Cardiovascular and cortisol reactions to acute psychological stress and cognitive ability in the Dutch Famine Birth Cohort Study

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Abstract

Given evidence linking blunted cardiovascular and cortisol reactions to acute stress and a range of adverse behavioural outcomes, the present study examined the associations between cardiovascular and cortisol reactivity and cognitive ability measured independently of the stress task exposure. Cognitive ability was assessed using the Alice Heim-4 test of general intelligence and two memory tasks in 724 men and women who were part of the Dutch Famine Birth Cohort Study. Blood pressure and heart rate, as well as cortisol, reactivity were measured to a battery of three standard acute stress tasks. Poorer cognitive ability was associated with lower cardiovascular reactions to stress and lower cortisol area under the curve. Our results are consistent with recent findings implicating low physiological stress reactivity in a range of adverse behavioural and health outcomes.

Descriptors: Blood pressure, cognitive ability, cortisol, heart rate, stress reactivity
The reactivity hypothesis proposes that large magnitude cardiovascular reactions to acute psychological stress contribute to the development of cardiovascular pathology. Evidence in support comes from a number of large scale cross-sectional and prospective observational studies that show positive associations between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure and hypertension status (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll, Smith, Shipley, Steptoe, Brunner & Marmot, 2001; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999), markers of systemic atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson, et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews, et al., 1998), and left ventricular mass and/or hypertrophy of the heart (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku, et al., 1999; Murdison, et al., 1998). Thus, the prevailing evidence implicates excessive cardiovascular reactivity in the development and expression of inflammatory cardiovascular disease.

There is now substantial evidence that hypertension is associated with poorer cognitive function (Elias, Wolf, D’Agostino, Cobb, & White, 1993; Launer, Masaki, Petrovich, Foley, & Havlic, 1995; Singh-Manoux, Ferrie, Lynch, & Marmot, 2005; Waldstein, 2003), as well as evidence implicating systemic inflammation more generally in cognitive impairment. Little is known about the association between cardiovascular stress reactivity and cognitive function. If excessive reactivity contributes to inflammatory cardiovascular disease and inflammation is associated with poor cognitive function, we might expect reactivity to be negatively associated with cognitive ability, i.e. higher cardiovascular reactivity would be related to poorer cognitive function.
Few previous studies have examined the association between reactivity and general cognitive ability. In a study of infants, greater suppression of a heart period based index of vagal tone during the cognitive challenge afforded by the Bayley Scale of Infant Development was associated with more mature cognitive skills and more coordinated motor behaviour (DeGangi, DiPietro, Greenspan, & Porges, 1991). A broadly similar outcome emerged from a more recent study of cardiovascular reactions to a task in which young adults were required to identify a target stimulus among a variety of distractor items (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009): R-wave to pulse interval, an index of sympathetic activity, was negatively associated with task performance, whereas respiratory sinus arrhythmia, an index of vagal tone, was positively related to performance. The authors interpret these outcomes as suggesting an association between enhanced sympathetic and reduced vagal cardiovascular influences and improved cognitive-attentional functioning. In contrast, no association between cardiovascular reactivity to memory tasks and task performance has been reported in studies of young (Backs & Seljos, 1994) and older adults (Wright, Kunz-Ebrecht, Iliffe, Foese, & Steptoe, 2005), although in the latter study, superior memory performance was associated with faster heart rate recovery following task exposure. Given the variations in study samples, the physiological parameters measured, and the cognitive tasks employed, it is not surprising that no clear consensus emerges from these studies. With one exception (Wright et al., 2005), all of the studies were small scale and did not adjust for potential confounding variables. More importantly, all of these previous studies measured cognitive ability as performance on the stress reactivity challenge. Stronger tests of the association between cognitive ability and cardiovascular reactivity to mental stress would be afforded by using measures of cognitive ability that are independent of the mental stress task employed to elicit reactivity.
In only one published study to date was cognitive ability measured independently of from mental stress task exposure (Ginty, Phillips, Der, Deary, & Carroll, 2011). Cognitive ability was assessed using the Alice Heim-4 test of general intelligence in 409 55 year-olds enrolled in the West of Scotland 20-07 Study. Blood pressure and heart rate reactions to an acute mental arithmetic stress task were measured seven years later. Following statistical adjustment for a wide-range of covariates including baseline cardiovascular activity, socio-demographics, body mass index, and medication status, cognitive ability and stress reactivity were positively associated. It was low cardiac reactivity which was characteristic of those with relatively low cognitive ability.

