSM-V* criteria, when applicable). Laboratory tests performed included complete blood count, electrolytes, fasting glucose, liver function, urea, creatinine, and thyroid function, and, if abnormalities were detected according to the exclusion criteria, the participant would be excluded.

In the next phase, all selected participants were evaluated in the on phase, or within 1 h of taking the medication. All underwent the Fatigue Severity Scale (FSS), with those with scores higher than 4 (FSS>4) considered fatigued and those with lower scores (FSS≤4) allocated to the group of patients without fatigue. The FSS was recommended for screening and quantifying the severity of fatigue, which is a scale composed of 9 items with the total score representing the average score of each of the 9 items, resulting in a score range between 1 and 7, higher scores indicate a higher level of fatigue[13]. According to the literature, we used an average score greater than 4 points to define clinically significant fatigue[13,14]. To assess the degree of motor impairment, all participants underwent the third part of the UPDRS (UPDRS-III)[15]. To measure the impact of fatigue on quality of life, the 39-item Parkinson's Disease Questionnaire (PDQ-39)[16] was used.

Frequency, mean, and standard deviation of the variables will be exposed. To verify if the measures of

age, disease duration, LEDD, HYS, UPDRS-III, FSS, MMSE, and PDQ-39 were superior, inferior, or equal between the fatigued or not groups, two tests were used. First, Fisher's F-test was used to identify the equality of variances. Subsequently, Student's t-test was used for equal variances or different variances. For all these tests, a significance level of 5% was adopted. Among continuous variables, Pearson's correlation was used. The $\chi^2$ test was used to compare gender distribution. SPSS version 18 and Microsoft Excel 2010 software were used to compile the analyses and tests.

## RESULTS

From a population of 237 individuals diagnosed with PD, using data from medical records, initially 155 patients were excluded according to the inclusion and exclusion criteria. The remaining 82 patients were invited to participate in this study. After applying the aforementioned scales and carrying out laboratory tests, 29 participants were excluded, so 53 made up the final sample, who were selected and separated into two groups, according to the score obtained on the FSS, as explained in the "Assessment" section. A total of 32 (60.37%) patients constituted the non-fatigued group (FSS≤4) and 21 patients formed the fatigued group (FSS>4), observing a prevalence of fatigue of 39.62% in the evaluated population (n=53). The mean±standard deviation of the FSS was 5.26±0.85 for the fatigued group and 2.31±1.00 for the non-fatigued group (p=0.00). The study population included more men than women (67.92 vs. 32.07%). The mean age of the sample was 65.13±7.94 years, with a mean duration of disease of 7.45±4.20 years. All patients were on antiparkinsonian therapy and the mean LEDD was 714.45±371.72. The mean MMSE score was 27.28±2.02 points.

The fatigued (n=21) and non-fatigued (n=32) groups had the same proportion of male and female patients ($\chi^2$=0.03; p=0.87). Still comparing the groups, we observed that the patients had a mean age (64.75±7.23 vs. 65.71±8.72; p=0.99), disease duration (7.25±3.64 vs. 7.76±4.82; p=0.43), LEDD (711.06±353.66 vs. 719.61±389.24; p=0.94), and UPDRS-III (19.18±10.34 vs. 22.23±13.14; p=0.36) were similar. Not surprisingly, fatigued patients had worse quality of life scores on the PDQ-39 total score (32.87±12.71 vs. 18.11±13.21; p=0.00) and in all dimensions, except "stigma," as shown in Table 1 and Figure 1. No correlation was identified between disease duration (r=0.11; p=0.43), age (r=0.00; p=0.99), and UPDRS-III (r=0.20; p=0.16) with the presence of fatigue. Disease duration correlated with LEDD (r=0.59; p=0.00) (Figure 2).

## DISCUSSION

Estimated data on the prevalence of fatigue in PD patients vary widely in the literature, around 33–58%[1,3,4]. This is due to the different criteria adopted for case selection and assessment methods used, as well as the definition of fatigue, which it is still heterogeneous in the literature. This reinforces the need to use similar criteria to define fatigue cases, the most recent being defined by the Movement Disorders Society[2]. We observed a prevalence of fatigue in 39% of our evaluated patients. However, our study sought to eliminate confounding factors, that is, factors other than PD that could be associated with fatigue, showing a more crystalline result and corroborating the concept that fatigue is a primary or independent symptom in PD. It is important to know that the coexistence of non-motor symptoms such as anxiety, EDS, depression, and fatigue is very common, with up to 59% of patients presenting two or more of these symptoms, that is, in addition to overestimating fatigue prevalence data, if these factors of confusion are not removed, the therapeutic approach will be impaired, as the treatment of depressive disorder, for example, is associated with a reduction in fatigue[17]. Another important observation is that these non-motor symptoms associated with fatigue are extremely common in PD. According to literature data, up to 35% of patients with PD have depressive symptoms (17% of them with a diagnosis of major depression)[18], 17–60%[19] have apathy, and up to 50% have EDS[20]. So far, especially after the publication of the 2016 case definition recommendations[2], we did not identify studies with exclusion criteria similar to this one, with the majority having determined the prevalence of fatigue in PD patients without excluding the main causes related to this symptom, and which, as described, are quite common. Thus, we show the high prevalence of fatigue, reinforcing the greater need for health professionals to assess this symptom.

A key point in understanding fatigue as a subjective symptom is to differentiate it from objective fatigue, which is more easily measurable. This point was difficult to understand by the patients evaluated and can also be misinterpreted by health professionals, who commonly confuse fatigue with disability related to the motor symptoms of the disease. An intuitive and mistaken reasoning would be to imagine that the greater the motor impairment, the greater the degree of fatigue; however, fatigue occurs unpredictably in PD and may even be a premotor symptom[21]. It is also important to note that other pathologies that involve the nervous system, such as stroke, even though they do not lead to motor disability, may be associated with fatigue[22], suggesting alternative mechanisms to the impairment of the motor

pathways in the pathophysiology of subjective fatigue. This can be corroborated by neuroimaging studies that show that fatigue in PD is associated with the involvement of non-dopaminergic extrastriatal areas[23,24].

Corroborating the concepts described above, we found similar mean motor impairment scores, through the UPDRS-III, in both groups (FSS>4, 22.23±13.14 vs. FSS≤4, 19.18±10.34; p=0.37) and no correlation between UPDRS-III and fatigue (r=0.20; p=0.16). Likewise, we found similar mean HYS scores between groups (FSS>4, 2.45±0.41 vs. FSS≤4, 2.39±0.38; p<0.59). Similarly, in a recent systematic review, Siciliano et al.[25] observed, through the UPDRS-III and HYS, a small difference between fatigued and non-fatigued patients, about 5 and 0.33 points, respectively.

We observed a similar mean age between fatigued and non-fatigued patients (FSS>4, 64.75±7.23 vs. FSS≤4, 65.71±8.72, p=0.99), with no correlation between these two variables (r=0.00; p=0.99). As we have sometimes emphasized, fatigue is an independent

**Table 1.** Clinical and demographic characteristics and Parkinson Disease Questionnaire-39 comparisons between groups.

| Clinical and demographic characteristics | | | | | |
|---|---|---|---|---|---|
| | | Non-fatigued (FSS≤4) n=32 | Fatigued (FSS>4) n=21 | | |
| Sex (male:female), % | | 68.75:31.25 | 66.67:33.33 | | |
| Age, years, mean±SD | | 64.75±7.23 | 65.71±8.72 | | |
| HYS (n) | Stage 2 | 14 | 8 | | |
| | Stage 2.5 | 11 | 7 | | |
| | Stage 3 | 7 | 6 | | |
| **Groups comparisons** | | | | | |
| **Variable, mean±SD** | | **Non-fatigued (FSS≤4) n=32** | **Fatigued (FSS>4) n=21** | **95%CI** | **p-value** |
| | | | | **Lower** | **Upper** |
| LEDD | | 711.06±353.66 | 719.61±389.24 | -203.05 | 220.17 | 0.94 |
| MMSE | | 27.41±1.86 | 27.10±228 | -1.46 | 0.84 | 0.59 |
| UPDRS-III | | 19.18±10.34 | 22.23±13.14 | -3.58 | 9.68 | 0.36 |
| Disease duration | | 7.25±3.64 | 7.76±4.82 | -1.88 | 2.90 | 0.43 |
| **PDQ-39** | | | | | |
| **PDQ-39 domain, mean±SD** | | **Non-fatigued (FSS≤4) n=32** | **Fatigued (FSS>4) n=21** | **95%CI** | **p-value** |
| | | | | **Lower** | **Upper** |
| Total | | 18.1 ±13.21 | 32.87±12.71 | 7.29 | 22.25 | 0.00* |
| Mobility | | 17.73±19.03 | 36.54±24.05 | 6.65 | 30.98 | 0.00* |
| Activities of daily living | | 22.52±20.69 | 37.30±23.23 | 2.28 | 27.27 | 0.02* |
| Emotions | | 19.92±14.57 | 33.13±20.67 | 3.30 | 23.13 | 0.01* |
| Stigma | | 16.01±23.43 | 22.91±19.22 | -5.66 | 19.47 | 0.28 |
| Social support | | 7.81±14.11 | 20.23±19.51 | 2.16 | 22.69 | 0.02* |
| Cognition | | 12.85±15.41 | 30.65±14.92 | 9.05 | 26.55 | 0.00* |
| Communication | | 8.62±12.56 | 20.23±16.77 | 2.72 | 20.51 | 0.01* |
| Bodily discomfort | | 36.19±23.71 | 52.77±22.76 | 3.16 | 30.00 | 0.02* |

