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No association between cardiometabolic risk and neural reactivity to acute psychosocial stress

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ABSTRACT

Background: Exaggerated reactivity to acute psychosocial stress is associated with an increased risk of cardiovascular and metabolic disease. A dysfunction of the cortico-limbic network coordinating the peripheral adaptation to acute stress exposure may constitute a brain mechanism underlying this association. We opted to characterize the changes of this network associated with acute psychosocial stress exposure in individuals with low and high cardiometabolic risk (CMR).

Methods: In 57 subjects without overt cardiac or cerebral disease, the Framingham risk score and presence/absence of type 2 diabetes or metabolic syndrome defined CMR. Psychosocial stress was induced during functional magnetic resonance imaging (fMRI) of brain activity by an established social threat paradigm. Measurements of heart rate, blood pressure and saliva cortisol quantified the peripheral stress reaction. Regression analyses for the anterior cingulate cortex, hippocampus, amygdala, insula and regulatory prefrontal regions evaluated the association of stress-associated brain activation and CMR.

Results: Psychosocial stress exposure was associated with an increased activity of a brain network including anterior and posterior cingulate cortex, putamen, insula, parahippocampus and right hippocampus. Psychosocial stress-associated brain activation did neither covary with Framingham risk score nor differ between groups with low or high CMR.

Conclusion: Exposure to acute psychosocial stress induces the activation of a well-defined cortico-limbic network. However, we did not find an association between CMR and this network's stress reactivity.

1. Introduction

Increased psychosocial stress exposure is associated with a higher incidence and prevalence of cardiovascular disease (CVD), classifying this variable as a cardiometabolic risk (CMR) factor (Brotman et al., 2007; Steptoe and Kivimaki, 2012). The deleterious health effects equal that of conventional risk factors, including smoking, arterial hypertension and hypercholesterolemia (Rosengren et al., 2004). However, the pathophysiological processes are incompletely understood. Environmental challenges represent a ubiquitous phenomenon, and the mechanisms regulating the perception of a stimulus as stressful remain uncertain. Current knowledge suggests that several brain areas process incoming information, validate it against stored knowledge, and judge it as benign or threatening (Ulrich-Lai and Herman, 2009). These brain areas form a cortico-limbic circuitry, composed of the anterior cingulate cortex (ACC), adjacent medial prefrontal cortex (mPFC), amygdala, hippocampus, insula and other components (Pruessner et al., 2010). If a stressor is taxed as threatening, efferent projections of this brain network induce a host of adaptation responses, including changes in stress hormone level, autonomic nervous and cardiovascular activity, and behaviour (Muscatell et al., 2016; Myers and Ulrich-Lai, 2017). It has been posited that a functional bias in this brain network contributes to the appraisal and encoding of a neutral stimulus as threatening and that this neural bias represents a marker of cardiovascular disease risk (Gianaros and Wager, 2015). Thus, in vulnerable subjects, altered neural stress responses may initiate adaptation processes that mismatch the needs of an anticipated or experienced stressor (Ginty et al., 2017).

The functionality of the elements of this stress-responsive cortico-

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limbic network is not readily disentangled. Rather, there seems to be considerable overlap in their contribution to the detection and appraisal of psychosocial stimuli as well as the downstream initiation of cardiovascular or metabolic responses (Myers, 2017; Eisenberger and Cole, 2012; Tost et al., 2015). However, some aspects of these elements' specific roles shall be discussed. Current evidence highlights the ACC as an important regulatory component of the circuitry, which integrates input from brain networks processing cognition, emotion and motivation and facilitates error detection, conflict monitoring and emotional self-control (Allman et al., 2001; Bush et al., 2000; Kerns et al., 2004; Etkin et al., 2006). Specifically, the peri- and subgenual aspects of the ACC are involved in stress-related cardiovascular regulation, as their activity correlates with blood pressure and heart rate variability (Gianaros et al., 2005; Gianaros et al., 2004). Conversely, the amygdala is central to threat detection and generation of fear and flight responses (LeDoux, 2000). It processes emotional and motivational appraisal of social stimuli, such as the emotional meaning of facial expressions Adolphs et al. (1994). Anatomically, this region is composed of several nuclei with distinct functionality and innervates (pre)motor and brainstem autonomic regulative centres, thereby facilitating immediate adaptive reactions to threatening stimuli prior to cortical processing (LeDoux et al., 1988). Also, the insular cortex seems to be strongly involved in cardiovascular regulation, and insular cortex activity is associated with blood pressure control (Gianaros et al., 2005). Impairments of this structure induced by stroke, epilepsy or stress may result in cardiac dysfunction, ranging from subtle electrocardiographic changes to severe cardiac arrhythmias, cardiomyopathy, or even cardiac death (Oppenheimer and Cechetto, 2016). This damage may also be mediated by CVD itself (white matter lesion, infarcts), compromising responses to exteroceptive and interoceptive stimuli and thus leading to further mismatch of stressor severity and autonomic responses. The hippocampus acts as an interface between psychosocial stress processing and memory consolidation and exhibits a high glucocorticoid receptor density. It also participates in cardiovascular regulation, as hippocampus stimulation is associated with decreases of mean arterial pressure and heart rate in an animal model (Ruit and Neafsey, 1988). Finally, it has been proposed that the mPFC acts as coordinator of the neural stress response by integrating the input from other brain regions and initiating context-specific responses on multiple levels including hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) activity (McKlveen et al., 2015).

