Indian J Physiol Pharmacol 2017; 61(1) : 14–22

Original Article

Does Heart Rate Variability Predict Human Cognitive Performance at Higher Memory Loads?

Suriya Prakash Muthukrishnan, John Preetham Gurja and Ratna Sharma*

Stress and Cognitive Electroimaging Laboratory,
Department of Physiology,
All India Institute of Medical Sciences,
New Delhi, India

Abstract

Background: Literature suggests an association between heart rate variability (HRV) and human cognitive performance. However, their correlation has not been worked out yet. The effect of cognitive load on HRV has not been investigated using visuospatial working memory (VSWM) task.

Objective: The objective of this study conducted on healthy human subjects was to explore the relationship between HRV (which reflects the autonomic activity) with cognitive performance (which is cortically mediated) using a visuospatial working memory paradigm.

Methods: Since humans have to routinely cope with many aspects of memory simultaneously, a VSWM task that involved various elements of memory simultaneously was designed. Twenty-four healthy subjects performed the VSWM paradigm that had three tasks of increasing memory loads. ECG was recorded simultaneously for the quantification of HRV. Time and frequency domain analysis of HRV was performed. Multivariate analysis was performed to evaluate the effect of memory load (3 memory loads) on HRV measures. Pearson correlation analysis was performed to study the association between the HRV measures with the performance at each memory load.

Results: The results showed that HRV decreased with an increase in memory load. Low HRV was found to be associated with poor performance.

Conclusion: The results imply an 'integrated' neural network of adaptive regulation that controls cognitive performance and autonomic functions. HRV could potentially serve as an index of healthy individual's cognitive capacity.

***Corresponding author :**

Ratna Sharma, Stress and Cognitive Electroimaging Laboratory, Department of Physiology, All India Institute of Medical Sciences, New Delhi, India, Tel.: +91-11-26594682; Fax: +91-11-26588641, Email : ratnaaiims@gmail.com

(Received on April 12, 2016)

Introduction

An integrative model of health and disease must incorporate cognitive, affective, behavioural and physiological factors that contribute to inter-individual differences. There has been great amount of evidence in the literature on the role of individual differences in the beat-to-beat variations of heart rate in the health and disease (1–5). The current study was conducted to explore the relationship between the autonomic mediated heart rate variability (HRV) with the cortically mediated cognitive performance using a visuospatial working memory (VSWM) paradigm that simulates day to day routine activity.

Previous neuroimaging studies have reported increased activity in the prefrontal cortex during working memory tasks and have suggested an important role played by the prefrontal cortex in determining individual's working memory capacity (6, 7). Thayer et al. (8) showed that the prefrontal cortex activity could modulate the heart rate and HRV. Recent meta-analysis report suggests that HRV could index the strength of integrity between medial prefrontal cortex (mPFC) with the brainstem nuclei that regulate the heart rate (4). These evidences suggest for the possibility of determining prefrontal cortex controlled human cognitive performance from an easily quantifiable HRV measures.

Previous studies have investigated HRV during various components of cognition such as attention, memory performance, mental workload, executive and planning tasks (9-17). These studies have reported variable results with some reporting high HRV with better cognitive performance and vice versa by the other studies. Therefore, the consensus regarding the relation between HRV and cognitive performance has not been reached till date and needs further investigation.

Most studies have reported decrement in HRV with increase in cognitive load (9, 11, 14, 16, 17). However, evidence suggests less reliability of HRV measures for the assessment of cognitive load (18). Futhermore, Luft et al. (19) reported significant difference in the HRV response between various cognitive tasks used in their study. Therefore, the effect of cognitive load on HRV needs to be investigated using a task that simulates daily routine activity.

Visuospatial working memory (VSWM) refers to the cognitive ability that is essential to encode, maintain, manipulate and retrieve information in the visual space to facilitate the execution of ongoing activity (20). Apart from being an essential cognitive component for routine activity, good VSWM is crucial for professionals such as drivers, sailors, aviators and naval officers. Moreover, VSWM is affected in various disease states such as autistic spectrum disorders, Alzheimer's disease, Parkinson's disease and schizophrenia (21–24). Hence, a convenient tool for predicting and assessing the VSWM performance in the health and disease is the need of the hour. To the best of our knowledge, no previous study has investigated the effect of VSWM load on HRV in healthy human adults.

VSWM tasks used by the previous studies, were N-Back task, Modified Sternberg memory paradigm and delayed match-to-sample task (6, 25-32). These tasks require memorizing the sample items displayed during the encoding period, merely maintain for a few seconds in the delay period and then respond by comparing the test item with the sample items in the retrieval period. Mohr and Linden (27) suggested that the passive and active processes in the VSWM should be distinguished as well. Passive processes are recruited by the tasks that require recall of the information in the same format as it was memorized, while the active processes are recruited by the tasks that require the information to be modified, transformed, integrated or otherwise manipulated (27). Hence, with the physiological point of view, we found that the VSWM has to be investigated using a better task which involves active memory processes. Due to the fact that we humans encounter all the elements of memory simultaneously in our daily life, we designed a VSWM task that involved various elements of the memory simultaneously.

In the current study, we aimed to explore the relationship between the autonomic mediated heart rate variability (HRV) with the cortically mediated cognitive performance in the healthy human subjects using a VSWM paradigm that involved retention, retrieval, manipulation, recoding and task execution simultaneously.

Materials and Methods

Participants

Twenty-four healthy male volunteers (mean age (SD) 27.63 (3.004); all right handed) participated in this experiment after giving written informed consent. Participants recruited were the post-graduate students in the institute. The study was approved by the Institution Ethics Committee, All India Institute of Medical Sciences, New Delhi, India.

Task Design

The current study was designed with an objective to investigate the effect of memory load on the neural substrates of VSWM using a task that involves simultaneous encoding, retention, manipulation, retrieval and execution of the goal in the healthy human subjects. Participants were requested to give their best possible performance in the task by keeping the error rate to the minimum. Participants performed a VSWM task which had three memory loads (3, 6 and 8 pairs of identical abstract pictures). Pictures used in the task were multi-coloured abstract designs. Abstract pictures were used to minimize the verbal memory contribution for performing the VSWM task. In each memory load, an array with the pairs of abstract pictures in different spatial location was presented for 10 seconds during which the spatial location of the abstract pictures had to be encoded. After 10 seconds of encoding, the abstract pictures were hidden in the array. The pictures in the hidden array turned unhidden with the mouse click.

Matching trial: Matching trial starts with a mouse click to turn open a picture in the array for 1 second after which participant starts searching for the matching picture located elsewhere in the array. Then, the participant clicks open a picture chosen as the matching picture which is displayed for 1 second. Successful matching trial makes the pair of abstract pictures to disappear from the array (Fig. 1). After a matching trial, the display turns blank for 200 ms, after which the array appears with the hidden pictures yet to be matched. All pairs of abstract pictures in the array have to be matched correctly to complete each block of the memory loads.

Matching trial involves simultaneous retrieval of the matching pair of pictures, retention of the spatial position of the remaining abstract pictures in the array, updating the spatial position of the pictures opened in the trial, recoding the spatial position of the pictures clicked open in the incorrect matching trials and execution of the goal i.e. matching the pair of abstract pictures in the array. Moreover, this VSWM task could possibly require the participants to strategize and decide the pair of abstract pictures in the array to be opened in sequence to give their best performance. Hence, the matching trial of VSWM task used in this study could involve simultaneous retention, retrieval, active manipulation (by demanding the participants to update, recode and possibly strategize) and execution of the goal. Matlab R2012b (The MathWorks, Inc., Natick, USA) software was used for stimulus presentation and to mark the events in the online EEG recording. Different sets of abstract pictures were used for each memory load to avoid repetition of the abstract pictures used already in the task. Array was displayed in the grey background at the centre of the monitor screen. Participants were seated at a distance of 70 cm from the monitor screen. Each picture in the array subtended a visual angle of 4.2° and 4.5° in the horizontal and the vertical axis, respectively.

ECG Recording

Lead II ECG was recorded using polygraph input box (PIB; Electronic Geodesic Inc., Eugene, OR, USA). ECG recording was done in a silent electrically noise free room. Five minutes' baseline ECG recording was taken followed by simultaneous ECG recording during VSWM paradigm. Participants took a mean (SD) duration of 1 min 32s (11s), 2 min 18s (18s) and 2 min 48s (16s) to complete memory load I, II and III, respectively. The total duration of VSWM paradigm was 6 min 48s (29s). Data was acquired using Net Station 4.5.6.