SD: standard deviation; 95%CI: 95% confidence interval; HYS: Hoehn-Yahr Scale; UPDRS-III: Unified Parkinson's Disease Rating Scale part III; PDQ-39: Parkinson Disease Questionnaire-39; LEDD: Levodopa Equivalent Daily Dose; MMSE: Mini-Mental Status Examination; *statistically significant.

non-motor symptom that may even precede the motor symptoms of PD, that is, it is part of the pathophysiological process of the disease, which can occur in a wide age range. It is known that with advancing age, chronic conditions associated with fatigue may arise, which we sought to exclude from this study[26]. Studies in the literature that correlated mean age and the presence of fatigue presented varied results. Stocchi et al.[27] observed a small difference between the mean age (68.0±9.2 vs. 66.3±8.7 years; p=0.044) in fatigued patients compared to non-fatigued patients, the same as observed by Siciliano et al.[25], through a systematic review by meta-analysis, which observed a mean age 1.7 years higher in fatigued patients (95%CI 0.77–2.12). Alves et al.[28] also did not observe a statistically significant difference in mean age between the fatigued and non-fatigued groups (74.2±7.9 vs. 72.6±8.8; p=0.216).

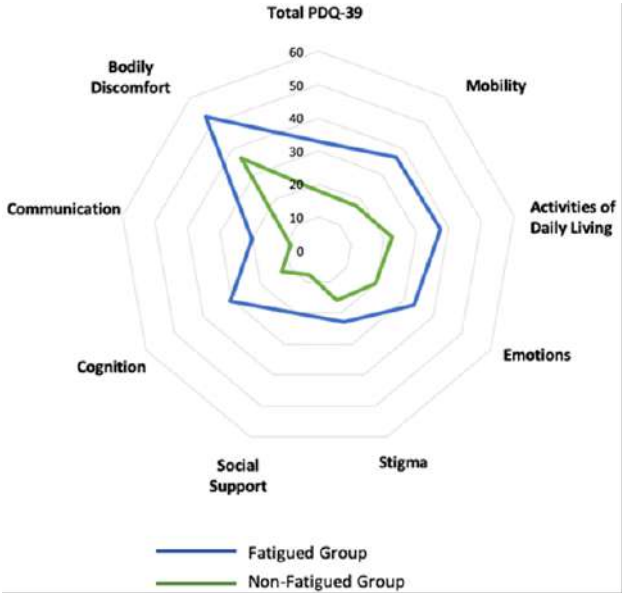


**Figure 1.** Total Parkinson Disease Questionnaire-39 and domain comparison between fatigued and non-fatigued patients.

In this study, both fatigued and non-fatigued groups had a similar LEDD (FSS>4, 711.06±353.66 vs. FSS≤4, 719.61±389.24; p=0.94). Despite the great benefit that dopaminergic drugs provide in the motor symptoms of PD, other non-dopaminergic mechanisms are probably related to fatigue, such as the decrease in serotonin in the basal ganglia and limbic system[24]. Kang et al.[29] correlated diffusion tensor imaging values and FSS score in patients with PD and demonstrated that the gray matter volume and striatal dopaminergic activity in PD with fatigue were not different from PD without fatigue, corroborating the involvement of alternative circuits in the pathophysiological process of fatigue. The subclassification of non-motor phenotypes in PD is a relatively recent concept that may result from variable

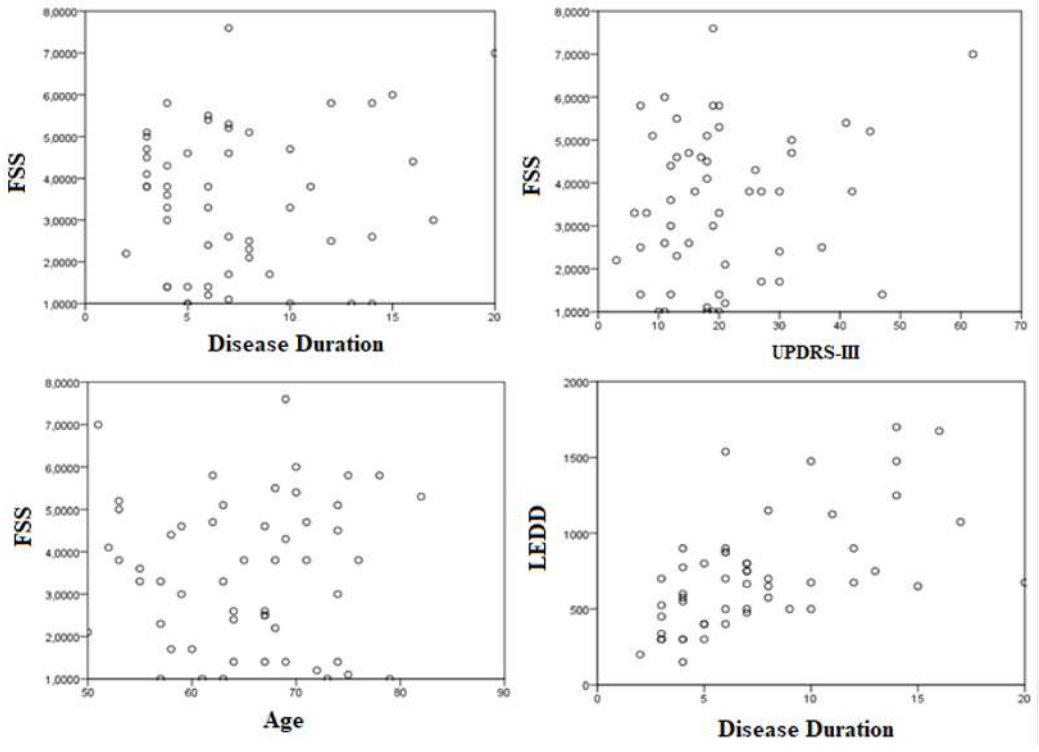


**Figure 2.** Negative correlation between age, disease duration, Unified Parkinson's Disease Rating Scale part III, and fatigue.

rates of Lewy body deposition and neurodegeneration in different areas of the central nervous system, for example, a higher degree of disease in the limbic system could lead to serotonergic deficit, which is related to a characterized clinical phenotype by fatigue[30].

Few studies evaluated the impact of dopaminergic drugs in fatigue. The ELLDOPA trial[31] showed less progression of fatigue in the patient group treated with levodopa than placebo, but it remains unclear if this was a direct effect of levodopa or possibly secondary to other differences such as activity levels. Specialists agree that fatigue does not respond to levodopa in clinical practice[32]. In the RECOVER study[33], rotigotine, a dopamine agonist with high affinity for all dopaminergic, α-adrenergic, and serotonergic receptor subtypes, improved some non-motor symptoms, such as fatigue, depression, anhedonia, and apathy in patients with PD. Conversely, fatigue can be associated with pramipexole use[34]. In a pilot study with a small sample, rasagiline reduced the levels of fatigue; however, there is a need for further studies to use it for this purpose[35,36]. No patients in our study were using this medication. The exact distinction between fatigue and disability generated by motor symptoms is important, as the use of dopaminergic medications will not lead to an improvement in the former and may lead to the appearance of side effects.

Patients in both groups had a similar mean disease duration (FSS<4, 7.25±3.64 vs. FSS≥4.7.76±4.82; p=0.43), with no correlation between this variable and the presence of fatigue (r=0.11; p=0.43).

As already mentioned, fatigue can be a premotor symptom in PD[21] and some studies have shown its prevalence in newly diagnosed patients with the disease, untreated, and its possibility of progression or appearance over the years. Ongre et al.[37] observed that these patients had more fatigue than the control subjects, both at baseline and at follow-up after 1 year, showing the precocity of the symptom within the course of the disease. In a 9-year follow-up of the same study, the authors observed an increase or decrease in fatigue levels, as well as the emergence of new cases, showing an unpredictable behavior of this symptom[38]. In the ELLDOPA study[31], with the same profile of patients, fatigue was identified in one-third of these. In week 42, fatigue still persisted in 50% of patients. Recently, Sciliano et al.[39] evaluated predictors of fatigue severity in newly diagnosed patients with PD and treatment-naïve over a year and, in addition to observing an initial prevalence of 22%, identified that fatigue can persist and increase over time, with its severity being related to baseline levels of fatigue, apathy, and EDS.

As noted, the presence of fatigue does not depend on the duration of the disease, being observed even in newly diagnosed patients, and it may or may not appear or worsen over the clinical course of the disease. In our study, in accordance with a recent meta-analysis[25], it was not observed that longer disease duration indicates a higher prevalence of fatigue.