A number of studies have examined the relationship between cortisol reactivity and cognitive ability. However, there is no clear consensus regarding the direction of any association. One study reported that higher reactivity was associated with poorer cognitive performance (Wright et al., 2005), although another study observed the association only for men (Wolf, Schommer, Hellhammer, McEwen, Kirschbaum, 2001). However, the converse has also been observed; higher cortisol reactivity has been found to be associated with better memory performance (Domes, Heinrichs, Reichwald, & Hautzinger, 2002). Further, poorer declarative memory performance has been reported before and after a stressful task exposure for those who showed a smaller cortisol stress response (Lupien et al., 1997). High cortisol reactivity has also been observed to be related to better cognitive executive function (Blair, Granger, & Razza, 2005) and better dichotic listening performance (al’ Absi, Hugdahl, & Lovallo, 2002). As far as we are aware, no substantial cohort study has examined the association between cortisol stress reactivity and cognitive ability.
The opportunity to re-address the issue of stress reactivity and cognitive ability is afforded by data from the Dutch Famine Birth Cohort Study (Painter et al. 2005; Ravelli et al. 1998). Cardiovascular and cortisol reactivity was measured to a battery of three stress tasks and cognitive ability was assessed cross-sectionally, but independently, using the Alice Heim-4 test and, additionally, two memory tasks. The sample size was substantial and the richness of the data set again allowed us to adjust statistically for a wide-range of covariates. Based on the balance of previous evidence, including a recent substantial study finding a retrospective positive association between cardiac reactivity and cognitive ability, it was hypothesized that lower cardiovascular stress reactivity would be associated cross-sectionally with poorer cognitive ability. With regard to cortisol reactivity, we had no such clear expectations, given the variations in the findings of previous research.

Method

Participants

Participants were selected from the Dutch Famine Birth Cohort, which consists of 2414 men and women who were born in Amsterdam, the Netherlands, between November 1943 and February 1947. The selection procedures and subsequent loss to follow up have been described in detail elsewhere (Painter et al. 2005; Ravelli et al. 1998). All 1,423 members of the cohort who lived in the Netherlands on 1 September 2002 and whose current address was available were invited to the clinic to participate in a stress testing session; a total of 740 attended. The study was approved by the local Medical Ethics Committee and carried out in accordance with the Declaration of Helsinki and the informed written consent of the participants.
General Study Parameters

Trained research nurses undertook anthropometric measurements and conducted a standardized interview in which information was obtained about socio-economic status (SES), educational level, lifestyle, and use of medication. Height was measured twice using a fixed or portable stadiometer and weight twice using Seca and portable Tefal scales. Body Mass Index (BMI) was computed as weight (kg) / height (m²) from the averages of the two height and weight measurements. SES was defined according to the International Socio-Economic Index (ISEI)-92, which is based on the participant’s or their partner’s occupation, whichever has the higher status (Bakker & Sieben 1997). Values in the ISEI-92 scale ranged from 16 (low status) to 87. Participants were considered to consume alcohol if they drank at least one alcoholic beverage per week. Educational level was measured on a 10-point scale (1 = primary education not completed, 10 = university completed).

Cognitive Function

Cognitive function was assessed using the fourth version of the Alice Heim test (AH-4) (Heim, 1970) measuring general mental ability and a paragraph encoding and recall task measuring episodic memory. Participants were tested individually and both tests were performed in the morning. The AH-4 is a measure of general mental ability (Deary, Der, & Ford, 2001), and was administered and scored as described in the test manual (Heim, 1970). The test comprises 12 practice questions followed 33 items measuring numerical reasoning ability and 32 items measuring verbal reasoning ability. The test has been used in other population studies of individuals in the same age range (Singh-Manoux et al., 2005; Rabbitt, Diggle, Smith, Holland, & McInnes, 2001). Participants were given 10 minutes to answer as
many items as possible and the percentage of correct responses was taken as the AH-4 score.

