Psychobiological Processes: Pathways Linking Social Factors with Disease

Andrew Steptoe
Department of Epidemiology and Public Health
University College London
http://www.ucl.ac.uk/psychobiology/
Department of Epidemiology and Public Health

- Whitehall and Whitehall II epidemiological studies
- English Longitudinal Study of Ageing (ELSA)
- Health Survey for England
- National Child Development Study (1946 birth cohort)
- Psychosocial factors in Eastern Europe (HAPIEE)
- Ethnic minority psychiatric illness rates (EMPIRIC) study
Issues:

- What are psychobiological processes?
- Why are they relevant?
- What types of study?
- What measures are useful in health care research?
Psychobiological pathways

The pathways through which psychosocial factors stimulate biological systems via central nervous system activation of autonomic, neuroendocrine and immunological responses
Psychobiological responses

<table>
<thead>
<tr>
<th>Category</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine</td>
<td>cortisol, epinephrine, testosterone, norepinephrine</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Blood pressure, heart rate</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>C-reactive protein, interleukin (IL-6), fibrinogen</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Lipids, glucose, insulin</td>
</tr>
<tr>
<td>Hemostatic</td>
<td>Platelets, coagulation factors</td>
</tr>
<tr>
<td>Immune</td>
<td>Lymphocyte counts and activity, natural killer cells, immunoglobulins</td>
</tr>
</tbody>
</table>
Hypothalamic-Pituitary-Adrenal Axis (HPA)

- Hypothalamus
  - CRF
  - Pituitary gland
    - ACTH
    - Adrenal cortex
      - Cortisol

Sympatho-Adrenal Axis

- Brain
- Hypothalamus
  - Sympathetic nervous system
    - Norepinephrine
  - Adrenal medulla
    - Epinephrine
Some effects of cortisol

• Stimulation of glucose production in the liver
• Release of free fatty acids from fat stores
• Regulation of water balance
• Stimulation of anti-inflammatory responses
• Immune regulation
Some effects of sympathetic activation

- Increased blood pressure and heart rate
- Reduced gut motility and salivation
- Stimulation of clotting processes
- Acute immune activation
- Release of free fatty acids from fat stores
When are psychobiological responses hazardous?

- Heightened reactions or failure of post-stress adaptation
Biological stress responsivity

- Size of the response

- Rate of recovery
Origin of variation in psychobiological responses

- Genetic factors
- Early life experience
- Adult life factors – adversity, temperament
- Appraisal and coping factors
Gianaros,

*Psychosom Med*

2005
When are psychobiological responses hazardous?

- Heightened reactions or failure of post-stress adaptation
- Sustained or repeated exposure to conditions eliciting responses
McEwen, *NEJM* 1998
Some effects of high cortisol

Potentially damaging effects

• Increased lipid (LDL-cholesterol) in the blood
• Suppression of immune function
• Decalcification of bone
• Deposition of abdominal fat
• Damage to the hippocampus
• Muscle wasting
• Impaired reproductive function
Issues:

- What are psychobiological processes?
- Why are they relevant?
- What types of study?
- What measures are useful in health care research?
Psychosocial factors associated with disease incidence or progression in prospective observational cohort studies

- Chronic life stress
  High demand/low control at work; effort-reward imbalance; financial strain; marital conflict; caregiving

- Social environment
  Social isolation; emotional support

- Psychological factors
  Depression, anger/hostility, anxiety/distress
Prevalence of Conventional Risk Factors in Men with Coronary Heart Disease
(n=87,869)

- No Risk Factors: 43.0%
- 1 Risk Factor: 27.8%
- 2 Risk Factors: 19.4%
- 3 Risk Factors: 8.9%
- 4 Risk Factors: <1%

Khot et al, 2003
JAMA
Work stress and cardiac mortality

25 year follow-up, adjusted for age, sex, smoking
Physical activity, blood pressure, cholesterol, body mass

Kivimäki, 2002
Metabolic syndrome markers (ATPIII)

Three or more of:

- Waist circumference $> 102$ cm (men) or $88$ cm (women)
- Fasting triglyceride $\geq 150$ mg/dl
- Fasting HDL-cholesterol $< 40$ mg/dl (men), $< 50$ mg/dl (women)
- Blood pressure $\geq 130 / 85$ mmHg
- Fasting glucose $\geq 110$ mg/dl
Marital satisfaction and the metabolic syndrome

