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Cardiac stress reactions and perseverance: Diminished reactivity is associated with study non-completion

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Highlights

Blunted cardiovascular stress reactions may signal poor behavioral regulation
Heart rate reactivity to mental stress was recorded in 176 high school students
Diminished heart rate reactivity predicted failure to complete follow-up testing
Blunted heart rate reactivity may signal lack of behavioral perseverance

Abstract

Blunted cardiovascular stress reactions may be a marker for poor behavioural regulation. The present study examined the association between heart rate reactivity and perseverance, operationalized as the failure to complete a subsequent follow-up assessment. The heart rate (using electrocardiography), cardiac output (using Doppler echocardiography) and blood pressure (using a semi- automatic sphygmomanometer) of 176 high school students were measured before and during exposure to a standard 10-minute mental arithmetic stress. A year later all participants were contacted to complete a simple and undemanding on-line assessment. Despite repeated promptings, 44 failed to do so. Diminished heart rate and cardiac output stress reactions predicted failure to complete the follow-up. This result adds to the emerging characterisation of those who exhibit blunted stress reactions by revealing associated deficiencies in perseverance. It may also have prognostic implications for the completion of multi-session interventions, as well as for selection bias in stress reactivity studies with follow-up designs.

1. Introduction

Exaggerated cardiovascular reactions to acute psychological stress are associated with an increased risk for cardiovascular disease morbidity and mortality (Carroll et al., 2012). Although, this would imply that diminished or blunted cardiovascular stress reactions should be benign, accumulating evidence suggests otherwise. Blunted stress reactions are associated with a range of adverse health and behavioural outcomes such as obesity (Carroll et al., 2008; Phillips et al., 2012; Singh and Shan, 2013), depression (Brindle et al., 2013; Carroll et al., 2007; de Rooij et al., 2010; Phillips et al., 2011; Salomon et al., 2009; Schwerdtfeger et al., 2011), bulimia (Ginty et al., 2012; Koo-Loeb et al., 1998), and childhood conduct disorders (Ortiz & Raine, 2004; Pesonen et al., 2011). Further, both smokers (Ginty et al., 2014; Girdler et al., 1997; Roy et al., 1994; Sheffield et al., 1997; Straneva et al., 2000) and those dependent on alcohol (Dai et al., 2007; Panknin et al., 2002; Sinha et al., 2011) are characterised by diminished stress reactivity. Indeed, blunted stress reactivity is a predictor of relapse from smoking and alcohol cessation (al'Absi et al., 2005; Junghanns et al., 2003). Finally, diminished reactions to stress would also appear to be a feature of exercise dependence (Heaney et al., 2011) and gambling addiction (Paris et al., 2010). It has been argued that blunted stress reactivity is linked to these seemingly diverse outcomes because it is a peripheral marker of an under-recruitment of central brain systems during situations, such as acute psychological stress exposures, that require motivated action, i.e., blunted stress reactivity signals a dysregulation of the neural systems in the brain that support motivation and goal directed behaviour (Carroll et al., 2009, 2011; Lovallo, 2011). A recent study demonstrated that individuals with blunted cardiac stress reactions have reduced activation in the anterior midcingulate cortex and insula, areas that support motivation and goal directed behavior, during a challenging task compared with a control task. (Ginty et al., 2013).

If blunted stress reactivity is, indeed, a marker of such central dysfunction it should be associated with other more general manifestations of poor behavioural regulation. This has received little attention, although there is some evidence linking diminished cardiovascular reactivity to impaired response inhibition (Bennett et al., 2014) and impulsivity (Allen et al., 2009). Persistence and perseverance are key components in achieving many goals in daily life, and are

related to greater academic and career progression (Andersson and Bergman, 2011) and the ability to refrain from unhealthy behaviours (Quinn et al., 1996). In addition, as with blunted stress reactivity, lack of perseverance is associated with relapse from smoking cessation (Lopez-Torrecillas et al., 2014), obesity (Murphy, Stojek & Mackillop, 2014), and conduct disorder (Marmorstein, 2013). To the best of our knowledge, however, no studies have examined the association between stress reactivity and perseverance outside the context of relapse in cessation studies. A casual observation from a stress reactivity study that involved repeated testing of exaggerated and blunted stress reactors was that it was more difficult to retain blunted reactors in later sessions (Ginty et al, 2013). A recent study in which we measured both cardiac and blood pressure reactions to acute psychological stress and which also entailed a fairly undemanding 1-year follow-up allowed us to more formally explore the link between cardiovascular stress reactivity and perseverance; we hypothesised that blunted stress reactors would be less likely to complete the follow-up.