Although the motor symptoms of PD are clearly associated with a negative impact on quality of life, the presence of non-motor symptoms enhances this impact, bearing in mind that, in general, patients with PD have more than one of these symptoms[17]. This study showed that fatigued patients have higher total scores on the PDQ-39, as well as in all domains evaluated, with the exception of the "stigma" domain. These findings are similar to those found by Herlofson et al.[40], who observed that PD patients with fatigue reported more distress in the dimensions of emotional well-being, mobility, and PDQ summary index and is also in agreement with the study by Okuma et al.[41], whose results also showed that PDQ total score and score for mobility were significantly associated with fatigue. Other studies, through PDQ-39 and other scales, and a systematic review also corroborated with the negative impact of fatigue in quality of life[25,42].

Among the limitations of this study, we point out the small sample size; however, previous studies that had larger samples did not exclude confounding factors such as this one. Despite this, the result obtained is in accordance with current literature. Other non-motor symptoms that were not evaluated can also interfere with quality of life, so although fatigue is certainly an important negative factor, it is not the only aggravating factor.

Fatigue is still a symptom neglected by health professionals. Its subjectivity, added to the absence of well-established diagnostic criteria and the lack of studies, make its diagnosis and management quite challenging. Future studies should be more homogeneous, as we now have a case definition established in the literature. The search for secondary factors is of fundamental importance, as some are potentially treatable. The distinction between fatigue and motor impairment must be made precisely so that there is no confusion between complaints and inadequate treatment. We saw that its absence in a first evaluation does not exclude the possibility of its appearance in a second moment, as well as several other non-motor symptoms, its behavior being unpredictable. Unfortunately, we still have less information about its pathophysiology and treatment, and this study seeks help in this regard.

**Authors' contributions.** DVN: conceptualization, investigation, methodology, project administration, visualization, writing – original draft, and writing – review & editing. JSP: project administration, supervision, and writing – review & editing

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Dement Neuropsychol 2022 June;16(2):244-248

Short Communication

https://doi.org/10.1590/1980-5764-DN-2021-0081

# The Autism Spectrum Quotient in a sample of Brazilian adults:
## analyses of normative data and performance

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**ABSTRACT.** Autism spectrum disorder (ASD) is characterized by difficulties in social interaction and inflexible behaviors/interests. To quantify ASD traits in adults with preserved intelligence, the Autism Spectrum Quotient (AQ) was developed, which is a self-report instrument and one of the most used and recommended tools. **Objectives:** We aimed to present a descriptive analysis of the AQ in a sample of Brazilian adults with neurotypical development (n=385) and investigate how the scale performs in a clinical subsample (n=33). **Methods:** We recruited 1,024 participants. They answered the Self-Reporting Questionnaire-20 (SRQ-20), AQ, and about their psychiatric record. Then, we selected 385 participants without any psychiatric diagnosis to describe the distribution of the ASD traits. To investigate the AQ performance, we evaluated 33 adults with ASD and 19 adults with neurotypical development from the total sample (n=1,024). **Results:** ASD traits were normally distributed in the population, with high internal consistency. Of a total of 91 men, volunteers with 32 points (clinical cutoff point) or more scored higher than 93% of the control sample. Of a total of 294 women, those who got a clinical score on the scale scored higher than 97%. In the clinical subsample (n=33), the positive predictive value (PPV) of the AQ was 0.84, and the negative predictive value (NPV) was 0.7. **Conclusions:** The study population has a different profile compared to the original study regarding the AQ scale. ASD traits were normally distributed in the neurotypical sample, and the scale seems to have a satisfactory performance to predict ASD. Future studies are required to adequate the use of the scale in the Brazilian population.

**Keywords:** Autism Spectrum Disorder; Asperger Syndrome; Cross-Cultural Comparison.

**O QUOCIENTE DO ESPECTRO DO AUTISMO EM UMA AMOSTRA DE ADULTOS BRASILEIROS: ANÁLISES DE DADOS NORMATIVOS E DE DESEMPENHO**

**RESUMO.** O transtorno do espectro do autismo (TEA) é caracterizado por dificuldades na interação social e comportamentos/interesses inflexíveis. Com o intuito de quantificar os traços de TEA em adultos com inteligência preservada, foi desenvolvido o quociente do espectro do autismo (QA), um instrumento de autorrelato muito utilizado e recomendado. **Objetivos:** Nosso objetivo foi apresentar uma análise descritiva do QA em uma amostra de adultos brasileiros com desenvolvimento neurotípico (n=385) e investigar o desempenho da escala em uma subamostra clínica (n=33). **Métodos:** Foram recrutados 1.024 participantes, que responderam ao Self-Reporting Questionnaire-20 (SRQ-20), ao QA e a questões sobre o seu histórico psiquiátrico. Em seguida, selecionamos 385 participantes sem qualquer diagnóstico psiquiátrico para descrever a distribuição dos traços de TEA. Para investigar o desempenho do QA, avaliamos 33 adultos com TEA e 19 adultos com desenvolvimento neurotípico da amostra total (n=1024). **Resultados:** As características do TEA apresentaram distribuição normal na amostra, com alta consistência interna. Do total de 91 homens, os voluntários com 32 pontos (ponto de corte clínico) ou mais pontuaram acima de 93% da amostra de controle. De 294 mulheres, aquelas que obtiveram pontuação clínica na escala pontuaram acima de 97%. Na subamostra clínica (n=33), o valor preditivo positivo do QA foi de 0,84 e o valor preditivo negativo foi de 0,7. **Conclusões:** A população estudada apresenta um perfil diferente comparada à população do estudo original, no que se refere à escala QA. Os traços de TEA foram normalmente distribuídos na amostra neurotípica, e a escala parece ter um desempenho satisfatório para predizer autismo. Estudos futuros são necessários para adequar o uso da escala na população brasileira.

**Palavras-chave:** Transtorno do Espectro Autista; Síndrome de Asperger; Comparação Transcultural.

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** This study was financed by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG).

Received on August 10, 2021; Received in its final form on November 26, 2021; Accepted on December 11, 2021.

## INTRODUCTION

People with autism spectrum disorder (ASD) present difficulties in social interaction associated with inflexible and repetitive thoughts and behaviors[1]. Those characteristics can be perceived in early development[2,3]. The prevalence of ASD is about 1% worldwide[1], and evidence suggests that autistic traits are normally distributed in the general population[4].

The severity of ASD is very heterogeneous, and according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V)[1], it should be seen as a spectrum[5]. Autistic traits impact individual's functionality in different domains, including relationships, professional life, and academic outputs[6]. Individuals with autism receive a diagnosis of anxiety disorder twice as much as the general population[7]. Moreover, they also report more mood symptoms and suicidal thoughts[8].

A team of multidisciplinary professionals should diagnose autism. Those professionals should be trained and be aware to identify ASD characteristics, especially when the patient is an adult with a milder clinical condition and preserved intelligence. In addition, individuals with autism could develop social compensatory strategies, which probably influence the diagnosis and clinical outcome[9,10]. The lack or delay in diagnosing this population will directly impact the access to interventions and better treatments, contributing to worse outcomes across life[11]. Studies pointed out the importance of early diagnosis in ASD for better improvement of language, cognitive, and social abilities, and adaptive skills[12].

The use of instruments, such as questionnaires, could be a welcome or, sometimes, a necessary strategy to support the diagnostic process[13]. The assessment of ASD traits in childhood is well documented in the literature[14,15]. However, this scenario is different when we consider ASD in adulthood.

To quantify ASD traits in individuals aged older than 18 years with intelligence quotient in the average range or above, Baron-Cohen et al.[16] developed the Autism Spectrum Quotient (AQ), a self-reported questionnaire with 50 items. The use of AQ is an efficient tool to screen key symptoms and signs, detecting who should be referred for further assessment[13].

Due to the clinical importance of this instrument, we aimed to present a descriptive analysis of the AQ in a sample of Brazilian adults with neurotypical development, followed by the performance analysis of the AQ scale in a sample of adults with autism previously diagnosed or with suspected autism.

## METHODS

This study was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (UFMG), and all volunteers agreed and consented to participate in the research. Data collection was performed from 2017 to 2018.

The research was organized in different stages. In the first stage, we adopted an online platform for data collection. Subjects were invited by direct mailing and social media. We received 1,024 responses. All volunteers answered the Self-Reporting Questionnaire-20 (SRQ-20)[17], a screening scale that evaluates depressive, anxiety, and somatic symptoms, and about medication use and mental and neurological conditions. In addition, volunteers responded to the AQ[16], which has 50 items divided into 5 different domains: social skills, imagination, communication, attention switching, and attention to detail. The total score is obtained from the sum of the items, and the higher scores indicate a higher presence of autistic traits. The scale was adapted to many languages, including Brazilian Portuguese[18], and is a helpful instrument in a research context because it presents a good accuracy to discriminate autism features among individuals in the general population[19].

The exclusion criteria applied in this initial sample were as follows: age below 18 years, self-reported history of mental disorders or neurological diseases, use of psychotropic medication, and scores above the cutoff score for mental disorders (>7) in the SRQ-20[17]. After applying those criteria, we selected 385 individuals (294 women) with a mean age of 34.3 years (standard deviation [SD]=11.3, range=18–68).