Data Analysis

Recent evidence suggests that the mental stress could be monitored reliably by HRV analysis with time window as short as 50s (33). Several other studies also indicate high accuracy and reliability of

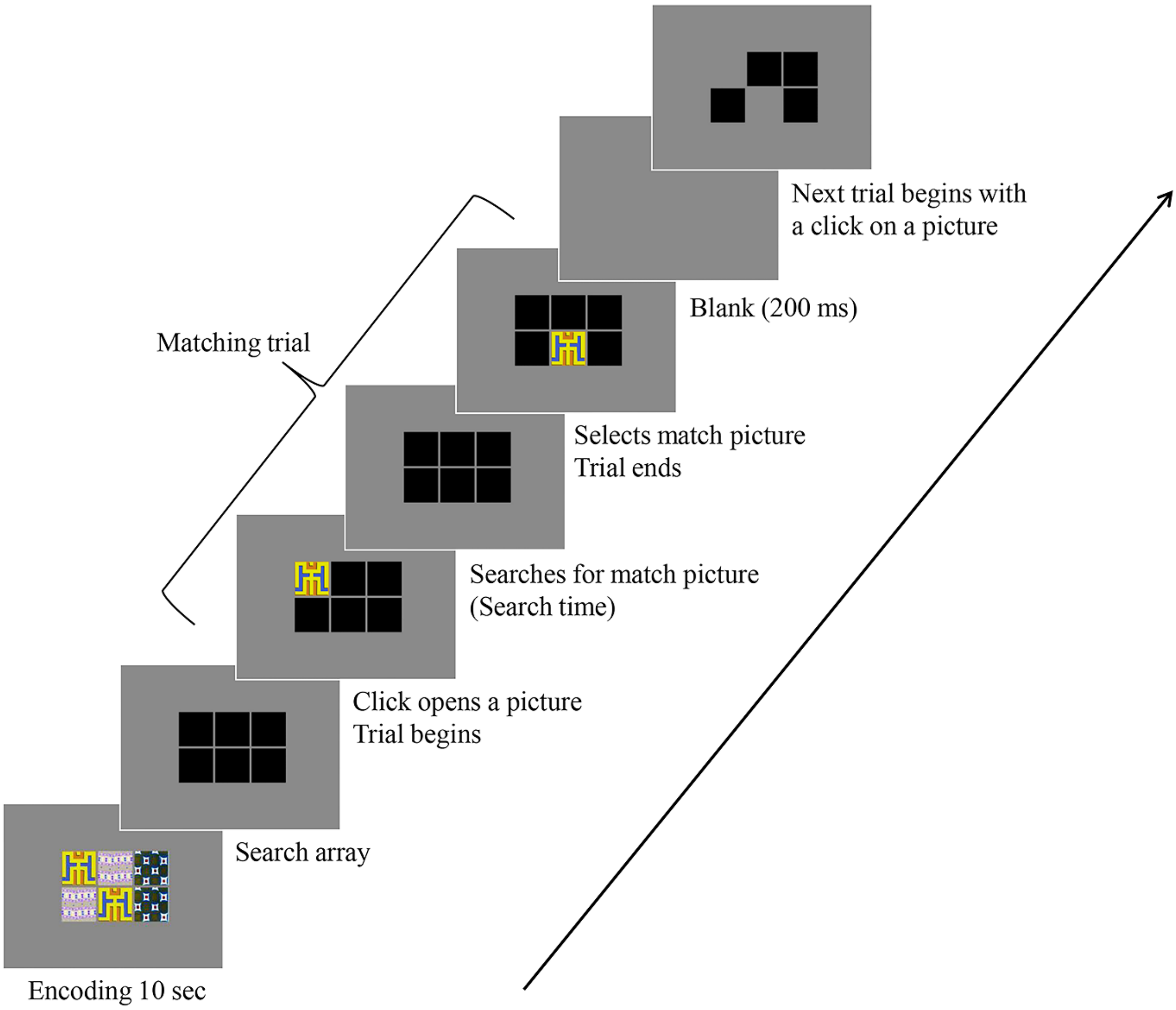

Fig. 1 : Design of the VSWM task used in this study.