Together, this circuitry forms an evolutionarily conserved “alarm system” to apparent threat. Thus, exaggerated reactivity of the system to psychosocial stimuli may induce repeated or enduring CMR adaptations with negative health consequences. For example, exaggerated cardiovascular responses enable inadequately high increases in heart rate, blood pressure or cardiac output (Gianaros and Sheu, 2009). In individuals with pre-existing atherosclerosis, this hyperreactivity may lead to coronary plaque rupture. Indeed, an increased incidence of coronary syndromes associated with acute stress exposure has been observed in the context of natural catastrophes (Leor et al., 1996), acts of war (missile attacks) (Meisel et al., 1991), strong emotional involvement in competitive sport activities (Wilbert-Lampen et al., 2008), and episodes of intense negative emotions (Mostofsky et al., 2014). Acute stress hyperreactivity also predisposes to chronic conditions, such as inflammation (Rohleder, 2014), arterial hypertension (Carroll et al., 2001) and left ventricular hypertrophy (Georgiades et al., 1997), and to increased cardiovascular mortality (Carroll et al., 2012). Furthermore, abnormally prolonged cardiovascular activation has been linked to adverse cardiovascular outcomes and all-cause mortality (Chida and Steptoe, 2010; Panaite et al., 2015). Also, there is some evidence linking exaggerated HPA system stress reactivity with increased CMR. In elderly subjects, drawn from the Whitehall II cohort, heightened cortisol levels to laboratory-induced psychosocial stress were associated with more extensive coronary artery calcification (Hamer et al., 2010). Women with increased visceral fat accumulation, a predictor of increased CMR, showed heightened stress-associated cortisol levels (Marin et al., 1992; Epel et al., 2000). Vice versa, offspring from long-living families had lower cortisol levels during social stress exposure (Jansen et al., 2016). To the best of our knowledge, prospective data exploring the association between stress-induced HPA reactivity and CMR are lacking.

However, as most studies report on cross-sectional data, it seems important to note that a causal relationship or any other clear direction of effects between exaggerated stress reactivity and CMR elevation cannot be assumed. The relationship of these two variables may also be strictly correlative, e.g. when they are both governed by a hitherto unassessed background variable. Alternatively, a “body-to-brain” direction of effects may be possible, when biological processes associated with arterial hypertension, diabetes mellitus and other CMR factors alter neural psychosocial stress processing. For example, enhanced silent cerebrovascular disease detectable on MRI in healthy asymptomatic older adults has been found to be associated with greater stress-induced BP reactivity (Waldstein et al., 2004). It may be assumed that these lesions compromise vagal activity, leading to an enhanced sympathetic outflow and in consequence to increased blood pressure reactivity. However, an increasing amount of longitudinal data on healthy individuals indicates that exaggerated stress reactivity is observed before the emergence of cardiovascular sequelae with follow up (Markovitz et al., 1998; Carroll et al., 1998; Matthews et al., 1998), arguing for increased stress reactivity as the initial event.

According to the arguments outlined above, subjects with a higher CMR profile are expected to differentially react to an acute psychosocial stressor, as compared to their low-risk counterparts. We put forth the hypothesis that during stress exposure, these subjects exhibit a distinct pattern of brain activation, leading to a different activation of cardiovascular and hormonal response systems. To test this hypothesis, we exposed individuals with differing degrees of CMR to a psychosocial stress task and compared their neural, cardiovascular and cortisol responses. Considering the significant role of ACC, hippocampus, amygdala, insula and prefrontal regulatory regions in governing these responses as outlined above, we also specifically analysed differences in stress-associated activity between these regions. We excluded subjects with a known prior coronary or cerebral event, as this has been found to be associated with profound and enduring changes of stress system activity (Graham et al., 2002), acceleration of atherosclerosis (Dutta et al., 2012) and possible worsening of cardiac function.

2. Material and methods

The study was approved by the ethics committee of Heidelberg University and registered in the German Register for Clinical Trials (study number, DRKS 00005362) before starting the enrolment phase. Participants were studied after all procedures had been explained to them in person and written informed consent had been obtained. Subjects received a monetary compensation for study participation.