2. Methods

2.1. Participants

Final year high school students (N= 185) were recruited from schools proximal to the University of Birmingham. Data from nine participants were unusable due to signal acquisition problems, resulting in a final sample of 176 participants (age, M = 18.02, SD = 0.43; 82% female). Exclusion criteria included history of cardiovascular disease and participants were required to refrain from alcohol and vigorous exercise 12h, caffeine 2h, and food and drinks other than water 1h before testing. At the time of recruitment participants were informed that the study consisted of both a laboratory visit (Phase 1) during their final year of high school and a follow-up on-line questionnaire assessment (Phase 2) approximately six months into their first year of university. Participants were asked to volunteer for the study only if they were willing to commit to both the initial laboratory visit and the follow-up assessment. Both the study information sheet and study consent form included information about the follow-up portion of the study. All participants and legal guardians, if participants were under 18, gave informed consent. Participants received £10 for study participation. The study was approved by the University Ethics Committee.

2.2 Laboratory Procedure

Participants completed questionnaires in a quiet room upon arrival to the laboratory. After questionnaire completion, participants were asked to lay in a semi lateral decubitus position on a standard hospital bed with their back supported by pillows for comfort while electrocardiograph (ECG) electrodes were applied in a three lead configuration and a blood pressure cuff was attached. The Doppler echocardiography probe was then positioned and the experimenter assessed the quality of the image. Participants then sat quietly for 10 min (adaptation phase), this was followed by a further formal 10-min resting baseline period, after which participants were read instructions regarding the PASAT and completed a brief practice to ensure they understood the task. Participants then completed the 10 min stress task followed by a 10 min recovery period (recovery data not reported here). Cardiovascular measurements were averaged for each 10 min phase (baseline, stress). Afterwards, participants completed a brief questionnaire regarding task stressfulness, difficulty, and their engagement. Participants responded on a standard Likert scale ranging from 0-6 anchored by “not at all” and “extremely”.

2.3 Acute psychological stress task

Participants completed the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977), which has been shown to significantly perturb cardiac activity (Mathias et al., 2004; Ring et al., 2002) and demonstrate good test-retest reliability (Ginty et al., 2013; Willemsen et al., 1998). Briefly, during the 10-minute stress phase, participants were presented with a series of single-digit numbers by CD recording and were asked to add consecutive single-digit numbers while remembering the most recent number so it could be added to the next number presented. Participants verbally said their answers. Participants began with 1000 points and lost five points for every wrong or unanswered question. The final score was calculated and used as an index of task performance. For further details see Ginty et al., 2012.

2.4 Cardiovascular measurements and data processing

Heart rate (HR) was measured continuously by electrocardiography (ECG) with spot electrodes placed on the lower left rib and the right and left clavicle. Raw ECG data was collected using a Grass P511 amplifier (Grass Instruments, USA), CED Power1401 digital to analogue converter, and Spike 2 software at a sampling frequency of 1000 Hz. Each trace was visually inspected for

artefacts and using Kubios HRV, a software suite designed for analysing human heart rate, artefacts were removed. Average HR for each test phase (baseline, stress) was calculated from inter-beat intervals using Kubios HRV using the full 10 min of data from each phase. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured discontinuously (minutes 2, 4, 6, 8 of each period) using a semi-automatic sphygmomanometer (Critkon Inc., Tampa, FL). Echocardiograph measurements were performed using a Philips Sonos 7500 ultrasound machine with an S3 two-dimensional transducer (1-2 MHz) and digital images of spectral waveforms were recorded discontinuously for later analysis. For each measurement point, averages were obtained from three or more spectral waveforms recorded; measurements for aortic blood flow to be averaged across 60s-intervals. An apical five-chamber view of the heart was used with Doppler mode to identify flow through the aortic valve during systole. The velocity profile of the aortic flow was obtained using pulse wave spectral mode at a screen sweep speed of 100 mm s^{-1} , Doppler sampling of the flow was taken immediately below the orifice of the aortic valve. The flow was quantified automatically using the velocity time integral, which is the mean distance through which blood travels in the outflow tract during ventricular contraction. Each velocity time integral was made from at least three velocity profiles taken towards the end of expiration. The diameter of the aortic valve was measured from a parasternal long axis view and the aortic valve area was calculated. Cardiac output (CO) was calculated as $\text{HR} \times (\text{velocity time integral} \times \text{aortic valve area})$. CO data was only available for 151 participants due to image acquisition difficulties. There were no demographic or cardiovascular differences between those who had full CO data and those who did not, nor were there any differences in likelihood to complete Phase 2.

