RESTING HEART RATE VARIABILITY AS A POSSIBLE MARKER OF COGNITIVE DECLINE

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Review
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Abstract:

Cognition is a major subject to be addressed nowadays due to the increasing number of cognitively affected people in most societies. Because of a lack of pharmaceutical therapies treating cognitive decline, its indicators should be diagnosed before it becomes prevalent. Scientific evidence indicates a relationship between cognition and the nervous system, especially its autonomic part. Heart rate variability (HRV) as an indicator of the autonomic nervous system functioning has been studied as a biological marker for the evaluation of cognitive performance. Therefore, HRV is a possible indicator of cognitive impairment. The aim was to provide a systematic literature review about the association between resting HRV and the cognitive performance. Five cognitive functions were analysed separately: executive functions, memory and learning, language abilities, visuospatial functioning, and processing speed. Furthermore, the global cognitive function evaluated with cognitive test batteries was considered as well. An electronic database search was conducted with five databases. Three search fields comprised HRV, cognitive performance, and adult subjects. The final dataset consisted of 27 articles. Significant correlations in each cognitive function were found, except for processing speed, suggesting a positive association between resting HRV and cognitive performance. Mechanisms underlying this association between cardiovascular health and cognition are discussed. For the future, HRV could be used in diagnostics as an indicator of cognitive impairment before symptoms of dementia get apparent. With a timely diagnosis, preventative tools could be initiated at an early stage of dementia.

Key words: *autonomic nervous system, cognition, dementia diagnosis*

Introduction

Cognition is a prerequisite to participate successfully in social and everyday life. In fact, cognitive functions usually decrease in late life (Bugg, DeLosh, Davalos, & Davis, 2007; Wild-Wall, Falkenstein, & Gajewski, 2011) and a very strong decline leads to dementia in older age. One of the biggest health problems in our future is the increasing number of elderly people and concordant increasing number of people with dementia. Medical care of the population is based on early diagnosis, treatment of reversible conditions in an attempt to restore any mental function but, in many cases, it is just a palliative care. So far, neither medications nor drastic interventions can heal or prevent diseases like dementia; except for some evidence pointing out to physical activity (Blondell, Hammersley-Mather, & Veerman, 2014). Then, prevention may be a better option.

The heart rate variability (HRV) describes the beat-to-beat variation of RR-intervals. It is a common diagnostic tool to assess the cardiac autonomic system and it has been used as a biological indicator for recognizing emotions (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012). In some other clinical situations, including diabetic neuropathy and congestive heart failure, HRV is used as a non-invasive diagnostic tool as well (Stein & Kleiger, 1999; Sztajel, 2004). Beside genetic factors (Singh, Larson, O'Donnell, Tsuji, Evans, & Levy, 2001), the environment (Togo & Takahashi, 2009), lifestyle (Valentini & Parati, 2009), neuropsychological factors (Fatisson, Oswald, & Lalonde, 2016), age also exerts influences on HRV (Almeida-Santos, et al., 2016; Jandackova, Scholes, Britton, & Steptoe, 2016). Regular physical exercise has positive effects on HRV and can even attenuate the age-induced decline (Hottenrott, Lauenroth, & Schwesig, 2004; Melo, et al., 2005). In the context of professional sports training, HRV is a popular diagnostic tool to prevent overtraining (Makivić, Nikić, & Willis, 2013).

In general, a high variation in heart rate reflects a good state of health. McCraty and Shaffer (2015) stated that "too little variation indicates age-related system depletion, chronic stress, pathology, or inadequate functioning in various levels of self-regulatory control systems" but too much variation indicates "arrhythmias and nervous system chaos [which] is detrimental to efficient physiological functioning and energy utilization" (Stein, Domitrovich, Hui, Rautaharju, & Gottdiene, 2005).

The heart-beat variations are the result of a complex interaction between sympathetic and parasympathetic activity (Billman, 2011). Sympathetic activity leads to a reduction of time between heart beats and energy mobilization, whereas parasympathetic activity has the opposite effect and is associated with vegetative and restorative functions. An optimal HRV reflects a balanced state of the autonomic nervous system (Thayer, Yamamoto, & Brosschot, 2010). The *Neurovisceral Integration Model* appears to be an important framework for understanding the mechanism underlying the association between HRV and cognition (Kemp, Koenig, & Thayer, 2017). According to that model, neural structures responsible for affective, cognitive, and physiological regulation are associated with vagally mediated cardiac function, indexed by HRV (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Especially the prefrontal cortex is associated, through its connection with the amygdala, with the cardiovascular system (Thayer & Lane, 2009). Vagally mediated HRV is supposed to be linked with "a set of neural structures that have been implicated in cognitive, especially executive, function" (Thayer, et al., 2009). Therefore, a greater vagally mediated HRV reflects a good prefrontal neural function, leading to better executive functioning.

