Archives of Gerontology and Geriatrics 73 (2017) 1–7

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Functional magnetic resonance imaging response as an early biomarker of cognitive decline in elderly patients with metabolic syndrome

Nadia Shigaeff[a,*], Edson Amaro[b], Fabio G.M. Franco[c], Alessandro F. Jacinto[d], Gabriela Chiochetta[e], Maysa S. Cendoroglo[f], Vanessa A. Citero[e]

[a] Psychiatry Department, Escola Paulista de Medicina, Universidade Federal de São Paulo and Hospital Israelita Albert Einstein, Rua Borges Lagoa, 570, CEP:04038-030, São Paulo, SP, Brazil
[b] Hospital Israelita Albert Einstein, Avenida Albert Einstein, 627, Sao Paulo, Brazil
[c] Hospital Israelita Albert Einstein, Rua Madre Cabrini, 462, CEP:04020-001, São Paulo, SP, Brazil
[d] Psychiatry Department, Escola Paulista de Medicina, Universidade Federal de São, Paulo and Internal Medicine Department, Faculdade de Medicina de Botucatu, Universidade Estadual de Sao Paulo Julio de Mesquita Filho, Rua Borges Lagoa, 570, CEP:04038-030, São Paulo, SP, Brazil
[e] Psychiatry Department, Escola Paulista de Medicina, Universidade Federal de São Paulo, Rua Borges Lagoa, 570, CEP:04038-030, São Paulo, SP, Brazil
[f] Geriatric Division – Internal Medicine Department, Escola Paulista de Medicina, Universidade Federal de São Paulo, Rua Francisco de Castro, 105, CEP:04020-050, São Paulo, SP, Brazil

ARTICLE INFO

Keywords:
Metabolic syndrome
Elderly
Biomarker
Neuropsychological assessment
Cognitive impairment
Functional magnetic resonance

ABSTRACT

Objectives: We assessed whether potential changes in brain activation patterns of elderly individuals with metabolic syndrome (MetS) who were cognitively healthy (without mild cognitive impairment or dementia) were associated with cognitive decline in executive function in the short-term.
Method: We analyzed 43 individuals (23 MetS, 20 controls) using a global geriatric evaluation, a neuropsychological battery, and task-related (attention) fMRI exam. Correlation analysis between the fMRI signal at baseline and cognitive impairment after 1 year was based on the voxel-based Pearson coefficient, corrected for multiple comparisons.
Results: At baseline, MetS patients showed reduced brain response in frontal and parietal regions compared to controls. After one year, the MetS group also showed a decline in verbal fluency performance. fMRI response in the right dorsolateral prefrontal cortex and bilateral parietal lobes was negatively correlated with verbal fluency decline in the MetS group.
Discussion: Our results provide an early biomarker of the possible development of cognitive impairment, particularly in the executive function, of elderly individuals suffering from MetS. These findings also point to an up or down regulation which could be interpreted as compensatory mechanism for possible brain tissue burden caused by MetS.

1. Introduction

Metabolic Syndrome (MetS) involves a series of clinical and laboratory abnormalities that increase the risk of cardiovascular disease. MetS has been best described as a set of symptoms that, altogether, are associated with greater cardiovascular risk compared to the risk of each factor in isolation (Rigo, Vieira, Dalacorte, & Reichert, 2009).

Although much research has evaluated the association of MetS with cardiovascular risk, particularly cerebrovascular accidents (CVA) (De Silva et al., 2009; Haley, Gonzales, Tarumi, & Tanaka, 2012; Park & Kwon, 2008; Zhang et al., 2010), there is growing interest in the potential impact of MetS on cognitive impairment. In fact, elderly individuals diagnosed with MetS have shown poorer scores on cognitive tests compared to matched adults without MetS (Collinson, Tong, Loh, Chionh, & Merchant, 2014; Rouch et al., 2014), especially MetS patients with higher inflammatory activity (Cavalieri et al., 2010; Dik et al., 2007; Roberts et al., 2010). Similar findings were obtained with longitudinal studies using screening tests, which have shown a gradual development from normal to mild cognitive impairment (MCI) or even direct evolution of MCI to dementia in elderly individuals with MetS followed from two to 16 years (Bruce et al., 2008; Creavin et al., 2012; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; McEvoy et al., 2012; McGuire, Ford, & Ajani, 2006; Niwa et al., 2006; Raffaitin et al., 2011)

However, the extent to which the risk of cognitive impairment in

* Corresponding author.
E-mail addresses: nadia.shigaeff@yahoo.com.br, nadia.shigaeff@einstein.br (N. Shigaeff), edsonjr@einstein.br (E. Amaro), ffranco@einstein.br (F.G.M. Franco), alessandrojacinto@uol.com.br (A.F. Jacinto), gabrielatch@yahoo.com.br (G. Chiochetta), maysa.seabra.cendoroglo@gmail.com (M.S. Cendoroglo), vcitero@uol.com.br (V.A. Citero).

http://dx.doi.org/10.1016/j.archger.2017.07.002
Received 26 July 2016; Received in revised form 18 June 2017; Accepted 3 July 2017
Available online 08 July 2017

Table 1
Cognitive Performance of elderly individuals with and without MetS.