In the second approach, from the first group (n=1,024), we selected individuals with a clinical score on the AQ (<32, international cutoff score) who reported a previous diagnosis of ASD to a diagnostic interview following the DSM-V[1] criteria. Those individuals were living in the city where the project was conducted. This clinical subsample was composed of 33 volunteers (23 women), with a mean age of 33.3 years (SD=8.2). The mean of AQ score was 35.4 points (SD=5.5). The presence of moderate or severe traits of autism was included as exclusion criteria.

The control subsample had 19 volunteers (16 women) with neurotypical development, with a mean age of 30.9 years (SD=10.6). The mean of AQ score was 20.2 (SD=4.1). They were paired with the volunteers from the clinical subsample according to age, level of education, and sex. The exclusion criteria applied were as follows: clinical score in the AQ scale and the presence or suspect of autism diagnosis. For both groups, exclusion criteria

were age below 18 and above 60 years, medical records of neurological diseases, and intellectual disability.

We made a checklist to investigate the presence of autistic traits and the clinical and daily impairments of the disorder which should be present since childhood. The psychiatric interview was performed by a trained professional (ALCA) and discussed with a clinical neuropsychologist (JJP) and a psychiatrist (MAR-S).

This study used the original version with 50 items from the AQ scale and provided a descriptive analysis, which is the distribution of the AQ scores in our sample, according to the original and the Brazilian-adapted versions. Normative values were defined using percentile scores. To ensure test reliability, we computed Cronbach's alpha. In the second stage, the interview based on DSM-V criteria was considered as a gold standard for the volunteer's diagnostic interview. Then, we calculated the positive predictive value (PPV) and the negative predictive value (NPV) of the AQ scale.

## RESULTS

Based on the AQ responses, we computed descriptive parameters using standard scores and percentiles following the original[20] and Brazilian-adapted[18] scoring systems. AQ scores showed a normal distribution according to histogram analysis, with a mean score of 20.9 (SD=8.8).

We found high internal consistency in both genders ($\alpha$=0.85 and 0.87), which means that the items reliably measured the same construct. Of a total of 91 men in our first sample (n=385), volunteers with 32 points or more (the cutoff score proposed by Baron-Cohen et al.)[20] scored higher than 93% of the control sample. Of a total of 294 women, those who obtained 32 points or more scored higher than 97% (Table 1). In the original study[20], 32 points represented the 98th percentile (computed from the mean and SDs reported in the original paper). The distribution of AQ scores according to this method is shown in Table 1.

Regarding the interview, in the clinical subsample (n=33), 20 volunteers had suspected of ASD and also had AQ clinical score, and 13 volunteers had a previous diagnosis of ASD. The suspected group was divided into 14 adults with a clinical score on the AQ scale, 2 adults with a borderline score (32 points), and 4 adults with more than 32 points. However, through the diagnostic interview, we observed inconsistency regarding the social dimension in this last group. Although impairments in social interactions and emotional expression, we concluded that they showed symptoms better explained by social phobia and generalized anxiety. Therefore, after the interview, the suspected group had 16 adults with ASD diagnosis confirmed.

**Table 1.** Descriptive data of Autism Spectrum Quotient scores stratified by scoring method and sex.

| | Baron-Cohen et al.[16] | | Egito et al.[18] | |
|---|---|---|---|---|
| | Male (n=91) | Female (n=294) | Male (n=91) | Female (n=294) |
| Mean | 25 | 20 | 62 | 54 |
| SD | 8 | 9 | 12 | 13 |
| Min | 5 | 3 | 40 | 28 |
| Max | 43 | 45 | 86 | 94 |
| Pc.5 | 5 | 5 | 40 | 38 |
| Pc.10 | 10 | 7 | 44 | 41 |
| Pc.20 | 14 | 11 | 47 | 44 |
| Pc.30 | 16 | 13 | 50 | 46 |
| Pc.40 | 18 | 15 | 52 | 48 |
| Pc.50 | 20 | 17 | 54 | 50 |
| Pc.60 | 22 | 19 | 56 | 52 |
| Pc.70 | 24 | 21 | 58 | 54 |
| Pc.80 | 27 | 23 | 60 | 52 |
| Pc.90 | 30 | 27 | 64 | 59 |
| Pc.95 | 34 | 30 | 66 | 62 |
| Reliability* | 0.87 | 0.85 | 0.76 | 0.82 |

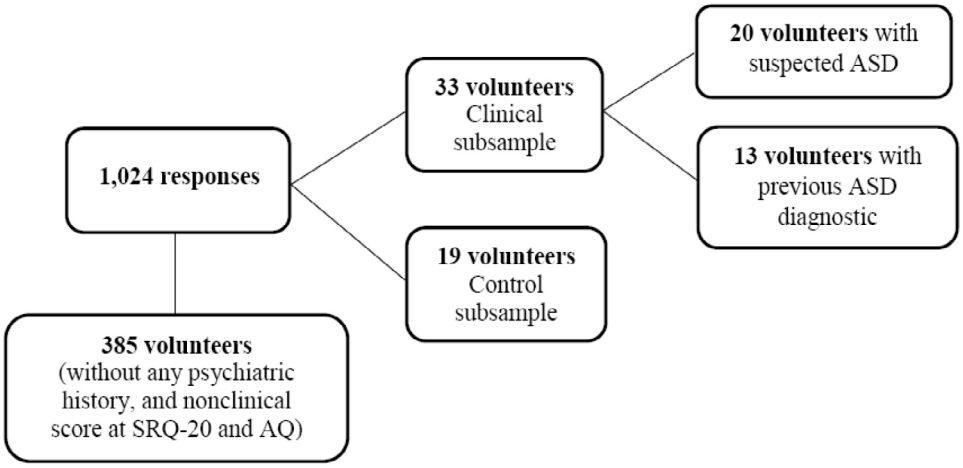
SD: standard deviation; *Cronbach's alpha. Pc.: Percentile.

Of those 13 volunteers with a previous diagnosis, 7 adults also received a clinical AQ score, but 6 received a nonclinical score despite ASD being confirmed. The control subsample was also interviewed, and we judged that none of them had an ASD diagnosis.

According to that, the PPV was 0.84, which means that there is an 84% of probability that the volunteer with an AQ clinical score truly has ASD. In addition, the NPV was 0.7, which means that there is a 70% of probability that a nonclinical score is compatible with the absence of a diagnosis. The study design is detailed in Figure 1.

## DISCUSSION

In DSM-V, ASD was recognized as a dimensional clinical condition, which varies according to symptoms,




ASD: Autism Spectrum Disorder; SRQ-20: Self-Reporting Questionnaire-20; AQ: Autism Spectrum Quotient.
**Figure 1.** Diagram of the study design.

severity, and the need for support[13]. As a screening instrument, the AQ identifies autistic adults with lower impairment and preserved intelligence[21]. The knowledge about ASD traits enables the clinicians to manage the assessment of symptoms to minimize the impairments, offer adequate support, and provide better guidance to the family[22].

As observed in other populations[23,24], AQ scores were normally distributed in our neurotypical sample. The scale also showed a good reliability using the original[16] and adapted[18] scoring systems. This study conducted by Egito et al.[18] examined the factorial structure of the Brazilian version of the scale. The authors proposed a three-factor model instead of five and a reduced version (25 items) with a different way to correct it. In addition, a different cutoff score of suggestive ASD diagnosis was not considered.

In our clinical and control subsample, positive and negative predictive values were calculated to investigate the performance of the AQ identifying cases of ASD. The results suggest that the scale had a satisfactory performance, which is consistent with other studies[25,26]. However, questionnaires are still a support for professionals and do not replace the clinical interview[27]. Although the AQ seems to be helpful to discriminate autism features among individuals in the general population[19], its use to differentiate ASD from other psychiatric conditions needs caution. Studies pointed that the scale does not present the same discriminating power due to ASD having overlap symptoms with other diagnoses, such as ADHD and schizophrenia, which also share similar impairments[28,29].

Another point that should be mentioned and require attention is the use of self-report questionnaires in clinical contexts with individuals who present difficulties in reporting their own symptoms, which is common with autistic individuals[30], because of their lower levels of insight and self-consciousness compared to individuals with neurotypical development[31]. Thus, according to these factors, the scale should be used as a screening tool, with a descriptive aim, to complement the diagnostic interview[32].

Our results also suggest that the study population has a different profile than the original study because our sample's clinical scores occurred at a lower percentile. Despite this, autistic traits were normally distributed in the neurotypical population, and the scale seems to have a satisfactory performance predicting ASD in our clinical sample. In conclusion, those results provide findings of ASD features and the use of a self-report instrument in a sample of neurotypical and autistic Brazilian adults. We considered that this is relevant due to the presence of few studies in Brazil with autistic adults.

Some limitations should be mentioned. We had a sampling bias because we counted with a small sample of volunteers during the in-person interview, and we reached more women than expected. We suspect this is a consequence of online data collection. Therefore, future studies are required with a larger sample and with a similar distribution of gender to produce more reliable analyses about predictive values and also to adequate the use of AQ in the Brazilian population, such as defining a cutoff score that

could better consider its culture and peculiarities. Furthermore, more studies are essential to increase the knowledge in this area.