2.1. Study subjects

Recruitment of participants followed a two-staged strategy. First, subjects with two or more CMR factors were contacted in their general practitioner's or internist's office and motivated for study participation. High CMR subjects were also addressed through public lectures, informative events, newspaper advertisements and flyers specifically targeting CMR factors. Second, low CMR subjects were recruited by inviting a random sample of the Mannheim city population for study participation. Intentionally, we did not sample low CMR subjects in fitness clubs or other organizations promoting healthy behaviour, as this may have compromised sample homogeneity.

Calculation of sample size was based on our prior work (Lederbogen et al., 2011). Assuming the previously reported effect size $f^2 = 0.52$ of stress responses within the bilateral amygdala and an uncorrected

alpha-level of 0.002 (α-level of 0.05 with FWE-correction for multiple testing) in the current calculation, we estimated a sample size of N = 44 subjects necessary to detect the experimental effects in a linear multiple regression.

Inclusion criteria were an age range of 40 to 65 years, the absence of a major or unstable general medical condition or mental disorder and the ability to comply with the study procedures. Exclusion criteria included knowledge of present or past coronary heart disease as defined by angina pectoris, positive treadmill test, a > 50% stenosis of a major coronary artery visible on cardiac catheterization, history of an acute coronary syndrome, or history of coronary artery narrowing necessitating stent placement. Further exclusion criteria were history of cerebral injuries, including stroke, significant head trauma, brain operation, meningitis, dementia or Parkinson' s disease and conditions prohibiting magnetic resonance imaging, including unsuitable metal implants, claustrophobia or large tattoos. Finally, subjects were excluded if they reported conditions affecting the stress response system including Cushing's syndrome, Addison's disease or glucocorticoid intake. On study day 1, each participant underwent a thorough clinical examination including electrocardiogram and a routine blood panel. A standardized clinical interview yielded information on personal, clinical, and social variables. Absence of major general medical conditions or mental disorders was assessed by the Cumulative Illness Rating Scale (Linn et al., 1968) and the structured clinical interview mini-DIPS (Margraf, 1994). To measure subjective social status, participants completed the Mac Arthur Scale of Subjective Social Status ("social ladder") (Adler et al., 2000). To assess HPA-function, participants were asked to collect saliva specimen for determination of cortisol concentration on two regular week-days. Sample times were at wake-up (F0) and at 15, 30, and 45 min as well as 16 h (F1/4, F1/2, F3/4, F16) after wake-up. A detailed description of the sampling procedure is given elsewhere (Lederbogen et al., 2010). Using the average of the two corresponding samples, we computed the secretion indices cortisol awakening reaction (CAR), both as difference score (F1/2 minus F0) and area under the curve (F0 through F3/4) (Pruessner et al., 2003), and slope of the diurnal decline.

2.2. Assessment of cardiometabolic risk

We applied two estimates of CMR: First, the 10-year risk of developing atherosclerotic cardiovascular disease (CVD) was quantified by use of the Framingham risk score lipids model (https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php, n.d.). This score uses age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure and presence of diabetes mellitus and provides a continuous measure of 10-year CVD risk (D'Agostino et al., 2008). Its validity has been tested extensively with prospective clinical data (D'Agostino et al., 2001). Although an overestimation of CVD risk in the German population has been noted (Hense et al., 2003), the Framingham risk score has been established as one of the most precise and most widely used tools for quantifying CMR. As the Framingham risk scores were not normally distributed, we included a log transformation in our analyses. The second strategy of CMR assessment implied assigning participants to two medical conditions associated with elevated CMR, type 2 diabetes and metabolic syndrome. Presence of type 2 diabetes was assumed if fasting blood glucose level was 126 mg/dl or higher, or if a diagnosis of the disorder had previously been made by a physician. The definition of Alberti and colleagues (Alberti et al., 2009) was used for assessment of metabolic syndrome. A positive diagnosis was made with the presence of three or more of following factors: central obesity, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure and elevated fasting glucose.

2.3. Stress paradigm

On study day 2, subjects participated in an fMRI session including a psychosocial stress task. The session's time window was held constant at 1:00–4:00 PM. The maximum time interval between study day 1 and 2 was four weeks. After arrival and explanation of study procedures, participants were allowed to reach equilibrium by resting for 30 min in a partially darkened, quiet room. After taking the baseline blood sample, a training session provided subjects with knowledge on the task before entering the scanner. Our psychosocial stressor consisted of the well-established Scan STRESS paradigm, described in detail elsewhere (Streit et al., 2014). This paradigm is composed of repeated 60 s experimental and control blocks that are preceded by 5 s instruction phases and followed by 20 s pauses. In both blocks, participants had to solve either mental arithmetic or spatial rotation tasks, and to provide solutions by a response box held in the right hand. In the experimental condition, time pressure was created by a visual countdown. Furthermore, the program automatically adjusted task speed and difficulty to the individual's performance in order to induce preprogrammed failure. In the control blocks, we asked subjects to complete simple matching tasks, which had to be solved without time pressure. The paradigm was composed of two sequences, each with two experimental and two control blocks. During the entire paradigm, two experimenters in white coats were presented to the participant by live video stream. While experimenters remained passive in the control blocks, they gave disapproving feedback during the experimental blocks (visual feedback) and between the sequences (visual and standardized verbal feedback). Including preparation of the participant and anatomical imaging, the session lasted approximately 50 min. After the test procedure subjects received detailed debriefing.

