Positive affect and health-related neuroendocrine, cardiovascular, and inflammatory processes

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Negative affective states such as depression are associated with premature mortality and increased risk of coronary heart disease, type 2 diabetes, and disability. It has been suggested that positive affective states are protective, but the pathways through which such effects might be mediated are poorly understood. Here we show that positive affect in middle-aged men and women is associated with reduced neuroendocrine, inflammatory, and cardiovascular activity. Positive affect was assessed by aggregating momentary experience samples of happiness over a working day and was inversely related to cortisol output over the day, independently of age, gender, socioeconomic position, body mass, and smoking. Similar patterns were observed on a leisure day. Happiness was also inversely related to heart rate assessed by using ambulatory monitoring methods over the day. Participants underwent mental stress testing in the laboratory, where plasma fibrinogen stress responses were smaller in happier individuals. These effects were independent of psychological distress, supporting the notion that positive well-being is directly related to health-relevant biological processes.

cortisol | well-being | fibrinogen | heart rate

There is growing evidence that affective states are associated with physical health. A metaanalysis of 25 prospective studies of adults with follow-up periods ranging from 2 to 16 years showed a consistently increased risk of mortality for both clinical and subclinical depression (1). Negative affective states such as depression are associated with increased risk of coronary heart disease, type 2 diabetes, and disability (2–4). Research in positive psychology is beginning to identify effects of psychological well-being on health as well (5, 6). For example, Danner *et al.* (7) reported a longitudinal analysis of a sample of Catholic nuns, in which the positive emotional content of writings at the age of 22 was associated with longevity during a 60-year period. A negative relationship between life satisfaction and mortality has been described in a 20-year study of initially healthy Finnish adults that was independent of marital status and social class (8). Whittington and Huppert (9) showed that 7-year mortality in a British cohort was more consistently associated with the absence of positive well-being than with the presence of symptoms of psychological distress. Other studies have reported that a lack of positive affect rather than heightened negative affect predicts mortality (10), stroke (11), and the development of disability (12) in older adults.

Two sets of mechanisms could theoretically mediate the relationship between affective states and physical health. First, positive well-being might be associated with favorable health habits and prudent lifestyles. For example, cigarette smoking is associated with psychological distress (13), and depression and anxiety are inversely related to leisure-time physical activity (14). The second possibility is that associations are mediated through psychobiological processes, defined as the pathways by which psychosocial factors stimulate biological systems through central nervous system activation of autonomic, neuroendocrine, inflammatory, and immune responses. Depressed mood has been linked with increased levels of C-reactive protein and inflammatory cytokines (15), prolonged norepinephrine responses to stress (16), and deficient immune responses after vaccination (17).

The biological correlates of positive affective states are only beginning to be described. Positive affect is associated with greater degrees of left compared with right superior frontal EEG activity at rest (18). Tugade and Fridrickson (19) demonstrated that the rate of cardiovascular recovery after stress is more rapid in individuals expressing positive emotionality. Lindfors and Lundberg (20) reported a small study involving 23 individuals in which salivary cortisol sampled every 2 h over the working day was inversely related to scores on eudaimonic psychological well-being scales. No associations were observed with urinary catecholamines or blood pressure. Psychological well-being ratings have also been positively associated with cytokine production after vaccination for influenza and hepatitis (21).

We assessed the biological correlates of positive affective states both in everyday life settings and under standardized stress testing conditions. We were interested in health-related biological indicators, so we measured cortisol during the day, ambulatory blood pressure and heart rate, and plasma fibrinogen responses to challenging behavioral tasks. Most research on affective states relies on global evaluations of positive or negative affect taken on a single occasion. The limitations of such measures for estimating subjective experience include recall bias, memory distortion, and the dominant influence of current state (22). A preferable method is momentary experience sampling, in which participants are prompted to record what they are currently feeling on several occasions for one or more days. We aggregated momentary ratings of happiness sampled repeatedly over the working day to derive a more robust estimate of positive affect than might be generated on a single occasion. We hypothesized that positive affect would be inversely associated with cortisol, ambulatory blood pressure, and heart rate, and with reduced fibrinogen stress responsiveness, independently of other factors known to influence these biological variables. A second aim of this analysis was to discover whether associations between happiness and biological responses were independent of psychological distress. Participants completed the General Health Questionnaire (GHQ), a well established screening instrument for psychiatric disorders that measures psychological distress (23), that has been found to predict coronary heart disease prospectively (24). We expected GHQ scores to be negatively associated with happiness ratings and reasoned that if positive affective states are independently related to health-related biological factors, then effects should persist after statistical control for psychological distress.