A lot of different methods to measure the HRV exist (Shaffer, McCraty, & Zerr, 2014). Due to the supposed relationship between vagally mediated HRV and cognitive performance, the parameters HF (power in high frequency range, 0.15–0.4 Hz), HF nu (HF power in normalized units:

HF / [Total Power – very low frequency] * 100)

and RMSSD (root mean square of successive differences between normal heart beats; in ms) are considered in this review (Shaffer, et al., 2014; Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012). HF is also called respiratory band because it corresponds to the respiratory cycle. Changes in heart rate elicited through respiration are known as respiratory sinus arrhythmia (Shaffer, et al., 2014). Parasympathetic influences on the heart rate are prevalent over all possible frequency ranges but sympathetic influences are prevalent only up to 0.15Hz (Thayer, et al., 2012). Therefore, the power in low frequency range (LF, 0.04-0.15 Hz) cannot clearly be ascribed to either the sympathetic or parasympathetic system and were not considered in this review (Billman, 2013).

Alzheimer's Disease (AD) is an increasing problem for the health care system. Markers that diagnose AD in preclinical stages are necessary to initiate prevention at an early stage. Beside cognitive performance tests, HRV could be such a diagnostic marker because of the previously mentioned connections between cognition and heart rate regulation. Although the knowledge of this connection has existed for over 150 years (Thayer & Lane, 2009), research about the association between HRV and cognitive performance only arose about 15 years ago. For using HRV as a marker for mental health, a relationship with the cognitive performance must be confirmed. Thus, the aim of this review is to provide an overview of the existing literature considering the relationship between resting HRV and cognitive performance.

Methods

Search strategy

A search request, consisting of three search fields, was implemented to identify all relevant studies. The search fields were connected with AND. The terms within the fields were connected with OR. This procedure guaranteed that at least one term in each field was found by the databases search engines. The first search field comprised terms relating to HRV. The second field comprised terms relating to cognition. The last field specified the subjects' age characteristic to exclude studies with infants or children. This revie wfollowed the guidelines for writing systematic reviews (Moher, Liberati, Tetzlaff, & Altman, 2009).

Search string

Search string: "heart rate variability" OR "HRV" OR "heart rate variance" OR "cycle length variability" OR "RR variability" OR "heart period variability" OR "beat-to-beat variation" OR "beat-to-beat variability" OR "cardiovascular fluctuation" OR "cardiovascular fluctuations" OR "heart rate oscillation" OR "heart rate oscillations"

AND

"cognition" OR "cognitive performance" OR "cognitive function" OR "cognitive functions" OR "memory" OR "executive function" OR "executive functioning" OR "executive functions" OR "cognitive state" OR "cognitive impairment" OR "dementia" OR "Alzheimer" OR "cognitive neurodegeneration" OR "cognitive processing" OR "cognitive process" OR "cognitive processes"

AND

"senior" OR "seniors" OR "elderly" OR "adult"

Search process

The search process was undertaken with electronic databases on August 18, 2017. Five databases were searched (Scopus, Pubmed, Web of Science, Cochrane Library, Medline). In Scopus, the search was limited to the categories title, abstract and keywords. Articles were considered as a possible document type and journal as a source type. Title and abstract were used in Pubmed. In the Cochrane Library, the search was undertaken in the categories title, abstract, and keyword, and was limited to trials. No restrictions were possible in Medline and Web of Science. All articles were downloaded in the citation manager Citavi 5 and duplicates were removed.

Inclusion and exclusion criteria

We considered all age groups except infants and children. Studies with animals were excluded as well. Articles published before 1980 were not considered for this review. Further inclusion criteria for eligible articles were the following:

- Measurement of HRV in resting state (short- or long-term) but not during tasks
- Conduction and presentation of the results of at least one cognitive task or comparison between groups with divergent cognitive states
- Correlation analysis between HRV and cognition or comparison between groups with different HRV levels
- Written in English language
- Full-text available
- Studies that did not include depressive and/or anxiety patients, or patients with psychiatric illnesses
- No drug trials
- Intervention studies if HRV was measured pre- and post-intervention and compared with cognitive performance
- Duplicates with the same study sample were used only once
- Only published original articles were considered, meaning we did not consider conference papers, reviews, letters, articles in press and notes
- No beta blockers users nor persons with congestive heart failure, myocardial infarction, or cardiac arrhythmias.