**Authors' contributions.** ALCA: conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing – original draft and writing – review & editing. JJP: conceptualization, data curation, formal analysis, investigation, methodology, supervision and writing – review & editing. DMM: funding acquisition, resources, validation and writing – review & editing. MARS: funding acquisition, resources, supervision, validation and writing – review & editing.

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Dement Neuropsychol 2022 June;16(2):249-252

Case Report

https://doi.org/10.1590/1980-5764-DN-2021-0105

# Lithium Intoxication as a cause of reversible dementia mimicking FDG PET features of Alzheimer's disease

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**ABSTRACT.** Rapidly progressive dementia (RPD) is a rare neurological disorder. Drug toxicity is among the differential diagnoses, including the use of lithium, in which an overdosage might cause cognitive dysfunction. Clinical suspicion, laboratory confirmation, and drug interruption are key points in the management of lithium intoxication. We described a 66-year-old female patient under treatment with lithium who developed an RPD associated with parkinsonian symptoms. $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) showed an "Alzheimer-like" pattern, while cerebrospinal fluid biomarkers for the disease were negative. There was a significant clinical and radiological improvement after lithium interruption. Lithium intoxication is a potentially reversible cause of RPD, as demonstrated in this case report. Drug discontinuation should be considered even in patients with normal levels of this metal, if cognitive impairment is detected. $^{18}$F-FDG PET/CT images may show an "Alzheimer-like" image pattern in acute intoxication and are useful for monitoring these patients.

**Keywords:** Lithium; Positron Emission Tomography Computed Tomography; Bipolar Disorder.

**INTOXICAÇÃO POR LÍTIO COMO CAUSA DE DEMÊNCIA RAPIDAMENTE PROGRESSIVA: UM RELATO DE CASO E REVISÃO DA LITERATURA**

**RESUMO.** Demência rapidamente progressiva é uma condição rara, cujos diagnósticos diferenciais incluem intoxicação por drogas como lítio, podendo causar importante disfunção cognitiva. A suspeita clínica, a confirmação laboratorial e a interrupção do uso medicamentoso são elementos fundamentais em seu diagnóstico e manejo. Trata-se de paciente feminina, de 66 anos de idade, que apresentou quadro demencial após intoxicação por lítio. Tal quadro foi acompanhado de sintomas parkinsonianos, além de Tomografia por Emissão de Pósitrons com 18F-Fluodeoxiglicose ($^{18}$F-FDG PET/CT) compatível com padrão "*Alzheimer-like*". Houve melhora objetiva de parâmetros clínicos e imaginológicos após a interrupção do uso medicamentoso. A intoxicação por lítio é uma causa potencialmente reversível de demência rapidamente progressiva. A descontinuação da droga deve ser considerada também em pacientes com níveis normais do metal no sangue se alterações cognitivas forem encontradas. Imagens $^{18}$F-FDG PET/CT podem demonstrar achados sugestivos de doença de Alzheimer na intoxicação aguda e parecem ser um método útil no seguimento.

**Palavras-chave:** Lítio; Tomografia por Emissão de Pósitrons combinada à Tomografia Computadorizada; Transtorno Bipolar.

## INTRODUCTION

Rapidly progressive dementia (RPD) is a neurological condition characterized by a decline in more than one cognitive domain with functional impairment in less than 1–2 years. Specific diagnosis is crucial, since 20–30% of the cases can be related to potentially reversible disorders[1-3]. There are several possible etiologies for RPD, including iatrogenic causes, such as medication toxicity.

Lithium is a widely used drug for preventing manic and depressive recurrences in bipolar disorder (BD). Although lithium is effective in the treatment of this disease, it has a narrow therapeutic ratio, and overdoses are potentially neurotoxic. Despite its potential effect on the

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**Disclosure:** The authors report no conflicts of interest.

**Funding:** São Paulo Research Foundation (FAPESP) grant 2018/15571-7.

Received on October 31, 2021. Accepted on November 19, 2021.

prevention of cognitive dysfunction and dementia, high serum lithium levels are associated with the development of RPD[3-5], and it should be considered among the iatrogenic causes of this condition.

Serum lithium dosage and clinical improvement after treatment interruption are necessary for the diagnosis, and the interruption of the medication can lead to the recovery of dementia symptoms.

We reported a case of lithium intoxication leading to RPD with $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) features of Alzheimer's disease (AD), which was discarded due to normal cerebrospinal fluid biomarkers. There was a significant improvement in clinical and imaging aspects after lithium's discontinuation.

## CASE REPORT

A 66-year-old female patient developed an RPD syndrome associated with asymmetric parkinsonian symptoms 6 months before hospitalization. She progressively developed asymmetric resting tremors (initially on the superior right limb), psychomotor slowing, inattention, language problems, echolalia, shuffling gait, and postural instability with frequent falls. After a few weeks, the patient presented with executive and visuospatial dysfunctions, as well as anterograde amnesia and disorientation. An acute episode of diarrhea and dehydration worsened these clinical manifestations. Personal background included hypertension, hypothyroidism, smoking, and chronic pulmonary obstructive disease. The patient was also under psychiatric follow-up at another service due to bipolar affective disorder. Lithium carbonate, prescribed as 600 mg/day, was among the drugs taken for at least 1 year, although we are not sure whether the patient had taken the prescribed dose. Other medications included quetiapine, hydrochlorothiazide, irbesartan, venlafaxine, esomeprazole, amlodipine, clonazepam, tiotropium, and formoterol.

Cognitive and functional examination revealed the following results: Mini-Mental Status Examination=7, Montreal Cognitive Assessment (MoCA)=5, and Pfeffer's Functional Activities Questionnaire=28. Mixed transcortical aphasia, apraxia, and mild inattention were also present, while resting tremor, postural instability, hypertonia, and bradykinesia were associated with parkinsonian clinical features.

After the initial ambulatory consultation, the patient was hospitalized aiming for a diagnostic workup. Several screening tests were then performed: simple blood tests and metabolic panel were normal; brain magnetic resonance imaging (MRI) revealed white matter microangiopathy (Fazekas scale=2); $^{18}$F-FDG PET/CT demonstrated severe bilateral hypometabolism of the parietal lobes, including the precuneus, and moderate hypometabolism of the frontal lobes, the common findings in AD (Figure 1A). Of note, there was no hypometabolism of the posterior cingulate gyrus and temporal lobes, both of which were usually involved in AD. Cerebrospinal fluid tested negative, including normal AD biomarkers — amyloid beta=661 ng/L (normal: 562–1018), phosphorylated Tau=30.84 ng/L (normal: 35.84–66.26), and slightly elevated total Tau protein=398 ng/L (normal: 116–370). High lithium serum levels were detected (2.6 mmol/L; normal: 0.5–1.20 mmol/L). These findings that were associated with cognitive and parkinsonian clinical features suggested lithium intoxication.

Six days after lithium withdrawal, serum levels decreased to 1.48 mmol/L and clinical improvement was observed. $^{18}$F-FDG PET/CT was repeated, and the images showed marked improvement of glucose metabolism in the left parietal lobe, including the precuneus. However, hypometabolism persisted in right parietal lobe and frontal lobe (Figure 1B). Four days later (a total of 10 days without lithium), the patient showed a significant improvement in attention, memory, and executive functions. There was also an improvement in the MoCA score from 5 to 14 points, as well as almost complete remission of the symptoms of parkinsonism. The patient was discharged from the hospital and was scheduled for outpatient follow-up.

Thirty days after lithium withdrawal, the patient returned to consultation presenting with complete resolution of parkinsonian symptoms. MoCA score was 23/30. Executive and visuospatial function and memory had substantially improved. New PET/CT performed for 2 months after lithium discontinuation showed a complete resolution of the parietal lobes, including the precuneus, with only mild hypometabolism of the frontal lobes persisting (Figure 1C).

## DISCUSSION AND LITERATURE REVIEW

Several studies have evaluated the cumulative lithium effects in the central nervous system. Although BD patients are at increased risk of developing dementia, intake of chronic lithium seems to present a protective effect[4,6].

However, treatment with lithium may be harmful in some circumstances. The particular pharmacokinetics of the drug can make its therapeutic and toxic levels very close to each other. Intoxication is a relatively common event, especially in patients with dehydration and renal failure. Patients using other medications are at higher risk of intoxication due to drug interaction. Both acute and chronic forms may occur, depending on the dose

of lithium and the patient's risk factors[1,7]. In this case report, an important cognitive dysfunction occurred after at least 12 months of lithium intake, with worsening of cognitive symptoms after an episode of diarrhea and dehydration. Although the patient evolved with complete resolution of parkinsonian symptoms and with improvement in executive/visuospatial functions and memory, the mild cognitive deficit persisted. In fact, glucose metabolism of the frontal lobes remained reduced, despite a complete normalization of the parietal metabolism, as shown by PET/CT images.

