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Blunted cardiac stress reactivity relates to neural hypoactivation

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Abstract

The present study examined neural activity differences between previously determined blunted (N = 9) and exaggerated (N = 8) cardiac stress reactors using fMRI and examining reactions to well-established stress and control task conditions. Exaggerated cardiac reactors exhibited significant increases in heart rate from control to stress, whereas blunted reactors showed no reaction. Blunted cardiac reactors displayed blunted activation in the anterior midcingulate cortex (aMCC) and insula compared to exaggerated cardiac reactors during the stress phase, and a greater deactivation in the amygdala. The biological differences between groups in response to the stress task could not be explained by subjective measures of engagement, stressfulness, or difficulty. This study supports the notion that blunted peripheral physiological stress reactivity may be a marker of some form of biological disengagement in brain areas supporting motivated behaviour.

Descriptors: heart rate, stress reactivity, fMRI

There is cumulative and consistent epidemiological evidence (Chida & Steptoe, 2010; Gerin et al. 2000; Schwartz et al., 2003; Taylor, Kamarck, & Dianzumba, 2003; Treiber et al., 2003) indicating that individuals who exhibit large magnitude or 'exaggerated' cardiovascular reactions to acute psychological stress exposures are at increased risk for clinical hypertension and premature elevations in blood pressure (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Everson, Kaplan, Goldberg, & Salonen, 1996; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999; Treiber, Turner, Davis, & Strong, 1997), markers of systemic atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998), ventricular hypertrophy (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Murdison et al., 1998), preclinical and clinical cerebrovascular disease (Everson et al., 2001; Waldstein et al., 2004), and are at increased risk of dying from cardiovascular disease (Carroll et al., in press).

Based on this body of evidence, it has long been presumed that individuals who exhibit smaller magnitude or 'blunted' cardiovascular reactions to acute psychological stress are at decreased risk for poor cardiovascular health, as compared with their more reactive counterparts. Contrary to this presumption**,** however, emerging evidence suggests that blunted cardiovascular stress reactions relate to unfavourable physical health outcomes and behavioural phenotypes that engender disease risk. For example, blunted cardiovascular, and cortisol, reactions to acute psychological stress characterize both smokers (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Kirschbaum, Strasburger, & Langkrar, 1993; Phillips, Der, Hunt, & Carroll, 2009) and those with alcohol and other substance addictions (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002). Indeed, blunted physiological stress reactions predict relapse in smokers who have

quit (al'Absi et al., 2006; al'Absi, Hatsukami, & Davis, 2005) and are also evident among adolescent offspring of alcoholic parents (Moss, Vanyukov, Yao, & Kirillova, 1999; Sorocco, Lovallo, Vincent, & Collins, 2006). Additionally, blunted cardiovascular stress reactions are associated with symptoms of bulimia (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012a) and exercise addiction (Heaney, Ginty, Carroll, & Phillips, 2011). Further, blunted cardiovascular stress reactivity has been linked in epidemiological studies to obesity, depressive symptomatology, and poorer self-reported health, both cross-sectionally and prospectively (Carroll, Phillips, & Der, 2008; Carroll, Phillips, Hunt, & Der, 2007; De Rooij, Schene, Phillips, & Roseboom, 2010; Phillips, Hunt, Der, & Carroll, 2011; De Rooij & Roseboom, 2010; Phillips, Der, & Carroll, 2009). In sum, such emerging evidence suggests that blunted physiological stress reactivity may have prognostic value for health and behaviour that is less favourable than previously assumed.

Although it may be premature to fully integrate the varied correlates of blunted physiological reactivity under a unified theoretical model, it appears that the existing correlates of blunted reactivity may commonly reflect problems in goal-directed behaviour and motivation. Accordingly, it has been proposed that blunted physiological stress reactivity may be a peripheral marker of central motivational dysregulation (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, 2011; Lovallo, 2011). In this regard, central motivational dysregulation refers to the suboptimal functioning prefrontal and limbic brain systems that jointly support motivated and goal-directed behaviour, as well as peripheral physiological control processes. Hence, the behavioural and health correlates of blunted stress reactivity may be characterized by 'hypoactivation' of these brain systems. In apparent support of this conjecture, there is functional magnetic resonance imaging (fMRI) evidence of reduced activation in frontal and subcortical limbic regions during inhibitory control tasks that engage executive function processes and emotional perception tasks that engage