All studies, 220 of them, that did not meet these criteria were removed and excluded from further analysis because they did not fulfil the above described criteria for eligibility. The cognitive tasks were classified into the following cognitive functions, based on a report of Levy (1994):

- Executive functions
- Memory and learning
- Language ability
- Visuospatial functioning
- Processing speed
- Global cognitive function.

This classification should ensure a presentation of a broad spectrum of different cognitive abilities. The global cognitive function was used as an additional category because some studies presented only the total score of a cognitive test battery (e.g. MMSE) without differentiating between particular cognitive functions. There are only a few cognitive tasks measuring one specific cognitive function. Therefore, we assigned the cognitive tasks to the function that was suggested as the primary cognitive function by the study authors. If no specific function was mentioned, or the task was not described, we looked in the references of the article and assigned it according to these references.

Data extraction

After reading the abstracts and method sections of the 493 identified articles, 220 articles that did not meet the inclusion criteria were excluded and the full texts of the relevant articles were examined. The cognitive tasks were then classified according to their evaluated cognitive function. Figure 1 describes the search process. The five databases revealed 948 articles. After removing duplicates, 493 remained. Twenty-seven studies met the inclusion criteria and were described in the tables with the following data: first author, year of publication, characteristics of study sample (number of subjects, mean age or age range with standard deviation, if available, and state of health), measured HRV parameters, cognitive tasks, and results.

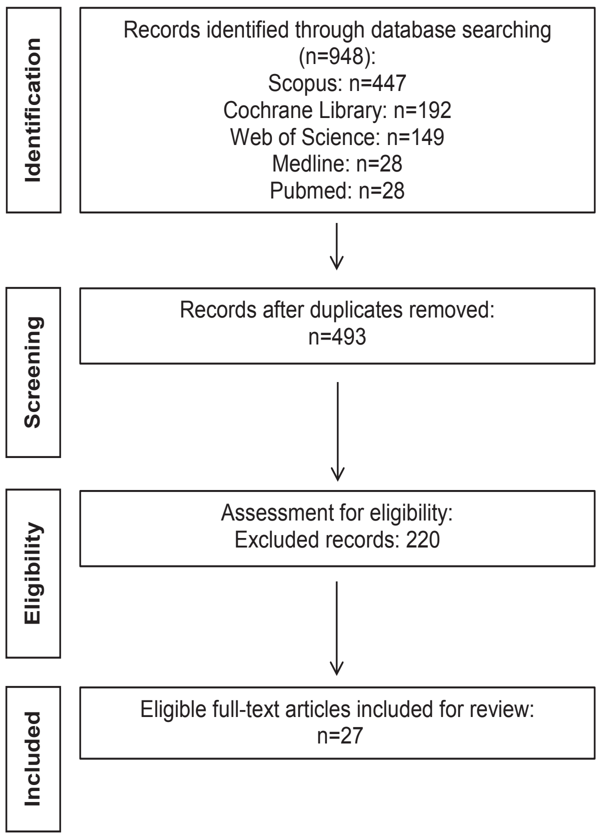

Figure 1. Flow chart of the screening process (n=number of articles)

Results

Executive functions

Table 1 summarizes all studies using executive function tasks. A typical executive task is the task Stroop. Positive correlations were found with HF (Hovland, et al., 2012; Jennings, Allen, Gianaros, Thayer, & Manuck, 2015), but two other studies found no association with HF (Mathewson, et al., 2010; Nonogaki, Umegaki, Makino, Suzuki, & Kuzuya, 2017). Stenfors, Hanson, Theorell, and Osika (2016) showed that the association with RMSSD and HF diminished after considering age and sex. Albinet, Abou-Dest, André, and Audiffren (2016) found no association with RMSSD and HF. The study samples comprised young and healthy but also elderly subjects and patients with AD. Therefore, positive relations cannot be limited to specific groups of people.

Two-back is another important executive task. Three studies showed significant associations with HF and RMSSD (Hansen, Johnsen, & Thayer, 2003; Hansen, Johnsen, Sollers III, Stenvik, & Thayer, 2004; Hansen, Johnsen, & Thayer, 2009), but Albinet et al. (2016) and Stenfors et al. (2016) did not find any correlations for the same parameters. WCST (Wisconsin Card Sorting Test) is a further popular executive task. Two studies found positive correlations: Albinet, Boucard, Bouquet, and Audiffren (2010) for RMSSD and HF, and Hovland et al. (2012) for HF. In the Trail-Making-Test B, positive associations (Kemp, et al., 2016) and no associations (Jennings, et al., 2015; Nicolini, et al., 2014; Stenfors, et al., 2016) with HF were found. Positive correlations were found for the CPT (Continuous Performance Test) with HF and RMSSD (Hansen, et al., 2003, 2004, 2009). A Psychomotor Vigilance Task showed better results in a group with higher RMSSD (Luque-Casado, Zabala, Morales, Mateo-March, & Sanabria, 2013). HF and RMSSD were positively associated with better results in a Flanker Test (Williams, Thayer, & Koenig, 2016). However, another version of the Flanker Test was not associated with HF (Alderman & Olson, 2014). No relationships were detected in some other familiar tasks testing executive functions, e.g. Raven Colored Progressive Matrices (Incalzi, et al., 2009; Nicolini, et al., 2014), d2 (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009), Hayling-Test (Albinet, et al., 2016), and Alice-Heim 4-I (Britton, Singh-Manoux, Hnatkova, Malik, Marmot, & Shipley, 2008). Finally, Yang, Tsai, Hong, Yang, Hsieh, and Liu (2008) detected positive relationships between RMSSD and results of the CASI (Cognitive Abilities Screening Instrument). Some other studies showed no correlations between HRV parameters and executive functions (Frewen, Finucane, Savva, Boyle, Coen, & Kenny, 2013; Giuliano, Gatzke-Kopp, Roos, & Skowron, 2017; Kimhy, et al., 2013).

Table 1. HRV parameters and executive functions

Author	Year	Participants (number/ age in M±SD or/and range in years)	HRV parameters	Cognitive task	Result
Albinet et al.	2010	24/70.7±4.2; sedentary	RMSSD, HF	WCST	↑
Albinet et al.	2016	36/60-75; sedentary	RMSSD, HF	Stroop	↔
			RMSSD, HF	Random Number Generation-Test	↔
				Hayling-Test	↔
				Spatial Running Span-Test	↔
				2-back-Test	↔
				Verbal Running Span-Test	↔
				Dimension-switching-Test	↔
				Plus-Minus-Test	↔
				Digit-Letter-Test	↔
Alderman & Olson	2014	56/18-25; healthy	HF	Eriksen Flanker-Test	↔
Britton et al.	2008	5375/55.5 (men), 55.8 (women)	HF	Alice-Heim 4-I	↔
Duschek et al.	2009	60/24.5±3.7; healthy	HF	d2	↔
Frewen et al.	2013	4763/61.7±8.3; healthy	HF	MOCA	↔
Giuliano et al.	2017	42 women/30.42±6.54; stressed	HF	visual change detect test	↔
Hansen et al.	2004	37 men/19.1; healthy	HF	CPT: executive functions	↑
				2-back	↑

Author	Year	Participants (number/ age in M±SD or/and range in years)	HRV parameters	Cognitive task	Result
Hansen et al.	2003	53 men/23; healthy	RMSSD	CPT: executive functions	↑
				2-back	↑
Hansen et al.	2009	65/23.1; healthy	HF	CPT: executive functions	↑
			HF	2-back	↑
Hovland et al.	2012	36/18-50; panic disorders	HF	WCST	↑
				Stroop	↑
Incalzi et al.	2009	54/69.1±7.7; COPD	HF nu	Raven Coloured Progressive Matrices	↔
Jennings et al.	2015	440/43±7.3; healthy	HF	Stroop	↑
				WMS II + III: SP-BACK, DGT-BACK	↔
				DIGVIG1+2	↔
				Trail-Making Test B	↔
Kemp et al.	2016	8114/51.17±8.81; healthy	RMSSD, HF	Trail-Making Test B	↑
Kimhy et al.	2013	817/57.11±11.15; healthy	HF	Digits backward span	↔
				Category fluency	↔
				Number series	↔
				SGST	↔
Luque-Casado et al.	2013	26 men/19.5; fit & unfit group	RMSSD	Psychomotor vigilance task	↑
			RMSSD	Temporal orienting task	↔
			RMSSD	Duration discrimination task	↔
Mathewson et al.	2010	76/30.6; healthy	HF	Pictorial Stroop	↔
Nicolini et al.	2014	80/78.6; 40 MCI, 40 CG	HF nu	digit cancellation and bell test	↔
				digit span backward	↔
				Trail-Making Test B	↔
				Weigl's colour-form sorting test	↔
				Raven's coloured progressive matrices	↔
				Letter fluency	↔
Nonogaki et al.	2017	78/77.1±6.2; AD	HF	Category fluency test	↔
				Letter fluency test	↔
				Wechsler: digit symbol subtest	↔
				Clock drawing test	↔
				Stroop	↔
Stenfors et al.	2016	119/47.98±10.49; 25-66; healthy	RMSSD, HF	2-back	↔
				Trail-Making Test B	↔
				Stroop	
			RMSSD, HF	Letter Digit Substitution Task	
Williams et al.	2016	104/19.25±1.43 healthy	HF, RMSSD	Modified flanker test	↑
Yang et al.	2008	63 men/78.3±3.9; healthy	RMSSD	CASI	↑