A recent study comparing measurements of cardiac output using impedance cardiography and Doppler echocardiography concluded that the latter provided a more reliable and clinically acceptable and accurate method of measuring cardiac activity during haemodynamic challenge (Fellahi et al., 2009).

2.5 Questionnaires

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). The HADS is a well-recognized assessment instrument that

comprises 14 items, 7 measuring depression and 7 measuring anxiety. The HADS has good concurrent validity and test-retest reliability (Bramley et al., 1988; Hermann, 1997).

Neuroticism was measured by the Eysenck Personality Questionnaire Revised-Abbreviated (EPQR-A; Francis et al., 1992). The neuroticism subscale has demonstrated good levels of internal consistency (Francis et al., 1992).

2.6. Follow-up (Phase 2)

All participants were sent an e-mail on March 6, 2013 asking them to complete Phase 2 of the study, which consisted of an on-line questionnaire. Participants were told they could complete the secure on-line questionnaire from any computer, tablet, or phone with internet access and would receive a £10 voucher upon completion. In the absence of a timely response, four follow-up e-mails and three follow-up text messages were sent over a period of three months. The mean time lag between Phase 1 and initial Phase 2 contact was 1.08 (SD = 0.20) years.

2.7. Statistical analysis

Reactivity for each cardiovascular measure (HR, SBP, DBP, CO) was calculated as the difference between baseline average and stress task exposure average. Repeated-measures ANOVAs, using baseline and task values, were undertaken to confirm that the PASAT perturbed cardiovascular activity. Characteristics of non-completers and completers were compared using one-way ANOVA and chi-square. The major analysis of the link between cardiovascular reactivity and likelihood of study completion was by a series of binary logistic regressions. All alpha levels were set to $p < .05$.

3. Results

Two-way (baseline, stress) repeated measures ANOVAs indicated that on average cardiovascular activity was substantially higher during stress than baseline (See Table 1). Despite repeated prompting, 44 of the 176 participants having full HR and BP data (38 with full CO data) did not complete Phase 2 of the study. The average time lag from Phase 1 to initial Phase 2 contact was 1.08 (0.20) for non-completers and 1.07 (0.21) years for completers, $p = .85$. The characteristics of the completers and non-completers are summarized in Table 1. Non-completers showed significantly lower HR reactivity and CO reactivity than completers. There were no other

significant differences between completion groups. Binary logistic regression confirmed the association between HR reactivity and completing the study, Odds Ratio (OR) = 1.06, 95% CI, 1.02 – 1.11, $p = .006$. Every one standard deviation increase in HR reactivity is associated with an 81.0% greater odds of completing the study. There was also a significant association between CO reactivity and completing the study, OR = 1.71, 95% CI, 1.15-2.57, $p = .009$. Every one standard deviation increase in CO reactivity is associated with 83.5% greater odds of completing the study. For illustration purposes quartiles of HR and CO reactivity were created and plotted against percentage of participants who completed the study (see Figure 1a and Figure 1b). Given that non-completers tended to be older ($p = .089$) and have poorer performance on the stress task ($p = .052$), a further regression model was tested with these as covariates. The association between HR reactivity and likelihood of completion was only slightly attenuated, OR = 1.05, 95% CI, 1.00 – 1.10, $p = .03$. Neither of the covariates was significant in this model. The association between CO reactivity and likelihood of completion was reduced, OR = 1.50, 95% CI, 0.99-2.27, $p = .05$. Neither of the covariates was significant in this model. There were no significant associations between either SBP reactivity ($p = .69$) or DBP reactivity ($p = .25$) and likelihood of completing the study.