motivational and behavioural salience processes in participants at risk for (Mannie, Taylor, Harmer, Cowen, & Norbury, 2011) and diagnosed with depression (Holsen et al., 2011), at risk for (Andrews et al., 2011; Glahn, Lovallo, & Fox, 2007) and diagnosed with alcoholism (Beck et al., 2009), and those diagnosed with bulimia (Joos et al., in press; Marsh et al., 2011). Hypoactivation of prefrontal and limbic regions has also been observed among obese individuals (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008), individuals showing an accelerated gain in weight over time (Stice, Yokum, Blum, & Bohon, 2010) and among those with a higher body mass index (Batterink, Yokum, & Stice, 2010).

To date, however, there has been scant research addressing the question of whether reduced neural activity in prefrontal or limbic brain regions relates directly to the phenotype of blunted physiological reactivity among individuals. Previously, lower levels of regional cerebral blood flow within orbital and ventral areas of the prefrontal cortex have been shown to correlate across individuals with smaller changes in salivary-cortisol and heart rate to a mental arithmetic task (Wang et al., 2005). Reduced neural activity in the pregenual region of the anterior cingulate cortex has also been shown to relate to smaller heart rate reactions evoked by social evaluative stress (Wager et al., 2009a). Finally, smaller blood pressure stress reactions have been associated with reduced neural activity in pregenual and mid-anterior regions of cingulate cortex and insula (Gianaros, Derbyshire, May, Siegle,, Gamalo, & Jennings, 2005), the posterior cingulate cortex (Gianaros, May, Siegle, & Jennings, 2005), and the amygdala (Gianaros et al., 2008). Importantly, across these prior studies theoretical interest was almost exclusively directed at characterising the neural correlates of exaggerated peripheral stress responses, presumably because of their epidemiological association with markers of disease risk (Gianaros and Sheu, 2009). As a result, little attention has been directed at characterizing and interpreting the neural correlates of blunted stress reactivity,

particularly within an individual difference framework emphasizing central motivational dysregulation.

Thus, given the paucity of research characterizing the specific neural correlates of blunted physiological reactivity, the present study tested the hypothesis that individuals who exhibit one form of blunted physiological reactivity, namely reduced cardiac reactivity determined by Doppler echocardiography, to standard laboratory stress tasks would also exhibit reduced activation in prefrontal and limbic regions of the brain. To test this hypothesis fMRI scanning was undertaken while administering a behaviourally-demanding task that involves executive function, reliably evokes individual differences in cardiovascular reactivity, and engages the cingulate, insula, and amygdala areas of the brain that are involved in peripheral physiological regulation, goal-directed behaviour, and motivational salience processing (Bush et al., 2008; Bush & Shin, 2006; Sheu, Jennings, & Gianaros, 2012).

Methods

Participants

Twenty-two healthy male undergraduate and postgraduate students (11 exaggerated and 11 blunted cardiac reactors) were recruited. Their mean (SD) age was 20.9 (1.56) years and their mean (SD) body mass index was 23.0 (1.52) kg/m^2. The high and low reactors did not differ in terms of age ($p = .96$) or BMI ($p = .40$). None of the participants smoked, and none had a history of cardiovascular disease, a current endocrine or immune disorder, an acute infection or other chronic illness, nor were any of the participants taking prescribed medication. All participants provided informed consent and the study was approved by the University of Birmingham Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Selection of participants

Ten (4 exaggerated and 6 blunted reactors) participants were selected from a temporal stability study in which cardiac reactions to a mental stress task, a 10-minute version of the paced auditory serial arithmetic test (PASAT; Gronwall, 1977), were measured using Doppler Echocardiography and electrocardiography on four separate occasions. A full description of the version of the PASAT used is provided elsewhere (Ginty et al., 2012). Briefly, participants were presented with a series of single digit numbers and required, in each case, to add any given number to the number previously presented and call out the answer. The intervals between the numbers were 4.5 seconds for the first 2 minutes and shortened by .5 seconds every subsequent 2 minutes. The task also involved elements of competition, harassment, and social evaluation. As can be seen in Figure 7.1a and 7.1b, the exaggerated cardiac output and heart rate reactors, although showing some adaptation of response over sessions, remained high reactors throughout; the blunted reactors continued throughout to show low cardiac responses.

