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Merrill F. Elias
University of Maine, mfelias@maine.edu

Rachael V. Torres

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The Renaissance of Heart Rate Variability as a Predictor of Cognitive Functioning

Merrill F. Elias and Rachael V. Torres

Heart rate variability (HRV) is defined as variation in the time interval between heartbeats. It is determined by interactions between the sympathetic and parasympathetic branches of the autonomic nervous system. Low HRV is an indicator of autonomic dysfunction and is associated with cardiovascular (CVD) risk factors and events that are also related to lower levels of performance on cognitive tests. Poor cognitive performance associated with reduced HRV may thus be a consequence of HRV-associated risk factors or, more directly, the failure of the autonomic nervous system to properly regulate brain perfusion. The article by Zeki Al Hazzouri et al. in this issue of the American Journal of Hypertension signifies the rebirth of interest in relations between HRV and cognition.

There were an estimated 261 published articles on blood pressure and cognitive functioning in 2011, but few on HRV. Table 1 identifies the major studies cited by Zeki Al Hazzouri et al. including possibly the earliest well-controlled study by Kim et al. in 2006. A review by Richard and Casey traces the study of HRV back to 1973 where HRV was employed as an index of attention. In these early studies, both variables were often measured concurrently and HRV was found to index orientation and attention in infants, children, and adults. More recently, Mukherjee et al. found that HRV was associated with different levels of mental workload. More importantly, Luft et al. found difference in HRV during performance of executive functioning (EF) vs. non-EF tasks. These studies are pertinent to the design of current studies in this area of research because they indicate need for temporal separation between measurements. The 5-year prospective design of the study by Zeki Al Hazzouri et al. is thus a major strength. Additional strengths are the large sample, control for CVD risk factors associated with HRV, and exclusion of persons with arrhythmias.

Zeki Al Hazzouri et al. utilized data from 2,118 participants of the Coronary Artery Risk Development in Young Adults study that had no electrocardiogram-based evidence of arrhythmias (mean age 45.3 years; 57.7% female; 43% African American). HRV measures were created from a 10-second, 12-lead electrocardiogram conducted in 2005 and were used to predict cognitive function, which was assessed in 2010. Two HRV measures included the SD of normal-to-normal intervals (SDNN) and the root mean square of successive differences (RMSSD). Cognitive tests utilized were the Rey Auditory Verbal Learning Test (indexing verbal memory), the Digit Symbol Substitution Test (indexing processing speed), and the Stroop Interference Test (indexing EF). The RMSSD index of HRV was not associated with any cognitive outcomes, although quartile of SDNN was related to performance on the Stroop Test with adjustment for demographics and CVD risk factors (i.e., smoking status, physical activity, body mass index, blood pressure, antihypertensive medication use, diabetes, history of stroke or myocardial infarction, and depressed mood). In these analyses, participants in SDNN quartiles 2 (range 17.4–26.6 ms) and 3 (26.6–40.7 ms) performed significantly better than those in quartile 1 (range 2.7–17.4 ms). Zeki Al Hazzouri et al. conclude that low HRV is associated with reduced EF. The broad definition of EF is set of processes that have to do with managing oneself and one’s resources in order to achieve a goal. They rely heavily on fluid intellectual ability and involve working memory, mental flexibility, and inhibition of incorrect responses as task demands shift. Thus, we prefer a narrower interpretation of the specific construct measured by the Stroop Interference Test because it more specifically measures ability to sustain attention and respond appropriately to shifting task demands.

Low HRV was also significantly associated with lower Digit Symbol Substitution Test score, reflecting mainly speed and to a lesser extent memory. However, this was only true for analyses adjusting for demographics. Absence of findings with adjustment for CVD risk factors may indicate that CVD risk factors may be important mediators of relations between processing speed and cognition. No significant associations...
between HRV and performance on the Rey Auditory Verbal Learning Test were observed.

The resurrection of interest in HRV and cognition stimulated by Zeki Al Hazzouri et al. and related literature (Table 1) leads us to consider some interesting directions this work could take in the future. It is inevitable that this research will include studies involving new controls. Among these we recommend statistical adjustment of early-stage and late-stage chronic kidney disease, as Brotman et al. have found that low HRV is associated with early-stage chronic kidney disease and chronic kidney disease–related hospitalization. We also hope to see more longitudinal studies. The study by Zeki Al Hazzouri et al. was prospective, but not longitudinal. Does change in HRV over time relate to changes in cognitive performance?

Our curiosity as to nonlinear relations is stimulated by the Zeki Al Hazzouri et al. finding that participants in SDNN quartiles 1 and 4 (the lowest and highest HRV, respectively) did not differ in performance on the Stroop Test (P > 0.05), although study participants in quartiles 2 and 3 exhibited significantly lower scores than persons in quartile 1. This appears in Figure 1 of the Zeki Al Hazzouri et al. study as an asymmetric inverted-U shaped function between SDNN and cognition. Assuming this relation will be repeated, what does it mean and what are its implications for management of HRV?