Note. AD – Alzheimer's disease; CASI – Cognitive Abilities Screening Instrument; COPD – hypoxemic chronic obstructive pulmonary disease; CPT – continuous performance test; DGT-BACK – digit span raw score; CG – control group; DIGVIG – digit vigilance; HF – power in high frequency range; MCI – mild cognitive impaired; MOCA – Montreal Cognitive Assessment; nu – normalized units; RMSSD – root of the mean square of the differences of successive intervals; SD – standard deviation; SGST – Stop & Go Switch Task; SP-BACK – spatial span backward raw score; WCST – Wisconsin card sorting test; WMS – Wechsler Memory Scale. ↑: significant positive correlation. ↔: no correlation detected.

Memory and learning

Memory and learning seem hardly related to HRV parameters (Table 2). There are some studies that found no connections (Britton, et al., 2008; Incalzi, et al., 2009; Jennings, et al., 2015; Nicolini, et al., 2014; Stenfors, et al., 2016). Only one study detected correlations: Nonogaki et al. (2017) showed that the Wechsler Memory Tasks were related to HF. There was a trend for HF in the verbal SRT (Selective Reminding Test) (Shah, et al., 2011).

Language ability

Language abilities were assessed in four studies (Table 3). Two of them showed no correlations (Britton, et al., 2008; Incalzi, et al., 2009). In the study by Britton et al. (2008), HF of 5375 subjects with a mean age of 55 years was measured. The study of Incalzi et al. (2009) measured patients with hypoxemic chronic obstructive pulmonary disease (COPD) and used two language tasks. Frequency-domain parameters did not correlate with task performance. But the language part of two cognitive test batteries showed correlations with HF: MOCA (Montreal Cognitive Assessment) (Frewen, et al., 2013) and CASI (Yang, et al., 2008). In both studies, healthy elderly people were tested.

Visuospatial functioning

The relationship between HRV and visuospatial functioning was investigated in three studies (Table 4). Frewen et al. (2013) found no association in 4763 healthy elderly subjects. Nicolini et al. (2014) found no correlation either. Here, healthy elderly people and subjects with MCI (mild cognitive impairment) were investigated. On the other hand, Incalzi et al. (2009) found a connection with frequency-domain

Table 2. HRV parameters and memory and learning

Author	Year	Participants (number/ age in M±SD or/and range in years)	HRV parameters	Cognitive task	Result
Britton et al.	2008	5375/55.5 (men), 55.8 (women)	HF	20-word free recall test	↔
Incalzi et al.	2009	54/69.1±7.7; COPD	HF nu	Rey auditory 15-word learning test	↔
				Immediate visual memory	↔
Jennings et al.	2015	440/43±7.3; healthy	HF	4WRD-STM	↔
Nicolini et al.	2014	80/78.6; 40 MCI, 40 CG	HF nu	Digit Span Forward	↔
Nonogaki et al.	2017	78/77.1±6.2; AD	HF	Wechsler Memory	↑
Shah et al.	2011	416 men twins/55.1±2.9	HF	SRT	↔
				Visual SRT	↔
Stenfors et al.	2016	119/47.98±10.49; 25-66; healthy	RMSSD, HF	Reading Span Task	↔

Note. 4WRD-STM – Four-Word Memory Test; CASI – Cognitive Abilities Screening Instrument; CG – control group; COPD – hypoxemic chronic obstructive pulmonary disease; HF – power in high frequency range; MCI – mild cognitive impaired; nu – normalized units; RMSSD – root of the mean square of the differences of successive intervals; SRT – Verbal Selective Reminding Test. ↑: significant positive correlation. ↔: no correlation detected.

Table 3. HRV parameters and language ability

Author	Year	Participants (number/ age in M±SD or/and range in years)	HRV parameters	Cognitive task	Result
Britton et al.	2008	5375/55.5 (men), 55.8 (women); healthy	HF	Mill Hill Vocabulary Test	↔
				Phonemic fluency	↔
				Semantic fluency	↔
Frewen et al.	2013	4763/61,7±8.3; healthy	HF	MOCA	↑
Incalzi et al.	2009	54/69.1±7.7; COPD	HF nu	Verbal fluency test	↔
				Sentence construction	↔
Yang et al.	2008	63 men/78.3±3.9; healthy	HF	CASI	↑

Note. CASI – Cognitive Abilities Screening Instrument; COPD – hypoxemic chronic obstructive pulmonary disease; HF – power in high frequency range; MOCA – Montreal Cognitive Assessment; nu – normalized units; SD – standard deviation. ↑: significant positive correlation. ↔: no correlation detected.