For the paragraph encoding (memory task part 1) and recall test (memory task part 2), two paragraphs were orally presented (pre-recorded on tape). Participants were told to remember as many story elements as possible and asked to reproduce the story immediately (part 1) and 30 minutes later (part 2). In each case, the number of correctly retrieved elements was recorded.

**Psychological Stress Protocol**

The stress protocol, which started in the afternoon between the hours of 12:00-14:00, approximately one hour after a light lunch, lagged the cognitive assessment by mean (SD) 3 hours and 11 minutes (50 minutes). It began with a 20-minute baseline period after which three psychological stress tasks were performed: Stroop, mirror tracing and a speech. Each stress task lasted 5 minutes with 6 minutes in between and 30 minutes of recovery following the final stress task. The Stroop task consisted of a single-trial computerized version of the classical Stroop colour-word conflict challenge. After a short introduction, participants were allowed to practise until they fully understood the requirements of the task. Errors and exceeding the response time limit of 5 seconds triggered a short auditory beep. For the mirror-tracing task, a star had to be traced that could only be seen in mirror image (Lafayette Instruments Corp, Lafayette, IN, USA). Every divergence from the line triggered an auditory stimulus. They were allowed to practice one circuit of tracing. Participants were instructed to prioritize accuracy over speed and were told that most people could perform five circuits of the star without divergence from the line within the given 5 minutes. Prior to the speech task, participants listened to an audio taped instruction in which they were told to imagine a situation in which they were falsely accused of pick pocketing. They were then given 2
minutes to prepare a 3-minute speech in which they had to respond to the accusation. The speech was videotaped and participants were told that the number of repetitions, eloquence, and persuasiveness of their performance would be assessed by a team of communication experts and psychologists. After completion of the stress protocol, participants completed 7-point rating scale of stress task impact, including participants’ commitment to the tasks.

Continuous blood pressure (BP) and heart rate (HR) recordings were made using a Finometer or a Portapres Model-2 (Finapres Medical Systems, Amsterdam, the Netherlands). There were no differences in reactivity as a function of the two different measuring devices. Six periods of 5 minutes were designated as the key measurement periods: resting baseline (15 minutes into the baseline period), Stroop, mirror-tracing, speech task (including preparation time), recovery 1 (5 minutes after completing the speech task) and recovery 2 (25 minutes after completing the speech task). Mean systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were calculated for each measuring period. A total of seven saliva samples were collected using Salivettes (Sarstedt, Rommelsdorf, Germany): at 5 and 20 minutes of the baseline period, at 6 minutes following completion of the Stroop task and the mirror tracing task, and at 10, 20 and 30 minutes after completion of the speech task. Salivary cortisol concentrations were measured using a time-resolved immunofluorescent assay (DELFIA) (Wood et al, 1997). The assay had a lower detection limit of 0.4 nmol/l and an inter-assay variance of 9-11% and an intra-assay variance of less than 10%.

**Statistical Analyses**

Baseline cortisol was computed as the mean of the first and the second cortisol concentration measures during the baseline period. Cortisol reactivity was calculated as cortisol area under
the curve (AUC) using the average baseline and the five subsequent measures, and applying the trapezoid method grounded to zero (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Because the distribution of AUC values were skewed, they were log\(_{10}\) transformed for the purposes of analyses. Baseline cardiovascular activity was the average of values recorded in the 5-minute period 15 minutes into the baseline. BP and HR measures were averaged for each of the three stress tasks and the highest 5-minute average was used to determine peak stress reactivity. Cardiovascular stress reactivity was defined as the difference between these peak averages during stress and baseline for each of the three cardiovascular variables. The SES measure had eight missing values; we imputed these values using the SPSS linear trend at point method. The AH-4 score and cortisol had skewed distributions and are summarized with medians and inter quartile ranges (IQR) and geometric means and standard deviations respectively.

