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# TABLE OF CONTENTS

Abbreviations and Acronyms ........................................................................................................ iii

Executive Summary ......................................................................................................................... v

Positive Psychological Factors and Health ..................................................................................... v

Known Biological Factors ............................................................................................................. vi

Research Areas That May Suggest Novel Biological Factors .......................................................... viii

Critical Issues ................................................................................................................................ ix

Positive versus Negative Factors .................................................................................................. ix

Methodological Issues ................................................................................................................ x

Areas for Future Research ............................................................................................................ x

Health As the Capacity to Adapt ................................................................................................... xi

Conclusions .................................................................................................................................. xii

Workshop SUMMARY .................................................................................................................. 1

Introduction .................................................................................................................................. 1

Session 1: Positive Psychological Factors and Health ................................................................. 3

Introduction .................................................................................................................................. 3

Positive Psychological Wellbeing and Health .............................................................................. 4

Salubrious Social Connections ...................................................................................................... 7

Pause and Plan: Effects of Self-Regulation on Peripheral Physiology ............................................. 10

Discussion ..................................................................................................................................... 12

Session 2: Known Biological Factors ............................................................................................ 13

Restorative Biological Processes and Health: A Useful Concept? ................................................ 13

The Healing Power of Love: an Oxytocin (OT) Hypothesis .......................................................... 15

Heart Rate Variability (HRV) As an Integrative Index of Resilience: Insights from a Neurovisceral Integration Perspective .............................................................................................................. 17

Immunity and Positive Psychobiology .......................................................................................... 19

Exploring the Neural Correlates of Receiving and Giving Social Support .................................. 23

Discussion ..................................................................................................................................... 26

Session 3: Research Areas That May Suggest Novel Biological Factors ......................................... 28

Setting the Stage for Novel Biological Factors .............................................................................. 28

Sleep as a Source of Resilience and Restoration ......................................................................... 28

Physical Activity: Implications for Brain and Cognitive Health ................................................... 32

Dopamine (DA), Motivation, and the Decision to Expend Effort .................................................... 35

Role of Microbiome Gut Brain Interactions in Resilience ............................................................... 38

Genomic Approaches .................................................................................................................... 40

Discussion ..................................................................................................................................... 41

Brainstorming ................................................................................................................................. 42

Appendix 1 – Workshop Agenda .................................................................................................... 44

Appendix 2 – List of Participants .................................................................................................... 47

Appendix 3 – List of Suggested Readings ....................................................................................... 50
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
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<tr>
<td>APC</td>
<td>antigen-presenting cell</td>
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<tr>
<td>AVP</td>
<td>arginine vasopressin</td>
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<tr>
<td>BA25</td>
<td>Brodmann area 25 (an area of the cerebral cortex)</td>
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<tr>
<td>BAC</td>
<td>blood alcohol concentration</td>
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<tr>
<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
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<tr>
<td>CARDIA</td>
<td>Coronary Artery Risk Development in Young Adults</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
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<td>CHD</td>
<td>coronary heart disease</td>
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<td>CNS</td>
<td>central nervous system</td>
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<td>CREW</td>
<td>Center for Research on Experience and Wellbeing</td>
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<td>CTRA</td>
<td>conserved transcriptional response to adversity</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>DA</td>
<td>dopamine</td>
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<td>dACC</td>
<td>dorsal anterior cingulate cortex</td>
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<td>DAMPs</td>
<td>damage-associated molecular patterns</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>DTH</td>
<td>delayed-type hypersensitivity</td>
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<tr>
<td>EE</td>
<td>enteroendocrine</td>
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<td>EEFRT</td>
<td>Effort-Expenditure for Rewards Task</td>
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<td>ENS</td>
<td>enteric nervous system</td>
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<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<td>GH</td>
<td>growth hormone</td>
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<td>HDL</td>
<td>high-density lipoprotein</td>
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<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenal</td>
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<tr>
<td>HRS</td>
<td>Health and Retirement Study</td>
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<td>HRV</td>
<td>heart rate variability</td>
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<td>IBS</td>
<td>irritable bowel syndrome</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>IGF</td>
<td>insulin-like growth factor</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>iTreg</td>
<td>inducible T-regulatory cell</td>
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<tr>
<td>MHC-SF</td>
<td>Mental Health Continuum Short Form</td>
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<tr>
<td>MIDUS</td>
<td>Midlife Development in the United States</td>
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<tr>
<td>mPFC</td>
<td>medial prefrontal cortex</td>
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<tr>
<td>NAA</td>
<td>N-acetylaspartate</td>
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<tr>
<td>NAcc</td>
<td>nucleus accumbens</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
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<td>NIA</td>
<td>National Institute on Aging</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>OT</td>
<td>oxytocin</td>
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<td>PAMPs</td>
<td>pathogen-associated molecular patterns</td>
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<tr>
<td>PBMC</td>
<td>peripheral blood mononuclear cell</td>
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<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
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<td>PPF</td>
<td>positive psychological functioning</td>
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<td>PPWB</td>
<td>positive psychological wellbeing</td>
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<tr>
<td>preSMA</td>
<td>pre-supplemental motor area</td>
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<tr>
<td>REM</td>
<td>rapid eye movement</td>
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<tr>
<td>RFA</td>
<td>request for applications</td>
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<tr>
<td>SA</td>
<td>septal area</td>
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<tr>
<td>SES</td>
<td>socioeconomic status</td>
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<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
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<td>SWS</td>
<td>slow-wave sleep</td>
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<tr>
<td>Th</td>
<td>Th-helper (cells)</td>
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<tr>
<td>TSST</td>
<td>Trier Social Stress Test</td>
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<tr>
<td>vmPFC</td>
<td>ventromedial prefrontal cortex</td>
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<tr>
<td>VO2max</td>
<td>maximal oxygen consumption</td>
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<tr>
<td>VS</td>
<td>ventral striatum</td>
</tr>
<tr>
<td>VTA</td>
<td>ventral tegmental area</td>
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<tr>
<td>WGBH</td>
<td>Boston public broadcasting</td>
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EXECUTIVE SUMMARY

There is increasing recognition that positive psychological functioning (PPF; including constructs such as optimism, positive emotions, and social connectedness) influences health above and beyond negative psychological functioning (including constructs such as depression, anxiety, and loneliness). Most research on the relationship between PPF and markers of health to date has focused on deteriorative biological processes and related health outcomes. Significantly less is known about restorative biological processes that may underlie health-relevant aspects of PPF. It seems possible that the biology associated with PPF is not merely the inverse of the processes associated with negative psychological functioning, particularly because the absence of negative psychological functioning does not necessarily indicate the presence of PPF. Despite greater exploration in recent years of the relationship between PPF and physical health, understanding of the underlying mechanisms is still limited.

To address this need, the Princeton University Center for Research on Experience and Wellbeing (CREW), an Edward R. Roybal Center for Translation Research in the Behavioral and Social Sciences of Aging funded by the National Institute on Aging (NIA), hosted the Workshop on Positive Psychobiology in Miami, Florida, on March 12 and 13, 2013. A diverse group of experts gathered to review the status of the field, discuss current challenges, and identify future research priorities.

The workshop comprised three sessions, the first of which reviewed examples of known connections between PPF and health. The second session focused on biological factors known to be associated with PPF. The third session explored other research areas that may suggest biological processes with restorative or adaptive features that have not yet been investigated in relation to PPF.

A detailed report of the presentations and discussions can be found in the full workshop summary. The agenda can be found in Appendix 1, a list of all participants is provided in Appendix 2, and a list of suggested readings can be found in Appendix 3.

POSITIVE PSYCHOLOGICAL FACTORS AND HEALTH

Laura D. Kubzansky reviewed consistent findings linking PPF to increased likelihood of better health that hold even after taking into account potentially confounding effects of poor psychological functioning, drawing primarily on evidence in relation to cardiovascular disease (CVD), but also considering other outcomes such as cancer, pulmonary function, and all-cause mortality. Researchers have also begun to disentangle behavioral and biological pathways linking PPF to reduced likelihood of disease by investigating associations of PPF with health-related behaviors as well as with pre-morbid conditions and biomarkers. Kubzansky noted that effects are evident in relation to both healthy and patient populations and that research further suggests that the absence of a deficit is not the same as the presence of an asset. In light of these findings, she suggested that traditional public health prevention efforts may have over-
emphasized the importance of reducing stress and missed opportunities to develop new interventions aimed at building strengths.

Tara Gruenewald highlighted the importance of social connections for human wellbeing. She noted the strong meta-analytic support for multiple facets of social connectedness as predictors of disease-specific and all-cause mortality risk. She also reviewed ongoing efforts to assess social connectedness and biomarkers related to disease risk in large longitudinal studies. Preliminary data suggest that social connectedness influences multiple biological systems, including heart rate variability (HRV), inflammation, and metabolic pathways. Gruenewald emphasized the complexity in modeling links between social connectedness and better health. She also noted that current public health interventions focusing on social connectedness are limited compared to those aimed, for example, at smoking.