Methods

Participants. Participants were 116 men and 100 women who took part in the Whitehall II psychobiology study. The Whitehall II

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Abbreviations: GHQ, General Health Questionnaire; BMI, body mass index.

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cohort is a sample of 10,308 London-based civil servants recruited in 1985–1988 when 35–55 years old to investigate demographic, psychosocial, and biological risk factors for coronary heart disease (25). The psychobiology study involved 228 volunteers (123 men and 105 women) who underwent laboratory stress testing, 227 of whom carried out ambulatory blood pressure and heart rate monitoring over a working day (26, 27). Participants were of white European origin, 45–59 years old, living in the London area, not planning to retire for at least 3 years, no history or objective signs of coronary heart disease, and with no previous diagnosis or treatment for hypertension. All women were peri- or postmenopausal. Grade of employment was used as the marker of socioeconomic status, and participants were systematically recruited from higher, intermediate, and lower grades. The study was approved by the University College London/University College London Hospital's Committee on the Ethics of Human Research.

Procedures. ***Blood pressure and heart rate monitoring.*** Blood pressure and heart rate monitoring was carried out by using the SpaceLabs (Redmond, WA) 90217 monitor, an instrument that satisfies international instrumentation protocols (28). Ambulatory monitoring was carried out during a working day, beginning from 0730 to 0930 hours (depending on the work schedules of the participants) and continuing until bedtime. Readings were automatically triggered every 20 min, and the participant was instructed to keep still during cuff deflation. Blood pressure and heart rate readings were stored and not available to the participant at the time. Each reading was accompanied by an entry in a diary in which the participant recorded location and activity during the past 5 min.

Salivary cortisol measurement. Eight saliva samples were collected over the same working day and eight on a leisure day (Saturday or Sunday). Samples were taken at 2-h intervals from 0800–0830 to 2200–2230 hours. Tubes were returned to the investigators personally or by mail, and cortisol was analyzed by immunoassay at the University of Düsseldorf (Düsseldorf, Germany).

Assessment of positive affect. Positive affect was recorded after each ambulatory blood pressure and heart rate measurement when the participant was asked to give a rating of happiness during the past 5 min on a five-point scale where 1 = low and 5 = high. Ratings of stress, control, and tiredness were also obtained. An average of 33.0 ± 6.8 happiness ratings was obtained from each person on the working day. Monitoring typically began at 0900 hours and ended at 2200 hours, giving a total of 39 possible ratings, so the average response was 84.6%. Nearly half of the ratings (47 ± 37.9%) were positive (scores of 4 or 5 on the five-point scale). We therefore computed the proportion of positive happiness ratings for each individual. This proportion ranged from 0% to 100%. Two hundred sixteen of the 227 men and women who carried out ambulatory monitoring produced adequate happiness data, and they were the individuals analyzed in this study. The remaining 11 people either did not carry out ambulatory monitoring for the complete day and evening or did not fill in the diaries that accompanied cardiovascular measurements. The main analyses of associations between happiness and biological responses were carried out by dividing the sample into quintiles of happiness over the working day (percentage of ratings of 4 and 5) and treating happiness quintile as a between-subject factor in analysis of variance and logistic regression analyses.

Psychological distress measure. Psychological distress was assessed with the GHQ 30, a standard measure designed for use in population studies (23). The Cronbach α in the present sample was 0.93. Scores could range from 0 to 30 with higher scores indicating greater distress. Additionally, a score of 5 or more was defined as a positive GHQ case on the basis of the receiver operating characteristic analysis described by Stansfeld *et al.* (29), in which it was found that at this threshold, the GHQ has a sensitivity of 72.7% and a specificity of 78% against the clinical interview schedule for the identification of psychological distress of a severity that could be classified as a psychiatric disorder.

Laboratory mental stress session. The stress testing session involved assessment of subjective, cardiovascular, and inflammatory responses to the performance of moderately stressful behavioral tasks (26, 30). The two behavioral tasks were computerized color-word interference and mirror tracing. The color-word task involved the presentation of a series of target color words in incongruous colors. At the bottom of the computer screen were four names of colors displayed in incorrect colors, and the task was to press a computer key that corresponded to the position at the bottom of the screen of the name of the color in which the target word was printed. Mirror tracing involved the tracing of a star seen in mirror image with a metal stylus. Participants were told that the average person completed five circuits of the star in the time available and were asked to give accuracy priority over speed on both tasks.