Ten further participants (5 exaggerated and 5 blunted cardiac reactors) were recruited from a study examining the inter-task consistency of cardiac stress responses, using the same measurement techniques as above. Since the PASAT is unsuitable for the fMRI part of the study, cardiac reactions to the PASAT were compared to reactions to a fMRI compatible task, the modified Multi Source Interference Task (MSIT; see later for description). The cardiac reactions of 48 participants were examined to the PASAT and MSIT, presented in a counter-balanced order. Although the PASAT elicited stronger reactions than the MSIT, t (47) = 5.03, $p < .001$ and t (47) = 6.26, $p < .001$, for cardiac output and heart rate reactivity respectively, reactions to the two tasks were highly correlated: r (46) = .61, $p < .001$ and r (46) = .56, $p < .001$, for cardiac output and heart rate reactivity respectively. The remaining two participants (2 exaggerated reactors) were recruited from a heart rate reactivity study conducted by

colleagues. The HR reactions to the PASAT of these two participants were 45 and 33 beats per minute.

[Insert Figure 1a and 1b. about here]

Multi source interference task

The MSIT (Bush & Shin, 2006; Gianaros et al., 2009) was comprised of two conditions: a congruent condition and an incongruent condition. The two conditions, each lasting 52-60 seconds were administered in a blocked design, and each was preceded by a 10-17 second rest period where participants fixated on a crosshair. In both MSIT task conditions participants were presented with three numbers in single trials; one number was different from the other two, which were identical. Participants selected the different number by pressing one of three buttons on an fMRI compatible response box. For all trials in the congruent condition, the different number in the display appeared in a location that was aligned with its spatial position on the response box. Thus, there was a one-to-one correspondence between the stimulus position and the correct response option. For the incongruent trials, the different number, was incongruent its spatial location on the response box, such that there was now no alignment between the stimulus position and the correct response option. In this condition, performance was titrated and maintained at *circa* 60% correct by adjusting the inter-trial intervals. For each of three trials, the incongruent and congruent conditions were each presented four times in an alternating order, separated by the resting crosshair condition; the incongruent condition always preceded the congruent condition. In all, the task lasted 9 minutes and 20 seconds. A fuller description of this task is provided elsewhere (Gianaros et al., 2009; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012).

Procedure

Blunted and exaggerated reactors were required to abstain: from alcohol 12 h, vigorous exercise 12 h, caffeine 2 h, and food and drink other than water 1 hour before fMRI testing. Participants were tested between 11am and 3pm at the Birmingham University Imaging Centre. On arrival at the imaging centre, they were provided with a description of the experiment and familiarized with the fMRI equipment. Participants were instrumented for the non-invasive measurement of heart rate using a MRI compatible pulse oximeter (InVivo 4500 MRI; Invivo Research Corp., Orlando, FL, USA) which was recorded throughout. As indicated above, participants were studied in the fMRI under three conditions: rest, congruent MSIT, and incongruent MSI. The first of these conditions allowed the acquisition of structural MRI images (for approximately 8 minutes). The last of these conditions served as the stress task exposure whereas the congruent version of the MSIT served as the non-stress control. At the end of the fMRI session, participants completed a brief questionnaire rating how difficult, stressful, and engaging they found the stress task, as well as how well they thought they performed on the task and how stressful they found being in the fMRI scanner; responses were made on a 7-point Likert scale in which 0 indicated "not at all" and 6 indicated "extremely."

Structural and functional magnetic resonance imaging acquisition

Neuroimaging data were acquired using a Philips 3 T Achieva system. Structural images were acquired using TITFE technique (TR=8.4, FoV=232 mm, flip angle=60° 288x288 matrix, 175 slices). Blood oxygenated level dependent (BOLD) contrast weighted echoplanar images (EPI) were generated (repetition time TR=3000 ms, echo time TE=3500 ms, FoV=220mm, 52 slices, 3.0 isotropic voxels) during functional scans. Participants completed the MSIT during functional scans as detailed above.