Zeki Al Hazzouri et al. correctly point out that absence of a significant relationship between the HRV and their test of memory (the Rey Auditory Verbal Learning Test) does not allow us to conclude that memory is unrelated to HRV, as the Rey Auditory Verbal Learning Test does not measure all dimensions of memory. For example, episodic and semantic memory abilities have not been examined in any investigation relating HRV to cognition (Table 1). Semantic memory includes information acquired from personal experience over the lifetime and episodic memory is memory from personal events, e.g., who, what, or when. These 2 types of memories are critical to the recognition of individuals who are on a trajectory to Alzheimer’s disease.

Just as is true for memory, EF needs to be indexed by more than a single cognitive test in future studies. The 7 most frequently used test of EF primarily measure mental flexibility, planning, verbal fluency, inhibition of incorrect response (Stroop). The Stroop Interference Test targets only one of these aspects of the broad construct defined as EF and this is why we prefer a narrower interpretation of the test results obtained using this test.

The word impairment is often used in a comparative sense (i.e., persons with lower scores are described as impaired). In our view, impairment must be defined relative to established clinical criteria. It is surprising that there have been so few prospective studies relating HRV to impaired performance using defined and established criteria for mild cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer’s Disease. We found a single study with findings indicating that low HRV was related to conversion from mild cognitive impairment to vascular Alzheimer’s Disease, but not Alzheimer’s Disease, although these findings are not yet available in a full-length article.

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### Table 1. Summary of major studies cited by Zeki Al Hazzouri et al. relating HRV to cognitive performance

<table>
<thead>
<tr>
<th>Study</th>
<th>Design(s)</th>
<th>Participants</th>
<th>HR measurement</th>
<th>Cognitive measures</th>
<th>Findings with adjustment for CV-RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>Kim et al., 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>311 physically disabled females (≥65 years of age)</td>
<td>2-hour ambulatory ECG</td>
<td>The Mini-Mental State Examination (MMSE)</td>
</tr>
<tr>
<td>2.10</td>
<td>Britton et al., 2008&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Cross-sectional longitudinal prospective</td>
<td>5375 males (55 ± 6 years of age) and females (61 ± 6 years of age)</td>
<td>5-minute supine resting ECG</td>
<td>20-word free recall test, 1-minute free recall of ‘S’ words, 1-minute free recall of animal names, the Alice-Heim 4-1 and the Mill Hill Vocabulary Test</td>
</tr>
<tr>
<td>2.15</td>
<td>Shah et al., 2011&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>416 male twins (55 ± 2.9 years of age)</td>
<td>24-hour ambulatory ECG</td>
<td>Visual and Verbal Selective Reminding Tests (SRT)</td>
</tr>
<tr>
<td>2.20</td>
<td>Frewen et al., 2013&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>4763 participants (62 ± 8 years of age, 55% female)</td>
<td>Two 5 min supine resting ECGs</td>
<td>The Montreal Cognitive Assessment (MOCA)</td>
</tr>
<tr>
<td>2.25</td>
<td>Zeki Al Hazzouri et al., 2014&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>869 Mexican Americans (76 ± 6 years of age, 59% female)</td>
<td>6-min supine resting ECG</td>
<td>The Modified MMSE (3MSE) and the Spanish English Verbal Learning Test (SEVLT)</td>
</tr>
<tr>
<td>2.25</td>
<td>Mahinrad et al., 2016&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Cross-sectional longitudinal</td>
<td>3583 participants (75 ± 3 years of age, 53% female)</td>
<td>10-s supine resting ECG</td>
<td>The Stroop test, the Letter-Digit Coding (LDC) test and the Picture-Word Learning Test</td>
</tr>
<tr>
<td>2.25</td>
<td>Zeki Al Hazzouri et al., 2017&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Prospective</td>
<td>2118 participants (45 ± 4 years of age, 58% female)</td>
<td>10-s supine resting ECG</td>
<td>The Stroop test, the Digit Symbol Substitution Test and the Rey Auditory Verbal Learning Test</td>
</tr>
</tbody>
</table>

**Abbreviations:** CV, cardiovascular; ECG, electrocardiogram; HR, heart rate; HRV, heart rate variability.
Family and twin studies also indicate a major genetic contribution to resting HRV (heritability estimates between 25% and 75%).

While Zeki Al Hazzouri et al. cite work indicating the validity of 10-second electrocardiogram, some data support the argument that recordings should last for at least 30 seconds to accurately detect arrhythmias and 60 seconds when heart rate is rapid. Zeki Al Hazzouri et al. exclude participants with arrhythmias detected within 10 seconds, but it is possible that some cases were undetected because of the short record. This would probably have minimal influence on study results, as the prevalence of steady state and paroxysmal atrial fibrillation is relatively low in the age group studied, but longer electrocardiogram records may become more important in studies with older individuals where the prevalence of atrial fibrillation is 2.3 percent in persons over 40 years of age and rises to 5.9 percent in persons over 65 years.

Of all of the recommendations we make, the use of comprehensive test batteries including multiple domains of cognition and longitudinal studies may be the most difficult to achieve. Achieving these goals places demands on investigator time and increases subject burden and therefore necessitate fewer subjects or, alternatively, longer studies. If we wish to determine which cognitive domains are susceptible to HRV, it is imperative that we meet these goals. They have been achieved in studies of blood pressure and are most assuredly achievable in studies of HRV.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES