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Insulin resistance and carotid intima-media thickness mediate the association between resting-state heart rate variability and executive function: A path modelling study

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ABSTRACT

Background: Research has linked high-frequency heart rate variability (HF-HRV) to cognitive function. The present study adopts a modern path modelling approach to understand potential causal pathways that may underpin this relationship.
Methods: Here we examine the association between resting-state HF-HRV and executive function in a large sample of civil servants from Brazil (N = 8114) recruited for the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). HF-HRV was calculated from 10-min resting-state electrocardiograms. Executive function was assessed using the trail-making test (version B).
Results and conclusions: Insulin resistance (a marker of type 2 diabetes mellitus) and carotid intima-media thickness (subclinical atherosclerosis) mediated the relationship between HRV and executive function in seriatim. A limitation of the present study is its cross-sectional design; therefore, conclusions must be confirmed in longitudinal study. Nevertheless, findings support that possibility that HRV provides a 'spark' that initiates a cascade of adverse downstream effects that subsequently leads to cognitive impairment.

1. Introduction

An increasing body of research highlights important links between cardiac function and cognition, resonating with Aristotelian thinking (Gross, 1995) on the functional role of the heart. Vagal nerve stimulation in humans has been shown to influence higher-order cognitive processing including executive function (Sackeim et al., 2001; Vonck et al., 2014). Other studies have demonstrated that reduced high-frequency HRV (HF-HRV) – an index of cardiac vagal function (Cacioppo, Tassinary, & Berntson, 2007) – is associated with a 6.7-fold increase in odds for cognitive impairment in older women (Kim et al., 2006), and that experimental modulation of HRV improves prefrontal cognitive function in both young (Hansen, Thayer, Johnsen, Sollers, & Stenvik, 2004) and older (Albinet, Boucard, Bouquet, & Audiffren, 2010) participants. Furthermore, recent epidemiological studies have shown that poor cardiovascular health is associated with future cognitive

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impairment (Reis et al., 2013; Thacker et al., 2014). Therefore, efforts to improve cardiovascular health – consistent with the American Heart Association strategic goals for 2020 and beyond (Lloyd-Jones et al., 2010) – may have important implications for cognitive outcomes later in life, including delaying onset of dementia. Here we examine the association between resting-state HF-HRV – an important marker of cardiac health – and executive function in civil servants recruited in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) (Aquino et al., 2012; Schmidt et al., 2014) using a modern path modelling approach (Hayes, 2013).

Despite an increasing body of evidence linking HRV to cognitive function, the underlying pathways mediating this relationship remain unclear. Despite this, the available evidence provides a solid framework on which potential mechanisms may be explored. Vagal nerve function – commonly indexed by HF-HRV – plays an important role in regulating the inflammatory reflex (Tracey & Pavlov, 2012; Tracey, 2002a), a neural mechanism involved in metabolic homeostasis and rapid control of innate immune responses, just as it controls heart rate and other vital functions. In this regard, reduced resting-state HRV may reflect a poorly functioning anti-inflammatory reflex (Jarczok, Koenig, Mauss, Fischer, & Thayer, 2014; Kemp & Quintana, 2013; Tracey & Pavlov, 2012), leading to chronic inflammation and the development of insulin resistance (Donath & Shoelson, 2011; Hotamisligil, 2006), a syndrome that subsequently contributes to progressive atherosclerosis (DeFronzo, 2010) and cognitive impairment (Zhong et al., 2012). Decreased vagal nerve function leads to impaired hepatic vagal nerve signalling and baroreflex sensitivity that is causally associated with insulin resistance (Miller, Sims, Canavan, Hsu, & Ujhelyi, 1999; Ribeiro, Lautt, Legare, & Macedo, 2005; Tracey and Pavlov, 2012). Insulin resistance is a hallmark of type 2 diabetes mellitus and is strongly associated with a cluster of metabolic and cardiovascular risk factors including dyslipidaemia, hypertension, obesity, glucose intolerance and endothelial dysfunction (DeFronzo, 2010; Kashyap & Defronzo, 2007), and these components may actually contribute to predementia syndromes and the evolution of dementia (Panza et al., 2012).