HRV analysis performed using time window of 40s-60s in various scenarios such as rest state, high altitude, exercise and atrial fibrillation (34-36). Therefore, ECG data acquired were segmented to extract 1 minute data segments from each condition (baseline, Memory load I, II & III) using Net Station 4.5.6. Segmented data were exported in MAT file format for further analysis in Matlab R2012b (The MathWorks, Inc., Natick, USA). HRV analysis was performed using Kubios HRV software package (37 Tarvainen et al., 2009). Time and frequency domain analysis of HRV measures were performed. The time domain HRV measures included for analysis were SDNN (Standard deviation of all NN intervals), rMSSD (Square root of the mean of the squares of differences between adjacent NN intervals) and pNN50 (Percentage of differences between adjacent NN intervals that are greater than 50 ms). Frequency domain measures included for analysis were LF (Total spectral power of all NN intervals between 0.04 and 0.15 Hz), HF (Total spectral power of all NN intervals between 0.15 and 0.4 Hz) and LF/HF (Ratio of low to high frequency power).

The SDNN is the standard deviation of the normal (NN) inter beat interval, i.e. the square root of variance measured in millisecond, which represents parasympathetically mediated respiratory sinus arrhythmia (38). The RMSSD is the root mean square of successive differences between normal heartbeats. The NN50 is the adjacent NN intervals that differ from each other by more than 50 ms and pNN50 is the percentage of NN50 (38). RMSSD and pNN50% are used to estimate the parasympathetically mediated changes reflected in HRV (38). The HF power, LF power and LF/HF ratio are considered to represent parasympathetic activity, sympathetic activity and sympatho-vagal balance, respectively (39-43).

Statistical Analysis

Baseline HRV measures were subtracted from the HRV measures during the memory load I, II and III of the VSWM paradigm. Normality of data was tested using Kolmogorov-Smirnov test. Parametric tests were applied since data was under normal Gaussian distribution. One-way ANOVA test was used to determine the effect of memory load (3 memory loads) on the error rate of the participants. Multivariate analysis was performed to evaluate the effect of memory load (3 memory loads) on HRV measures. The P-values were adjusted according to the Bonferroni correction. Correlation analysis was performed to study the relation between the HRV measures with the performance at each memory load. The parametric Pearson correlation coefficient was used to describe the relationship between the HRV measures of 2 memory load conditions (Memory load II and III) with the error rate of the respective load conditions. As only 4 out of 24 participants committed errors in the memory load I, we did not perform correlation analysis of error rate with the HRV measures for the same. Statistical significance was accepted at $P<0.05$. All the analyses were performed using Statistical Package for Social Sciences version 20.0.

Results

Effect of working memory load on error rate

The working memory load had significant effect on the error rate ($F(2, 66) = 81.046$, $p<0.001$), (Fig. 2). Bonferroni's multiple comparison revealed that the error rate was significantly high in the memory load III when compared with the memory load I & II (p (I vs. III) < 0.001, p (II vs. III) < 0.001).

Effect of working memory load on heart rate variability

Among the HRV measures analyzed, SDNN, pNN50%, LF power and LF/HF ratio showed significant changes in the working memory loads (Table I, II). Further post-hoc analysis revealed that

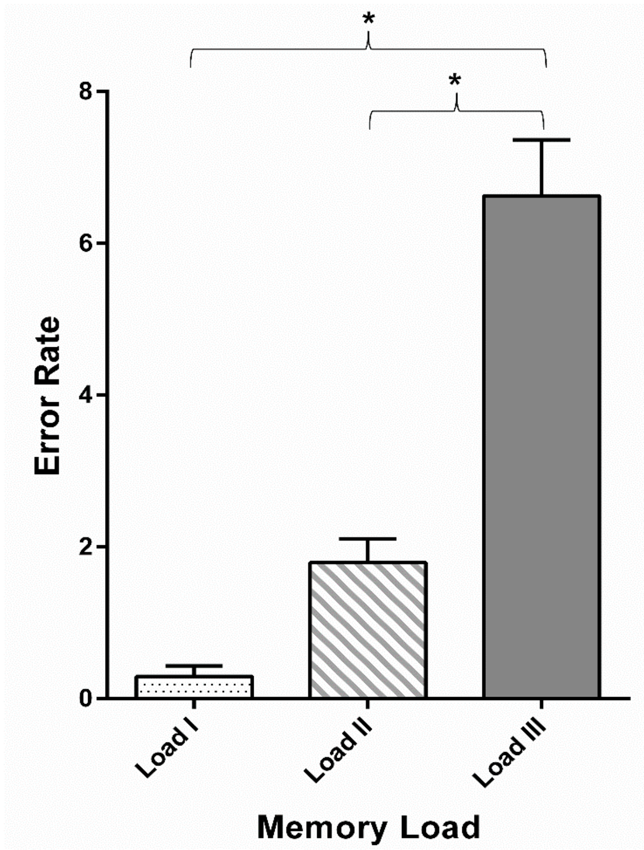

Fig. 2 : Error rate plotted against memory load conditions. Error bars represent±standard error of the mean. * represents Bonferroni corrected p value < 0.05.