Suzanne C. Segerstrom described the “pause and plan” phenomenon, which refers to the conservation of energetic resources via downregulation of metabolic activity of organ systems. This conservation is linked to self-regulatory effort and might have arisen because self-regulation (e.g., planning, inhibition) implies future energetic need (e.g., action). Understanding these mechanisms might help researchers understand seemingly paradoxical observations. Optimists, for example, have been shown to have a more robust immune response under most circumstances, but may have a less robust response during self-regulatory challenges, because they tend to actively engage these challenges, causing the body to assume a “pause and plan” state.

**KNOWN BIOLOGICAL FACTORS**

Negative psychological states may impair restorative biological processes by slowing down the rate of repair, by diminishing the quality of available biological materials, or by disrupting normative processes. Ted Robles described these processes and noted that an understanding of the possible benefit of enhancing restorative functions beyond the normal range is currently missing. He offered the parasympathetic nervous system, growth hormone (GH), and insulin-like growth factor (IGF) pathways as possible candidates for future studies of restorative biological processes and concluded his talk by pointing to the importance of studying the impact of health behaviors (e.g., diet, exercise) on these pathways.

Sue Carter posited that the mother-child interaction is the archetype of human love. The hormone oxytocin (OT) is critical for this interaction and, therefore, may be critical for the experience of love. OT is important for birth, lactation, sharing, and bonding, while the related hormone arginine vasopressin (AVP) controls defensiveness, vigilance, and arousal. The interplay between these two molecules likely plays a role in shaping human sociality. Carter noted that understanding the causes and consequences of mammalian sociality will lead to a deeper understanding of the biology of human emotion and natural factors (e.g., social support, love) that contribute to human health and wellbeing. She reviewed scientific evidence for healing effects of OT (although it may have damaging effects in certain contexts as well), which are posited to be conveyed by its anti-inflammatory and anti-oxidant properties.
Research on the underlying pathways may provide a better understanding of complex human behaviors.

Julian F. Thayer focused his presentation on HRV as an indicator of resilience and as a peripheral index of changes in neural regulation of autonomic response. The prefrontal cortex (PFC) is involved in modulating threat response, and lack of prefrontal inhibitory tone leads to an undifferentiated and more frequent stress response. The neurovisceral integration model stipulates that higher HRV is associated with a greater prefrontal inhibitory tone. Higher levels of resting HRV are also associated with better self-regulation and the ability to generate an emotional response that is appropriate with regard to the environmental demand. HRV has been associated with better health in the physiological, emotional, and cognitive domains. Individuals with greater HRV may be able to occupy a broader range of physiological states and therefore may have greater response flexibility and be better prepared for facing adverse events and challenges. Brain imaging studies have begun to disentangle the brain concomitants of alterations in HRV and improved self-regulation. Research on HRV therefore might provide a useful proxy for research on changes in brain connectivity.

In reviewing the role of innate and adaptive immune responses in restorative immunological processes, Marian Kohut pointed to the balance between danger responses and repair responses as important aspects of immunological regulation. Antigen presenting cells (APCs), macrophages, and T cells can all tip this balance one way or the other. Kohut also reviewed interactions between immune, neuroendocrine, and metabolic pathways. She noted the association of optimism with improved immune function and concluded her presentation by outlining future priorities for research in immunology and trans-disciplinary approaches involving psychobiology.

Naomi I. Eisenberger reviewed research regarding the physiological benefits of social support and the underlying neural correlates. She specifically considered work examining whether social support activates safety-related neural regions. Current work is evaluating whether suppression of a conditioned fear response by social support, for example, is associated with activity in the ventromedial prefrontal cortex (vmPFC) in humans, and whether the ventral striatum (VS) and septal area (SA) are involved in the suppression of threat responses when one is giving social support to others. These regions are parts of a larger reward circuit, providing further evidence for an inverse relationship between reward and threat in the human brain. Eisenberger noted that both giving and receiving social support have effects on stress response system and the immune system, and are important for health outcomes. She concluded that an important next step for this research is to link neural circuitry associated with giving and receiving social support to peripheral pathways including autonomic, neuroendocrine, and immune responses.

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RESEARCH AREAS THAT MAY SUGGEST NOVEL BIOLOGICAL FACTORS

Orfeu M. Buxton focused on sleep as a source of resilience. Sleep deprivation has many known detrimental effects on human health, and sufficient sleep has important implications for cognitive performance and learning. There is a strong link between lack of sleep, obesity, and diabetes risk. Buxton noted the importance of objective measures of physical activity and sleep (e.g., pedometers, actigraphy) for future longitudinal studies. Public health education efforts focusing on sleep and workplace factors that could foster healthful sleep habits are an important future direction for research in the domain of sleep.

Art Kramer reviewed known effects of exercise on neurobiology and behavior. Animal studies have revealed a large number of molecular and cellular changes in the brain occurring in response to exercise, and modern imaging techniques now allow researchers to begin to validate these findings in the human brain. Sophisticated neuroimaging methods have recently become available to study brain connectivity and neural activation networks. Kramer presented recent research in human subjects that has identified correlations between increased brain volume and memory in response to exercise. In addition, exercise may lead to more robust networks of neuronal activity. Building such networks by exercise may, therefore, provide increased resilience to adverse psychological or biological events.

David Zald discussed work aimed at finding the neural substrates of motivation and understanding the effects of positive affect. He discussed how, in animal models, simple paradigms such as physical barriers can be employed to test motivation to overcome obstacles. Testing these concepts in humans, while allowing simultaneous measurements in brain scanners, requires more sophisticated designs. Zald developed the Effort-Expenditure for Rewards Task (EEfRT) to study brain activation in humans while they are engaged in weighing the costs and benefits of activity and reward-seeking behaviors. Consistent with the work in animals, humans showed activations in the medial prefrontal cortex (mPFC), dorsal anterior cingulate cortex (dACC), and pre-supplemental motor area (preSMA) when deciding to invest effort in a task (i.e., being motivated). Additional work has demonstrated in humans that dopaminergic manipulations indeed alter willingness to exert effort for reward. Moreover, individuals with high ventral striatal dopamine (DA) release have greater motivation to pursue rewards and novelty. Although these types of studies cannot be integrated easily into large epidemiological investigations, they might provide important clues about motivational aspects of wellbeing and related functional circuits and pathways.

Emeran Mayer noted the emerging importance of microbiota-gut-brain interactions in health and disease. Studies into these complex bidirectional mechanisms in humans have recently become possible by applying advanced multimodal brain imaging techniques to identify brain signatures and genetic and molecular techniques to characterize the gut microbiome. The gut microbiota use elaborate signaling systems to communicate with each other and with the host, including signaling of gut microbes to the enteric nervous system in the gut and to the brain via the vagus nerve. The brain, in turn, can alter the composition of the gut microbiome via mediators of the stress system (e.g., cortisol and catecholamines). Based on these interactions, it has been proposed that bidirectional gut-brain interactions may play an important role in
wellness and disease, and that distinct signatures of these closely connected systems may become as relevant as more conventional biomarkers. Distinct gut metabolomics signatures based on the characterization of microbial communities and their metabolic products may become useful tools to identify disturbances in the gut microbiome that underlie a variety of chronic diseases. For example, gut microbial diversity has been suggested to predict resilience and to protect against obesity. In rodent models, alterations in microbial metabolites have been implicated in obesity and in several brain disorders including anxiety, Parkinson’s disease, and autism, even though such evidence in humans is not available. Advancing this knowledge might allow researchers to better understand links between gut function and wellbeing.

Steve Cole has been studying gene expression patterns and how they might inform our understanding of effects of the social and psychological factors on health. Recent studies on social isolation have revealed a pattern of gene activation and silencing in white blood cells that is also found in response to a large number of other psychosocial deficits. Because of its consistent emergence during adverse conditions, this gene regulation pattern has been called the conserved transcriptional response to adversity (CTRA). When studying correlations of gene expression patterns with brief measures of hedonic and eudaimonic wellbeing, Cole found suggestive evidence of a stronger inverse link between CTRA and eudaimonic versus hedonic wellbeing. These findings suggest one set of pathways by which eudaimonic wellbeing protects health and further may indicate a larger role for eudaimonic wellbeing in relation to physical health. Cole concluded that studying the genome to better understand biological changes and effects of interventions will be of increasing importance in the future.

CRITICAL ISSUES

The workshop participants engaged in lively discussion on critical issues regarding concepts, methodology, and future research. This section provides a summary of the main themes that arose during these discussions.