We assessed cardiovascular and HPA system responses to stress exposure according to previously described procedures (Lederbogen et al., 2011). Heart rate during fMRI was continuously monitored by pulse oxymetry, and blood pressure was recorded before and after sessions by an aneroid sphygmomanometer. HPA system reactivity was determined by saliva cortisol sampling, with samples taken on participant's arrival (T1), after 30 min rest (T2), before entering (T3) and immediately after leaving the scanner (T4). The last 3 samples were collected every 15 min after leaving the scanner (T5-T7). Hormonal reactivity during the stress task was analysed by subtracting saliva cortisol concentration at T3 from the highest value at T4, T5 or T6. Subjective feeling of both stress and sense of control were measured via visual analogue scales before and after the session, with a possible range of 0–10, "0" indicating absence of any stressor as well as maximum control and "10" maximum stress intensity and complete loss of control.

2.4. Image acquisition and analysis

Details of image acquisition and analysis have been described previously (Lederbogen et al., 2011; Streit et al., 2014). Blood-oxygen-level-dependent (BOLD) fMRI was performed on a 3.0 Tesla Siemens Trio scanner using an echo-planar-imaging (EPI) sequence (repetition time = 2000 ms, echo time = 30 ms, flip angle = 80°, 64 × 64 matrix, 32 3 mm axial slices with 1 mm gap). Images were preprocessed and analysed using SPM12 (www.fil.ion.ucl.ac.uk/spm, n.d.). Images were slice time corrected and realigned to a mean image by a 6-parameter rigid body transformation, spatially normalized to the standard Montreal Neurological Institute EPI template including resampling into 3 mm^3 voxels and finally smoothed with a 9 mm full-width at half-maximum Gaussian kernel. For each subject we defined one general linear model containing regressors for the control and experimental conditions of both task phases (arithmetic calculation and mental rotation) as well as for the respecting announcement phases leading to a sum of 6 task regressors. To account for motion artefacts we included the 6 motion regressors of the realignment step as regressors of no

interest. Data sets were excluded from further analysis if head movement was excessive (> 5 mm translation, > 4° rotation). To address the concern that in high CMR individuals, clinically silent white matter lesions alter psychosocial stress processing, we scored periventricular and deep white-matter lesions in the anatomical images according to the methods described by Fazekas and collegues (Fazekas et al., 1987) and included this variable in our analysis.

2.5. Data analysis

On a first-level analysis, we calculated one t-contrast image of experimental minus control condition across both task phases (mental rotation and arithmetic calculation) for each subject. Considering possible habituation effects during the task, we calculated two additional models, one assuming habituation over the complete paradigm and the other assuming habituation over each of the two sequences. In these models, task phases were contrasted with control conditions. To see if anticipation of stress differentiates between groups, we also calculated contrasts of the announcement phases and the control conditions. These models were used in subsequent second-level analyses.

In second-level analyses, two strategies were performed to test for an association of CMR with brain function: First, contrast images were analysed in a multiple regression to test for an effect of CMR using the (log) Framingham risk score as covariate of interest. Second, groups with low versus high CMR (type 2 diabetes, metabolic syndrome yes/no) were compared using two samples *t*-tests. All models were corrected for age, sex and smoking status by including these variables as covariates of no interest. As these three variables were already included in the Framingham risk score, we also computed the corresponding analyses without these covariates. To check for correlations between stress-responsive brain function and peripheral stress indicators (cortisol reactivity, changes in heart rate, blood pressure and subjective stress level), separate multiple regression analyses were conducted for the respective variable of interest. To assess the effect of subjective social status on neural stress processing, we re-run the main analyses (main group effect, comparison of low versus high CMR subjects, multiple regression with (log) Framingham risk score) with the social ladder score as additional covariate of no interest.

2.6. Statistical inference

Imaging results were considered significant at a threshold of $p < .05$ after voxelwise family-wise error (FWE) correction for multiple comparisons. For main task effects, correction was performed across the whole brain. For testing the association of brain function and CMR, FWE-correction was applied within the a priori selected bilateral anatomical regions of interest ACC, hippocampus, amygdala, insula as well as the prefrontal regulatory regions orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (VLPFC), and dorsolateral orbitofrontal cortex (DLPFC), based on automated anatomical labelling (Tzourio-Mazoyer et al., 2002) retrieved from the WFU Pickatlas. Final analyses used one combined ROI including amygdala, insula, ACC and hippocampus. Small volume corrected analyses of prefrontal regulatory regions were conducted separately. Considering the association of stress-induced brain activation and CMR beyond the a priori selected brain regions, we performed FWE-corrected whole brain analyses in an exploratory intention. Fazekas score did not significantly affect stress-associated brain activation and was therefore not included in the statistical model.