Data pre-processing

The object of the analysis was to describe BOLD response in the high and low reactors and compare differences in BOLD response between the exaggerated and blunted reactors during performance of the MSIT. To these ends, the following pre-processing procedures were performed using statistical parametric mapping software (SPM8; Wellcome Trust Centre for the Study of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm). Slice timing correction was used to correct for the time difference in slice acquisition. Head movement between scans was corrected by aligning all subsequent scans with the first and an unwarp function applied to minimise artifacts from the head motion. Each realigned set of scans from every subject was co-registered with their own hi-res structural MRI image and then reoriented into the standardized anatomical space of the average brain provided by the Montreal Neurological Institute. To increase the signal to noise ratio and accommodate variability in functional anatomy, each image was smoothed in X, Y, and Z dimensions with a Gaussian filter of 8 mm (FWHM).

Data analyses

Group (exaggerated and blunted cardiac reactors) differences in self report were examined using one-way ANOVAs. To provide summary heart rate data for analyses, heart rate values were averaged separately for each of the three conditions across the first two trials. The averages generated were then subject to a 2 groups (exaggerated and blunted reactors) x 3 conditions (rest, congruent, incongruent) ANOVA. Group by condition interactions were followed up with simple effects tests and pairwise comparisons between conditions for each group.

Assessment of regional brain activation

For each subject, a boxcar model with a hemodynamic delay function was fitted to each voxel to contrast the incongruent with congruent conditions and generate a statistical parametric map. Baseline drifts were removed by applying a high-pass filter. Contrast images

for each individual subject were then combined at the second level to generate maps indicating within and between group effects. This random effects implementation corrects for variability between subjects so that outlying subjects cannot drive the result. A whole brain grey matter mask was applied using WFU Pickatlas to exclude white matter and ventricles from the analysis. Brain regions with a large statistic correspond to structures whose BOLD response shares a substantial amount of variance with the conditions of interest. Images were thresholded at $p < 0.001$ with an extent threshold of 50 contiguous voxels, which provides a reasonable balance of protection against false-positives, without artificially concealing the real profile of activation. *A priori* analyses of hypothesis-driven regions of interest (ROIs) involved examination of the insula and amygdala regions (Critchley et al., 2005; Gianaros et al., 2005), thresholds were set at p < .05 with an extent threshold of 10 contiguous voxels.

Results

Self-report and cardiac stress responses

Three exaggerated cardiac reactors and two blunted cardiac reactors data were excluded because of excessive movement artifacts in their functional neuroimaging data; thus, the final analyses included 17 participants (8 exaggerated reactors and 9 blunted reactors). There were no significant differences between high and low reactors in how difficult ($p = .39$), stressful ($p = .45$), or how engaging ($p = .45$) they found the MSIT task. There were also no group differences in how well they thought they performed ($p = .39$) or how stressful they found being in the scanner ($p = .53$). With regard to heart rate during the session, there was a significant main effect of condition (baseline, congruent, incongruent), $F (2, 30) = 13.45$, $p = .001$, $_p\eta^2 = .473$, and a significant main effect of group, $F (1, 15) = 12.38$, $p = .003$, $_p\eta^2 = .452$. There was also a significant group x condition interaction, $F (2, 30) = 11.66$, $p = .002$, $_p\eta^2 = .437$. Pairwise comparisons revealed that high reactors increased slightly between baseline and the congruent ($p = .051$), and increased significantly between

baseline and incongruent (p = .001) and between congruent and incongruent (p < .001). In contrast, the heart rate of low reactors did not change significantly between baseline and congruent, baseline and incongruent , and between congruent and incongruent (p > 0.10 in all cases). Figure 7.2 displays each group's average change from baseline to the congruent and incongruent conditions.