Differences in cognitive function scores between men and women and those from a lower and higher SES background were examined with Mann Whitney (sex) and Kruskal Wallis (SES) tests in the case of AH-4 score and t-test (sex) and ANOVA (SES) in the case of memory scores. Correlations were calculated between AH-4 score (Spearman) and memory scores (Pearson) and general study parameters. Linear regression models were applied to analyze the associations between the cognitive function measures and baseline physiological activity and stress reactivity. Associations between cognitive function measures and baseline activity were adjusted for sex and SES. The stress reactivity regression models were first run without adjustment, then with adjustment for sex, SES, educational level and age and, secondly, with additional adjustment for BMI, alcohol consumption, smoking, use of anti-hypertensive, anti-depressant and anxiolytic medication, commitment to the stress tasks, and baseline
physiological activity. These covariates were selected as they have been shown to be directly or indirectly associated with reactivity in previous studies (Ginty et al., 2011; Phillips, Hunt, Der, & Carroll, 2011; Carroll, Phillips, & Der, 2008; Lovallo, 2011). In the case of cortisol AUC, because it was grounded to zero, baseline cortisol adjustments were made in all three of the cortisol AUC regression models for reach of the cognitive ability measures. Differences were considered to be statistically significant if $p$-values were ≤ .05. SPSS 16.0 (SPSS Inc, Chicago, IL) was used to perform the statistical analyses.

Results

Study Population

Of the 740 cohort members who participated in the study, 725 completed the psychological stress protocol. Fifteen persons were unable to participate in or finish the stress protocol due to logistical problems ($n = 5$) or because they were feeling unwell ($n = 10$). Due to technical problems, BP and HR recordings were unavailable for four individuals. A total of 270 participants had one or more missing cortisol value as a result of insufficient saliva, and were excluded from the cortisol analyses. A total of 724 participants had complete data on at least one of the two cognitive tests. Forty-seven percent ($n = 342$) of the study population was male; the mean age was $58.3 \pm 0.9$ years. The mean SES level was $49.7 \pm 14.1$ and the mean educational level was $4.5 \pm 2.2$. A total of 67.5% consumed at least one alcoholic beverage every week; 23.9% were smokers; 23.5% were using anti-hypertensive medication and 12.0% were using anti-depressant or anxiolytic medication.

Cognitive Function
The overall median AH-4 score was 72.4 ± 18.9 (IQR). The overall mean score on the first part of the memory task was 21.5 ± 6.9 and on the second part of the memory task was 17.9 ±7.0. Table 1 shows the results for the three measures of cognitive function according to sex and SES level. Men had a significantly higher AH-4 score than women \( (p < .001) \). Those from a higher SES background had a higher AH-4 score \( (p < .001) \), higher memory 1 \( (p = .02) \) and memory 2 \( (p = .01) \) scores compared to those from a lower SES background. AH-4 score was positively correlated with educational level \( (r = .46, p < .001) \) and negatively with alcohol consumption \( (r = -.13, p = .001) \) and smoking \( (r = -.15, p < .001) \). Memory score 1 and 2 were both positively correlated with educational level \( (r = .29, p < .001, r = .30, p < .001) \) and negatively with age \( (r = -.12, p = .002, r = -.11, p = .01) \), alcohol consumption \( (r = -.09, p = .03, r = -.09, p = .04) \) and smoking \( (r = -.12, p = .003, r = -.14, p < .001) \).

[Insert Table 1 about here]

**Stress Reactivity**

The psychological stress protocol significantly perturbed cardiovascular activity and cortisol (all \( p < .001 \)). Table 2 shows that mean SBP reactivity was 47.6 ± 20.7 mmHg, DBP reactivity 21.4 ± 9.1 mmHg, HR reactivity 11.8 ± 9.5 bpm and the geometric mean for cortisol AUC was 448.5 ± 1.8. In the subsequent cortisol AUC analyses, as indicated, we adjusted for baseline cortisol. Men and women did not differ in SBP, DBP and HR stress reactivity, but women had lower cortisol reactivity \( (p < .001) \) compared to men. Those from a higher SES background had higher SBP \( (p = 0.01) \) and HR \( (p < .001) \) reactivity, and cortisol AUC \( (p = .03) \) than those from a lower SES background.
Educational level was positively correlated with SBP ($r = .14, p < .001$), HR ($r = .14, p < .001$). BMI was negatively correlated with HR reactivity ($r = -.20, p < .001$) and cortisol AUC ($r = -.11, p = .02$). Alcohol consumption was negatively correlated with HR reactivity ($r = -.11, p = .004$) and cortisol AUC ($r = -.11, p = .02$). Smoking was negatively correlated with SBP ($r = -.20, p = .002$), DBP ($r = -.09, p = .01$), HR ($r = -.19, p < .001$) reactivity and cortisol AUC ($r = -.12, p = .01$). Use of anti-hypertensive medication was negatively correlated with HR reactivity ($r = -.08, p = .04$) and use of anti-depressant or anxiolytic medication was negatively associated with SBP ($r = -.12, p = .002$) and DBP ($r = -.10, p = .01$) reactivity.