POSITIVE VERSUS NEGATIVE FACTORS

Participants agreed that the workshop’s focus on positive factors was meant to increase considerations about an often-neglected side of psychobiology. They cautioned against excluding negative factors from future research priorities and also against reducing the positive to a mere “lack of negative.” Positive and negative factors can be independent or lie on a continuum, and strictly partitioning by valence would be highly problematic as evidenced by the following:

- Scales or questionnaires assessing eudaimonic and hedonic wellbeing often contain both positively worded and negatively worded items.
- Challenging or stressful experiences can be contexts for the growth of eudaimonic wellbeing.
- A strict division of biological processes as anabolic versus catabolic (or restorative versus deteriorative) would ignore processes that are dynamic, interacting, and overlapping (e.g., wound healing).
METHODOLOGICAL ISSUES

The strongest future studies should address causality. Cross-sectional data may be useful for pilot studies designed to obtain preliminary data, but more sophisticated designs are also necessary. When possible, studies should use multi-modal interventions and outcomes. Positive psychological states may act as mediators in these studies, rather than as predictors or outcomes. Furthermore, studies should not focus on single-item outcomes or biomarkers, but consider a spectrum of outcomes or composites of outcomes. A balance must be found in conducting powerful studies at a reasonable cost. Efforts that are too narrow or small may not have sufficient theoretical or statistical power to gain new knowledge.

All speakers noted the importance of measurement for both psychological and biological processes, and the variety of challenges associated with developing or achieving accurate measurement. Several speakers stressed the value of objective assessment of restorative processes, particularly when predictors of interest are derived from self-report measures. Some participants suggested that self-report is the best and possibly the only way to assess positive psychological wellbeing, which is subjective. Not all participants agreed and noted that second-person narratives may provide an important additional source of assessing wellbeing or an individual’s connectedness with others.

Future measurement tools should consider the possibility of receiving guidance from big data and biological profiles.

Repeated measurements in everyday and naturalistic settings will provide opportunities to study the dynamic adjustments that biological systems make continuously. The simultaneous adjustment of multiple bodily systems may increase the likelihood of establishing a healthier trajectory.

Moreover, little is currently known about the physiological ranges of biomarkers and the effects of changes within these ranges. For example:

- What are the optimal ranges for enhancing physiological function?
- How do the different physiological systems balance and adjust each other?
- How can systems be modified to improve overall function and health?

AREAS FOR FUTURE RESEARCH

Participants noted that exercise has a very large number of positive effects on health and wellbeing. Future research should further investigate the underlying mechanisms, as well as other questions of interest:

- To what extent do healthy individuals improve further by exercising more?
- Are there processes in sleep and exercise to which the field has not paid enough attention?
The strong social component of wellbeing may allow studies to consider the inter-relationship between wellbeing and social integration. For example:

- Are there very happy people who live in complete isolation?
- If so, how do such people differ from others psychologically and biologically?

Optimism received a lot of attention during the workshop, as did the “Big Five” personality traits (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism). In particular, conscientiousness is a powerful predictor of mortality.

Sexual activity is an often-overlooked pillar of health. It is restorative, while sharing similarities with exercise. Deprivation leads to major decreases in perceived “humanness.” Targeted interventions to promote high-quality sexual activity are missing because researchers are often afraid to talk about sex.

Efforts to improve health need to focus on not only the individual, but also the social environment. However much health professionals try to motivate an individual, they will not be successful if they do not also modify the environment. In addition, researchers must do a better job thinking about structural constraints and inequalities; people may have limited capacity to choose their health behaviors. Modifying external structures may be a crucial step for increasing wellbeing.

The behavior of other individuals can also have substantial influences on health. Worries about the work status of spouses, for example, are associated with decreased wellbeing. Hostility in a partner can be more highly correlated with coronary heart disease (CHD) than any other measure in the individual.

The concept of self-efficacy appears important when predicting adherence or attrition to interventions and deserves more attention.

The pursuit of short-term versus long-term goals must be better understood. Humans must make very frequent cost-benefit calculations, for example: should I rest or should I exercise? Greater knowledge of these processes will allow researchers to design interventions that can push people to do what they cognitively know is the best thing to do.

HEALTH AS THE CAPACITY TO ADAPT

Several participants endorsed the idea of thinking about periods of positive health and functioning as times during which resource capacity is being built. The restorative process of “storing” PPF may resemble the mechanism of fat storage in times of food abundance. The built-in redundancy in neural systems and linkages between biological systems may provide additional functional capacity that goes beyond survival. An organism so constructed may have a better ability to react and adapt to a changing environment and the best chance to survive and thrive. Additional questions relevant to this issue include:

- How can an organism prepare for dealing with stress and challenge?
• What can **Eastern philosophy** (e.g., mindfulness) teach researchers about processes relevant to making tradeoffs between short-term versus long-term gains?

A significant objective of being human is to **maintain meaning and purpose** in the face of adversity. Challenges are often thought of as major life events (e.g., losing one’s job, getting divorced), but many challenges occur on a day-to-day basis (e.g., commuting to work, meeting a work deadline). Being able to effectively adapt in the context of challenge may be the key to health. PPF then, may provide indicators of an individual’s ability to effectively adapt.

**CONCLUSIONS**

Participants agreed that the field is moving away from the notion that individual biomarkers will serve as magic bullets in the understanding of complex human behaviors and their relation to health. Interdisciplinary exchanges such as the current workshop are important ways to promote simultaneous research on multiple systems.

An interesting notion that emerged from the workshop was that of adaptability, that is, health as the ability to capitalize on opportunities to build restorative capacity and prepare for adverse events. Further research about biological mechanisms underlying this capacity is warranted.

The design of future interventions is a very important challenge. Participants noted the importance of integrating interventions across several levels, including the individual, family, neighborhood, or workplace to promote positive health and restorative capacity. Efforts that target individuals in isolation of their usual social surroundings are likely to fail. Interventions should provide individuals with adequate resources on many different levels so that they are better protected against the detrimental effects of adversity. The field can also move forward by finding effective ways to add targeted new measures to existing interventions and longitudinal studies without putting an excessive burden on research subjects. Changes in the physical environment and human societies provide further opportunities for natural experiments.

Participants expressed optimism regarding future opportunities for big data (e.g., genomics, proteomics, metabolomics) to inform biological assessment. More accurate measures that are grounded in validated biological pathways will provide additional power to disentangle complex psychobiological constructs.

They also noted the importance of bidirectionality in all processes and the need to consider the role of balanced states (e.g., sense of safety versus sense of threat).

The ideas discussed herein are by no means comprehensive of all relevant issues. The workshop was designed to consider innovative and emerging biological markers worthy of exploration, and to identify relevant research questions that can be addressed now. An ongoing dialogue about workshop themes and ideas will help lay the foundation for future research on the biological processes underlying PPF and adaptive aging.
INTRODUCTION

Lis Nielsen, National Institute on Aging (NIA)
Arthur Stone, Stony Brook University and Princeton University

In her opening remarks, Lis Nielsen reviewed the main motivations for the NIA to engage in the current workshop. All participants are experts on the effects of psychological factors on health-relevant outcomes. The main focus of this gathering was on biological factors that are or may be linked with PPF and how such biological factors set people on trajectories toward better health. The ultimate goal is to obtain a comprehensive understanding and full life-course perspective on the link between PPF and health. As a life stage—rather than disease-focused institute, the NIA is interested in advancing our understanding of the processes that shape life course trajectories of health and wellbeing. Better health can be achieved not only by reversing unhealthy trajectories or developing compensatory mechanisms, but also by establishing healthy or positive trajectories of development and aging.

Two developments are of significance for this workshop:

- Researchers now have access to a strong foundation of national and international biosocial surveys. Recent additions of comprehensive biomarker assessments in numerous behavioral and social surveys of aging allow greater understanding of how psychosocial factors are linked to health, as well as underlying biological processes. These types of studies allow researchers to understand how the cumulative impact of our psychosocial environment may manifest in health or disease. The Midlife Development in the United States (MIDUS)\(^2\) study and the Health and Retirement Study (HRS)\(^3\) are two examples of such ongoing and growing NIA-funded resources for which data are publicly available.

- The NIA has also invested in the development of new measurements of subjective wellbeing, both in the eudaimonic and hedonic domains, and in the assessment of momentary wellbeing. Nielsen noted that CREW has been a leader in the development of momentary-based measures.