HRV. Regarding visuospatial functioning, there are too little studies to make any conclusions.

Processing speed

Six studies investigating the relationship between processing speed and HRV (Table 5) were identified. In none of them significant correlations between vagally mediated HRV and processing speed were detected. Specifically, there was no correlation with the non-executive part of CPT (Hansen, et al., 2003, 2004, 2009), Trail-Making Test A (Nicolini, et al., 2014; Stenfors, et al., 2016), and backward counting (Kimhy, et al., 2013).

Global cognitive functioning

Some authors did not differentiate between single cognitive functions but used general cognitive tests or presented only the total score of a cognitive test battery (Table 6). The MMSE (Mini Mental Status Examination) is one of the most widespread cognitive test batteries. One study showed positive associations between the total score of MMSE and RMSSD (Kim, et al., 2006). Associations with the frequency-domain parameters were found in the same study and a non-significant trend in the study by Mellingsæter, Wyller, Ranhoff, Bogdanovic, and Wyller (2015), but not in the study by Allan et al.

Table 4. HRV parameters and visuospatial functioning

Author	Year	Participants (number/ age in M±SD or/and range in years)	HRV parameters	Cognitive task	Result
Frewen et al.	2013	4763/61,7±8.3; healthy	HF	MOCA	↔
Incalzi et al.	2009	54/69.1±7.7; COPD	HF nu	CDL	↓
Nicolini et al.	2014	80/78.6; 40 MCI, 40 CG	HF nu	Rey-Osterrieth complex figure-delayed recall	↔

Note. CDL – copying of drawing landmarks; CG – control group; COPD – hypoxemic chronic obstructive pulmonary disease; HF – power in high frequency range; MCI – mild cognitive impaired; MMSE – Mini-Mental-Status-Examination; MOCA – Montreal Cognitive Assessment; nu – normalized units; SD – standard deviation. ↑: significant positive correlation. ↔: no correlation detected.

Table 5. HRV parameters and processing speed

Author	Year	Participants (number/ age in M±SD or/and range in years)	HRV parameters	Cognitive task	Result
Hansen et al.	2004	37 men/19.1; healthy	HF	CPT	↔
Hansen et al.	2003	53 men/23; healthy	RMSSD	CPT	↔
Hansen et al.	2009	65/23.1; healthy	HF	CPT	↔
Kimhy et al.	2013	817/57.11±11.15; healthy	HF	Backward counting	↔
Nicolini et al.	2014	80/78.6; 40 MCI, 40 CG	HF nu	Trail-Making Test A	↔
Stenfors et al.	2016	119/47.98±10.49; 25-66; healthy	RMSSD, HF	Trail-Making Test A	↔

Note. CG – control group; CPT – continuous performance test; HF – power in high frequency range; MCI – mild cognitive impaired; nu – normalized units; RMSSD – root of the mean square of the differences of successive intervals; SD – standard deviation. ↑: significant positive correlation. ↔: no correlation detected.

Table 6. HRV parameters and global cognitive function

Author	Year	Participants (number/age in M±SD or/ and range in years)	HRV parameters	Cognitive task	Result
Allan et al.	2005	114/>65; 80 healthy, 14 AD, 20 VAD	HF	MMSE	↔
Allan et al.	2007	177/>65; 39 AD, 30 VAD, 30 DLB, 40 PDD, 38 CG	HF	CAMCOG	↑
Kim et al.	2006	311 women/65-85 disabled	HF, RMSSD	MMSE	↑
Mellingsæter et al.	2015	62/14 AD or MCI (73.6), 48 CG (72); >65	HF	MMSE	↑

Note. AD – Alzheimer's disease; CAMCOG – Cambridge Examination for Mental Disorders in the Elderly; CG – control group; DLB – dementia with Lewy bodies; HF – power in high frequency range; MCI – mild cognitive impaired; MMSE – Mini-Mental-Status-Examination; PDD – Parkinson's disease dementia; RMSSD – root of the mean square of the differences of successive intervals; SD – standard deviation; VAD – vascular Alzheimer's disease. ↑: significant positive correlation. ↔: no correlation detected.

(2005). Allan et al. (2007) detected correlations between HF and the total score of the test battery CAMCOG (Cambridge Examination for Mental Disorders in the Elderly) in 177 elderly people.

Discussion and conclusion

The purpose of the current review was to summarize the existing literature exploring the cross-sectional correlation between resting HRV and cognitive functions. Possible reasons for both the detected and not detected correlations are presented.