[Cognitive Function and Baseline Cardiovascular and Cortisol Activity]

Memory score 1 was negatively associated with baseline cortisol. Per unit increase in memory score 1, baseline cortisol increased 0.8 % ($p = 0.04$). There were no other significant associations between cognitive function and baseline cardiovascular and cortisol activity.

[Cognitive Function and Cardiovascular and Cortisol Reactivity]

AH-4 score, memory score 1 and memory score 2 were all significantly positively associated with SBP, DBP and HR reactivity: the lower the reactivity the lower the cognitive ability. Effect sizes and other statistics of these associations are presented in Tables 3 (SBP reactivity), 4 (DBP reactivity) and 5 (HR reactivity). Table 3 also shows that, firstly, adjustment for sex, SES, educational level and age and then, additionally, for BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or
anxiolytic medication, commitment to the stress tasks, and baseline SBP/DBP/HR, did not
abolish associations for SBP and HR, but did attenuate DBP findings to non-significance.
Although effect sizes became somewhat smaller, in all cases the associations remained
statistically significant. The associations are illustrated by plotting tertiles of cognitive ability
scores against reactivity in Figures 1 (SBP reactivity), 2 (DBP reactivity), and 3 (HR
reactivity). We also analysed the cardiovascular reactivity data as mean cardiovascular
reactivity (mean activity across the three tasks – baseline). The outcomes were almost
identical to those reported from the peak response analyses above, with one exception, the
previously significant association between memory 2 performance and SBP reactivity, was no
longer statistically significant ($p = .06$, whereas previous it was $p = .05$).

In the models adjusting only for baseline cortisol, all three of the cognitive ability tasks were
positively associated with cortisol AUC: the flatter the AUC the lower the cognitive ability.
These associations are illustrated by plotting tertiles of cognitive ability scores against AUC
in Figures 4. For this illustration, actual arithmetic mean (SE) cortisol AUC values were
used. For memory 1 and memory 2 tasks the associations between cognitive ability and
cortisol AUC remained statistically significant in the two models adjusting for additional
covariates. However, in the case of AH-4, additional adjustment attenuated the associations
to non-significance. The summary statistics for the regression models are presented in Table
6.

[Insert Tables 3, 4, 5, and 6 and Figures 1, 2, 3, and 4 about here]
This study examined the cross-sectional association between cardiovascular and cortisol stress reactivity and cognitive ability, as indexed by scores on the AH-4 test of verbal and numerical reasoning and by two memory tasks: immediate and delayed recall. Low SBP, DBP, and HR reactions to acute stress were associated with low AH-4 test scores and poorer performance on the two memory tasks. Post hoc analyses of tertiles of AH-4 and memory task scores indicated a positive dose-response relationship between cognitive ability and cardiovascular reactivity. These associations between cardiovascular reactivity and cognitive ability remained statistically significant in regression models that adjusted for age, sex, socio-economic status, educational level, BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline cardiovascular activity. The fact that the positive associations between cardiovascular reactivity and cognitive ability, with one exception, survived adjustment for stress task commitment suggests that present results cannot be accounted for by participants of low cognitive ability disengaging from the stress challenges. Low cortisol AUC was also associated with poorer AH-4 scores and memory performance. These associations survived adjustment for additional covariates in the case of memory performance but not in the case of AH-4 scores. Post hoc analyses using tertiles of cognitive ability suggest a dose response relationship between memory performance and cortisol stress reactivity as indexed by AUC.

It is noteworthy that there were no significant associations between cognitive ability and baseline cardiovascular levels, given the extant literature indicating a relationship between resting blood pressure and cognitive function (Elias, Elias, Robbins, & Budge, 2004; Waldstein, Giggey, Thayer, & Zonderman, 2005; Waldstein, 1994; Robbins, Elias, Elias, &
Budge, 2005). However, cognitive deficits may be manifest mainly in those with hypertensive or borderline hypertensive blood pressure levels (Novak & Hajjar, 2010). In addition, both cross-sectional and longitudinal relationships to blood pressure have been found to be predominately non-linear and moderated by a range of factors including age, education, and anti-hypertensive medication (Waldstein, et al. 2005). With one exception, there was also no association between cognitive ability and baseline cortisol.