3. Results

3.1. Description of study subjects and general aspects of stress exposure

We included 68 subjects in our study. Of these, two did not successfully complete the stress task, one for claustrophobia and one for unwillingness to comply with study procedures. In two subjects, an incidental finding of a cerebral pathology, and in seven participants, major motion artefacts, as defined above, precluded further examination of fMR images. Thus, data from 57 subjects were available for final analysis (Table 1). According to the inclusion of high CMR subjects intended per study protocol, 28% of the sample ingested antiglycemic and 40% antihypertensive drugs; further details on medication status are given in Table 1 and Supplementary Table 2. Baseline circadian cortisol measures outside the lab (Table 1) were within the normative reference values derived from a large number of unselected individuals (Miller et al., 2016); no associations with CMR emerged (results not shown). Exposure to psychosocial stress was associated with significant increases in heart rate, blood pressure, salivary cortisol and feeling of subjective stress as well as loss of control, indicating that stress was successfully induced (Table 2). Analyses of absolute answer counts indicated that task motivation was not associated with CMR (regression analysis with (log)Framingham risk score as independent variable: $r = 0.23$, $p = .1$, comparison of answer counts between groups with and without diabetes, 105 ± 19 vs 111 ± 26, $t = 0.9$, $p = .38$, and between groups with and without metabolic syndrome 106 ± 20 vs 113 ± 28, $t = 1.2$, $p = .23$).

Table 1
Characteristics of subjects: clinical and biochemical variables, circadian cortisol secretion and CMR markers.

Clinical variables	
Age – yr	54.8 ± 5.8
Female/male sex	25/32
Living with partner no/yes	23/34
Houshold – number of persons	2.2 ± 1.3
Education – yr	11.6 ± 2.1
Current employment no/yes	20/37
Current smoker no/yes	35/22
Smoking status (never smoked/former smoker/current smoker)	29/6/22
Systolic blood pressure – mmHg	136.6 ± 18.4
Diastolic blood pressure – mmHg	86.3 ± 12.0
Heart rate – min^{-1}	72.7 ± 10.7
Body mass index – kg/m^2	28.0 ± 5.9
Waist circumference – cm	96.8 ± 16.7
Female	89.6 ± 17.6
Male	102.4 ± 13.7
Comorbidities – CIRS-Index	4.6 ± 3.3
Physical activity – (hours per week) (N = 49)	3.4 ± 4.1
Antiglycemic drug	16
Antihypertensive drug	23
Lipid-lowering drug	11
Antidepressant	8
Other medication	23
Biochemical variables (fasting state)	
Total cholesterol – mg/dl	201.0 ± 38.6
High density lipoprotein – mg/dl	58.4 ± 21.0
Low density lipoprotein – mg/dl	114.0 ± 35.1
Triglycerides – mg/dl	152.6 ± 85.7
Glucose – mg/dl	119.4 ± 46.3
Circadian cortisol secretion	
F0 [nmol/L] (N = 54)	7.2 ± 3.2
F¼ [nmol/L] (N = 54)	9.6 ± 3.9
F½ [nmol/L] (N = 54)	11.7 ± 4.0
F¾ [nmol/L] (N = 54)	10.9 ± 4.4
F16 [nmol/L] (N = 54)	1.6 ± 1.8
CAR – difference score [nmol/L] (N = 42)	4.6 ± 3.7
CAR – AUC [nmol/L] (N = 44)	490.3 ± 144.4
Slope [nmol/L/h] (N = 41)	0.38 ± 0.20
Cardiometabolic risk markers	
Diabetes – no/yes	37/20
Metabolic syndrome – no/yes	24/33
Metabolic syndrome – factor count	2.7 ± 1.5
Framingham Risk Score (individual risk) – %	20.1 ± 16.4

N = 57, unless otherwise indicated.
Values are given as N or means ± SD.
CIRS denotes Cumulative Illness Rating Scale, CAR cortisol awakening reaction and AUC area under the curve.

Table 2
Effect of psychosocial stress exposure on stress indicators.

	N	Baseline	Stress exposure	Delta	Analysis p-value*
Subjective feeling of					
Stress	57	1.3 ± 1.4	7.1 ± 2.2	5.9 ± 2.5	< 0.01
Control	57	7.8 ± 2.5	3.7 ± 2,6	−4.1 ± 3.0	< 0.01
Heart rate – min^{-1}	53	77 ± 12	89 ± 15	12 ± 10	< 0.01
Blood pressure – mmHg					
Systolic	55	134 ± 19	153 ± 20	19 ± 20	< 0.01
Diastolic	55	86 ± 12	94 ± 13	8 ± 11	< 0.01
Saliva cortisol concentration – nmol/L	56	3.6 ± 1.9	6.0 ± 4.4	2.4 ± 3.9	< 0.01

Values are means ± SD.
* Paired samples *t*-test, two-sided.