Participants were tested individually in either the morning or afternoon in a light- and temperature-controlled laboratory. They were instructed not to have drunk tea, coffee, or caffeinated beverages or to have smoked for at least two hours before the study, and not to have consumed alcohol or exercised on the evening before or the day of testing. Body weight, height, and waist and hip circumference were measured by a research nurse by using standardized methods. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Data concerning marital status and smoking were collected by questionnaire. Blood pressure and heart rate were monitored continuously from the finger by using a Portapres-2 (TNO-BMI, Amsterdam) (31). A 21-gauge venous cannula was inserted, and the participant rested for 30 min, at the end of which a baseline blood sample was drawn. Blood pressure and heart rate were averaged over minutes 25–30 of the baseline period to constitute resting levels. Participants rated their current level of stress on a seven-point scale from 1 (low) to 7 (high). The two tasks were then administered for 5 min each in random order. After each task, ratings of stress, task involvement, difficulty, and controllability were obtained on seven-point scales. A second blood sample (stress measure) was drawn immediately after the two tasks had been completed. Blood pressure and heart rate monitoring was continuous throughout the task trials. Clottable fibrinogen was measured from frozen samples by an automated Clauss assay in a MDA-180 coagulometer (Organon Teknika, Cambridge, U.K.) by using the manufacturer's reagents and the International Fibrinogen Standard (32). Hematocrit was assessed immediately after each blood sample was drawn by using a microhematocrit centrifuge and reader (Hawksley-Gelman, Lancing, U.K.).

All participants carried out the laboratory stress session first. At the end of the session, the ambulatory monitoring procedure was explained and scheduled for a few days later. The leisure day monitoring of saliva followed the working day assessments.

Results

Affective States. The sample was divided into quintiles based on happiness ratings during the working day. Participants in the lowest quintile (quintile 1) gave virtually no positive happiness ratings, whereas those in the highest quintile (quintile 5) rated themselves as happy almost all of the time (Table 1). There was no association between happiness and age, gender, marital status, or socioeconomic position. There was a positive correlation between happiness ratings on the work and leisure days ($r = 0.65$, $P < 0.001$), so the classification of participants on the basis of happiness during the working day generalized to the leisure day. Comparison of happiness ratings on work and leisure days showed a happiness quintile by day interaction ($P < 0.001$).

Table 1. Ratings of happiness and psychological distress for participants in the five happiness quintiles

		Happiness quintiles				
	Gender	1	2	3	4	5
Happiness ratings, %						
Workday	Men	1.4 ± 2.2	16.7 ± 6.7	41.2 ± 8.2	81.3 ± 11.3	99.0 ± 1.4
	Women	1.1 ± 1.9	16.7 ± 7.3	40.4 ± 7.3	80.2 ± 13.9	99.4 ± 1.3
Leisure day	Men	12.5 ± 19.0	37.3 ± 41.0	78.1 ± 36.4	84.6 ± 29.9	95.5 ± 12.7
	Women	22.4 ± 30.4	53.0 ± 48.7	62.5 ± 38.5	77.6 ± 33.7	89.4 ± 23.9
Mean GHQ rating		4.34 ± 6.6	4.18 ± 5.4	4.48 ± 6.6	2.69 ± 5.0	1.26 ± 3.3

Post hoc analyses indicated that happiness ratings in the top two quintiles did not differ between work and leisure days, whereas individuals in the lower three workday quintiles were happier on leisure than work days ($P < 0.001$). Psychological distress scores on the GHQ averaged 3.39 ± 6.5, and 53 (24.5%) of participants had ratings above the GHQ case threshold. GHQ scores were inversely related to the happiness quintile ($P = 0.004$), confirming that happier individuals reported lower psychological distress (Table 1). The proportion of participants with positive GHQ case status was 29.3%, 31.8%, 31.8%, 18.6%, and 11.6% for respondents in happiness quintiles 1 to 5, respectively. The odds adjusted for age and gender of a positive GHQ case score were 3.21 (95% confidence interval 1.00–10.3) for individuals in the lowest happiness quintile, 3.56 (1.14–11.1) for quintile 2, and 3.45 (1.11–10.7) for quintile 3 compared with the highest happiness quintile. Men and women did not differ significantly in any of these analyses.