Acute lithium intoxication may present with gastrointestinal (e.g., nausea, vomiting, and diarrhea), cardiovascular (e.g., bradycardias and QT interval prolongation), and neurological manifestation (e.g., ataxia, tremors, myoclonus, fasciculations, confusion, and even encephalopathy). Nevertheless, patients who were chronically intoxicated might present the Syndrome of Irreversible Lithium Effectuated Neurotoxicity (SILENT) syndrome. It is associated with high lithium doses and a lack of improvement after drug discontinuation. Symptoms include parkinsonism, dementia,

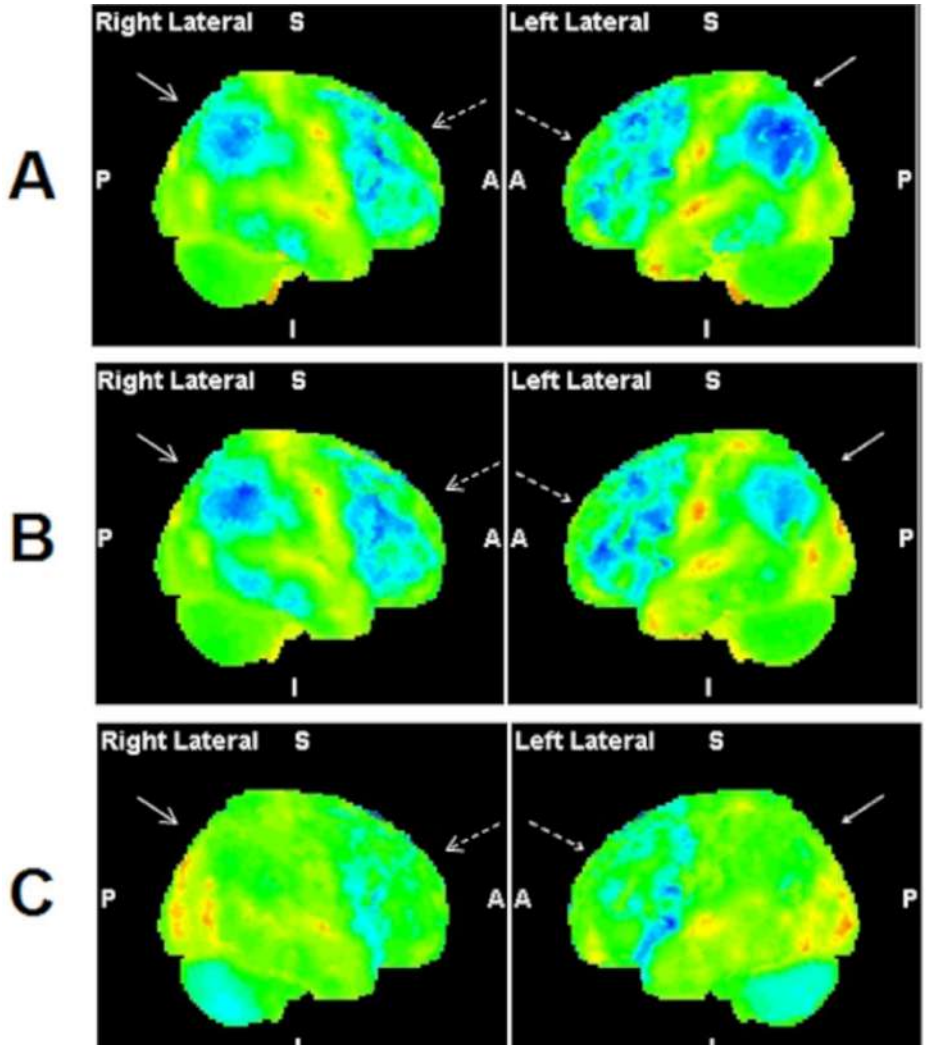


**Figure 1.** Quantitative analysis of the $^{18}$F-FDG PET/CT images (Scenium® software, Siemens CTI Molecular Imaging, Knoxville, TN, USA). The software conducts a voxel-by-voxel statistical comparison of patient's PET/CT with a control group. The quantitative analysis delineates areas of significant hypometabolism (>2 SDs from the mean) and depicts them in color tridimensional images. Regions with normal and reduced glucose metabolism are displayed in green and blue, respectively. (A) Right and left lateral projections of quantitative images obtained during acute lithium intoxication show marked bilateral hypometabolism of the parietal lobes (arrows) and moderate hypometabolism of frontal lobes (dashed arrows). (B) Images obtained on the sixth day after lithium withdrawal show a significant improvement of glucose metabolism in the left parietal lobe (arrow), with hypometabolism persisting in the right parietal and frontal lobes (dashed arrows). (C) Two months after lithium discontinuation, complete resolution of glucose metabolism is evident in the parietal lobes (arrows), with only mild hypometabolism of the frontal lobes persisting (dashed arrows).

cerebellar, and brainstem dysfunction[1,7]; they may persist over months or years after lithium interruption. This case report, as well as others in the literature, presented an association between RPD and extrapyramidal symptoms. Within 30 days of lithium withdrawal, the patient had substantial clinical improvement, with significant recovery of cognitive functions, differently than the expected in SILENT syndrome[8,9].

The diagnosis of lithium intoxication is based on clinical features and serum lithium levels. A high dosage strongly suggests intoxication. In contrast, some patients may evolve with RPD syndrome and normal serum lithium levels with clinical improvement after discontinuation of medication. In this clinical case, treatment with lithium dosage was performed on the peak of cognitive manifestations, highly suggesting toxicity. Thus, in the case of patients who take lithium chronically, even with normal lithium levels, the interruption of the medication should be considered if the patient presents cognitive symptoms. Soni[9] described a patient who had been taking lithium for 25 years and developed cognitive manifestations despite the 18-month normal serum levels, suggesting that high lithium levels are not essential for intoxication diagnosis[8,9].

Several tests have been described for the differential diagnosis of RPD. The investigation approach includes electroencephalogram (EEG), brain MRI, $^{18}$F-FDG PET/CT, cerebrospinal fluid analysis, and AD biomarkers together with the measurement of lithium serum levels[1]. EEG has been described as an important follow-up method. There was an EEG improvement in encephalopathy after drug withdrawal, according to previous reports.

An "Alzheimer-like" pattern of glucose metabolism was found in FDG PET/CT images of the present patient at the initial presentation. This finding was previously reported[2,10]. Interestingly, although there was a marked hypometabolism of the parietal lobes, including the precuneus, and to a lesser extent, of frontal lobes, the temporal lobes and posterior cingulate gyri were spared, differently than previous reports[2,10]. AD was ruled out by screening biomarkers in cerebrospinal fluid, which tested negative. A gradual and complete recovery of parietal metabolism was demonstrated by PET/CT images after lithium suspension. These imaging findings might be related to specific mechanisms of the pathophysiology of acute lithium toxicity in the central nervous system. This also suggests FDG PET/CT as a potential tool for monitoring lithium intoxication.

In this case report, a mild hypometabolism of the frontal lobes persisted after 2 months of lithium suspension. This could be explained by a slower recovery of this region or irreversible lithium neurotoxicity[2]. Furthermore, an additional subclinical neurodegenerative disease cannot be excluded.

In conclusion, lithium intoxication is among the several causes of RPD, and both acute and chronic presentations have been described. Drug withdrawal potentially leads to symptoms regression. Lithium suspension should be considered even in patients with normal serum levels presenting with neurocognitive impairment. $^{18}$F-FDG PET/CT may identify an "Alzheimer-like" image pattern in acute lithium intoxication and appears to be useful for monitoring these patients, especially in those like this case report, who had negative cerebrospinal fluid Alzheimer's biomarkers.

**Authors' contributions.** AMM, VCA, GML, MLFB, RRT: conceptualization, data curation, formal analysis, investigation, funding acquisition, methodology, visualization. MLFB: resource, supervision, validation. TBM, CDR: investigation, data curation, methodology, software, writing – original draft. AMM, GML, MLFB: writing original draft. AMM: review & editing.

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- Abstracts: Author(s).Title, followed by (Abstr). Journal year; volume (Supplement and number if necessary):page(s) or, in case of abstracts not published in journals: Title of the publication. City where published: publisher, year:page(s).
- Works consulted on the internet: link and date of the consult.

**Tables.** Up to 5 tables are allowed in original manuscripts (up to **3** tables in short communications, history note or case reports), each presented on a separate page together with its title, notes and sequence number. Tables should contain all information required to be understood by the reader. Vertical lines should not be used for separating data within the table. Type each table double spaced on a separate page. Do not submit tables as photographs. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations used in each table. For footnotes use the following symbols, in this sequence: *, +, §, ||, ¶, **, ++, etc. The editor, on accepting a manuscript, may recommend that

additional tables containing important supporting data too extensive to publish be deposited with an archival service, such as the site of the journal (www.demneuropsy.com.br), or be made available by the authors. In this case, an appropriate statement will be added to the text. Submit all tables for consideration together with the manuscript.

**Illustrations.** Up to 4 figures, graphs or photos are allowed, with their title and notes on separate pages (up to 3 illustrations in short communications, history note or case reports). Figures must be submitted in JPEG or TIFF format, with the following resolutions: a) Artwork in black and white: 1,200 dpi/ppi; b) Half-tones: 300 dpi/ppi; c) Combination of half-tones: 600 dpi/ppi.