[Insert Figure 2. about here]

Exaggerated cardiac reactors condition-related brain activation and deactivation

BOLD signal increases and decreases during the incongruent (stress) condition compared to the congruent (control) condition for exaggerated cardiac responders are shown in Table 7.1 and Table 7.2, respectively. During the stress condition, exaggerated cardiac responders had significantly greater BOLD activation in the occipital and parietal lobe; these analyses survived family wise error corrections. There were significantly greater BOLD activation responses in several other areas including the brainstem, cerebellum, anterior midcingulate cortex (aMCC), caudate, and inferior frontal gyrus. Exaggerated cardiac responders had significantly less BOLD activation during the stress condition compared to the control condition in the superior frontal gyrus, an effect which survived family wise error correction, and in the posterior cingulate cortex; thus, these areas showed evidence of de-activation during stress exposure. In addition to Tables 7.1 and 7.2, the outcomes for exaggerated cardiac reactors are illustrated in Figures 7.3 and 7.4.

Blunted cardiac reactors condition-related brain activation and deactivation

BOLD signal increases and decreases during the incongruent (stress) condition compared to the congruent (control) condition for blunted cardiac reactors are shown in Tables 7.1 and 7.2, respectively. BOLD increases were seen in the occipital and parietal lobes, and parahippocampal gyrus during the stress condition compared to the control condition, and the effects again survived family wise error correction. Additionally, there

were significantly greater BOLD responses in other areas of the brain including the frontal lobe and the posterior cingulate cortex. There were several areas of the brain where blunted cardiac responders displayed decreases in BOLD responses to stress, i.e., greater activation during the control condition relative to the stress condition. Deactivation, surviving family wise error correction, was seen in the parietal and temporal lobes, and in the hippocampus. Deactivation also occurred in the amygdala, posterior cingulate cortex, superior frontal gyrus, and anterior cingulate. The outcomes are illustrated in Figure 7.3 and 7.4.

[Insert Tables 1 and 2 and Figures 3 and 4 about here]

Group differences in condition-related regional brain activity

A whole-brain ANOVA showed that exaggerated cardiac reactors also expressed greater activation of the aMCC (BA 24) during the incongruent compared with the congruent condition, group x condition cluster $F (1, 15) = 33.96$, $p < .001$, voxel contiguity threshold = 50 voxels (Figure 7.5). A priori analyses of ROIs revealed significant group x condition differences for the amygdala $F (1, 15) = 11.66$, $p = .004$ and for the insula $F (1, 15) = 11.37$, $p = .004$. Blunted cardiac reactors exhibited greater deactivation in the amygdala and exaggerated reactors had greater activation during the incongruent compared with the congruent condition.

[Insert Figure 5. about here]

Discussion

The present study compared neural activation differences in pre-established exaggerated and blunted cardiac reactors. This is the first fMRI study to screen and select extreme cardiac reactors using Doppler echocardiography for cardiovascular measurements. As expected, during the fMRI testing session, exaggerated cardiac reactors displayed significant increases in HR during the stress task compared to resting baseline, while low reactors' HR did not change with stress exposure. There were no significant differences

between exaggerated and blunted reactors in how difficult, stressful, or engaging they found

the task or in their subjective assessment of their performance of the task. This indicates that

differences in HR reactivity and any potential differences in neural activation could not be

attributed to simple expedients such as group differences in task involvement. Participants in

the high and low reactor groups also did not differ in age or BMI.

The most notable difference between groups in neural activation during the stress task

compared to the control condition was in the aMCC; exaggerated reactors exhibited an

increase in aMCC activation during the stress task while blunted reactors did not. There were

also group differences in insula and amygdala responses to stress, confirming *a priori*

hypotheses. Exaggerated reactors had greater activation in the insula during stress and in

comparison blunted reactors exhibited hypo-activation. Blunted reactors also showed

deactivation of the amygdala during stress, i.e., they showed greater activity in the amygdala

during rest than during the stress task. Separate analyses examining the neural reactivity of

each group separately demonstrated more widespread and intense activation in the

exaggerated reactors during stress in the brain stem and cerebellum which blunted reactors

did not show. Both groups showed similar activation in the occipital and parietal lobes.

The results from the whole brain analyses are different than a previous study examining

neural responses of high and low systolic blood pressure reactors during stress exposure

(Gianaros et al., 2005), which found group differences in posterior cingulate activity. High

reactors exhibited increases in activation in the posterior cingulate during stress exposure

whereas low reactors showed decreases in the posterior cingulate. In the present study, there

were no differences between exaggerated and blunted cardiac reactors in the posterior

cingulate during stress exposure. A potential explanation could reside in the selection of high

and low reactors; Gianaros and colleagues selected extreme reactors based on systolic blood

pressure, while the present study used CO and HR reactivity as selection criteria and used a stricter cut-off to identify extreme reactors. Additionally, participants in the present study were all relatively young compared with the participants in the previous study. It should be noted that despite the differences seen in group comparisons, overall the stress task elicited responses in similar areas of the brain (Gianaros et al., 2005).