HRV and executive functions

Executive functions comprise working memory, inhibition and cognitive flexibility (Albinet, et al., 2016). Our results showed a partly relation between executive performances and HRV levels. Some studies detect associations with the vagally mediated HRV parameters HF or RMSSD (Albinet, et al., 2010; Hansen, et al., 2003, 2004, 2009; Hovland, et al., 20012; Jennings, et al., 2015; Kemp, et al., 2016; Luque-Casado, et al., 2013; Williams, et al., 2016; Yang, et al., 2008), but others did not find any associations (Alderman & Olson, 2014; Britton, et al., 2008; Duschek, et al., 2009; Frewen, et al., 2013; Giuliano, et al., 2017; Incalzi, et al., 2009; Kimhy, et al., 2013; Mathewson, et al., 2010; Nicolini, et al., 2014; Nonogaki, et al., 2017; Stenfors, et al., 2016).

Hansen et al. (2003) justified their positive results through the association between HRV and "efficient attentional regulation and greater ability to inhibit pre-potent but inappropriate responses". This statement underpins the supposed relationship between HRV and the prefrontal cortex and explains the positive association between vagally mediated HRV and executive function tasks like the task Stroop. Hansen et al. (2004) supposed that the positive relationship was the result of the increased efficiency of prefrontal neural function achieved through aerobic training. In particular, physical training leads to cardiovascular improvements and increased cerebral blood flow, which improves prefrontal functioning.

One explanation for the lack of correlations in other studies could be the big number of factors playing their roles in the relationship between cognitive performance and HRV (Alderman & Olson, 2014). Kimhy et al. (2013) mentioned a limited instrument sensitivity of the working memory task as one reason for the lack of correlation. Britton et al. (2008) stated that their test battery did not assess executive functions in detail. Nonogaki et al. (2017) called the old age of their subjects to account for the lack of correlations and maybe dementia hid possible correlations. However, Holzman and Bridgett (2017) noted that the relation between HRV and top-down self-regulation is stronger in older individuals. Nicolini et al. (2014) stated that autonomic dysfunction is revealed only when the autonomic system is challenged by changing from the supine position to the standing one. In summary, the results demonstrated a tendency of positive correlations between typical executive function tasks (Stroop and 2-back) and vagally mediated HRV.

HRV and memory learning

Memory was positively associated with vagally mediated HRV in only one study with AD patients (Nonogaki, et al., 2017). The authors argued that some parts of the brain (insular cortex, amygdala, hypothalamus, and *nucleus tractus solitarius*) regulate cardiac autonomic function and interact with the medial temporal lobes. These regions are responsible for memorizing things but get impaired in case of a central autonomic dysfunction, which is the case in AD. Karlamangla et al. (2014) confirmed this by revealing a positive relationship between cardiovascular function and memory. Shah et al. (2011) mentioned an impaired baroreflex as a possible mechanism because it is responsible for the cerebral blood flow and is an important component of the autonomic nervous system. In summary, the results indicate a weak connection between memory and HRV.

HRV and language ability

Language ability includes comprehension and word finding (Levy, 1994). In two studies, positive correlations with HF were detected (Frewen, et al., 2013; Yang, et al., 2008). Frewen et al. (2013) mentioned the fornix, a connective part for the hippocampus in the brain, as a possible location underlying the association between HRV and cognition. Moreover, the cholinergic anti-inflammatory pathway could explain this relationship as well.

HRV and visuospatial functioning

Regarding the visuospatial functioning, one study detected significant correlations. Incalzi et al. (2009) explained their results with a dysfunction of the right insular in COPD patients and concluded that "neurogenic heart diseases" are an expression of cardiac abnormalities related to problems in the brain-heart connection.

HRV and processing speed

Processing speed was added as a non-executive function, measuring the reaction time in simple choice tasks that do not require challenging cognitive functions. None of the six relevant studies found significant correlations. There was at least a trend in the Trail-Making Test A (Nicolini, et al., 2014; Stenfors, et al., 2016). Stenfors et al. (2016) suggested using the parameter QTVI (QT variability index) because it showed the best correlations between HRV and cognitive functions. In the study of Hansen et al. (2004), curiously, the low HRV group had faster reaction times compared to the high HRV group in a non-executive task.

HRV and global cognitive functions

In three out of four studies, positive correlations between total cognitive scores and HRV were detected. HF correlated significantly with the scores of the MMSE (Kim, et al., 2006; Mellingsæter, et al., 2015) and the CAMCOG (Allan, et al., 2007). Additionally, RMSSD showed a positive correlation with the MMSE (Kim, et al., 2006). These results implicate that HRV reflects broad cognitive functions and not only specific ones.