In our cohort, the Framingham risk score was 20.1 ± 16.4% (range 1.9–72.6%), with 42% of individuals showing a < 10% 10-year CVD risk, 18% a 10–20% risk and 40% a > 20% risk, indicating the bimodal risk distribution intended per study protocol (for further details, see Supplementary Fig. 1).

3.2. Effects of stress exposure on brain activity

Consistently with prior findings we observed significant stress-related increases in brain activity (stress > control contrast) in right and left ACC, right and left posterior cingulate cortex, right and left putamen, right and left insula, right and left parahippocampus and right hippocampus (all p < .05, FWE-corrected for multiple comparisons across the whole brain, see Fig. 1 and Supplementary Table 1). We did not observe any stress-related decreases in brain activity (control > stress contrast) after FWE-correction.

3.3. Associations of brain activity, Framingham risk score and peripheral stress markers

We did not observe any significant correlations between individual CMR indicated by the Framingham risk score and stress-related changes in brain activity in the a priori defined regions of interest ACC, hippocampus, amygdala, insula, OFC, VLPFC and DLPFC after FWE correction. On exploratory FWE-corrected whole-brain analyses, activation of no other brain region appeared to be associated with CMR either quantified as Framingham risk score or conceptualized as high CMR condition. Analyses without inclusion of age, sex and smoking status as covariates of interest were virtually unchanged, as well as analyses considering subjective social status. Neither did we find significant changes using statistical models that considered habituation processes during the stress task or that assessed the announcement phases instead of the task phases.

Stress-associated brain activation in the a priori defined regions of interest ACC, hippocampus, amygdala, insula, OFC, VLPFC, and DLPFC was not correlated with the task-induced rise in cortisol, heart rate, blood pressure or subjective stress feeling (FWE corrected, all p-values > .1). Exploratory FWE-corrected whole-brain analyses gave no evidence of other brain regions to be associated with changes of these stress markers.

We noticed a negative correlation between CMR, expressed as Framingham risk score, and increase in heart rate during stress exposure (ANOVA: F = 2.9, p = .04, adjusted for age and sex). There were no significant relationships between CMR and other stress-related changes of blood pressure, cortisol, and subjective feelings of stress and loss of control (all p-values > .1).