Nielsen further identified three parallel efforts that intersect with the topics of the current workshop and represent priority areas of research for the NIA:

- In 2011, an NIA workgroup on Conscientiousness and Healthy Aging examined the mechanisms underlying conscientiousness, an adaptive personality trait with strong

\(^2\) [http://www.midus.wisc.edu/scopeofstudy.php](http://www.midus.wisc.edu/scopeofstudy.php)
\(^3\) [http://hrsonline.isr.umich.edu/](http://hrsonline.isr.umich.edu/)
predictive power for health and longevity, and explored possibilities for interventions to enhance this trait in midlife and beyond.\(^4\)

- The NIA recently convened an expert meeting on Motivation and Aging at the National Academies,\(^5\) in order to explore the extent to which harnessing positive, life stage appropriate, motivational states can enhance the effectiveness of interventions to promote adaptive aging. The extent to which motivational states may enhance neuroplasticity and create windows of opportunity during which change is possible is of considerable interest. Harnessing motivation and directing it toward adaptive goals may be a key ingredient in developing effective interventions to get people, particularly during midlife, to develop healthier behavioral patterns.

- A third NIA initiative builds on a large body of research demonstrating that early adversity has a long reach into later life. It examines the psychological dispositions and biobehavioral risk mechanism responsible for biologically embedding early adverse social exposures, in order to understand the potential for reversing these adverse effects in later life. This NIA-funded Network on Reversibility,\(^6\) led by David Reiss (Yale University) and Stephen Suomi (Eunice Kennedy Shriver National Institute of Child Health and Human Development), while focused on negative events and their long-term consequences, is also focused on the malleability of the underlying pathways, where positive or restorative processes may play an important role. Nielsen mentioned that a request for applications (RFA) on reversibility would be announced in the near future.

Arthur Stone welcomed participants on behalf of Princeton University and CREW, which has existed for 9 years and has a mandate to support pilot studies and conferences such as the current one. CREW is an interdisciplinary unit within the Woodrow Wilson School of Public and International Affairs, and its affiliates consist mainly of economists and psychologists. Its work focuses on the area of hedonic wellbeing and on the development of new measurements of subjective experiences that can be added to population-based surveys. As a consequence of these efforts, the American Time Use Survey now includes new measures about experiences. The resulting data are publicly available for analysis.

CREW also seeks to shape new policies. It works nationally and internationally to help measure wellbeing and advises governments on the best use of these measures.

\(^4\) Link to the January 6-7, 2011 workshop report: \url{http://www.nia.nih.gov/about/events/2011/conscientiousness-and-healthy-aging-workshop}


\(^6\) Link to the September 10-11, 2012 workshop report: \url{http://www.nia.nih.gov/about/events/2012/network-reversibility-meeting}

Stone expressed his excitement about the field of positive psychobiology. The relationship between self-reports of wellbeing and biology is an important research interest for CREW, and increasing amounts of scientific data are becoming available to help researchers understand this relationship.

**SESSION 1: POSITIVE PSYCHOLOGICAL FACTORS AND HEALTH**

**INTRODUCTION**

*Julia K. Boehm, Ph.D., Harvard School of Public Health*

Julia Boehm introduced the speakers of the first session and provided a brief review of the state of the art in psychobiology, the challenges ahead, and the rationale for the focus of the current workshop. She noted that the connection between psychological and physical health is well established. A good understanding of health beyond the “absence of disease,” however, is still missing. Most previous research has demonstrated that poor psychological health (e.g., depression, anxiety) is associated with an increased risk for CHD and other chronic conditions. Much less effort has focused on optimal psychological states and how they might be linked with health and disease. Preliminary research suggests that PPF, the focus of the current workshop, is associated with improved health outcomes. The current discussions will, therefore, focus on psychological assets rather than deficits and specifically on:

- Positive psychological wellbeing
- Social connectedness
- Self-regulation

All humans strive for meaning and social connectedness and want to be able to self-regulate. Each of these three factors is, therefore, desirable in its own right. Additionally, each of these factors may be linked with physical health outcomes, and the current workshop aims to better understand relevant underlying biological processes. A further challenge lies in the question of how particular markers of PPF may have similar or dissimilar health correlates.

To study these questions, researchers use observational and experimental studies. Because most of the population-based studies have been cross-sectional, it often has been difficult to separate causes and effects. More recent efforts to conduct longitudinal studies over several decades while controlling for confounders will provide opportunities to determine the direction of effects. Studies of disease progression over time will provide further opportunities to gain insights into psychobiological pathways. Experimental designs can help to further disentangle causes and effects and reduce concerns about self-report bias encountered in observational studies.

Turning to possible risk pathways, Boehm noted that most attention has, historically, been given to PPF as a moderator of stress, either by reducing the amount of stress experienced or by attenuating the negative effects of stress on physiological systems. But PPF also may act on wellbeing through a more direct pathway—namely, by influencing biological pathways and
processes that directly modulate health. Researchers have speculated that this pathway may involve factors such as antioxidants and the parasympathetic nervous system. Compared to the links with stress, however, much less is known about these mechanisms, and focusing on these positive pathways during the current workshop might contribute to advancing the field in this direction.

One model posits that biological and behavioral processes can be characterized by deterioration (e.g., atherosclerotic plaque, cigarette smoking) or restoration (e.g., sleep, meditation). While a sharp delineation between deteriorative and restorative processes does not exist, this workshop mainly focuses on potentially restorative processes and how they might be linked with PPF and health outcomes.

POSITIVE PSYCHOLOGICAL WELLBEING AND HEALTH

Laura D. Kubzansky, Ph.D., M.P.H., Harvard School of Public Health

Laura Kubzansky defined positive psychological wellbeing (PPWB) as a broad umbrella term that reflects positive feelings and cognitions of those who function well in their lives and evaluate life favorably. It includes constructs such as optimism, life satisfaction, life purpose, positive emotions, and happiness.

She concurred with Boehm that most research to date has focused on the effects of stress and negative emotions, but she also noted a recent trend in the field to expand research to PPF and answer four main questions:

1. Does PPF have benefits for human health?
2. Are these effects independent of those caused by poor psychological functioning?
3. Can stress-buffering pathways explain the majority of these effects, or do other important pathways exist?
4. What are the exact underlying mechanisms?

Kubzansky reviewed possible roles for PPWB in physical health and noted that psychological states may precede physical health. Psychological states might further trigger or exacerbate symptoms, influence disease progression, and have important consequences for disease management in general. She remarked that the field too often reduces positive effects to nothing more than the absence of negative factors. Researchers investigating PPF routinely have to demonstrate that effects are independent of negatively oriented constructs (e.g., depression, anxiety), while the opposite is not always true.

Evidence from Kubzansky’s own work and the work of others indicates that independent effects of positive factors in relation to health exist:

Higher emotional vitality led to a significant risk reduction in CHD in a nationally representative sample of 6,900 men and women who were followed for 15 years. These findings were independent of conventional risk factors. A lot of this work has focused on heart disease because it has a clear onset and can be measured objectively, providing an advantage for studies of possible effects of psychological factors (often measured via self-report).

Using similar methods another study including 1,300 men followed for more than 10 years found reduced risk for CHD associated with higher levels of optimism. This study adjusted for known risk factors and for the presence of negative emotions. Kubzansky noted that this finding has been replicated at least three times in independent samples since its publication in 2001.

A Canadian study found that greater levels of positive affect were associated with up to 22 percent reduced risk for CHD. This study controlled for depressive symptoms, anxiety, hostility, and standard CHD risk factors. It also used external coders to rate the degree of outwardly displayed positive affect to minimize bias due to self report.

Incident diabetes shares precursors with CHD, and may therefore be associated with PPF in similar ways. Boehm et al. tested this hypothesis in the Whitehall II cohort, a sample of British civil servants. The authors found significant reductions in incident diabetes risk in individuals with high emotional vitality and high life satisfaction.

Research participants in an experimental study were infected with rhinovirus or influenza A virus. Positive emotional style reduced the likelihood that subjects became clinically infected. This study adjusted for the type of virus, viral-specific antibody levels, and negative emotional style.

A study on disease progression in neck cancer patients found that those with higher optimism were less likely to die during the 1-year follow-up period. Results remained significant after accounting for age and the disease stage.

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11 submitted manuscript

12 http://www.ucl.ac.uk/whitehallII/


• A study following 670 men over an 8-year period found that optimism protected against a rapid decline of pulmonary function, which is associated with greater health risks.\textsuperscript{15}

• Higher levels of optimism were associated with reduced all-cause mortality in a large Dutch cohort.\textsuperscript{16} This finding has been replicated several times, and a recent meta-analysis indicates up to a 20 percent risk reduction in total mortality.\textsuperscript{17}

Kubzansky noted that not all aspects of PPWB were equally protective, and that the strongest effects have been observed in studies of optimism. Associations have also been evident in samples of healthy individuals and patients, although PPWB’s effect seems to be larger among healthy participants. The available data suggest that effects are systemic and independent from poor psychological health.

The exact mechanisms linking PPWB with health outcomes are still poorly understood. Kubzansky further noted that the influence of PPWB on health behaviors (e.g., physical activity, diet, smoking, sleep, and alcohol consumption) must be taken into account. However, recent research suggests that health behaviors cannot fully account for the effects of PPWB.\textsuperscript{18}

Because most of the reviewed research is observational, no statements about causes and effects can be made. To overcome this problem, several investigators have studied the effect of PPWB on biological measures upstream of disease manifestation.