Chronic inflammation also plays an important role in the pathophysiology of metabolic risk factors (i.e. the metabolic syndrome) (Haffner, 2006). Longitudinal studies have demonstrated that the metabolic syndrome leads to cognitive decline over a 3-year period in an elderly Latino population, and these findings were especially pronounced in individuals with high serum levels of inflammation (median high-sensitivity C-reactive protein level $\geq$3.2 mg/L) (Yaffe et al., 2007). Insulin resistance also has proatherogenic effects at the level of the arterial wall, that subsequently lead to cellular events critical for plaque progression (Reddy, Singh, Bangit, & Batsell, 2010; Tabas et al., 2010Tabas, Tall, & Accili, 2010) (see also: Karrowni et al., 2013). Inflammation also contributes to the development of atherosclerosis (Ross, 1993, 1999), further suggesting an important role for reduced vagal function in the accumulation of lipids and hardening of the arterial wall.

Carotid intima-media thickness (IMT) is a non-invasive surrogate measurement for subclinical atherosclerosis (Touboul et al., 2012), associated with cognitive impairment and cognitive test performance ten years later (Zhong et al., 2012). In that study (Zhong et al., 2012), larger IMT was associated with longer time to complete the Trail-Making Test (part B) – a commonly employed measure of executive function employed in the present study – after multiple adjustments. The authors (Zhong et al., 2012) proposed three possible mechanisms for the association between carotid atherosclerosis and cognitive function including: 1) unstable plaque peeling off, causing cerebral emboli, stroke and vascular dementia, 2) silent stroke damaging the brain and causing cognitive impairment, and 3) chronic cerebral hypo-perfusion and ischemia, increasing the vulnerability of neurons and subsequently impacting on cognitive performance. Interestingly, it has recently been shown that low resting HRV is associated with decreased resting brain perfusion as measured by pulsed arterial spin labelling (Allen, Jennings, Gianaros, Thayer, & Manuck, 2015). We suggest here that the adverse, downstream effects of reduced HRV may include insulin resistance subsequently leading to increased atherosclerosis, which will contribute to cognitive impairment. This is the model we sought to test in the present study.

We hypothesised that insulin resistance and atherosclerosis would mediate the relationship between HRV and executive function in a relatively large cohort of individuals from Brazil. We further sought to determine whether a single serial pathway of multiple mediators, or multiple indirect pathways underpinned this relationship. For instance, it is possible that reduced HRV directly contributes to atherosclerosis, beyond any contribution from insulin resistance. It is also possible that insulin resistance itself contributes directly to impairment in cognitive function (McCrimmon, Ryan, & Frier, 2012; Talbot et al., 2012). While we expected an important role of insulin resistance and atherosclerosis as mediating factors between HRV and executive function, we sought to determine, which particular pathways best explain this association. To our knowledge this is the first study to explore the relationship between cardiac function and executive function using path modelling.

2. Methods

2.1. Participants

ELSA-Brasil is a cohort of 15,105 civil servants aged 35–74 enrolled between August 2008 and December 2010 at six cities (Belo Horizonte, Porto Alegre, Río de Janeiro, Salvador, São Paulo and Vitória). Exclusion criteria for the ELSA-Brasil study included current or recent pregnancy (within 4 months of first interview), intention to quit working at the institution in the near future, severe cognitive or communication impairment, and if retired, residence outside of a study centre's metropolitan area. ELSA-Brasil is an ongoing cohort study designed to investigate the development and progression of chronic diseases including cardiovascular diseases, diabetes and dementia (Aquino et al., 2012; de Passos, Caramelli, Benseñor, Giatti, & Barreto, 2014; Schmidt et al., 2014). The ethics committees of the participating universities approved the research protocol. All participants provided written informed consent after a complete description of the study.

Data from participants completing the Trail Making Test (TMT, version B) – a measure of executive function – was available for 13,142 participants after excluding participants (n = 1963) with a history of stroke or those using medications known to interfere with cognition (neuroleptics, anticonvulsants, anticholinesterase or antiparkinsonian agents), as well as those participants who were not able to complete the test within 5-min. Analyses were conducted on cases with complete data (N = 8114). (See section on Participant Characteristics for further information).

2.2. Procedure

Participants were asked to abstain from caffeine, alcohol and physical activity 12 h prior to assessments, described below. (See also Aquino et al., 2012; Schmidt et al., 2014).

2.3. Measures

2.3.1. Heart rate variability (HRV)

Ten-minute, resting-state electrocardiogram (ECG) was recorded from participants in the supine position during spontaneous breathing without task demands. The ECG was always