TABLE I : Descriptive data of HRV parameters during VSWM paradigm.

HRV Measures	*Load I*	*Load II*	*Load III*
SDNN (ms)	63.94(3.73)	49.63(4.59)	36.17(2.09)
RMSSD (ms)	41.02(4.38)	38.40(3.59)	37.84(3.41)
pNN50%	27.77(2.70)	18.3(3.23)	9.48(1.67)
LF Power (ms^2)	689.98(164.47)	865.35(230.06)	1755.19(281.37)
HF Power (ms^2)	619.07(132.79)	516.16(104.88)	625.37(116.69)
LF/HF	1.39(0.21)	2.0(0.42)	6.13((1.75)

Mean (SD) of the HRV parameters during memory load I, II and III are represented.

TABLE II : Effect of working memory load on HRV measures.

HRV Measures	*F value (2,69)*	*P value*	*Post-hoc Bonferroni correction (P<0.05)*		
			Load I Vs II	*Load II Vs III*	*Load I Vs III*
SDNN (ms)	14.70	<0.001	I > II	II > III	I > III
RMSSD (ms)	0.20	ns	ns	ns	ns
pNN50%	11.40	<0.001	I > II	ns	I > III
LF Power (ms^2)	6.15	0.003	ns	II < III	I < III
HF Power (ms^2)	0.27	ns	ns	ns	ns
LF/HF	6.06	0.004	ns	II < III	I < III

ns – Denotes not significant; I, II and III – Denotes memory loads I, II and III, respectively.

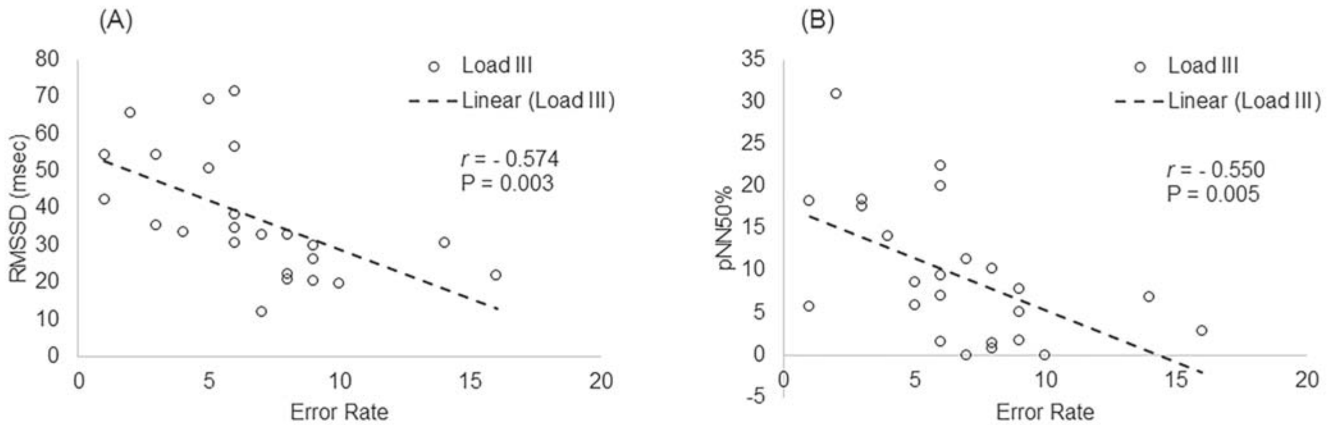

Fig. 3 : rMSSD (Fig. 3A) and pNN50% (Fig. 3B) showed significant linear relation with the error rate during memory load III.

all these variables decreased in higher working memory loads except LF/HF ratio which showed increase in higher memory loads (Table I, II).