Odds ratio

Satisfied | Moderately satisfied | Dissatisfied
---|---|---
1.5 | 1.2 | 4.0

11.5 year follow-up adjusted for baseline MS, age, race, education, Smoking, physical activity, alcohol, depression, anxiety

Troxel et al, 2005
Arch Intern Med
Social support and CHD

15 year follow-up, adjusted for smoking, blood pressure, cholesterol, triglycerides, BMI, waist/hip ratio, diabetes, family history, social class, stress

Rosengren, 2004
Psychobiology and Infection

- Infectious agent
- Adequate immune response
  - No illness
- Psychobiological stimulation
- Impaired immune response
- Illness

- Infectious agent
  - Impaired immune response
  - Illness
(Odds ratios are adjusted for control variables.)

Cohen et al, *JAMA*, 1997
Depression and physical illness

- Premature mortality
- Coronary heart disease
- Diabetes
- Disability
- Multiple sclerosis
- Rheumatic conditions
- Metabolic syndrome

Depression and Physical Illness
CUP, in press
Socioeconomic position and psychosocial factors

Lower socioeconomic position associated with

- Greater exposure to chronic stress (domestic, neighborhood)
- Greater financial strain
- Lower job control, higher job demands, effort-reward imbalance
- Greater social isolation and lower social support
- Lower sense of control
- Greater hostility
- Less use of active coping and planning responses
- More depressed mood, lower optimism
Psychosocial Factors

Adverse
- Work stress
- Neighbourhood
- Financial
- Domestic

Protective
- Social networks
- Coping responses
- Self-esteem

Health-compromising behaviours

Psychobiological processes

Psychological well-being

Physical disease risk

Affective disorders

Social position
- Occupation
- Education
- Income
Issues:

• What are psychobiological processes?
• Why are they relevant?
• What types of study?
• What measures are useful in health care research?
Applications of Psychobiological Measures

- Epidemiological studies
- Clinical studies
- Experimental studies
- Naturalistic monitoring studies
Epidemiological surveys

- Large samples
- Disease endpoints
- Prospective designs
Fibrinogen

Inflammatory and thrombogenic factor
Increases blood viscosity, stimulates atherogenic cell proliferation, platelet aggregation

Associated with:
• Low SES
• Low control at work, high effort/reward imbalance
• Social isolation
Epidemiological surveys

- Large samples
- Disease endpoints
- Prospective designs

Single measures under resting conditions
Limited information about mechanisms
Confounding issues in psychosocial studies
Experimental studies

• Stress-inducing tasks:
  Problem solving, emotional interviews, simulated public speaking

• Measurement of:
  Blood pressure, heart rate, hormones, cholesterol, blood clotting, inflammation, muscle tension

• Comparison of:
  Clinical groups;
  People high or low on psychosocial characteristics;
  Experimental conditions inducing low or high control, social support, etc
Laboratory mental stress testing

- Sophisticated biological measures
- Control of confounders
- Experimental manipulation of conditions
C-reactive protein

- Acute phase protein synthesized in liver
- Increases in response to inflammatory stimuli (cytokines), infection and tissue damage
- Antimicrobial, clears apoptotic cells, enhances phagocytosis
- Marker of chronic low grade inflammation
- Risk marker for CVD, functional significance debated
Work stress study

• 105 healthy nonsmoking men, mean age 32.1 years. Full-time employment
• Measures of effort-reward imbalance
• Responses to simulated public speaking and mirror tracing tasks
• Blood samples for C-reactive protein before and after tasks
Effort-reward imbalance and C-reactive protein stress responses

Adjusted for baseline C-reactive protein, age and BMI
Psychobiological responses and SEP

Participants
- 238 members of the Whitehall II (prospective) cohort aged 47-59 years in full-time employment.
  Sampled by grade of employment:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>49</td>
<td>41</td>
<td>90</td>
</tr>
<tr>
<td>Intermediate</td>
<td>44</td>
<td>37</td>
<td>81</td>
</tr>
<tr>
<td>Lower</td>
<td>36</td>
<td>31</td>
<td>67</td>
</tr>
</tbody>
</table>

Conditions
- Cardiovascular, neuroendocrine, cytokine and hemostatic responses to colour/word and mirror tracing tasks.
  Blood drawn at baseline, immediately post-task, and 45 minutes later.
Stress ratings by SEP