Mechanism linking HRV and cognitive function

The role of the HRV as a possible biomarker of the top-down self-regulatory mechanism was well discussed in a recent meta-analysis (Holzman & Bridgett, 2017). The present systematic review focuses on the cognitive part of self-regulation. Thayer et al. (2009) suggested that HRV served as an index of the functional capacity of brain structures "that support the effective and efficient performance of cognitive executive-function tasks including working memory and inhibitory control".

Two theories are the basis for the considered relation between HRV and top-down self-regulation that comprises cognitive functions: the *Neurovisceral Integration Model* (Thayer, et al., 2009) and the *Polyvagal Theory* (Porges, 2003). Both approaches stated a moderating role of the parasympathetic-mediated nervous system. The prefrontal cortex is supposed to play an important role thereby. This part of the brain forms together with cortical and subcortical brain structures an interconnected network and controls the heart rate being also responsible for the cognitive regulation (Thayer & Lane, 2009). Thus, a declining prefrontal activity leads to an increased sympathetic activity, heart rate and hence reduced HRV (Thayer & Lane, 2009). This inhibition of prefrontal activity and pronounced activation of the sympathetic system was beneficial for human survival in ancient times. However, nowadays, a tonic inhibition of the prefrontal cortex and a permanent sympathetic state are contradictory to adaptation and self-regulatory processes (McCraty & Shaffer, 2015). Thus, an optimal level of vagally mediated HRV is necessary for adaptation and cognitive functions.

The link between prefrontal cortex and cardiac system was mentioned in some studies and called upon as one explanation for the correlation between HRV and cognition. The functional state of the cardiac system depends on the level of brain perfusion that can be improved through aerobic training (Mahinrad, et al., 2016). Hansen et al. (2004) argued that the relationship is "mediated by a common set of neural circuits, the efficient functioning of which have inhibitory processes". Mahinrad et al. (2016) considered an autonomic dysfunction caused by dysregulation in cerebral perfusion as the link between low HRV and cognitive impairment. External factors like cardiovascular risk factors could be responsible for the association as well. Further, HRV could reflect an early manifestation of brain damage and future cardiovascular events which lead to cognitive decline. The baroreflex is another possible explanation for the relation between HRV and cognition (Kim, et al., 2006). It ensures proper blood flow through all organs and is regarded an indicator for the autonomic nervous system. High blood pressure variability is a sign of baroreflex disturbances and is associated with cognitive impairment (Meyer, et al., 2017). The relationship between blood pressure regulation and dementia was recently reviewed by O'Callaghan and Kenny (2016). They have described the phenomenon of *Neurocardiovascular Instability* (NCVI), which affects heart rate behaviour through abnormal neural control and is more prevalent in patients with MCI or AD. However, the direction of causality is still unclear. Another reason for the relationship may be a dysfunction of the cholinergic system, which impairs cognitive and parasympathetic system function (Frewen, et al., 2013; Yang, et al., 2008). Incalzi et al. (2009) have mentioned a dysfunction of the right insular as an additional reason for the relationship because the insular modulates sympathetic tone and is involved in integrating cognitive and emotional aspects. Allan et al. (2007) listed autonomic neuropathy as a possible explanation because frequency-domain HRV was lower in patients with Parkinson's disease, who showed higher prevalence of autonomic neuropathy.

Limitations

Some limitations have to be mentioned. First, the studies used different HRV measurement techniques and durations of recording the HRV. This could lead to inconsistency in the results. Second, different samples in terms of age-range and state of health were compared. This was done to offer a variety of studies with different sample characteristics. Otherwise, the number of studies would have been much smaller. And third, our classification of cognitive functions was restricted in the way that a lot of different tasks were used and therefore it was difficult to classify and compare them.

Conclusions

A summary of studies investigating the association between resting-state HRV and cognitive performance was provided. Theoretical models proposed a positive connection between HRV and cognitive performance through the link between cardiovascular regulating processes in the brain and cognition regulating processes located, especially, in the prefrontal cortex (McCraty, et al., 2015; Shaffer, et al., 2014; Thayer, et al., 2009). Some studies could confirm this relationship (e.g., Albinet, et al., 2010; Hansen, et al., 2009; Hovland, et al., 2012; Yang, et al., 2008), but others could not (e.g., Britton, et al., 2008; Nicolini, et al., 2014). The lack of a uniform measurement procedure, different cognitive tasks, and different sample characteristics (age, disorders) are possible reasons for the lack of a stronger relation. To take a step forward in diagnosing and preventing dementia, longitudinal studies are recommended to evaluate HRV as an indicator of cognitive impairment and to investigate the development of and interaction between HRV and cognitive performance throughout life.

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