• Optimism reduced the amount of carotid atherosclerotic progression occurring over a 3-year period in female subjects.\textsuperscript{19}

• A study on mental vitality and cardiovascular outcomes found lower likelihood of developing hypertension or hypercholesterolemia over a 1-year follow-up period in individuals with high mental vitality.\textsuperscript{20}

• Optimistic individuals were recently found to have higher levels of blood antioxidants\textsuperscript{21} and higher levels of high-density lipoprotein (HDL) cholesterol.\textsuperscript{22}


Kubzansky concluded her presentation by discussing the public health impact of these findings. She emphasized that the absence of a psychological deficit is not the same as the presence of a psychological asset. An asset may provide increased flexibility, rapid recovery, enhanced resources, and better coping skills. The challenge for the field is to identify those psychological assets that matter the most for health and focus more on building strengths instead of solely attempting to reduce stress or fix problems. This will lead to new targets for preventive medicine and interventions. Kubzansky encouraged the participants to think about physical outcomes of PPWB and what it means to function well.

SALUBRIOUS SOCIAL CONNECTIONS

Tara L. Gruenewald, Ph.D., M.P.H., Davis School of Gerontology, University of Southern California

Tara Gruenewald focused her presentation on the psychobiology of social connections. Her goals were to review the current state of the literature on social connections and health and to outline psychological, behavioral, and biological pathways through which social relationships may influence health.

The social connection hypothesis is very old. Aristotle, for example, stated in Politics (about 335-323 B.C.) that “Man is by nature a social animal.” As social animals, we have evolved so that our survival is dependent on each other.23 But empirical research was not carried out on this subject until the late 1970s, when highly influential reviews by John Cassel24 and Sidney Cobb25 jumpstarted the field of social epidemiology.

A population-based study in 1979 found a connection between social connectedness and mortality.26 Individuals with more connections (e.g., marital partner, friends, church membership, group affiliations) had less mortality. Remarkably, the effect sizes were large and in a similar range as those of smoking or exercise.

The notion that social connectedness was important for health outcomes received additional strong support in 1988, when a review found that low social integration was a risk factor for mortality in five prospective studies.\textsuperscript{27} Today, a wealth of data is available (recently reviewed in a meta-analysis of 148 studies),\textsuperscript{28} allowing researchers to separate structural from functional aspects of relationships. Across many different measures (e.g., social support, loneliness, social isolation, social integration), odds ratios for the association between connectedness and health outcomes typically range between 1.2 and 2.0. Gruenewald noted that predictive power increases with finer granularity of the measurements.

Additional research has been carried out in patient populations. Gruenewald pointed to results from studies on heart disease progression. A recent meta-analysis found substantial effect sizes; for each unit lower score on a social support measure, there was a 1.6-times greater hazard of death in those with CHD.\textsuperscript{29} A meta-analysis of 87 studies of cancer patients showed a substantial risk reduction associated with perceived social support, the presence of social networks, and marriage.\textsuperscript{30} A more recent meta-analysis documented the association between marital quality and health outcomes.\textsuperscript{31}

Gruenewald concluded from these studies that empirical analyses from the past 30 to 40 years have clearly shown that social connections are very important for health and survival. The focus of attention in the field is now shifting from determining whether these associations exist to understanding how they work. Many models have been developed, most of which share certain central pathways that fall into the behavioral (e.g., smoking, exercise, diet, drug use), psychosocial (e.g., stress, coping, cognitive-emotional, relational needs), and biological (e.g., autonomic, neuroendocrine, immune, cardiovascular, metabolic) domains. Many of the pathways are likely bidirectional.

A closer look at behavioral mechanisms suggests that social relationships can influence health-promoting and -damaging behavior. Extant research has, however, often treated behavior only as a covariate. With better measures of behaviors becoming available, effect size estimates of behaviors as mediators may become larger in the future.

Psychosocial mechanisms for improved health outcomes may include relationships as stress buffers, the promotion of cognitive and emotional wellbeing, and the fulfillment of relational

needs. There is good scientific evidence that relationships act as stress buffers.\textsuperscript{32} Social support also might lead to reduced perception of stress and directly reduce psychological and biological distress. Although this hypothesis is appealing, it is not supported by strong scientific evidence.\textsuperscript{33}

According to Gruenewald, important areas for future research on psychosocial pathways include a stronger focus on positive cognitive states. The study of social value and usefulness are therefore at the core of Gruenewald’s research efforts. Humans derive usefulness from their social activities. A study on older adults from the MacArthur Study of Successful Aging addressed the question of the meaning of relationships for people.\textsuperscript{34} Social usefulness was inversely related to morbidity and death. The finding has been replicated in the national sample of adults in MIDUS.

In her review of biological pathways, Gruenewald noted that because humans are social animals, social factors should influence most biological systems. Some social factors, however, may show stronger correlations with biological function than others. Possible targets to consider include the neuroendocrine system (e.g., OT, the autonomic (sympathetic and parasympathetic) nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and mechanisms relevant to survival and thriving (e.g., cardiovascular, respiratory, immune, metabolic, and reproductive pathways). A very large number of studies have researched these biological pathways, but a review was beyond the scope of Gruenewald’s presentation. She presented data from a collaboration with Teresa Seeman to analyze data from the Coronary Risk Development in Young Adults (CARDIA) study.\textsuperscript{35} This study offers unique measures of social integration, emotional support, and social demands combined with biomarkers, such as blood pressure, HRV, metabolic measures, inflammation, autonomic nervous system, and salivary samples. All bodily systems studied appeared to be sensitive to social connectedness. Individuals with low social integration showed the strongest risk in unhealthful levels of HRV, inflammation, and metabolism.


\textsuperscript{35} http://www.cardia.dopm.uab.edu/
Gruenewald noted the importance of further research to understand how the risk pathways work. Despite similar effect sizes for the association between social connectedness and health as the association between cigarette smoking and health, very little public health money is currently being invested in the former. The positive benefits of our social relationships are beyond doubt, but how this process works is still very poorly understood. Complex models will likely be necessary to understand and describe the intricate interplay between pathways and their mediators.

**PAUSE AND PLAN: EFFECTS OF SELF-REGULATION ON PERIPHERAL PHYSIOLOGY**

*Suzanne C. Segerstrom, Ph.D., University of Kentucky*

According to an epidemiological view of PPF, processes are deteriorative or restorative, although no sharp boundary can be drawn. Instead of following that categorization, Segerstrom encouraged her audience to think about self-regulation from an ecological perspective. According to the ecological view, processes are either adaptive or maladaptive with regard to the total functioning of the organism rather than the functioning of an individual system.

Energy from food has not always been as abundant as it is now. Not long ago, individuals who did not act economically had lower chance of survival. Instincts that evolved in a low-energy environment now make humans gain weight, because the body has evolved to be energetically conservative.

Every single cell in the body comes with a certain metabolic cost. This cost varies by different organ systems, but not all systems are equally important at all times. Very often, certain systems take priority over others. The human body, therefore, has to set priorities regarding which systems should be metabolically active. Internal and external demands together with motivation determine these prioritizations. Between-organ differences can be seen in basal metabolic rate: The brain and heart are “costly” organs that take up very little mass, yet use a lot of energy. “Cheap” organs include the muscle and skin. However, these costs can change depending on the demand. During a “fight or flight” response, for example, metabolic priority shifts to the heart and muscles.

Similarly, ecological immunology posits that it may not be ideal for the body to heal itself as fast as possible at all times. A maximum immunological response may not be the optimal defense if it comes at a substantial cost for other fitness-relevant traits. It is, therefore, not possible to

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obtain a full understanding of immunoregulatory processes without considering the organism and the internal and external environments in which the immune response takes place.\textsuperscript{38}

Optimism is usually conceptualized as a buffer against stressor-related changes in the immune system. Studies by Segerstrom suggest, however, that optimists who face conflicting goals are more likely to remain engaged with both goals.\textsuperscript{39} The cost for this behavior is impaired immunity during stressors.\textsuperscript{40} An experimental study that measured a skin test response lends further support to the idea that the immune response in optimists is better when they engage in simple tasks, but impaired when they face complex challenges.\textsuperscript{41} The importance of self-regulation as a mechanism of this effect (as opposed to threat or stress) is demonstrated by the reproduction of this interaction when substituting conscientiousness for optimism, but not when substituting neuroticism.