- **Higher**
- **Intermediate**
- **Lower**

- **Base**
- **CW**
- **MT**
- **Recovery**
Factor VIII, Stress, and SEP

Steptoe et al
*Thromb Haemo, 2003*
Laboratory mental stress testing

- Sophisticated biological measures
- Control of confounders
- Experimental manipulation of conditions

Small acute responses
Generalisation of acute responses into everyday life
Prediction of future health risk
**Blood pressure reactivity and atherosclerosis**

**TABLE 3. Prediction of Mean/Maximum Carotid IMT and Plaque Scores From SBP Reactivity**

<table>
<thead>
<tr>
<th>Source Variable</th>
<th>Mean IMT</th>
<th>Max IMT</th>
<th>Plaque Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Age</td>
<td>0.056</td>
<td>0.047</td>
<td>0.077</td>
</tr>
<tr>
<td>Education</td>
<td>−0.041</td>
<td>0.103</td>
<td>−0.042</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−0.047</td>
<td>0.099</td>
<td>−0.023</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.025</td>
<td>0.344</td>
<td>0.016</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.032</td>
<td>0.211</td>
<td>0.037</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.025</td>
<td>0.377</td>
<td>−0.038</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>0.024</td>
<td>0.511</td>
<td>0.056</td>
</tr>
<tr>
<td>Resting DBP</td>
<td>0.041</td>
<td>0.070</td>
<td>0.050</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.087</td>
<td>0.001</td>
<td>0.104</td>
</tr>
<tr>
<td>Previous carotid measure</td>
<td>0.699</td>
<td>&lt;0.001</td>
<td>0.586</td>
</tr>
<tr>
<td>SBP reactivity</td>
<td>0.059</td>
<td>0.026</td>
<td>0.084</td>
</tr>
<tr>
<td>Total $df$</td>
<td>12.675</td>
<td>...</td>
<td>12.675</td>
</tr>
<tr>
<td>$R^2$ for model</td>
<td>0.583</td>
<td>...</td>
<td>0.453</td>
</tr>
</tbody>
</table>

- Shows adjustment for cardiovascular risk factors and carotid measures taken 7 y earlier.
- *Standardized $\beta$ values.

**Jennings et al 2004 Circulation**
Whitehall Psychobiology Follow-up

• Assessment of 209 participants 3 years after mental stress testing (92% response rate)

• Measurement of
  ➢ resting blood pressure
  ➢ fasting lipid profiles
  ➢ BMI, waist and hip circumference
  ➢ Ambulatory BP in a subset (153)
3 year systolic BP increase ≥ 5 mmHg

Adjusted for baseline BP, age, gender, grade of employment, hypertensive medication, BMI, and smoking

Steptoe & Marmot
*J Hypertension, 2005*
Cholesterol response to acute stress

Adjusted for socioeconomic status, age, body weight, smoking, alcohol, and haematocrit
Steptoe & Brydon
*Health Psychol*, 2005

Cholesterol stress response and cholesterol 3-years later

Adjusted for gender, socioeconomic status, age, body weight, smoking, alcohol, and baseline cholesterol
Applications of Psychobiological Measures

- Epidemiological studies
- Clinical studies
- Experimental studies
- Naturalistic monitoring studies
Naturalistic / ambulatory monitoring studies

- Dynamic responses in everyday life
- Covariation of biology, events and reactions

Ambulatory blood pressure
Salivary cortisol
Ambulatory systolic pressure: working day

Adjusted for gender, age, occupational grade, smoking, bmi, and physical activity

Steptoe & Willemsen
J Hypertension, 2004
Cortisol and job control

Men, age-adjusted

Kunz-Ebrecht et al
Naturalistic / ambulatory monitoring studies

- Dynamic responses in everyday life
- Covariation of biology, events and reactions

Limited range of biological measures
Control for confounders
6 year risk of stroke in older men and women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk / ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive affect</td>
<td>0.74 (0.62-0.88)</td>
</tr>
<tr>
<td>Negative affect</td>
<td>1.01 (0.97-1.05)</td>
</tr>
<tr>
<td>Age</td>
<td>0.004</td>
</tr>
<tr>
<td>Education</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.008</td>
</tr>
<tr>
<td>Previous heart attack</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Ostir et al, Psychosom Med, 2001
### 10 year mortality in older men and women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conditional hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq 75$</td>
<td>1.78 (1.61-1.96)</td>
</tr>
<tr>
<td>Male</td>
<td>2.12 (1.91-2.36)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>1.30 (1.17-1.50)</td>
</tr>
<tr>
<td>Low education</td>
<td>1.22 (1.10-1.35)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>1.64 (1.45-1.87)</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>2.07 (1.87-1.28)</td>
</tr>
<tr>
<td>Low positive affect</td>
<td>1.12 (1.05-1.18)</td>
</tr>
</tbody>
</table>