A priori predictions regarding differential activation of the insula and amygdala during stress between the groups were confirmed. Evidence implicates the insula in cardiovascular regulation (Allen, Saper, Hurley, & Cechetto, 1991; Cechetto, 1994; Cechetto & Chen, 1990; Cechetto & Shoemaker, 2009; Oppenheimer, 1993; Ruggiero, Mraovitch, Granata, Anwar, & Reis, 1987; Verberne and Owens, 1998; Yasui, Breder, Saper, & Cechetto, 1991) and a recent meta-analysis consisting of cardiovascular stress reactivity neuroimaging studies identified the insula as one of three key regions associated with individual differences in stress-evoked cardiovascular reactions (Gianaros & Sheu, 2009). Group differences in the amygdala are also in line with previous studies which have demonstrated a relationship between the amygdala and cardiovascular control (Gianaros et al., 2008) and sympathetic arousal (Critchley, 2005; Bechara, Damasio, Damasio, & Lee, 1999). Additionally, fMRI studies have shown hypoactivation in the amygdala in individuals with depression (Holson et al., 2011) and at risk for alcoholism (Glahn et al., 2007), both of which have been related to blunted physiological reactions to stress (Carroll et al., 2007; Moss et al., 1999; Phillips et al., 2011; de Rooij et al., 2010; Salomon, Clift, Karslsdottir, & Rottenberg, 2009; Schwerdtfeger, & Rosenkaimer, 2011; Sorocco et al., 2006). What is most notable about the current results is that blunted cardiac reactors showed less activity in the amygdala during stress than during baseline. It would appear that individuals who show blunted peripheral stress reactivity are also unresponsive in a key neural component of emotion. It is worth noting that individuals

with a damaged amygdala are emotionally unresponsive (Adolphs et al., 2005; Buchanan, Etzel, Adolphs, & Tranel, 2006) and have impaired decision making and lower sympathetic reactivity when thinking about risky behaviour (Bechara et al., 1999). Blunted physiological reactions have been related to risky behaviours, such as addiction (Lovallo et al., 2000; Pankin et al., 2002) and impaired decision making such as reoffending among delinquent adolescents (de Vries-Bouw et al., 2011). The amygdala effects were modest, but nevertheless statistically significant. Research shows that tasks which involve non-emotional stimuli, such as the MSIT, show a stronger relationship between the anterior cingulate and sympathetic arousal than between the amygdala and sympathetic arousal (Bush et al., 2008; Bush & Shin, 2006; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Critchley et al., 2003).

The most robust group differences were in the anterior cingulate, specifically the aMCC, which has also been related to cardiovascular activation in response to stress (Critchley et al., 2000; Critchley et al., 2003); higher cardiovascular reactors have been found by others to have greater aMCC activation during stress (Gianaros et al., 2005a). Just as high reactivity to stress has been related to cardiovascular disease, greater activation of the aMCC has been found in patients with cardiovascular disease (Soufer et al., 1998). Thus, it is perhaps not unexpected that exaggerated reactors in the present study displayed greater activation in the aMCC during stress than blunted reactors. That blunted cardiac reactors failed to show activation in the aMCC during stress compared to the control condition is in line with a previous studies reporting that patients with damage to their anterior cingulate cortex displayed blunted autonomic arousal to cognitive and motor tasks (Critchely et al., 2003). Hypo-activation of the anterior cingulate has also been related to depression (Holson et al., 2011) and bulimia (Marsh et al., 2011; Joos et al., 2011), both of which are associated with blunted physiological reactions to stress (Carroll et al., 2007; Ginty et al., 2012; Koo-