Segerstrom then focused on heart rate as a target for regulation. She showed that self-regulatory efforts, such as resisting unhealthful food (e.g., a cookie), are accompanied by higher HRV and lower heart rate when compared with other kinds of effort (e.g., memorizing).\textsuperscript{42}

The liver uses a lot of energy but is difficult to study experimentally because of the potentially invasive nature of such investigations. Segerstrom had the opportunity to circumvent these limitations by collaborating with a researcher focusing on alcohol metabolism. In a within-subject design, subjects were asked to perform tasks low versus high in self-regulatory effort after being dosed with a small amount of alcohol. The combination of high self-regulatory effort and low trait self-control was associated with slower alcohol metabolism and blood alcohol concentration (BAC) decline, an effect mediated by appraisal of the high self-regulation tasks as difficult.\textsuperscript{43}

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Segerstrom concluded from these research examples that, overall, there is a slowing down of metabolism by a number of different organ systems under different self-regulatory conditions. But why does the body “pause and plan?” Why does self-regulation influence metabolism? It is unlikely that this is caused by the extra demand for glucose by the brain. More likely, this behavior may constitute a human version of the “freezing response” seen in some animals. The organism becomes aware that action must be taken, but the best action is uncertain. Another possible explanation is a manifestation of forward-looking conservatism. Anticipating a dearth of resources, the body may turn down metabolically expensive activity long before substrates are depleted. Such behavior may be linked to future availability of resources for action. Signals associated with self-regulation may thus cause the body to become more conservative.

DISCUSSION

Participants asked whether the pause is associated with a physical halt of motion in humans. Do people actually physically hold still when they are self-regulating? This is difficult to capture in daily life, but may be possible to study in the lab. A challenge will be to separate pause and plan from fight and flight. Segerstrom further explained that there is a strong but not perfect correlation between self-regulation and optimism. It is not yet understood why individuals with low optimism have higher immune responses during high-demand challenges than low-demand challenges.

Participants disagreed regarding the possibility to willfully become an optimist. Some noted that optimism is correlated with education and that there is good evidence that it is a learnable and modifiable trait. Others considered it a rather persistent character trait during the life course, noted a strong genetic component, and were pessimistic about the possibility of designing interventions directly aimed at modifying optimism.

Another important question is whether optimism directly affects health outcomes, or if early adverse events trigger optimism as well as these outcomes. Participants noted the current lack of appropriate data to answer this question.

Segerstrom pointed to a prospective study in adults that followed a sample of law students for 10 years. Initially optimistic individuals, in general, made more money and had greater social networks. Changes in optimism, conversely, were driven only by more social relationships. The test-retest measure for optimism was relatively low, which indicates that optimism is potentially malleable.44

Nielsen noted that similar questions have recently been discussed in the conscientiousness workgroup, which reviewed evidence for “bottom-up” personality change, i.e., changing personality by changing the thoughts, feelings, or behaviors that constitute a trait. There is a growing body of evidence from clinical research that such personality change may be possible.

Participants also discussed possible influences of cultural contexts. Latino populations, for example, have better health outcomes in spite of reduced access to health care and more risk factors. Could a greater prevalence of optimism in that population explain such differences? Furthermore, the question was raised why Buddhist monks do not live for 200 years. Can the results presented in this session, which have been based on Western cultures, be generalized to other populations? These questions remain to be answered, and ongoing international studies might be able to address these questions in the future.

**SESSION 2: KNOWN BIOLOGICAL FACTORS**

**RESTORATIVE BIOLOGICAL PROCESSES AND HEALTH: A USEFUL CONCEPT?**

*Theodore F. Robles, Ph.D., University of California at Los Angeles*

Ted Robles provided an overview of how to conceptualize restorative processes. His goal was to illustrate how examining restorative biological processes (e.g., sleep, wound healing) can expand knowledge of PPF and health.

Robles provided dictionary definitions of restorative and allostatic processes. Restorative processes return an organism to its original state, which it occupied prior to an environmental challenge. Allostatic processes temporarily change set points to adapt to an environmental challenge. Restorative processes include mechanisms such as sleep, energy storage, growth repair, antioxidant capacity, telomerase activity, and deoxyribonucleic acid (DNA) repair. Allostatic processes include the acute HPA/autonomic nervous system (ANS) responses, immune responses to antigens, and oxidative stress. Many of these mechanisms have been implicated in aging processes.

The concepts of allostatic and restorative processes are informed by many other concepts (e.g., entropy, metabolism, ANS biology). Organisms constantly have to counter entropy and fight disorder. For example, a balance of hormones in anabolic and catabolic processes is important for health. Furthermore, the sympathetic and parasympathetic nervous systems oppose each other, for example by acting inversely on insulin metabolism. These systems counteract each other in a beneficial way.

Both allostatic and restorative processes have been associated with health outcomes. In a very simplified model, restorative processes are characterized by low activity during a stressor and higher activity before and after a stressor, while allostatic processes show high activity primarily during the acute period of a stressor.

Thus far, most research regarding restorative processes has been done in the area of sleep and is cross-sectional. Measures are usually sleep quality and duration, mainly relying on subjective

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45 See Robles’ detailed bibliography on this subject available online at: [http://rhl.psych.ucla.edu/pdfs/restorative.pdf](http://rhl.psych.ucla.edu/pdfs/restorative.pdf)
self-reports. Other restorative factors have been studied to a lesser extent, and Robles noted that these should be given more attention in the future.

The difference between allostatic and restorative is not a sharp line. Wound healing, for example, is restorative at the macroscopic level, but when observing the different phases of healing in greater detail, the boundaries get softer.\(^\text{46}\) An early inflammatory phase, which constitutes an allostatic process, is followed by a restorative proliferative phase. Events in the early phase set the stage for the rest of the process; early delays create late delays. Psychosocial factors may play a role in both phases.

Robles then suggested three possible mechanisms by which psychosocial factors may impact restorative processes:

- **Slowing the rate of repair.** A meta-analysis of 11 studies found a fairly consistent and moderate association between stress and wound healing.\(^\text{47}\) Similar associations might apply to DNA and telomere repair.

- **Diminishing the integrity of materials.** A study of sleep and glucose metabolism showed that suppression of slow-wave sleep (SWS) after 3 nights leads to decreased insulin sensitivity.\(^\text{48}\) Disrupting sleep thus leads to a disruption of metabolic activity during daytime. Another study has shown that a greater stress burden is associated with lower telomerase activity in immune cells among caregivers.\(^\text{49}\)

- **Disrupting normative processes (overcompensation).** Increased programmed cell death, scarring, overeating following sleep loss, and disruptions in circadian rhythms all fall into this category.

Robles then focused on the most relevant research questions that remain to be answered:

1. Which factors predict normative restorative function despite adversity?

To answer this question, for example, one could explain the observed differences between caregivers and non-caregivers. Very large samples would, however, be necessary, because the expected effect sizes are small. Additionally, within subject designs could be helpful. If days with greater stress are associated with lower sleep efficiency, then it would be interesting to study what differentiates those days on which sleep efficiency is maintained despite a stressful


day. Recent research from Robles’ lab suggests that marital disclosure of thoughts and feelings to the spouse may be one factor.  

2. Can restorative functions be enhanced?

In a study by Robles and colleagues, individuals with high trait positive affect have shown faster skin barrier recovery compared to those with low trait positive affect. This phenomenon emerged only during exposure to stress, which appeared to elevate the response curve above normal levels. To determine whether individuals can be pushed above normal levels, a better understanding of normal ranges for many biological processes is required. Once the normal range is known, one can design interventions to try to elevate measures above this range.

3. Which novel mechanisms should be explored?

Robles noted that the parasympathetic nervous system would be an interesting candidate, because it regulates metabolism, digestion, and growth. GH and IGF pathways, as well as remodeling and repair mechanisms, might also be of interest. Much attention has been given to the inflammatory phase, but other mechanisms should also be considered. Finally, the impact of health behaviors such as diet, nutrition, and exercise on restorative processes should be studied.

THE HEALING POWER OF LOVE: AN OXYTOCIN (OT) HYPOTHESIS

*Sue Carter, Ph.D., Oxytocin Pathways LLC, and Department of Psychiatry, University of North Carolina, Chapel Hill*

Love is characterized by selective social relationships and bonds, which have broad consequences for an individual’s mental and physical health. Love is often described as an emotional state, and specific hormones are involved, one of which is OT. Remarkably little is known about its release mechanism. Sue Carter focused on the physiological and behavioral effects of OT, with a special focus on animal studies in prairie voles, a species of socially monogamous rodents.

Carter argued that the mother-child interaction is the archetype of love, and that OT is central to the understanding of the biology of social behavior, social bonds, social support, birth, lactation, and love. OT is a neuropeptide that is released in the blood stream. A simple molecule of nine amino acids, it has effects on social behavior, and even larger effects on autonomic and immune systems. OT is related to AVP, a molecule that differs from OT by only two amino acids. In fact, OT and AVP have some affinity for each other’s receptors. They

50 Kane, Slatcher, Reynolds, Repetti, and Robles. Presentation at the American Psychosomatic Society (APS) meeting 2013 in Miami.
evolved from an ancestral molecule prior to the split between vertebrates and invertebrates.\textsuperscript{52} Very simplified, OT is involved in love and sharing, while AVP is involved in defensive behaviors.