3.4. Comparison of subjects with and without type 2 diabetes or metabolic syndrome

Subjects with type 2 diabetes were older, more often male, and

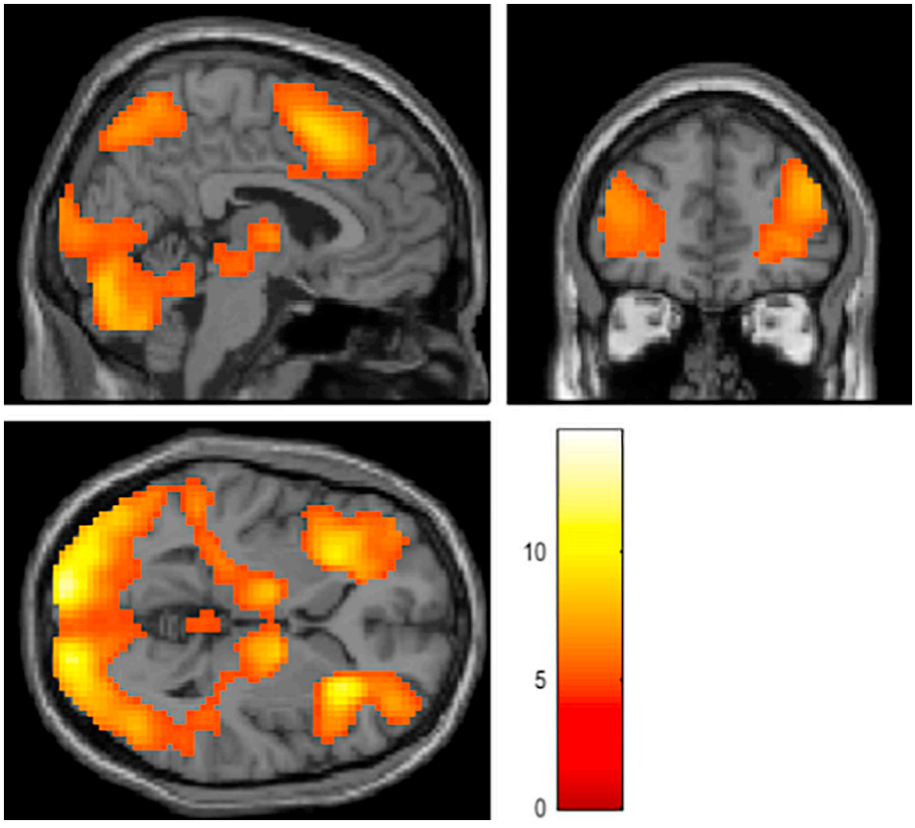

Fig. 1. Effect of psychosocial stress exposure on brain activity (N = 57). Significantly activated brain regions during psychosocial stress exposure (stress > control contrast), crosshairs at x = 6, y = 44, z = 0, see text for details. Whole brain analysis, p < .05 FWE corrected. Color bar represents t-values. A complete list of stress-induced brain regions is available in Supplementary Table 1.

showed the clinical and biochemical abnormalities associated with this disorder (Supplementary Table 2). Not surprisingly, diabetic subjects more often fulfilled the criteria of the metabolic syndrome, had an increased metabolic syndrome factor count, and a higher Framingham risk score. Comparing subjects with and without type 2 diabetes, no differences in stress-related brain activation between groups were noted for the contrasts diabetes > no diabetes and no diabetes > diabetes after FWE correction in the ROI ACC, hippocampus, amygdala, insula, OFC, VLPFC and DLPFC. Again, inclusion of subjective social status or stress task habituation effects as covariates did not change these results. In measures of cardiovascular and cortisol stress-related reactivity, subjects with diabetes showed descriptively smaller increases, but differences between groups did not reach statistical significance (Supplementary Table 3).

We did not observe any significant differences in stress-related brain activation between groups with and without the metabolic syndrome after FWE-correction. Similarly, no significant differences were observed in stress-related reactivity of cardiovascular, cortisol and subjective stress measures (all p-values > .1).

4. Discussion

In our cohort of subjects with low and high CMR, we successfully induced acute psychosocial stress during the measurement of brain activity in the fMRI scanner. Subjective feeling of stress increased fivefold, and there were significant surges in heart rate, blood pressure and cortisol secretion. Brain activity increased during stress exposure, as compared to the control condition, in a cortico-limbic network, confirming previous findings (Lederbogen et al., 2011).

However, when specific regions of this cortico-limbic system were marked as regions of interest and stress-associated activation of these areas was tested for covariation with CMR, no significant findings were noted. This result both emerged when CMR was indexed as Framingham risk score and conceptualized as type 2 diabetes or metabolic syndrome.

Several circumstances may explain the apparent absence of associations. First, increase of CMR associated with psychosocial stress exposure may rather be mediated by chronic than acute adaptional processes. It is well conceived that pathomechanisms differ between these two conditions Lagraauw et al. (2015). Chronic stress has distinct effects on cortico-limbic organization and morphology, including prefrontal hypofunction (McKlveen et al., 2016) and dendritic remodelling in hippocampal and amygdaloid neurons (Vyas et al., 2002). However, these changes may have little or no effect on brain activation associated with acute stress exposure.

Second, the size of our cohort may have been too small to detect differences in brain activation between low and high CMR subjects. However, a priori sample size calculation based on our previous work (Lederbogen et al., 2011) indicated that our cohort of N = 57 was reasonably sized to detect a potential effect. Furthermore, other significant functional MRI findings have been reported with similar or smaller group sizes. Soufer et al. (Soufer et al., 1998) noted exaggerated cerebral cortical responses in 10 coronary artery disease patients as compared to 6 normal controls; however, this group used different imaging and stress task conditions. If a very large group size would have detected a significant difference in stress-associated brain activation, it would be unclear whether this difference would indicate a clinical relevant pathomechanism.

Potentially, we did not include enough representative subjects with a high CMR profile in our sample. These individuals more often show depression, anger, social isolation and hostility (Brotman et al., 2007) and we assume that they typically do not volunteer for studies involving unpleasant performance tasks. Interestingly, in epidemiological research on cardiovascular risk factors, subjects who refused study participation had a higher cardiovascular mortality (Amann et al., 2016). However, 18% of our study subjects had a 10-year CVD risk of 10–20% and 40% a risk of > 20%, substantially exceeding CVD risk of comparable age groups in the general population, with corresponding figures of 25% and 4%, respectively (age group 50–59 years) (Ford et al., 2004). Also, the numbers of subjects with and without type 2 diabetes as well as with and without metabolic syndrome were evenly distributed between our groups, further arguing against underrepresentation of high CMR subjects as explanation of our finding.

Third, our study design (including CMR definition, stress task and analytic strategy) may not have been appropriate for detecting differences in psychosocial stress-evoked brain activation between low and high CMR subjects. The Framingham risk score defines CMR using the factors age, sex, blood pressure, indicators of lipid and glucose metabolism, and smoking. This definition encloses a wide range of both physiological and behavioural factors and may be too coarse to appropriately test our hypothesis. Furthermore, the CMR elevation associated with exaggerated psychosocial stress response may not be covered by this definition, as it maps on static, not dynamic variables. This notion is supported by the finding that stress-related brain activation was associated with stressor-evoked blood pressure elevation and but not with tonic resting blood pressure (Gianaros et al., 2017).