Loeb, Pederson, & Carroll, 1998; Moss et al., 1999; Phillips et al., 2011; de Rooij et al., 2010; Salomon et al., 2009; Schwerdtfeger, & Rosenkaimer, 2011; Sorocco et al., 2006). The aMCC has also been implicated in higher cognitive functions such as cognitive information processing and executive function (Bush, Luu, & Posner, 2000; Bush et al., 2008; Bush et al., 2002; Critchley, 2003; Williams et al., 1998; Shima & Tanji, 1998; Paus, 2001). Recent studies indicate a link between poor cognitive ability and blunted peripheral physiological stress reactivity (Ginty, Phillips, Der, Deary, & Carroll, 2011a, Ginty, Phillips, Der, Deary, & Carroll, 2011b; Ginty, Phillips, Roseboom, Carroll, & de Rooij, 2012b). One of the measures of cognitive ability, choice reaction time, involves both cognitive processing and executive functioning and has been regarded as a marker of cognitive aging (Nettelbeck & Rabbitt, 1992). Results showed that blunted cardiac reactions to stress predicted a decline in choice reaction time amongst the oldest participants in the study over a seven year period (Ginty et al., 2011a). Evidence from the present study suggests that blunted neural activation to stress may also be related to cognitive ability and that some sort of biological disengagement is occurring across multiple systems in blunted reactors when confronted by a stressful and cognitively challenging stimulus.

It is widely accepted that the amygdala, insula, and anterior cingulate work together as a network to evaluate and process the motivational and emotional aspects of psychologically stressful stimuli in the environment (e.g. aversive stimuli; uncontrollable stimuli); they then interact to elicit appropriate cardiovascular and motor responses (Bennarroch, 1997; Bush et al., 2000; Cechetto, 1994; Ongur & Price, 2000; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Gianaros et al., in press; Gianaros & Sheu, 2009; Hagemann, Waldstein, & Thayer, 2003; Koski & Paus, 2000; Resstel & Correa, 2006; Thayer, & Lane, 2000; Wager et al., 2009b). This network is vital for motivated behavioural responses and adaptations to the threat or challenge (Gianaros et al., 2012; Dampney, 1994;

Dampney et al., 2002). In the present study, participants with blunted cardiovascular reactions to stress displayed either blunted responses or deactivation in these areas of the brain when exposed to psychologically stressful stimuli. The current findings offer support to the hypothesis that blunted peripheral physiological reactions to acute psychological stress may be a peripheral marker for some form of dysregulation in those areas of the brain that are associated with motivation (Carroll et al., 2009; Carroll et al., 2011; Lovallo, 2011). Further, this biological disengagement may contribute to outcomes such as obesity, addiction (al' Absi et al., 2003; Lovallo et al., 2000), depression (Salomon et al., 2009; de Rooij et al., 2010), and other adverse behaviours (Ginty et al., 2012a). It is also worth noting that this biological disengagement is independent of participants' ratings of engagement with the stress task; such independence of self-report and biological measures has been observed previously (Ginty et al., 2012a; Heaney et al., 2011).

The present study is not without limitations. First, all of the participants tested were males. However, there is no reason to believe the results would be any different if female participants were included (Balanos et al., 2010; Carroll, Turner, Lee, & Stephenson, 1984; Gianaros et al., 2005). Second, only HR was measured during the fMRI protocol. However, participants were initially selected using both CO and HR using Doppler echocardiography, a highly sensitive and clinically accepted device (Balanos et al., 2010; Fellahi et al., 2009). Additionally, HR was recorded continuously throughout the scanning session which allows for a more definitive assessment of the relationship between neural and cardiac responses (Gianaros et al., 2005). Third, it could be argued that individual differences in cardiac reactivity is not stable over time and, accordingly, the present findings may not be truly representative. However, the temporal stability of exaggerated and blunted reactivity was tested prior to fMRI testing, providing further evidence for the temporal stability of cardiac reactivity (Carroll et al., 1984) and the stability of both cardiovascular and neural reactions to

the MSIT task (Sheu, Jennings, & Gianaros, 2012). Lastly, the sample size was relatively small. However, extreme groups were being examined and a large number of participants were screened to select these groups. In addition the sample size was similar in magnitude to other studies of this nature (Gianaros et al., 2005).