The table below presents a summary of the requirements defined for each type of contribution:

| Manuscript Types | Abstract | Keywords | Text | References | Tables and Figures |
|---|---|---|---|---|---|
| Original Article | Structured 250 words | 4 to 6 | 3.000 | 50 | 5 tables + 4 figures |
| Review Article | Unstructured 150 words | 4 to 6 | 5.000 | 150 | 5 tables + 4 figures |
| Short Communication | Structured 250 words | 4 to 6 | 2.000 | 30 | 3 tables + 3 figures |
| Case Report | Unstructured 150 words | 4 to 6 | 2.000 | 30 | 3 tables + 3 figures |
| Historical Notes | Unstructured 150 words | 4 to 6 | 2.000 | 30 | 3 tables + 3 figures |
| Neuroimaging through Clinical Cases | – | – | 750 | 20 | 1 table + 2 figures |
| Letter | – | – | 750 | 20 | 1 table + 2 figures |

## SEND OF THE MANUSCRIPTS

Submissions must be made online: https://mc04.manuscriptcentral.com/dn-scielo.

Manuscripts must be written in English, and present title, abstract and keywords in both English and Portuguese. For those who do not write in Portuguese, the editorial office will translate these items.

Submissions must be accompanied by a cover letter, declaration of Authorship Responsibility, Financial Disclosure and Copyright Transfer/Publishing Agreement. Studies involving humans should be accompanied by a copy of the Ethics Committee authorization from the institution involved. Clinical trial studies will be accepted for publication, pending the presentation of Clinical Trial Registers.

The authors may be asked for additional information regarding previous presentations at Scientific Meetings. This information can be supplied in the cover letter sent at the time of manuscript submission.

**Note.** Before submitting your manuscript, please go through the Author's checklist and complete the Authorship, non-financial, and financial disclosure forms in annex: Authorship Disclosure.

**There are no fees for manuscript submission or manuscript review.**

### Review Process

All submitted manuscripts are reviewed initially by Editors-in-Chief. Manuscripts with insufficient priority for publication are rejected promptly.

Initial screening will be performed by one of the Editors-in-Chief to verify the formal eligibility of the manuscript according to the editorial norms **Dementia & Neuropsychologia**. Submission of manuscripts that do not comply with the format described in this document may incur its return.

After approval of formal aspects, the manuscript is submitted to peer-review and to ad-hoc consultants, as well as international and national specialists. Each manuscript is evaluated by at least two reviewers.

Based on the reviewers' comments and the Associate Editors' recommendations, the Editors-in-Chief may: a) accept the publication of the manuscript; 2) ask authors to review and resubmit the manuscript – Minor or Major Revision; or c) reject and no longer consider the manuscript for publication.

To submit the revised version of the manuscript, authors will have **30** days for a minor review and **60** days for a major review.

The entire process is overseen by the Editor-in-Chief who determines the number of appropriate re-submissions, with a focus on the quality of the work being published at all times.

Authors will be informed by the Editor-in-Chief of the likely date of publication after their final decision.

The journal adopts the double-blind peer-review mode. In this way, peer reviewers' identities are kept confidential, and authors' identities are also not disclosed to reviewers.

# INSTRUÇÕES AOS AUTORES



## ESCOPO E POLÍTICA EDITORIAL

**Dementia & Neuropsychologia** é um periódico dedicado à publicação de pesquisas em ciências cognitivas e do comportamento, com foco em epidemiologia clínica, neurociências básicas e aplicadas e testes cognitivos desenvolvidos ou adaptados para populações com diferentes substratos culturais, educacionais e socioeconômicos.

**Dementia & Neuropsychologia** está particularmente envolvido com a publicação de pesquisas relevantes de países em desenvolvimento e também procura publicar artigos originais e disseminar revisões e relatos de caso que sejam contribuições importantes para o campo da neurociência cognitiva.

O periódico segue as recomendações do *International Committee of Medical Journal Editors - ICMJE*, intituladas de *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* (http://www.icmje.org/recommendations/), atualização de dezembro de 2019.

Para as questões éticas, o periódico segue o documento *Core Practices* elaborado pelo *Committee on Publication Ethics – COPE* (http://publicationethics.org).

Os conceitos e declarações contidos nos referidos manuscritos são de inteira responsabilidade dos autores.

### Autoria

Para ser incluído como autor, espera-se que a pessoa tenha feito uma contribuição significativa para o manuscrito submetido à **Dementia & Neuropsychologia**. Conforme recomendação do *International Committee of Medical Journal Editors (ICMJE),* a autoria se baseia nos seguintes critérios:

- Contribuição substancial para o desenho do projeto do estudo ou para a aquisição, análise e interpretação dos dados;
- Contribuição intelectual na redação do manuscrito ou sua revisão crítica;
- Aprovação da versão final a ser publicada; e
- Concordância em relação à responsabilidade por todos os aspectos do trabalho.

O texto completo das recomendações do ICMJE está disponível a partir de:
http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

### Conflito de interesse

Um conflito de interesse pode existir quando um autor (ou a instituição ou empregador do autor) tem relações financeiras e pessoais que possam inapropriadamente influenciar (ou enviesar) a decisão sobre a autoria do trabalho ou manuscrito. Todos os autores são requisitados a relatar potenciais conflitos de interesse, incluindo interesses financeiros específicos relevantes ao assunto do manuscrito, na sua carta de apresentação e no formulário de declaração financeira de interesses de Dementia & Neuropsychologia. Autores sem interesses financeiros relevantes, devem indicar a ausência de interesse no manuscrito.

São solicitadas aos autores informações detalhadas quanto ao suporte material e financeiro para a pesquisa a trabalho, incluindo fontes de fundos e provisão de equipamentos e suprimentos, não limitados ao auxílio pesquisa.

Espera-se que os autores forneçam informações detalhadas sobre qualquer interesse financeiro relevante ou conflitos financeiros até 5 anos atrás e num futuro próximo, particularmente, aqueles presentes durante a pesquisa e o período de publicação. Além disso, os autores que não tiverem

interesses financeiros devem providenciar uma declaração indicando não haver interesse financeiro relacionado ao material do manuscrito.

Estas regras de declarações de conflitos de interesse devem ser aplicadas a todos os manuscritos submetidos, incluindo cartas ao editor e relatos de caso.

### Consentimento informado

Para investigações experimentais em seres humanos ou animais, coloque na sessão de "Métodos" do manuscrito que um comitê institucional aprovou o projeto. Para aqueles investigadores que não possuam um comitê de ética em pesquisa formal (institucional ou regional) os princípios exibidos na Declaração de Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) devem ser seguidos. Uma carta de consentimento deve acompanhar todas as fotografias e/ou videos de pacientes na qual uma possível identificação possa ocorrer. Não é suficiente cobrir olhos para mascarar a identidade. Refira-se ao paciente por número (ou, em relatos anedóticos, por nomes fictícios). Nomes reais ou iniciais não devem ser usados no texto, tabelas ou ilustrações.

### Publicação prévia ou submissão duplicada

Manuscritos são recebidos entendendo-se que não estejam sob outra consideração para publicação. Esta informação deve ser inserida na carta de apresentação. Dementia & Neuropsychologia usa ferramentas para detectar semelhança de texto para verificar plágio. Quando é detectado plágio, a revista segue o documento intitulado *Core Practices* do *Committee on Publication Ethics – COPE* (http://publicationethics.org/).

### Ensaios clínicos

Em acordo com o ICMJE, **Dementia & Neuropsychologia** requer, como condição para consideração de publicação, o registro do ensaio clínico nos centros de registro. Os sites para registros de ensaio clínico aceitáveis incluem: http://clinicaltrials.gov, http://isrctn.org, http://actr.org.au, http://trialregister.nl , ensaiosclinicos.gov.br (REBEC-Registro Brasileiro de Ensaios Clínicos) http://www.umin.ac.jp/ctr. Para este propósito, o ICMJE define ensaio clínico como qualquer estudo que prospectivamente submete indivíduos a intervenções ou comparações de grupos para avaliar as relações de causa e efeito entre uma intervenção médica e a evolução do estado de saúde. O nome do ensaio registrado, sua URL e número de registro deverão constar ao final do resumo. Os ensaios devem ser registrados no início, ou antes, do recrutamento dos indivíduos. Em acordo com as recomendações da BIREME/OPAS/OMS para relato de ensaios clínicos, os autores deverão trabalhar seguindo as diretrizes recomendadas no CONSORT STATEMENT (www.consort-statement.org).

### Fundos e suporte e papel do financiador

Todo suporte financeiro e material para a pesquisa e trabalho deve ser clara e completamente identificado nos agradecimentos.

### Acesso aos dados e responsabilidade

Para ensaios clínicos financiados pela indústria farmacêutica, os autores devem relatar na sua carta de submissão que (1) eles tiveram total acesso aos dados, (2) tiveram o direito de publicar todos os dados e (3) tiveram o direito de obter análises estatísticas independentes. Manuscritos contendo avaliações estatísticas devem conter o nome e afiliação do revisor estatístico.

### Preprint

**Dementia & Neuropsychologia** aceita a submissão de manuscrito previamente depositados em repositórios de *preprint*. Para a submissão de manuscritos depositados, o autor deve indicar os dados do repositório na Carta de Apresentação.