Carter noted that love is specific to mammals, and not seen in reptiles. The capacity to show the traits associated with mammalian social behavior, including social engagement and social bonding, depend on adaptations acquired in the transition from reptiles to mammals. OT facilitates social engagement (e.g., love, empathy, compassion, relaxation), while AVP may allow selective sociality and defensiveness (e.g., vigilance, hypermobilization, arousal).

Carter explained that OT is one component of a complex and interactive system of feedback loops throughout the body. She then reviewed scientific evidence for OT’s healing effects (although OT may have damaging effects in certain contexts as well), which Carter posited are conveyed by its anti-inflammatory and anti-oxidant properties:

- Wound healing of small blisters was faster in individuals with high OT levels.\textsuperscript{53}
- Studies of monogamous prairie voles have been very helpful for OT research. In this model, acute stress has been found to increase plasma OT levels in male and female animals. Chronic stress showed a similar effect, but only in female animals. Expression of the receptor was not affected by acute stress, while chronic stress down-regulated receptor expression in males and females.\textsuperscript{54}

Carter further reviewed evidence from studies indicating that OT may regulate the ANS, facilitate parental behavior, and inhibit aggression:

- OT treatment (14 days) reversed or prevented the adverse effects of isolation on heart rate.\textsuperscript{55}
- Adult female prairie voles treated with OT showed increased parental behavior and reduced aggression.\textsuperscript{56}

Carter indicated that the endocrine effects of exposure to an infant provide a model for understanding the neurobiology of social support. In male prairie voles never exposed to

\textsuperscript{54} Pournajafi-Nazarloo, et al., manuscript submitted for publication.
infants, a single exposure to a pup can release a surge of OT.\textsuperscript{57} This model may be useful in the study of the role of endogenous OT.

Exogenous OT treatment increases endogenous OT synthesis in the hypothalamus.\textsuperscript{58} This regulation, Carter posited, is likely achieved by an epigenetic mechanism. Specifically, OT treatment increases methylation of the receptor gene, which is down-regulated. Too much OT may lead to too much down-regulation and a maladaptive state.

Carter concluded her presentation by noting that understanding the causes and consequences of mammalian sociality will lead to a deeper understanding of the biology of human emotion and natural factors (e.g., social support, love) that contribute to human health and wellbeing. A perceived sense of safety is necessary to allow the body to grow, heal, and restore itself under stress. OT allows birth to happen, supports maternal behavior, and supports oxygenation of the brain. It may, furthermore, play a critical role in allowing the human nervous system to gain a sense of safety. Ultimately, understanding how this molecule works might help to explain complex human behavior.

HEART RATE VARIABILITY (HRV) AS AN INTEGRATIVE INDEX OF RESILIENCE: INSIGHTS FROM A NEUROVISCERAL INTEGRATION PERSPECTIVE

\textit{Julian F. Thayer, Ph.D., The Ohio State University}

Mutual interactions between the brain and the heart have been known to exist since Darwin’s days. Julian Thayer focused his presentation on HRV as an adaptive mechanism that is associated with a wide range of health outcomes.

Currently, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) lists eight risk factors for heart disease and stroke: hypertension, diabetes, cholesterol, smoking, obesity, physical inactivity, family history, and age. Emerging risk factors include inflammation and psychosocial stress. Previous research by Thayer and his collaborators has shown that each of these risk factors is associated with decreased vagal activity.\textsuperscript{59}


Unpublished data further suggest that HRV can predict blood pressure. Low HRV precedes an increase in blood pressure.

HRV is also related to sleep, genetics, physical activity, serotonin, digestion, social connections, gender, and ethnicity; all of these are interesting but beyond the scope of the current presentation.

Thayer noted that autonomic balance is a predictor of mortality and morbidity, underlies a broad range of responses linked to allostatic load, and may explain how psychosocial factors are involved in physiology and disease. In his overview of the ANS, he focused on the vagus nerve as an integrator of afferent and efferent signals and feedback regulator. Regulation of heart rate appears important, because elevated heart rates show strong associations with all-cause morbidity and mortality.

Thayer then discussed the role of the physiological threat response. The default stress response prepares humans to prepare for the worst. But overstimulation by threats is maladaptive; the response must be appropriate for the context. The neurovisceral integration model stipulates that higher HRV is associated with a greater prefrontal inhibitory tone. A lack of this inhibition leads to an undifferentiated threat response. Because of the correlation between heart rate and prefrontal activity, HRV can be used as a proxy to understand changes in the brain. The vagus nerve is of special relevance in the threat context, because parasympathetic mediation is much faster (i.e., millisecond range) than sympathetic activation (i.e., seconds). HRV can be measured by observing beat frequency over time.

HRV has been associated with a multitude of outcomes:

- **Physiological health.** Decreased HRV is associated with higher levels of hypertension, diabetes, cholesterol, obesity, arthritis, and cancer.
- **Emotional health.** Decreased HRV is associated with increased depression and anxiety.
- **Attentional processes.** HRV decreases as attentional demands increase.
- **Cognitive health.** Increased HRV is linked to greater accuracy and faster reaction time during working memory tasks.

Thayer then discussed research on the pathways involved in a possible role for HRV as a marker of stress and health. A review of imaging studies revealed associations of HRV measures with

several areas of the vmPFC. Impaired stress recovery, measured by cardiovascular, endocrine, and immune markers, was found to be associated with low vagal tone. Thayer concluded from these data that HRV may act as a resilience resource. Higher levels of resting HRV are associated with better self-regulation. Increases in HRV during self-regulation are associated with more successful emotional regulation. This regulation requires the ability to generate an emotional response that is appropriate with regard to the environmental demand. This response involves inhibitory pathways originating from the PFC.

Based on the identified interactions between the PFC and HRV, low HRV is predicted to be associated with threat responses to safe stimuli. Thayer presented data that supported this view and pointed to results from an independent study that found that individuals with high resting HRV can, indeed, better regulate emotions.

Thayer noted that a further link between HRV and emotional regulation is the observation that cardiac vagal tone is decreased in depression. In a recent study (in press), Thayer studied the role of Brodmann area 25 (BA25), a brain area linked to depression. This area is the principal site of autonomic regulation in the frontal lobe. Results suggest that BA25 is implicated in affective state shifts and support the notion that dysfunction of BA25 and abnormalities in vagal tone in depression indeed are linked.

Thayer briefly reviewed several ongoing research efforts on the role of visceromotor networks in depression, the link between HRV, worries, and anxiety, and HRV associations with memory functions.

HRV is not static. It can be modified by exercise, diet (e.g., omega-3 fatty acids), stress, drugs, and vagus nerve stimulation. Thayer concluded his presentation by emphasizing the importance of the ability to adapt to a changing environment. HRV allows humans to adapt.

**IMMUNITY AND POSITIVE PSYCHOBIOLOGY**

*Marian Kohut, Ph.D., Iowa State University*

Marian Kohut focused her presentation on changes in immunity associated with positive psychobiology that are independent of stress and negative influences. She provided an overview of immune system function and noted that psychosocial studies have historically

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focused on a limited set of parameters. Other factors could, however, be important for restorative functions.

The immune response is usually divided into innate and adaptive responses. Recent research has led to a better understanding of the innate system and how it recognizes different pathogens.

The innate system may recognize and respond to pathogen-associated molecular patterns (PAMPs) or endogenous danger-associated molecular patterns (DAMPs). The response to PAMPs or DAMPs may result in activation of an intracellular signaling complex known as the inflammasome. Activation of the inflammasome results in the production of inflammatory cytokines. DAMP-related activation of inflammation may contribute to the pathogenesis of different disease states. For example, in chronic diseases such as obesity or diabetes, endogenous palmitate and ceramide may lead to inflammasome activation, contributing to inflammation. In view of the growing evidence for the role of the inflammasome in multiple chronic diseases, finding a means to limit activation of this pathway may confer health benefits.

The overall balance between inflammatory factors and anti-inflammatory factors is important in determining whether conditions favor immune-mediated tissue damage or anti-inflammatory processes that are essential in initiating repair and healing. There are several “control” points in the immune response that may result in a shift toward inflammation or toward repair. Kohut pointed to dendritic cells as an important bridge between innate immunity and adaptive immunity and an example of a critical control point. Dendritic cells have the ability to become APCs and present antigens to Th-helper \( (T_{h}) \) cells, which, in turn, activate other cells. An important feature is that the APC cells receive input from the innate system. The input received from the innate immune system directs the type of ensuing APC response. Subsequently, the type of APC response directs the pattern of adaptive immunity \( (T_{h} \) activation). Therefore, APC activation constitutes an important regulatory point, downstream of which \( T_{h} \) cell response may promote a pro-inflammatory or anti-inflammatory environment.