Blazer & Hybels, *JAGS*, 2004
Psychobiology and Happiness

Aims

• To assess associations between happiness and psychobiological responses relevant to health and disease risk

• To determine whether associations of psychobiological responses and happiness are independent of negative emotional states
Measurement of happiness

- Repeated sampling every 20 minutes from morning (07:30 – 09:30 start) until evening (22:30) on a working day
- Happiness on 5-point scale: 1 = very low to 5 = very high
- Division into 1-3 vs 4-5
- Proportion of happy ratings (4-5) over the day
Happiness in men and women

Steptoe et al
PNAS, 2005
Salivary cortisol – working day

8 samples (08:00 – 22:30)
Adjusted for gender, age, occupational grade, smoking, bmi, and GHQ

Happiness quintiles

1 Low 2 3 4 5 High

P = .009
Fibrinogen stress responses

Adjusted for gender, age, occupational grade, smoking, bmi, haematocrit, baseline fibrinogen, and GHQ

\( P = .003 \)
Happiness ratings - 3 years

Happiness quintiles (baseline)

% happy rating:

Men   Women

1 Low  2  3  4  5 High

Happiness quintiles (baseline)
Cortisol and happiness – 3 year

Happiness quintiles

1 Low 2 3 4 5 High

N = 144
Adjusted for gender, age, occupational grade, work at follow-up, smoking, bmi, GHQ

P = .064
Systolic BP and happiness – 3 year

Adjusted for gender, age, occupational grade, work at follow-up, smoking, bmi, GHQ. N = 160
Applications of Psychobiological Measures

- Epidemiological studies
- Clinical studies
- Experimental studies
- Naturalistic monitoring studies
Psychobiological measures:

- Cortisol
- Inflammatory markers: IL-6
- Heart rate variability
Cortisol:

- General marker of activation and associated with health outcomes
- Related to physical health outcomes, mental health (depression) and cognitive function (memory)
- Influenced by current and earlier life psychosocial factors
- Easy to measure in saliva, urine or blood
Cortisol and cognition:

- Wide variation in natural cortisol levels
- In aging, some increase, others decrease cortisol levels
- High increases in natural levels with aging associated with impaired memory, smaller hippocampal volume
  
Lupien, PNEC, 2005

- General cognitive function associated with higher cortisol in older men
  
MacLullich, PNEC, 2005
Acute cortisol responsivity and memory in old age

Adjusted for age, gender, education, chronic illness, medication, baseline cortisol and time of day

Wright et al, PNEC, 2005
Problems of interpretation of cortisol data:

- Variation over the day; single readings of limited value
Cortisol profile over working day
Problems of interpretation of cortisol data:

- Variation over the day; single readings of limited value
  - Cortisol awakening response
  - Levels over the day, slope
Cortisol waking response

Kunz-Ebrecht et al
PNEC, 2004
Cortisol waking response

Wright & Steptoe
PNEC, 2005
Cortisol waking response

Heightened response

• Depressive symptoms (Pruessner 2003)
• Patients with clinical depression (Bhagwagar 2003)
• Chronic work stress (Steptoe 2000)
• Working vs weekend days (Schlotz 2004)
• Loneliness (Steptoe 2004, PNEC)
• Abdominal adiposity (Steptoe, 2004, IJO)
Problems of interpretation of cortisol data:

- Variation over the day; single readings of limited value
- Which is bad – high or low level?
Buske-Kirschbaum et al
*Psychosom Med, 2003*
Cortisol waking response

**Heightened response**
- Depressive symptoms (Pruessner 2003)
- Patients with clinical depression (Bhagwagar 2003)
- Chronic work stress (Steptoe 2000)
- Working vs weekend days (Schlotz 2004)
- Loneliness (Steptoe 2004, PNEC)
- Abdominal adiposity (Steptoe, 2004, IJO)

**Reduced response**
- Chronic fatigue (Roberts 2004)
- Some physical illness groups (Kudielka 2003)
Cortisol and recent trauma:

- 190 low income women from urban Michigan
- Samples in clinic, on waking, 30 min after waking, and before bed
- 12 month exposure to trauma (assault, rape, car crash, sudden death of close friend etc)

Young et al, Biol Psychiatry, 2004
Cortisol and recent trauma:

- 163/190 clinic
- 170/190 waking
- 173/190 second morning
- 166/190 bedtime samples
- Second morning sample very late in more than a third
- Pooled data used
Inflammatory markers

- C-reactive protein
- Interleukin 6 (IL-6)
- Fibrinogen
- Tumor necrosis factor alpha
Interleukin 6

An ‘endocrine’ cytokine associated with
• Coronary heart disease
• Type 2 diabetes, insulin resistance, obesity
• Depression
• Disability
• Cognitive decline
IL-6 and depressed mood

3024 men & women aged 70-79

Penninx et al, *Biol Psychiat* 2005
IL-6 and cognitive impairment

4 year follow-up of 2632 men and women aged 70-79 years
Cognitive impairment, adjusting for baseline cognitive score, age, education, race, depression, alcohol, stroke and statins
• High inflammation RR: 1.66 (1.19 – 2.18)
• Low inflammation RR: 1.08 (0.89 – 1.30)

Yaffe et al
JAMA 2004
Interleukin 6

An ‘endocrine’ cytokine associated with
• Coronary heart disease
• Type 2 diabetes, insulin resistance
• Depression
• Disability

• Sensitive to acute and chronic stress
Caregiver stress and plasma interleukin-6

Kiecolt-Glaser et al
PNAS, 2003
Stress and plasma interleukin-6

Brydon et al
Brain, Behav Immun, 2004
Heart rate variability

- Beat-to beat variation in heart rate
- Interplay between sympathetic and parasympathetic (vagal) branches of autonomic nervous system

Assessed in the
- Time domain (R-R variability)
- Frequency domain (spectral analysis)
  - High frequency (parasympathetic)
  - Low frequency (sympathovagal balance)
  - Low/High (sympathovagal balance)
Low heart rate variability

- Higher risk of death or recurrent events in patients with CHD (Atrami study, 1998)
- Incident CHD in apparently healthy cohorts (Liao, 1997)
- Future hypertension (Schroeder, 2003)
- Post-stroke mortality (Makikillio, 2004)
- Depressive symptoms (Lim, 2005)
Low heart rate variability

- Poorer cognitive executive function (Hansen et al, 2003)
- Less effective impulse control in children (Allen et al, 2000)
- More negative moods in alcohol abuse (Ingjaldsson et al, 2003)
- Reduced sleep efficiency (Hall et al, 2004)
Whitehall autonomic function study

Low heart rate variability related to:

- Low employment grade
- Lower job control
- Smoking, inactivity, high alcohol intake
- Metabolic syndrome

Hemingway et al
Circulation, 2005
Low heart rate variability

- Social isolation (Horsten, 1999)
- High effort/reward imbalance (Vrijkotte, 2000)
- Depressive symptoms (Lim, 2005)
- Depression in post-MI patients (Carney, 2001)
Heart rate variability by grade
Psychosocial Factors

Adverse Work stress Neighbourhood Financial Domestic

Protective Social networks Coping responses Self-esteem

Health-compromising behaviours

Psychobiological processes

Psychological well-being

Physical disease risk
Affective disorders

Social position
Occupation Education Income
Conclusions

• Psychobiological processes are plausible mediators of social influences on disease development
• The involvement of psychobiological responses is determined by the interplay between individual differences in responsivity and exposure to positive and negative life experiences
• Some psychobiological responses appear to be relevant across a range of health outcomes
What we need to know

• The precise pathological significance of some psychobiological responses is poorly understood
• The full sequence from social factor to biological response to disease has seldom been documented
• Whether interventions along this sequence will block health effects and demonstrate causality
Acknowledgements

• University College London:
  Sir Michael Marmot, Professor Jane Wardle, Dr Sabine Kunz-Ebrecht, Dr Pamela J Feldman, Dr Natalie Owen, Dr Lena Brydon, Dr Mark Hamer, Bev Murray, Caroline Wright

• University of Dresden
  Professor Clemens Kirschbaum

• University of Glasgow
  Professor Gordon Lowe, Dr Ann Rumley

Medical Research Council
British Heart Foundation
Early life stress and adult cortisol stress responses

Heim et al, *JAMA*, 2000

ELS – history of childhood physical or sexual abuse
Depression – current major depressive disorder