Neuroendocrine and Cardiovascular Activity in Everyday Life. Cortisol aggregated over eight samples taken at 2-h intervals on the working day averaged 7.70 ± 2.8 nmol/liter and was slightly higher in men than women ($P = 0.043$). Cortisol concentration differed across the happiness quintiles after controlling for age, grade of employment, smoking status, and body mass index (BMI), and this effect remained significant after the GHQ was included as a covariate ($P = 0.009$). Cortisol levels also decreased across the day ($P < 0.001$), but there was no interaction between happiness and time of day. Cortisol was highest in quintile 1, and lowest in quintile 5, with values being an average 32.1% greater in the least happy compared with the happiest quintile (Fig. 1). The mean salivary cortisol over the leisure day was 7.22 ± 3.0 nmol/liter and did not differ between men and women. The difference in leisure-day cortisol across the happiness quintiles was also significant after the GHQ and other covariates were taken into account ($P = 0.026$). Levels were greatest in the lowest happiness quintile (adjusted mean 8.24 ± 4.1 nmol/liter), declining to 6.17 ± 1.8 nmol/liter in the highest happiness quintile (a 34% difference). Thus on both work and leisure days, higher levels of happiness were associated with lower cortisol levels, independently of psychological distress and other covariates.

Happiness was not associated with ambulatory blood pressure in this study. Transient episodes of activation stimulated by positive mood states may prevent any inverse association between broader positive experience and blood pressure from becoming apparent (33). Nevertheless, in men but not women, happiness was associated with ambulatory heart rate after controlling for age, grade of employment, smoking, BMI, and physical activity ($P = 0.020$). This effect remained significant after additional control for GHQ scores ($P = 0.033$). Heart rate averaged across the working day and evening was greatest in the low happiness quintile, and was less in happier men (Fig. 1).

Mental Stress Testing. In the laboratory phase of the study, subjective stress averaged 1.45 ± 0.75 during baseline, rising to 4.04 ± 1.4 for task trials. Systolic blood pressure averaged 114.6 ± 12.1 mmHg (1 mmHg = 133 Pa) during baseline, increasing to 140.9 ± 21.1 mmHg during task trials, whereas diastolic blood pressure rose from 70.1 ± 9.6 to 83.7 ± 11.4 mmHg. There were no differences across happiness quintiles in subjective stress, blood pressure, or heart rate responses to tasks, and ratings of task difficulty and controllability were also unrelated to happiness group.

Plasma fibrinogen concentration in blood drawn during the baseline averaged 2.87 ± 0.6 g/liter and was unrelated to happiness. Fibrinogen concentration increased after stress, and there were significant differences in stress responses across happiness quintiles after covarying for age, gender, grade of employment, smoking, BMI, and baseline fibrinogen ($P = 0.003$). Inclusion of the GHQ as an additional covariate did not change this result ($P = 0.011$), illustrated in Fig. 2. The increase in fibrinogen (adjusted for covariates) with stress averaged 0.12 g/liter in the lowest compared with 0.0097 g/liter in the highest happiness quintile. We found that 68.4% of participants showed an increase in fibrinogen concentration with stress, whereas there was no change or a decrease in fibrinogen between baseline and task trials in 31.6%. The odds of

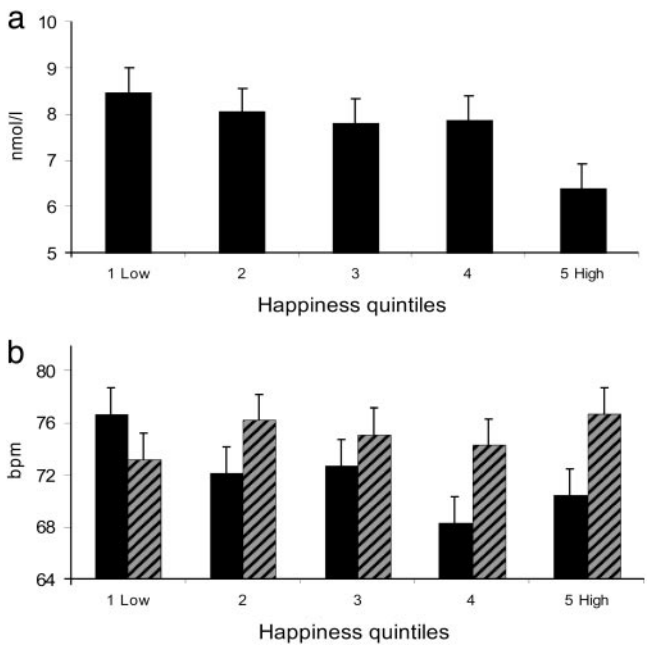

Fig. 1. Biological correlates of happiness over the working day. (*a*) Mean salivary cortisol averaged during the working day in relation to happiness quintile, adjusted for gender, age, grade of employment, BMI, smoking, and psychological distress. Error bars are standard errors of the mean (SEM). Cortisol levels were inversely related to happiness ($P = 0.009$), and there was no gender difference in this pattern. (*b*) Mean heart rate averaged during the working day in relation to happiness in men (black bars) and women (hatched bars). Values are adjusted for age, grade of employment, BMI, smoking, and physical activity, and error bars are SEM. The difference across happiness quintiles was significant for men ($P = 0.020$) but not for women.