Furthermore, our stress task may not have been appropriate for detecting differences in brain activation between low and high CMR subjects. By combining social-evaluative threat and uncontrollability, this paradigm reliably activates stress system activity (Dickerson and Kemeny, 2004). In our cohort, its effectiveness was proven by increases in subjective stress, heart rate, blood pressure, and cortisol secretion. Potentially, tasks tailored to challenge specific components of the stress processing circuitry are more useful. Other researchers (Gianaros et al., 2017) applied a task specifically designed for amygdala activation, through the presentation of angry or fearful faces, and found intima-media-thickness, a preclinical marker of atherosclerosis, to covary with greater amygdala reactivity and a more positive connectivity between amygdala and perigenual ACC. Analysis was controlled for traditional CVD risk factors, including many of those examined in our study. However, other observations did not fully confirm these findings (Gianaros et al., 2014), so the extent to which amygdala activation is associated with CMR is debatable. In addition, tasks suitable for reward system activation may be considered, as high CMR individuals have been found to hyperactivate mesolimbic reward pathways in response to visual food cues. These brain circuits are known to be involved in the pathophysiology of addictive behaviour and may mediate the association between increased food intake, reduction of physical activity and high CMR (Grosshans et al., 2012; Morris et al., 2015). Other pathomechanistic work linked stress hyperreactivity to increased signs of inflammation. This condition, evidenced by increased concentrations of specific cytokines and invasion of the vessel wall by monocytes and T-lymphocytes fuels the progression of atherosclerosis (Libby, 2012) (Libby, 2012). Recently, an increased level of inflammation, quantified by bone-marrow activity and C-reactive protein concentration, has been traced back to heightened amygdala activity (Tawakol et al., 2017). In the longitudinal part of this study, the presence of these factors predicted a higher incidence of acute coronary syndromes.

Furthermore, our strategy of brain activity analysis may not have been appropriate to detect differences between low and high CMR individuals. A recent novel analytical approach used multivariate analyses and machine learning to analyse psychosocial stress-evoked patterns of brain activation associated with blood pressure reactivity and heart rate or skin conductance responses (Gianaros et al., 2017; Eisenbarth et al., 2016). These brain activation patterns were subsequently used to predict these physiological responses in an independent sample and revealed that, despite some similarities, the brain patterns associated with distinct autonomic responses were largely different. This observation argued against a common stress response system hypothesis but provided evidence that different autonomic responses are associated with distinct patterns of brain activation. These reports also indicated that brain activation associated with psychosocial stress-

evoked autonomic responses showed moderate to good intra-individual, but only minor inter-individual correlation, explaining about 10% or less of variance in heart rate and blood pressure reactivity between individuals.

Finally, our strict criteria to control the imaging analyses for errors associated with multiple testing may have concealed a meaningful finding. However, increasing concern on liberal statistical thresholds weakened confidence in neuroscientific reports. Replication of our observation or demonstration of an alternative neural mechanism explaining the empirically found association of increased psychosocial stress reactivity and CMR would strengthen the confidence in rejecting our hypothesis.

We found cardiovascular stress reactivity to be inversely associated with CMR, with high CMR subjects showing lower increases in heart rate during stress exposure. There were also lower increases in blood-pressure and cortisol secretion during stress exposure in high CMR subjects, but these differences did not reach statistical significance, possibly due to insufficient group size. According to meta-analytic data, a reduced cardiovascular reactivity is associated with chronic psychosocial stressors (Chida and Hamer, 2008). More specifically, blunted stress reactivity seems more closely associated with the behaviorally mediated CMR factors obesity and smoking, but also with impulsivity, neuroticism, eating disorders, addiction and depression (Carroll et al., 2017). A model was proposed that classified blunted cardiovascular and cortisol reactivity as a marker of a syndrome centered on motivational dysregulation as the ultimate psychological determinant of adverse health and behavioural outcomes. Vice versa, exaggerated stress reactivity seems to be more closely correlated with CMR factors that appear less behaviourally influenced like arterial hypertension or (preclinical) atherosclerosis. Other researchers proposed that during chronic CMR exposure, an initial state of hyperreactivity is transformed into hyporeactivity by adaptional processes (Miller et al., 2007) that may also include alterations in brain function. However, the reasons for these divergent patterns of association are far from being clear.

5. Conclusion

Although it seems plausible that subjects with high CMR show different neural patterns of acute stress processing, in this study no differences in brain activity associated with stress exposure emerged between these subjects and their low-risk counterparts.

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Appendix A. Supplementary data

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