Correlation of error rate with heart rate variability

Error rate had significant negative correlation with rMSSD and pNN50 during memory load III condition (Fig. 3A and 3B). We did not find any significant relationship between the error rate and HRV measures during memory load II (Table III).

TABLE III : Correlation between the error rate with the HRV measures during memory load II & III.

HRV Measures	*Load II*		*Load III*	
	P value	*Pearson r*	*P value*	*Pearson r*
SDNN (ms)	0.1354	–0.3138	0.627	0.105
RMSSD (ms)	0.1113	–0.3335	0.003*	–0.574
pNN50%	0.1347	–0.4326	0.005*	–0.550
LF Power (ms^2)	0.2978	–0.2217	0.055	–0.396
HF Power (ms^2)	0.0713	–0.3746	0.051	–0.404
LF/HF	0.172	0.2882	0.676	0.090

* – denotes significant correlation (p<0.05).

Discussion

In the current study, we tried to explore the effect of memory load on HRV measures using VSWM task that involved various elements of memory simultaneously. The current study results showed that the error rate increased (performance of the subjects decreased) with an increase in the working memory load. This is in line with previous study that revealed the capacity limitation of human working memory (30).

The study results revealed decrease in HRV with an increase in the working memory load as SDNN and pNN50% decreased, LF power and LF/HF ratio increased at higher memory loads. This is in agreement with the previous studies which had also reported decrement in HRV with an increase in the task difficulty and memory load (9, 11, 44). Previous evidence suggests that the SDNN and pNN50% changes are primarily mediated by parasympathetic (Vagus) system (38). The LF power and LF/HF ratio was considered to represent sympathetic activity and sympatho-vagal balance, respectively (39-43). However, recent data challenge these interpretations on LF power and LF/HF ratio. It suggests that the HRV power spectrum, including its LF component, is mainly determined by the parasympathetic system (45). Previous evidences had also reported elimination of HF oscillations and reduction of LF power after vagal blockade (42, 46). Hence, in view of previous evidences, our results might suggest withdrawal of parasympathetic activity in response to high memory load.

Error rate correlated negatively with SDNN and pNN50% during memory load III. Therefore, good performance was associated with high SDNN and pNN50% and vice versa, only when challenged with higher working memory load. This is in agreement with the previous studies which had also reported association of HRV with the cognitive performance (11, 44, 47). SDNN and pNN50% changes are primarily mediated by parasympathetic (Vagus) system (38). Hence, our results indicate that the poor performance associated with low SDNN and pNN50% could be due to the withdrawal of parasympathetic vagal activity. From our results, it becomes apparent that HRV may be more than just an index of heart function, and might also indicate heathy individual's cognitive capacity. Thayer et al. (4) suggested a common reciprocal inhibitory cortico-subcortical neural circuit between mPFC and subcortical structures such as amygdala and brainstem nuclei to serve as the structural link between the psychological processes like memory with the physiological processes like heart rate. This integrated circuit is believed to control the sympatho-vagal balance to effectively respond to the psychological and physical challenges posed by the environment.

Evidence suggests that respiration could be affected by cognitive load (48) and respiration in turn is known to affect HRV (49). Hence, Simultaneous recording of ECG and respiration could have given more insights and helped in the interpretation of the current study results. This is the limitation of the current study and therefore future investigations on cognitive load need to be performed with simultaneous recording of ECG and respiration.

The current study results revealed that the poor cognitive performance in VSWM is associated with low HRV. This highlights the potential importance of HRV as a predictive tool for cognitive performance in VSWM. This could potentially be applied for the early detection of disease states with VSWM impairment, which would allow for the intervention methods to be applied sooner to slow or cease cognitive decline progression (50). Diet, exercise, biofeedback and stress reduction techniques such as meditation are some of the several behavioral strategies that can be used to increase HRV (51), which could also additionally benefit by improving cognition in the health and disease.

Conclusion

To summarize, the current study for the first time has investigated the relationship of HRV with the cognitive performance of the VSWM task that involved various elements of memory simultaneously in the healthy human subjects. The current study found two important findings. First, decrement in HRV was observed in response to increase in the memory load. Second, poor cognitive performance was found to be associated with low HRV and vice versa at higher memory load. Evidence supports the structural and functional existence of reciprocal inhibitory cortico-subcortical neural circuit between mPFC and subcortical structures such as amygdala and brainstem nuclei (4). The neural strategy underlying good performance could be the lesser stimulation of sympathetic activity and lesser withdrawal of parasympathetic activity by mPFC, which might have decreased arousal (eustress response) when challenged with higher memory loads. While poor cognitive performance could be due to relatively more sympathetic activation causing heightened arousal (distress response). Our results indicate that the HRV has the potential to predict the qualitative differences in the cognitive performance of healthy individuals.