## FORMA E PREPARAÇÃO DOS MANUSCRITOS

**Página de Título. Inclui o título do manuscrito e os nomes dos autores.** O título deve ser conciso e descritivo, com informação essencial sobre o conteúdo do manuscrito, com até 150 caracteres incluindo espaços. O nome dos autores deve incluir o primeiro nome. Ao final da página de título informe: o nome do departamento e instituição, com até 100 caracteres, cidade e país no qual o estudo foi conduzido, contribuição de cada autor ao elaborar o manuscrito e o número de ORCID de todos os autores, título acadêmico de cada autor e sua afiliação institucional, suporte financeiro, agradecimentos, nome e endereço (postal e eletrônico) para correspondência.

**Resumo.** Os resumos de artigos originais ou comunicações breves devem ser estruturados e conter os seguintes itens: embasamento, objetivo(s), métodos, resultados e conclusões. Os resumos podem conter até 250 palavras. Resumos de relatos de caso ou revisões não necessitam ser estruturados e podem conter até 150 palavras.

**Palavras-chave.** Adicione 4 a 6 palavras-chave, seguindo os DeCS – Descritores em Ciências da Saúde (http://decs.bvs.br/) ou MeSH – Medical Subject Headings (http://www.ncbi.nlm.nih.gov/mesh).

**Título, resumo e palavras-chave** devem ser fornecidos também em português. Aqueles que não escrevem na língua portuguesa, contarão com a tradução dos editores.

**Texto.** Os manuscritos originais deverão apresentar até 3000 palavras, contendo: introdução e objetivos; métodos (material e/ou casuística; método estatístico; menção à aprovação pelo Comitê de Ética, o nome desse Comitê e o consentimento informado); resultados; discussão (que deve incluir as conclusões); e agradecimentos. Os dados apresentados nas tabelas e ilustrações não devem ser repetidos no texto. Observações: O limite para comunicações breves, nota histórica e relato de caso é até 2000 palavras e para revisões até 5000 palavras; "Neuroimagem através de casos clínicos" até 750 palavras.

**Referências**. Até 50 para manuscritos originais, numeradas consecutivamente na ordem em que são citadas no texto. Para relatos de caso, nota histórica ou comunicações breves até 30, para "Neuroimagem através de casos clínicos" até 20, e nas revisões, até 150. No corpo do texto, as referências devem ser identificadas com algarismos arábicos, em expoente. A apresentação das referências dever estar de acordo com o padrão definido pelo *International Committee of Medical Journal Editors* – ICMJE (https://www.nlm.nih.gov/bsd/uniform_requirements.html) e os títulos dos periódicos deverão ser abreviados conforme *Index Medicus: abbreviations of journal titles* (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng).

- Artigos: autor(es), marque os seis primeiros e segue com et al.) . Título. Jornal ano; volume: páginas inicial-final e DOI .
- Livros: autor(es) ou editor (es). Título. Edição, se não for a primeira. Cidade de publicação: editora; ano: número de páginas.
- Capítulo de livro: autor (es). Título. In: Editores do livro seguido por (Eds),Título, edição, se não for a primeira. Cidade de publicação: editora, ano: páginas inicial e final.
- Resumos: autor(es). Título, seguido por (abstr). Jornal ano; volume (suplemento e seu número, se necessário): página(s) ou, no caso de resumos não publicados em jornais: Título da publicação. Cidade de publicação: editora, ano: página(s).
- Trabalhos consultados na internet: colocar o link e a data da consulta.

**Tabelas**. Até cinco tabelas em manuscritos originais (até três em comunicações breves ou relatos de caso), cada uma apresentada em página separada, com seu título, legenda e sequência numérica. As tabelas devem conter toda a informação requerida para compreensão do leitor. Não devem ser utilizadas linhas verticais para separar os dados dentro da tabela. Não submeta tabelas como fotografias. Numere a tabela consecutivamente em ordem de sua primeira citação no texto e forneça um breve título para

cada uma. Dê a cada coluna um cabeçalho curto ou abreviado. Coloque notas informativas no rodapé, não no cabeçalho. Explicite no rodapé todas as abreviações usadas em cada tabela. Para o rodapé use os seguintes símbolos, nesta sequência: *, +, §, ||, ¶, **, ++, etc. O Editor ao aceitar um manuscrito, pode recomendar que tabelas adicionais contendo dados importantes de suporte, muito extensos para publicação, possam ser deixadas num arquivo, tal como no sítio da revista (www.demneuropsy.com.br), ou que possa ser disponibilizado pelos autores. Neste caso, uma declaração apropriada será adicionada ao texto. Submeta todas as tabelas junto com o manuscrito.

**Ilustrações**. Até quatro figuras, gráficos ou fotos, com seu título e legenda em páginas separadas (até três ilustrações em comunicações curtas ou relatos de caso). As figuras deverão ser submetidas em formato JPEG ou TIFF, com as seguintes resoluções: a) arte em preto e branco: 1.200 dpi/ppi; b) combinação de meios-tons: 600 dpi/ppi; e c) meios tons: 300 dpi/ppi.

O quadro a seguir apresenta o resumo dos requisitos definidos para cada tipo de contribuição:

| Tipo de Manuscrito | Resumo | Palavras-Chave (Decs Ou Mesh) | Palavras no Texto | Referências | Tabelas e Figuras |
|---|---|---|---|---|---|
| Artigo Original | Estruturado, com até 250 palavras | 4 a 6 | 3.000 | 50 | 5 tabelas + 4 figuras |
| Artigo de Revisão | Não necessariamente estruturado, com até 150 palavras | 4 a 6 | 5.000 | 150 | 5 tabelas + 4 figuras |
| Comunicações Breves | Estruturado, com até 250 palavras | 4 a 6 | 2.000 | 30 | 3 tabelas + 3 figuras |
| Relato de Caso | Não necessariamente estruturado, com até 150 palavras | 4 a 6 | 2.000 | 30 | 3 tabelas + 3 figuras |
| Nota Histórica | Não necessariamente estruturado, com até 150 palavras | 4 a 6 | 2.000 | 30 | 3 tabelas + 3 figuras |
| Neuroimagem através de Casos Clínicos | – | – | 750 | 20 | 1 tabela + 2 figuras |
| Carta ao Editor | – | – | 750 | 20 | 1 tabela + 2 figuras |

## SUBMISSÃO DE MANUSCRITOS

As submissões de manuscritos deve ser realizada de forma online, a partir de: https://mc04.manuscriptcentral.com/dn-scielo.

Os manuscritos deverão ser submetidos no idioma inglês, incluindo título, resumo e palavras-chave em português.

Devem ser anexados: a carta de apresentação, declarações de responsabilidade de autoria, declaração financeira e transferência de direitos autorais. Cada uma destas três declarações deve ser lida e assinada por todos os autores. (Veja o formulário de autoria e um exemplo de carta de apresentação). Estudos que utilizem seres vivos devem submeter uma cópia da autorização pelo Comitê de ética da instituição envolvida. Ensaios clínicos serão aceitos para publicação, mediante apresentação do registro de ensaio clínico.

Os autores podem ser solicitados a fornecer informações adicionais sobre a apresentação prévia em encontros científicos. Esta informação pode ser dada na carta de apresentação, enviada na ocasião da submissão do manuscrito.

**Atenção.** Antes de submeter seu manuscrito, por favor, complete o *checklist* e as declarações de autoria, conflitos financeiros e não financeiros, disponíveis em: Formulário de Revelação de Autoria.

**Não há taxas para submissão ou para a publicação de manuscritos.**

### Revisão dos manuscritos

Os manuscritos submetidos são inicialmente avaliados pelos editores-chefes. Manuscritos com insuficiente prioridade para publicação serão prontamente rejeitados.

Na avaliação inicial, um dos editores-chefes também verificará a adequação formal dos manuscritos às normas editoriais adotadas pela **Dementia & Neuropsychologia**. A submissão de manuscritos em desacordo com o formato descrito neste documento, poderá incorrer em sua devolução.

Após aprovação dos aspectos formais, o manuscrito é submetido para revisão por pares e consultores *ad-hoc*, especialistas nacionais e internacionais. Cada manuscrito será avaliado por pelo menos dois revisores.

A partir dos comentários dos revisores e das recomendações dos Editores Associados, os Editores-chefes poderão: a) aceitar a publicação do manuscrito; 2) solicitar aos autores que revisem e submetam o manuscrito revisado– Menor ou Maior Revisão; ou c) rejeitar e não considerar mais o manuscrito para publicação.

Para a submissão da versão revisada do manuscrito, os autores terão 30 dias para uma revisão menor e 60 dias para uma revisão maior.

O processo inteiro é supervisionado pelos Editores- Chefes que determinam o número apropriado de submissões dos artigos corrigidos, quantas forem necessárias, sempre focando na qualidade do trabalho a ser publicado.

Os autores serão informados pelos Editores-Chefes da provável data de publicação após sua decisão final.

O periódico adota a modalidade de revisão por pares do tipo *duplo cego*. Desta forma, as identidades dos revisores serão mantidas confidenciais, a identidade dos autores não será informada aos revisores.