4. Discussion

Despite repeated prompts from the same researcher who conducted the earlier stress testing and a modest financial incentive, a quarter of our participants failed to complete what was a fairly undemanding 1-year follow-up. Diminished HR and CO reactions to an acute psychological stress were associated with non-completion. The association was independent of age and stress task performance, and completers and non-completers did not differ significantly in gender, ethnicity, baseline cardiac activity, and their perceptions of how stressful and difficult the stress task was, nor in the extent to which they were engaged during it. The relationship could not be explained by personality and/or mood factors such as depression, anxiety, or neuroticism. This is the first demonstration we know of that diminished stress reactivity is linked to a measure of perseverance rather than relapse.

The direction of our findings is in accord with those from a recent 4-year study of police officers routinely exposed to traumatic events. Officers who showed blunted reactivity to a laboratory

stress exposure during training showed less resilience when faced with stressful events on the job (Galatzter-Levy et al., 2014). The present results also resonate with previous research demonstrating a link between diminished stress reactivity and shorter time to relapse during smoking (al' Absi, Hatsukami, & Davis, 2005) and alcohol (Junghanns et al., 2003) cessation programs, as well as after inpatient cocaine treatment (Back et al., 2010). However, it should be conceded that these latter studies examined the ability to persist in refraining from something, rather than from continuing to actively participate in something. Nevertheless, their findings and those of the current study suggest that diminished reactivity may provide a prognostic marker for identifying individuals who are less likely to complete or fully engage with common multi-session behavioural intervention programmes (e.g., exercise, mindfulness, cognitive behaviour therapy, etc.). Measuring someone's reactivity to an acute psychological stress task may be an inexpensive, yet informative, tool for identifying individuals who may need extra support when enrolling in such programmes. Additionally, the present findings might also be of some significance for multi-session studies. A not unsubstancial number of stress reactivity studies have employed a subsequent follow-up, either questionnaire based or involving further stress testing. What the present results imply is that failure to complete the follow-up procedure may not be an arbitrary matter. Rather, it may be related to the stress reactivity status of the participant; those lost to follow-up may be more likely to be blunted stress reactors, with all the attendant health and behavioural corollaries.

HR and CO reactivity, but not BP reactivity, were associated with study non-completion. Both blunted HR and BP have been associated with adverse health outcomes such as depression and obesity (e.g., Salomon et al., 2009; Schwerdtfeger & Rosenkaimer, 2011; Carroll et al., 2007). However, it is HR reactivity that has been most strongly implicated in impulsivity (Bennett et al., 2014) and is the most consistent cardiovascular reactivity correlate of many of the other health and behavioural outcomes associated with blunted reactivity (see, e.g., Lovallo et al., 2013; Ginty et al., 2012). In healthy young adults, HR and CO reactivity to stress are highly correlated (e.g., Carroll et al., 2009). Low HR and CO reactivity have been associated with diminished anterior mid cingulate cortex (aMCC) activation (Ginty et al., 2013; Critchley et al., 2003) and damages to the aMCC have been associated with diminished autonomic arousal during cognitive demanding tasks (Critchley et al., 2003). Our findings support the hypothesis that blunted

cardiac stress reactivity may be a peripheral biological manifestation of a dysregulation of the neural systems in the brain that support motivation and goal directed behaviour (Carroll et al., 2009, 2011; Lovallo, 2011) and, accordingly, a marker of poor behavioural regulation. This certainly accords with findings also linking blunted stress reactions to poor response inhibition (Bennett et al., 2014) and greater impulsivity (Allen et al., 2009), as well as with what is now a substantial body of evidence of a negative association between stress reactivity and obesity, depression, bulimia, conduct disorders, and both substance and non-substance dependencies (see Phillips, Ginty, & Hughes, 2013, for a review). It is worth recalling that some of these latter outcomes have also been associated with lack of perseverance (Lopez-Torrecillas et al., 2014; Marmorstein, 2013; Murphy, Stojek & Mackillop, 2014).