The current study result implies an 'integrated' neural network of adaptive regulation, which controls cognitive performance and autonomic functions such as heart rate. HRV could serve as an index of this neural network and has the potential to serve as a tool for predicting healthy individual's capacity to effectively function in a complex environment such as the present modern world.

References

1. Berkoff DJ, Cairns CB, Sanchez LD, Moorman CT. Heart rate variability in elite American track-and-field athletes. *J Strength Cond Res Natl Strength Cond Assoc* 2007; 21(1): 227–231.
2. Kristal-Boneh E, Raifel M, Froom P, Ribak J. Heart rate variability in health and disease. *Scand J Work Environ Health* 1995; 21(2): 85–95.
3. Sleight P. The importance of the autonomic nervous system in health and disease. *Aust N Z J Med* 1997; 27(4): 467–473.
4. Thayer JF, Ahs F, Fredrikson M, Sollers JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev* 2012; 36(2): 747–756.
5. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol* 2010; 141(2): 122–131.
6. Edin F, Klingberg T, Johansson P, McNab F, Tegnér J, Compte A. Mechanism for top-down control of working memory capacity. *Proc Natl Acad Sci* 2009; 106(16): 6802–6807.
7. Grimault S, Robitaille N, Grova C, Lina J-M, Dubarry A-S, Jolicoeur P. Oscillatory activity in parietal and dorsolateral prefrontal cortex during retention in visual short-term memory: additive effects of spatial attention and memory load. *Hum Brain Mapp* 2009; 30(10): 3378–3392.
8. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med Publ Soc Behav Med* 2009; 37(2): 141–153.
9. Backs RW, Seljos KA. Metabolic and cardiorespiratory measures of mental effort: the effects of level of difficulty in a working memory task. *Int J Psychophysiol Off J Int Organ Psychophysiol* 1994; 16(1): 57–68.
10. Ekberg K, Eklund J, Tuvesson M-A, Örtengren R, Odenrick P, Ericson M. Psychological stress and muscle activity during data entry at visual display units. *Work Stress* 1995; 9(4): 475–490.
11. Middleton HC, Sharma A, Agouzoul D, Sahakian BJ, Robbins TW. Contrasts between the cardiovascular concomitants of tests of planning and attention. *Psychophysiology* 1999; 36(5): 610–618.
12. Phillips AC. Blunted cardiovascular reactivity relates to depression, obesity, and self-reported health. *Biol Psychol* 2011; 86(2): 106–113.
13. Porges SW, Raskin DC. Respiratory and heart rate components of attention. *J Exp Psychol* 1969; 81(3): 497–503.
14. Redondo M, Del Valle-Inclán F. Decrements in heart rate variability during memory search. *Int J Psychophysiol Off J Int Organ Psychophysiol* 1992; 13(1): 29–35.
15. Schellekens JM, Sijtsma GJ, Vegter E, Meijman TF. Immediate and delayed after-effects of long lasting mentally demanding work. *Biol Psychol* 2000; 53(1): 37–56.
16. Veltman JA, Gaillard AW. Physiological workload reactions to increasing levels of task difficulty. *Ergonomics* 1998; 41(5): 656–669.
17. Vincent A, Craik FI, Furedy JJ. Relations among memory performance, mental workload and cardiovascular responses. *Int J Psychophysiol Off J Int Organ Psychophysiol* 1996; 23(3): 181–198.
18. Wilson GF. An analysis of mental workload in pilots during flight using multiple psychophysiological measures. *The Int J Aviat Psychol* 2002; 12(1): 3–18.
19. Luft CDB, Takase E, Darby D. Heart rate variability and cognitive function: effects of physical effort. *Biol Psychol* 2009; 82(2): 164–168.
20. Baddeley A. The fractionation of working memory. *Proc Natl Acad Sci* 1996; 93(24): 13468–13472.
21. Bradley VA, Welch JL, Dick DJ. Visuospatial working memory in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989; 52(11): 1228–1235.
22. Fleming K, Goldberg TE, Binks S, Randolph C, Gold JM, Weinberger DR. Visuospatial working memory in patients with schizophrenia. *Biol Psychiatry* 1997; 41(1): 43–49.
23. Mammarella IC, Giofrè D, Caviola S, Cornoldi C, Hamilton C. Visuospatial working memory in children with autism: the effect of a semantic global organization. *Res Dev Disabil* 2014; 35(6): 1349–1356.
24. Quental NBM, Brucki SMD, Bueno OFA. Visuospatial function in early Alzheimer's disease-the use of the Visual Object and Space Perception (VOSP) battery. *PloS One* 2013; 8(7): e68398.
25. Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 1997; 35(10): 1373–1380.
26. Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, et al. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex N Y N* 1991. 1999; 9(1): 20–26.
27. Mohr HM, Linden DEJ. Separation of the systems for color and spatial manipulation in working memory revealed by a dual-task procedure. *J Cogn Neurosci* 2005; 17(2): 355–366.
28. Pessoa L, Gutierrez E, Bandettini P, Ungerleider L. Neural correlates of visual working memory: fMRI amplitude predicts task performance. *Neuron* 2002; 35(5): 975–987.
29. Smith EE, Jonides J. Neuroimaging analyses of human working memory. *Proc Natl Acad Sci* 1998; 95(20): 12061–12068.
30. Todd JJ, Marois R. Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature* 2004; 428(6984): 751–754.
31. Vogel EK, Machizawa MG. Neural activity predicts