	Moment	Group						P
		Control			MetS			
		Median	1° quartile	3° quartile	Median	1° quartile	3° quartile	
Sustained Attention (z-escore)	Baseline	−2,2	−4,9	−0,3	−3,7	−6,3	−1,4	0,099
	One year follow-up	−2,5	−5,1	−0,8	−3,0	−5,4	−1,0	0,448
Switch Attention (z-escore)	Baseline	−2,9	−5,9	−1,2	−4,2	−7,4	−2,1	0,244
	One year follow-up	−3,2	−6,7	−1,4	−4,0	−6,9	−2,4	0,385
Work Memory (z-escore)	Baseline	0,7	−0,6	1,5	0,7	0,0	2,3	0,365
	One year follow-up	0,0	−0,9	1,5	0,7	−0,9	1,3	0,821
Immediate Memory (z-escore)	Baseline	1,3	−0,4	2,2	1,3	0,4	2,2	0,976
	One year follow-up	1,3	0,4	2,2	1,3	0,4	2,2	0,794
Mental Flexibility (z-escore)	Baseline	−0,5	−0,5	0,5	−1,0	−1,0	1,0	0,172
	One year follow-up	−1,2	−1,8	−0,6	−1,8	−1,8	0,0	0,753
Long memory – immediate recall (z-escore)	Baseline	−0,1	−1,5	0,5	0,0	−1,5	0,3	0,899
	One year follow-up	0,2	−1,1	1,3	−0,3	−1,3	0,5	0,198
Long memory – delayed recall (z-escore)	Baseline	−0,1	−0,9	0,6	−0,6	−1,2	0,3	0,250
	One year follow-up	0,2	−0,9	0,6	−0,1	−1,0	1,1	0,982
Long memory – recognition (z-escore)	Baseline	−0,4	−1,2	0,2	−0,8	−2,8	0,2	0,198
	One year follow-up	−0,6	−1,4	0,3	−0,4	−2,6	0,7	0,691
Executive Function (z-escore)	Baseline	−0,7	−2,3	−0,3	−1,3	−3,6	−0,2	0,546
	One year follow-up	−0,6	−2,5	−0,1	−2,8	−4,6	−0,3	0,128
Constructive praxis (weighted)	Baseline	10,0	8,0	12,0	9,0	7,0	12,0	0,680
	One year follow-up	9,5	8,0	11,2	8,0	8,0	11,7	0,348
Naming ability (z-escore)	Baseline	0,0	−0,2	0,5	0,1	−1,2	0,4	0,213
	One year follow-up	0,4	−0,1	0,7	0,3	−0,5	0,7	0,384
Verbal fluency (z-escore)	Baseline	−0,1	−0,8	0,4	−0,4	−0,9	0,0	0,100
	One year follow-up	0,0	−0,5	0,6	−0,4	−0,9	−0,2	0,017

individuals with MetS is associated with functional changes in brain activity is not well established, and the impact of these changes on cognitive performance in the long-term is still unclear. To our knowledge, there have been only three studies that have explored this issue to date. A cross-sectional study concluded that MetS in elderly individuals without dementia or a history of stroke was associated with cognitive impairment, especially impairment of memory and executive function. Individuals with higher inflammatory activity also had higher chances of developing cognitive impairment; however, interestingly, there was no structural or functional abnormality in magnetic resonance imaging (MRI) (Cavalieri et al., 2010), even though ischemic alterations in cerebral tissue resulting from stroke are associated with cognitive impairment.

The second study, and the only one involving functional neuroimaging in MetS in a population without a history of vascular events, evaluated a sample of elderly patients with MetS and controls by BOLD (blood oxygen level dependent) effect during a working memory task. Patients with MetS showed a lower BOLD signal in the right superior frontal gyrus and in the right superior and left inferior parietal lobes during the task (Hoth et al., 2011), indicating a failure to produce the expected hemodynamic response in these regions. Lastly, we have previously shown in a cross-sectional study that MetS patients had a discrete reduction in performance in a specific attention task and reduced response in BOLD signal in the parietal and occipital lobes compared with matched controls (Shigaeff et al., 2012). However, the patients were considered cognitively healthy because they did not meet the criteria for mild cognitive impairment (MCI) or dementia. These results point to possible brain changes caused by MetS, and the possibility of progression to preventable neurovascular and cognitive damage in the long-term.

Because these studies were either restricted to a population with a history of stroke, examined only changes in memory function or employed cross-sectional design with no follow up of patients, it is not yet clear whether functional abnormalities in brain activation patterns can be used as an early marker of impairment risk across cognitive domains in elderly individuals with MetS. This is particularly important in light of the higher risk of neurodegenerative disease in patients with MetS.

In this study we aimed to evaluate whether brain activation patterns in cognitively healthy (without MCI or dementia) elderly individuals with MetS differ from those of matched healthy controls. We also evaluated whether these potential differences in activation pattern could predict cognitive decline in the short term. By showing that the MetS group exhibited reduced brain activation at baseline while having the same neuropsychological performance as controls, our results should help in the early diagnosis of neurodegenerative pathologies in this population. Indeed, we show that reduced pre-frontal fMRI signal at baseline is negatively associated with reduced verbal fluency performance after 1 year.

2. Methods

This was a cohort study with one-year follow-up of Brazilian elderly subjects from two sites: volunteers from the public health system attending the geriatrics and gerontology outpatient clinic of the *Universidade Federal de Sao Paulo*, and healthy elderly individuals from the *Serviço Social do Comércio* (Commerce Social Service Units), both in Sao Paulo. The assessments occurred between April 2010 and March 2013.

The inclusion criteria were: (1) age ≥ 65 years; (2) schooling level between one and four years; and (3) score on the Mini-Mental State Examination ≥ 22, as suggested by Brazilian validation (Brucki, Nitrini, Caramelli, Bertolucci, & Okamoto, 2003). Using this criteria, in both groups there are no subject with MCI. Exclusion criteria were: (1)