Our study is not without limitations. First, the effective sample was highly skewed in terms of gender; four fifths of the participants were women. However, the genders did not differ significantly in terms of either completion rates or HR reactivity. Second, the current measure of perseverance might be regarded as opportunistic. Clearly, replication with a more dedicated and deliberate assessment of perseverance is essential. Third, there was a trend towards lower score on the PASAT for non-completers versus completers. It could be that non-completers were less motivated to perform well on the PASAT. However, there were no differences between groups on self-report task engagement. Fourth, some other third variable could have influenced the relationship between blunted reactivity and study non-completion. Lastly, both the initial and follow-up visits occurred during a major transitional time. It could be that the timing of the follow-up was the cause of some attrition. However, participants were given multiple reminders over the course of a few months to complete the follow-up. Additionally, it could be argued that this time of transition is a time when the uptake of unhealthy behaviors requiring remediation occur and thus it is important to identify those who will persist with intervention programs.

In conclusion, diminished HR and CO reactions to stress predicted the failure to complete, despite repeated prompts, a subsequent relatively undemanding on-line assessment. The results add to accumulating evidence that both exaggerated and diminished reactions to stress are associated with adverse outcomes and suggest that moderate reactivity may represent optimal function. While exaggerated reactivity is associated with adverse cardiovascular outcomes,

blunted stress reactivity may be a manifestation of dysfunction in those brain areas that support motivation and, accordingly, a marker for poor behavioural regulation. It also suggests that blunted reactivity may be a useful prognostic marker prior to behavioural intervention and that caution may be warranted when assuming that a smaller follow-up sample is representative of the originally tested sample in terms of both biology and behaviour.

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Table 1. Mean (SD) values of HR, SBP, DBP, and CO during baseline and stress. Results are reported for two-way repeated measures ANOVAs.

	Mean (SD)		F	p	eta ²
	Baseline	Stress			
Heart rate (bpm)	74.49 (12.13)	90.68 (14.76)	470.86	<.001	.729
Systolic blood pressure (mmHg)	110.37 (10.64)	124.25 (14.02)	457.89	<.001	.726
Diastolic blood pressure (mmHg)	67.51 (6.22)	75.98 (8.36)	367.57	<.001	.680
Cardiac output (L/min)	5.37 (0.98)	6.99 (1.60)	288.76	<.001	.669

Table 2. Characteristics of completers and non-completers.

	Mean (SD)/N (%)		F/ χ^2	p
	Completers (N = 132)	Non-completers (N = 44)		
Age (years)	18.00 (0.43)	18.16 (0.42)	2.93	.09
Gender (% female)	111 (84%)	34 (77%)	0.30	.36
Ethnicity (% Caucasian)	73 (55%)	22 (50%)	0.37	.54
HADS Depression	4.46 (3.23)	4.34 (2.79)	0.05	.82
HADS Anxiety	9.23 (3.74)	8.41 (4.02)	1.52	.22
Neuroticism	1.32 (3.56)	1.82 (3.73)	0.66	.42
Score on PASAT	608.27 (177.18)	548.41 (172.86)	3.81	.05
PASAT engagement	4.09 (1.28)	4.15 (1.15)	0.07	.79
PASAT difficulty	4.22 (0.99)	4.16 (1.18)	0.11	.74
PASAT stressfulness	4.53 (1.07)	4.25 (1.16)	2.18	.14
Baseline heart rate (bpm)	74.53 (12.21)	74.36 (12.02)	0.01	.93
Baseline systolic blood pressure (mmHg)	109.85 (9.62)	112.32 (13.33)	1.78	.18
Baseline diastolic blood pressure (mmHg)	67.20 (6.01)	68.52 (6.75)	1.49	.22
Baseline cardiac output (L/min)	5.30 (0.95)	5.57 (0.98)	2.18	.14
Heart rate reactivity (bpm)	17.39 (9.71)	12.59 (9.68)	8.09	.005
Systolic blood pressure reactivity (mmHg)	14.02 (8.33)	13.42 (9.29)	0.16	.69
Diastolic blood pressure reactivity (mmHg)	8.77 (5.58)	7.59 (6.52)	1.31	.25
Cardiac output reactivity (L/min)	1.77 (1.16)	1.18 (0.99)	7.54	.007

Figure Caption

Figure 1a. Percent of participants who completed the study by quartiles of heart rate reactivity.

Figure 1b. Percent of participants who completed by quartiles of cardiac output reactivity.