individual differences in visual working memory capacity. *Nature* 2004; 428(6984): 748–751.

32. Xu Y, Chun MM. Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature* 2006; 440(7080): 91–95.
33. Salahuddin L, Cho J, Jeong MG, Kim D. Ultra short term analysis of heart rate variability for monitoring mental stress in mobile settings. *Conf Proc IEEE Eng Med Biol Soc* 2007; 2007: 4656–4659.
34. Boos CJ, Bakker-Dyos J, Watchorn J, Woods DR, O'Hara JP, Macconnachie L, Mellor A. A comparison of two methods of heart rate variability assessment at high altitude. *Clin Physiol Funct Imaging* 2016. doi: 10.1111/cpf.12334.
35. Esco MR, Flatt AA. Ultra-short-term heart rate variability indexes at rest and post-exercise in athletes: Evaluating the agreement with accepted recommendations. *J Sports Sci Med* 2014; 13(3): 535–541.
36. Salahuddin L, Jeong MG, Kim D. Ultra short term analysis of heart rate variability using normal sinus rhythm and atrial fibrillation ECG data. 9th International Conference on e-Health Networking, Application and Services. 2007; 240–243.
37. Tarvainen MP, Niskanen J-P, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV- Heart rate variability analysis software. *Comput Methods Programs Biomed* 2014; 113(1): 210–220.
38. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol* 2014; 5: 1040.
39. Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 1997; 34(6): 623–648.
40. Billman GE. Heart rate variability - a historical perspective. *Front Physiol* 2011; 2: 86.
41. Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. *Front Physiol* 2013; 4: 26.
42. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; 84(2): 482–492.
43. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; 59(2): 178–193.
44. Hansen AL, Johnsen BH, Thayer JF. Vagal influence on working memory and attention. *Int J Psychophysiol Off J Int Organ Psychophysiol* 2003; 48(3): 263–274.
45. Reyes del Paso GA, Langewitz W, Mulder LJM, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. *Psychophysiology* 2013; 50(5): 477–487.
46. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; 248(1): H151-H153.
47. Backs RW, Ryan AM, Wilson GF. Psychophysiological measures of workload during continuous manual performance. *Hum Factors* 1994; 36(3): 514–531.
48. Grassmann M, Vlemincx E, von Leupoldt A, Mittelstadt JM, Van den Bergh O. Respiratory Changes in Response to Cognitive Load: A Systematic Review. *Neural Plasticity* 2016; 2016: e8146809.
49. Aysin B, Aysin E. Effect of respiration in heart rate variability (HRV) analysis. *Conf Proc IEEE Eng Med Biol Soc* 2006; 1: 1776–1779.
50. Giblin LB, de Leon L, Smith LM, Sztynda T, Lal S. Heart rate variability, blood pressure and cognitive function: Assessing age effects. *River Publ* 2013; 3(3): 347–361.
51. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev* 2009; 33(2): 81–88.