The direction of the relationship between cognitive ability and cardiovascular reactivity is in line with that observed in two earlier studies, which found that lower cardiovascular reactivity was associated with poorer performance on the mental stress task (DeGangi et al., 1991; Duschek et al., 2009). However, it should be conceded that two other studies failed to find an association between reactivity and cognitive ability as revealed by performance on the stress task (Backs & Seljos, 1994; Wright et al., 2005). Only one other published study in the context has assessed cognitive ability independently of stress task performance; a recent analysis of a substantial cohort from the West of Scotland 20-07 found a positive retrospective association between AH-4 scores and cardiac reactions to a mental arithmetic stress seven years later (Ginty et al., 2011). The present analyses indicate that the positive relationship between cognitive ability and reactivity may extend to blood pressure, as well as cardiac, reactivity. That the relationship holds for memory task performance as well as AH-4 scores indicates the generality of the association between blunted cardiovascular reactivity and poor cognitive ability.

The present finding of a positive association between cognitive ability, particularly memory performance, and cortisol stress reactivity is in line with the results of three previous studies.
showing that low cortisol reactivity was associated with poorer performance on a variety of cognitive tasks (Domes et al., 2002; Blair et al., 2005; al’ Absi, 2002). In addition, there has also been an observation from a small scale study of elderly individuals that cortisol reactivity was lower in those with poorer declarative memory before and after the stressful exposure (Lupien et al., 1997). However, it should be conceded that other studies report a negative association between cognitive ability and cortisol reactivity, although for men, but not for women (Wolf et al., 2001), and in two instances for cognitive tasks that also served as the stress exposure (al’ Absi, 2002; Wright et al., 2005). In the present study, multivariate analyses abolished the positive association between AH-4 scores and cortisol AUC. It is possible that this reflected a reduction in power in the cortisol analyses as a function of missing data. However, our analyses included substantially more participants than previous studies of cortisol reactivity and cognitive ability. Accordingly, it is also possible that robust positive associations between cognitive ability and cortisol reactivity are found mainly for tasks that involve memory and recall. It is perhaps worth noting in this context that two of the four studies above reporting an association between low cortisol reactivity and poorer cognitive ability used a memory task to measure cognition (Domes et al., 2002; Lupien et al., 1997).

The present findings are also consistent with a growing body of cross-sectional and prospective evidence that low, not high, cardiovascular and/or cortisol reactivity are associated with a range of adverse health and behavioural outcomes, such as obesity (Carroll, Phillips, & Der, 2008; Phillips, 2011), symptoms of depression (Carroll, Phillips, Hunt, & Der, 2007; de Rooij, Schene, Phillips, & Roseboom, 2010; Phillips et al., 2011; Rottenberg, Clift, Bolden, Salomon, 2007; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; York, Hassan,
Li, Li, Fillingim, Sheps, 2007), and bulimia (Koo-Loeb, Pedersen, & Girdler, 1998; Ginty, Phillips, Higgs, Heaney, & Carroll, in press). Low reactivity has also been associated with tobacco and alcohol dependence, as well as risk of dependence (al’ Absi, 2006; al’Absi, Hatuskami, & Davis, 2005; Girdler, Jammer, Jarvik, Soles, & Shapiro, 1997; Lovallo, Dickensheets, Myers, Thomas & Nixon, 2000; Pankin, Dickensheets, Nixon, & Lovallo, 2002; Phillips, Der, Hunt, & Carroll, 2009; Roy, Steptoe, & Kirschbaum, 1994), and exercise dependence (Heaney, Ginty, Phillips, & Carroll, 2011).