In summary, extreme blunted cardiac reactors displayed blunted activation in the aMCC and insula compared to exaggerated cardiac reactors during an acute stress task, and a deactivation in the amygdala. The biological differences between groups in response to stress task could not be explained by subjective measures of engagement, stressfulness, or difficulty. This study supports the notion that blunted peripheral physiological stress reactivity may be a marker of some form of biological disengagement in those areas of the brain that support motivated behaviour.

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Table 1. Significant BOLD activation during incongruent (stress) compared to congruent (control) for exaggerated and blunted cardiac reactors, threshold $p < .001$, extent threshold 50 contiguous voxels.

Figure label	Side	Brain area	Exaggerated reactors			Blunted reactors		
			(x, y, z coordinates) region	Cluster size	t value	(x, y, z coordinates) region	Cluster size	t value
1	R	Medial premotor cortex	(6, 14, 58) BA 6	488	13.41	(36, 6, 58) BA 6	66	6.47
	L		(-32, -4, 66) BA 6	75	6.87	___	___	___
2	L	Anterior mid cingulate cortex (aMCC)	(0, 34, 26) BA 32	134	8.65	___	___	___
	R		(2, 18, 20)	134	5.12	___	___	___
3	L	Brainstem	(-12, 20, -4)	1554	9.87	___	___	___
	R		(14, -18, -6)	1554	9.20	___	___	___
4	R	Thalamus	(-9, -12, -2)	1554	7.81	(18, -22, 8)	474	9.35
5	R	Caudate	(32, -34, 4)	50	9.96	___	___	___
6	L	Posterior Cingulate Cortex	___	___	___	(-6, -24, 28) BA 23	133	12.73
	R		___	___	___	(8, 10, 32) BA 23	641	10.66
N/A	R	Insula	(38, 20, 16) BA 13	599	7.97	(44, 10, 16) BA 13	1452	10.91*

* ROI analyses of the insula revealed greater activation in exaggerated cardiac reactors during stress compared to rest, despite the peak voxel being higher in the blunted cardiac reactors.

Table 2. Significant BOLD dectivation during incongruent (stress) compared to congruent (control) for exaggerated and blunted cardiac reactors, threshold $p < .001$, extent threshold 50 contiguous voxels.

Figure label	Side	Brain area	High reactors			Low reactors		
			(x, y, z coordinates) region	Cluster size	t value	(x, y, z coordinates) region	Cluster size	t value
7	L	Ventral Posterior cingulate cortex (vPCC)	(-4, -50, 18) BA 30	78	5.97	(-8, -42, 36) BA 30	504	8.18
8	L	Medial frontal cortex	(-12, 58, 0) BA 10	482	5.96	(-10, 66, 26) BA 10	3207	11.34
9	L	Perigenual anterior cingulated cortex (pACC)	____	____	____	(-16, 42, 2) BA 32	3207	9.42
10	R	Amygdala	____	____	____	(-28, -12, -16)	80	13.75*
	L	Amygdala	____	____	____	(20, -10,-10)	51	10.08
11	L	Temporal cortex	____	____	____	(-50, -66, 26) BA 39	533	17.98*
	R		____	____	____	(36, 10, -36) BA 38	131	11.00
						(-58, -12, -8) BA 21	52	8.72

Figure Captions

Figure 1a. Heart rate reactivity of extreme exaggerated and blunted reactors over four independent laboratory sessions.

Figure 1b. Cardiac output reactivity of extreme exaggerated and blunted reactors over four independent laboratory sessions.

Figure 2. Change in heart from baseline to the congruent and the incongruent conditions for the MSIT for exaggerated and blunted cardiac reactors.

Figure 3. Sagittal slices showing BOLD activation (orange) and deactivation (blue) during the incongruent stress condition in comparison to the congruent control condition for both exaggerated and blunted cardiac reactors. Please refer to Tables 7.1 and 7.2 for figure labels.

Figure 4. Coronal slices showing BOLD activation (orange) and deactivation (blue) during the incongruent stress condition in comparison to the congruent control condition for both exaggerated and blunted cardiac reactors. Please refer to Tables 7.1 and 7.2 for figure labels.

Figure 5. Group (Exaggerated, Blunted) x Condition (Incongruent, Congruent) BOLD activation differences using a whole brain exploratory analysis, threshold $p < .001$, extent threshold 50 contiguous voxels.