Fig. 2. Happiness and fibrinogen stress responses. Shown is the mean increase in plasma fibrinogen after acute mental stress in the five happiness quintiles, adjusted for gender, age, grade of employment, BMI, smoking, baseline fibrinogen, and GHQ. Error bars are SEM. Differences in fibrinogen stress responses across happiness quintiles were significant ($P = 0.011$).

a stress-induced increase in fibrinogen were 3.72 (confidence interval 1.16–11.9) for participants in happiness quintile 1, adjusted for covariates including GHQ score, compared with the highest happiness quintile.

Discussion

This study is focused on the biological correlates of individual differences in affective well-being, and we aggregated momentary samples to generate a single measure of happiness. The complete range of possible happiness levels was covered from individuals who never rated themselves happy to those with positive happiness ratings on all samples. As might be expected, happiness levels were higher on the leisure than working day, and individual differences were consistent across days. People who were happy most of the workday were also happier during the leisure day. Aggregation of the momentary assessments appears therefore to have generated relatively robust estimates of positive affective state. A complementary approach is to study within-subject covariation of positive affect with biology, but this involves different analytic methods (33). As anticipated, happiness was inversely associated with psychological distress measured by using the GHQ. Substituting subjective stress ratings for the GHQ as an indicator of distress did not alter the associations between positive affect and biology.

The relationship between reduced cortisol and positive affect is potentially relevant to health. Cortisol is a key stress hormone related to a range of pathologies including abdominal obesity, Type 2 diabetes, hypertension, and autoimmune conditions (34, 35). The average difference in cortisol of 32.1% between the lowest and highest happiness quintiles is substantial and might contribute to health risk if it persists over months or years. Because high cortisol is characteristic of some depressed individuals (36), it is important to note that the link with happiness was independent of negative affect in this study.

Elevated heart rate has been shown to predict mortality and cardiovascular disease risk in prospective epidemiological studies (37, 38). The associations we found with happiness in men were independent both of standard covariates and of ratings of physical activity that have previously been shown to correlate with objective energy expenditure (27). The explanation of the gender difference in heart rate is not clear, but observational epidemiological studies have shown consistent associations between mortality and heart rate more in men than women (38).

The laboratory phase of the study involved assessment of subjective, cardiovascular, and inflammatory responses to standardized behavioral tasks. The advantages of this method of assessing psychobiological responses have been well documented (39). Laboratory stress testing permits the measurement of sophisticated markers of biological activation under controlled conditions, eliminating variability due to factors such as ongoing activities, physical environment, consumption of caffeine and tobacco, that complicate naturalistic ambulatory monitoring. Assessment of fibrinogen responses in everyday life would be very difficult because of the need to take repeated blood samples. By imposing standardized behavioral challenges, individual differences in stress responsiveness can be revealed. Interestingly, happiness was not related to subjective or cardiovascular stress responses, nor did appraisals of task difficulty and controllability vary with happiness. We had expected that happier individuals might feel less stressed by the behavioral tasks, but this was not the case. This finding reinforces the observation that happiness reports were partly independent of negative affect by showing that acute episodes of stress were not related to happiness. In analyses that have not been presented in detail, we failed to observe any association between happiness and poststress cardiovascular recovery, as reported by Tugade and Fredrickson (19).

Plasma fibrinogen is an inflammatory marker and predictor of future coronary heart disease, heightening risk through increasing blood viscosity, infiltration of the arterial wall, stimulation of atherogenic cell proliferation, and platelet aggregation (40, 41). Although the fibrinogen stress responses were small in absolute terms, the relative increase was >12 times greater in the lowest compared with highest happiness group. If differences of this magnitude are elicited in everyday life when people are exposed to daily hassles and challenges, the result could be a marked difference in cardiovascular disease risk.

Research in positive psychology has begun to document the significance of positive well-being to creativity, leadership, and the realization of human potential (5, 42). Our findings indicate that positive affective states are related to favorable profiles of functioning in several biological systems and may thereby be relevant to risk of development of physical illness. The participants in this study were in relatively good health, so no objective health outcomes were analyzed.

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