Further, our results are consistent with the recent contention that relatively low cardiovascular reactions to acute stress may be a peripheral marker of central motivational dysregulation (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, in press; Lovallo, 2011). By central motivational dysregulation we mean the suboptimal functioning of those systems in the brain, converging at the striatum and ventromedial prefrontal cortex, which appear to shape the motivation of our behaviour. These may be precisely the same circuits that support physiological reactivity (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, in press; Lovallo, 2011). As cognitive performance requires the integrity of such motivational systems (Busato, Prins, Elshout, & Hamaker, 2000; Dweck, 1986; McClelland, Atkinson, Clark, & Lowell, 1953; Pintrich & Schunk, 1986), it would be expected that lower rather than higher cardiovascular reactivity would be associated with poorer subsequent cognitive ability, which is precisely what was observed in the current study.

The present study is not without limitations. First, it should be acknowledged that the observed effect sizes are small. However, our effects for cardiovascular reactivity are of the same order as the positive associations between cardiovascular reactivity and future resting
blood pressure in other studies (Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll, et al., 2001; Carroll et al., 2003; Markovitz et al., 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999). Second, only blood pressure and HR reactivity were measured. It could have proved instructive to have a more comprehensive assessment of haemodynamics, such as that afforded by impedance cardiography. Further, a continuous rather than an intermittent assessment of blood pressure and HR would have permitted us to chart the time course of acute stress reactivity, as well as permitting measures that would throw light on the underlying mechanisms. Cardiovascular reactivity would appear to reflect both β-adrenergic and parasympathetic influences (Balanos et al., 2010; Sloan, Korten, & Myers, 1991). Thus, low cardiovascular reactivity could reflect reduced β-adrenergic drive or less withdrawal of vagal tone during the stress task. Regrettably, in the present study we cannot determine which of these was the predominant mechanism for low cardiac reactivity. Third, determining causality and the direction of causality in cross-sectional studies is impossible. Further, confounding by unmeasured variables can never be wholly discounted. However, we did adjust for a broad range of potential confounders, indeed more than any previous study. Fourth, at the time of testing no Dutch version of the AH-4 was not available, so it was translated internally (de Rooij, Wouters, Yonker, Painter, & Roseboom, 2010). Also, it was not possible to separate the verbal and numeric scores of the total AH-4 score. A separation of these subscales may have shown reactivity to stressors to be associated with one subscore more than with the other. However, a previous study has shown reactivity to be associated with both subscales (Ginty et al., 2011). Fifth, although we would argue that the separation of stress exposure from cognitive ability assessment in the present study should be regarded as a strength, it is also possible that the time limited AH-4 task itself acted as a stressor and illicited individual differences in reactivity that may have correlated with those
observed during the designated stress tasks. However, since stress reactivity was not measured during the AH-4 we have no way of determining whether this was the case. Sixth, this is a unique population and it has been suggested that early life adversity may predispose individuals to life-long vulnerability to stress. However, a previous study using this population showed individuals who experienced prenatal exposure to the Dutch Famine did not differ in cortisol stress reactivity from those who did not (De Rooij, Painter, Phillips, Osmond, Tanck, Bossuyt, & Roseboom, 2006). Finally, it was not possible to derive performance scores for the stress tasks used in this study. Nevertheless, we do have a measure of commitment to the task and have included this as a covariate in the fully adjusted analyses.

In conclusion, we observed a robust cross-sectional positive association between cardiovascular and cortisol reactivity and cognitive ability assessed independently of mental stress task performance. Our results are consistent with the notion low or blunted cardiovascular and cortisol stress reactivity may be associated with a range of adverse behavioural and health outcomes and low reactivity may not necessarily be adaptive.
References


Author Notes

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Table 1. Median (IQR) AH-4 and mean (SD) memory test (MT) scores by sex and socio-economic status.

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<th>MT score part 2</th>
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<td>342</td>
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<td>20.5 (6.5)</td>
<td>16.9 (6.8)</td>
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<tr>
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<td>380</td>
<td>75.4 (16.1)</td>
<td>22.3 (7.1)</td>
<td>18.8 (7.1)</td>
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MT = memory test; SES = socio-economic status.
Table 2. Mean (SD) cardiovascular and cortisol values for baseline, stress, and reactivity.

<table>
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<th>Reactivity</th>
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<td>720</td>
<td>127.9 (21.0)</td>
<td>175.4 (28.8)</td>
<td>47.6 (20.7)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>720</td>
<td>65.9 (12.0)</td>
<td>87.2 (14.4)</td>
<td>21.4 (9.1)</td>
</tr>
<tr>
<td>Heart Rate (HR)</td>
<td>720</td>
<td>74.3 (10.5)</td>
<td>86.0 (14.4)</td>
<td>11.8 (9.5)</td>
</tr>
<tr>
<td>Cortisol (nmol/l) *</td>
<td>455</td>
<td>4.4 (1.8)*</td>
<td>448.5 (1.8)**</td>
<td></td>
</tr>
</tbody>
</table>

* Data are given as geometric means ± SD.

**AUC
<table>
<thead>
<tr>
<th>Table 3. Regression models AH-4 and memory test scores and SBP reactivity.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AH-4 correct items</strong></td>
</tr>
<tr>
<td>Unadjusted</td>
</tr>
<tr>
<td>Model 1</td>
</tr>
<tr>
<td>Model 2</td>
</tr>
<tr>
<td><strong>Memory test score part 1</strong></td>
</tr>
<tr>
<td>Unadjusted</td>
</tr>
<tr>
<td>Model 1</td>
</tr>
<tr>
<td>Model 2</td>
</tr>
<tr>
<td><strong>Memory test score part 2</strong></td>
</tr>
<tr>
<td>Unadjusted</td>
</tr>
<tr>
<td>Model 1</td>
</tr>
<tr>
<td>Model 2</td>
</tr>
</tbody>
</table>

Model 1 includes sex, socio-economic status, educational level and age; Model 2 additionally includes BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline SBP.
Table 4. Regression models AH-4 and memory test and DBP reactivity.

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$</th>
<th>$R^2$ change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AH-4 correct items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.08</td>
<td>3.54</td>
<td>&lt;.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.09</td>
<td>3.32</td>
<td>.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.08</td>
<td>3.11</td>
<td>.002</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Memory test score part 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.19</td>
<td>3.64</td>
<td>&lt;.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.18</td>
<td>3.26</td>
<td>.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.17</td>
<td>3.07</td>
<td>.002</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Memory test score part 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.13</td>
<td>2.55</td>
<td>.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.12</td>
<td>2.19</td>
<td>.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.11</td>
<td>2.00</td>
<td>.05</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Model 1 includes sex, socio-economic status, educational level and age; Model 2 additionally includes BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline DBP.
Table 5. Regression models AH-4 and memory test and HR reactivity.

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$</th>
<th>$R^2$ change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AH-4 correct items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.10</td>
<td>4.08</td>
<td>&lt;.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.07</td>
<td>2.64</td>
<td>.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.06</td>
<td>2.24</td>
<td>.03</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Memory test score part 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.19</td>
<td>3.43</td>
<td>.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.14</td>
<td>2.47</td>
<td>.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.14</td>
<td>2.50</td>
<td>.01</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Memory test score part 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.21</td>
<td>3.97</td>
<td>&lt;.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.17</td>
<td>3.02</td>
<td>.003</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.15</td>
<td>2.79</td>
<td>.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Model 1 includes sex, socio-economic status, educational level and age; Model 2 additionally includes BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline HR.
Table 6. Regression models AH-4 and memory test and AUC for cortisol.

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>R² change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AH-4 correct items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.003</td>
<td>2.46</td>
<td>.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.001</td>
<td>0.74</td>
<td>.46</td>
<td>0.00</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.000</td>
<td>0.13</td>
<td>.90</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Memory test score part 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.011</td>
<td>3.53</td>
<td>&lt;.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.010</td>
<td>3.19</td>
<td>.002</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.009</td>
<td>2.83</td>
<td>.005</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Model 1 adjusts only for baseline cortisol; Model 2 additionally includes sex, socio-economic status, educational level and age; Model 3 additionally includes alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication and stress task commitment; $\beta$ in percent difference based on log-transformed AUC for cortisol.
Figure captions

Figure 1. Mean (SE) SBP reactivity for tertiles of cognitive ability scores
Figure 2. Mean (SE) DBP reactivity for tertiles of cognitive ability scores
Figure 3. Mean (SE) HR reactivity for tertiles of cognitive ability scores
Figure 4. Mean (SE) AUC cortisol for tertiles of cognitive ability scores

Note: a= significantly different from 2ⁿᵈ, b= significantly different from 3ⁿᵈ. *= p < .05, **= p < .005