The \( T_{h} \) cell phenotype plays a role in regulating inflammation or repair. For example, inducible T-regulatory cells (iTreg) may limit inflammatory cytokine production by other cells of the immune system, allowing for initiation of the repair process. Another example of phenotypic cellular changes that can shift the balance from inflammation to repair is the change from an M1 classical inflammatory type of macrophage to an M2 type alternatively activated macrophage.

In summary, the examples provided illustrate that the immune system itself has restorative features by regulating the balance between activation of inflammation and the activation of restorative repair processes.

The immune system does not act in isolation; it communicates with the neuroendocrine system in a bidirectional manner. Signals from the immune system (e.g., cytokines) to the brain induce sickness behaviors and activate the HPA axis. Under conditions such as stress, neuroendocrine factors may affect immune response. This bidirectional communication between the neuroendocrine system and immune system is well recognized and may have an important role
in response to infection as well as in chronic disease. More recently it has been recognized that metabolic-immune interaction at the cellular level may direct immune activation and/or influence the physiological response of metabolic tissues. For example, the degree of glucose uptake by T cells can determine whether T cells proliferate or undergo apoptosis. With respect to immune-mediated effects on metabolic tissue, inflammasome activation inhibits insulin signaling. Metabolic-immune communication adds yet another regulatory mechanism that can affect disease outcome and repair processes. Therefore, the input from the neuroendocrine system as well as metabolic signals can influence immune response and again play a role in the shift toward restoration or repair, although these processes are not well understood.

Kohut described several models of human immune function that have been used to study the influence of positive psychobiology. These include measurements of serum cytokines, peripheral blood mononuclear cell (PBMC)-cell typing, experimental infection, measurements of vaccine responses, delayed-type hypersensitivity (DTH), and wound healing.

Studies of the response to infection with respiratory viruses have demonstrated that stress increases the susceptibility to develop a cold and also the severity of symptoms. Positive emotional style has also been associated with a significantly decreased illness rate and fewer reported symptoms. Effects of chronic or perceived stress on immunization responses have been demonstrated in numerous studies. Optimism and positive affect have been shown to lead to a greater antibody response and increased interleukin (IL)-10 levels.


Kohut then reviewed her own recent data on wellbeing and response to vaccination. High positive affect was associated with increased t-cell proliferation and virus-specific interferon-gamma production by CD8+ cells. In another study, she carried out an exercise intervention and studied the effects on optimism and immunity. Exercise, which reduces stress and depression, increased optimism. Those individuals with the greatest change in optimism also had the lowest count of CD8+ CD28- cells, which are less responsive cells that may accumulate with aging. This mechanism may illustrate one restorative aspect of immunity in response to increased wellbeing.

Kohut concluded her presentation by outlining mechanisms of interest and priorities for future studies. The field’s current understanding of the mechanisms by which positive psychobiology influences immunity is very limited, but offers many opportunities for further research, such as:

- Greater positivity as a stress buffer
- The HPA axis and the sympathetic nervous system (SNS) alter immunity
- The influence of vagal tone on immunity
- A role for reduced danger signal activation
- Calculations of energy costs and metabolism/immune interactions

Current gaps in the understanding of the immune system that need to be filled in order to address these questions are:

- Understanding innate immunity (PAMPs and DAMPs)
- Roles of different T\(_h\) cell subsets
- Antigen presentation and co-stimulation

• The transition of macrophages from inflammatory to restorative states, repair by neutrophil cells, and the role of innate lymphoid cells
• Characterization of tissue repair metabolites
• Shifts in the balance between activation and resolution/repair

EXPLORING THE NEURAL CORRELATES OF RECEIVING AND GIVING SOCIAL SUPPORT

Naomi I. Eisenberger, Ph.D., University of California at Los Angeles

Naomi Eisenberger reviewed research on restorative neural processes and neural correlates of safety processing and mammalian caregiving. She noted that the links between social ties and good health are very well established. After decades of research, the field is beginning to understand the underlying mechanisms.

Given the workshop focus on positive effects, Eisenberger focused on results from research on the benefits of social support. Both giving and receiving social support have effects on stress response system and the immune system, and are important for health outcomes.67 Eisenberger noted that current research mainly focuses on central neural investigations and that an important next step will be to link these with peripheral systems.

Benefits of social support have been shown in studies on animals and humans. In animals, the presence of a companion during stress can reduce emotional and behavioral reactions to shock,68 and reduce HPA responses.69 Very similar responses have been observed in humans. Cardiovascular responses,70 cortisol release,71 and subjective physical pain72 have all been shown to be reduced by the presence of a supportive companion.

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Eisenberger then turned to the mechanisms involved and noted that knowing that others are available to help might reduce an individual’s sense of stress and induce a feeling of safety. Several studies have been undertaken to reveal the underlying neural correlates. One study let subjects believe that a tarantula was in close proximity to their feet. Increasing the distance from the foot led to increased activity in the vmPFC, suggesting that this region emits safety signals or expels fear. Additional experiments in humans have examined vmPFC’s association with threat reduction, measured by decreased fear responses, decreased heart rate and anxiety, and decreased pain. Animal experiments have provided additional evidence for a role of the vmPFC in threat reduction.

Eisenberger presented results from her own work on the question of whether social support may reduce distress in response to a negative event through the activation of this safety-related neural region. She recruited subjects in very supportive relationships and exposed the females to a heat stressor. Social support was simulated by showing subjects a picture of their partner; in the control condition, subjects viewed a picture of a stranger or a neutral object (e.g., chair). Subjects were then asked about pain levels. When subjects looked at pictures of their partner compared to pictures of a stranger or neutral object, Eisenberger found increased vmPFC activation. Subjects with greater activity in the vmPFC during pain also showed less activity in the dACC and less self-reported pain.

To further understand the downstream effects of such safety-related mechanisms, Eisenberger is now conducting studies on the role of social support in fear conditioning paradigms. She


quantifies fear response by galvanic skin response. Conditioning is accomplished by linking the fear response to visual presentation of a picture, which can be a picture of the partner, a stranger, or a neutral object. Preliminary data suggest that the picture of the stranger and the neutral picture elicit a conditioned fear response, but the picture of a social support person does not. Future studies will address whether this suppression of a conditioned fear response by social support is associated with increased activity in the vmPFC.

Eisenberger then focused on the effects of giving rather than receiving support. Individuals who give support may receive as much benefit as those who receive support, and those who give support have been shown to have better mental health, lower blood pressure and heart rate, and reduced overall mortality risk. The underlying mechanisms are still poorly understood.

Animal research has shown that maternal caregiving to offspring relies on neural regions involved in reward processing. These regions include the VS and SA. Pup exposure in maternal females leads to increased activity in the VS, and VS lesions disrupt maternal behavior. SA lesions also disrupt maternal behavior, and the SA plays a role in threat.

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reduction.\textsuperscript{85} Specifically, the SA has been shown to contribute to maternal behavior by reducing threat responding to facilitate caregiving during stress.\textsuperscript{86}

This mechanism is believed to reduce the perception of threats so that an individual can engage in adaptive caregiving in times of threat. To test whether the neural correlates of support giving in humans are the same as those identified in animals, Eisenberger studied individuals as they provided support to a partner. Thus, female subjects were scanned as they provided support to their male partner (held his arm) while he went through a negative experience (exposure to shock). The greatest activity in the VS and SA was, indeed, seen during support giving as opposed to control conditions.\textsuperscript{87} Furthermore, increased septal activation was associated with reduced amygdala activity.

Eisenberger is now examining whether giving support to others may reduce one’s own physiological stress responsivity. In a current study, support givers and control participants engage in the Trier Social Stress Test (TSST). Preliminary findings indicate a significant benefit of support giving in reducing stress (reduced blood pressure) during the TSST.

Eisenberger concluded her presentation by noting an interesting pattern: the regions mentioned above are typically considered part of a larger reward-related circuit. They all have connections with the amygdala. These findings might therefore provide further evidence for an inverse relationship between reward and threat, and the mechanisms by which reward reduces stress may be similar to those found in other paradigms (e.g., sucrose,\textsuperscript{88} erotic stimuli,\textsuperscript{89} monetary reward\textsuperscript{90}). Understanding the exact underlying mechanisms will be an interesting avenue for future research.

\section*{DISCUSSION}

Participants suggested that being helpful gives people a sense of purpose, which may link social support more closely with eudaimonic rather than hedonic wellbeing. Past social science


\textsuperscript{89} Creswell et al., Psychosom. Med., in press.

research may have underestimated the benefits of giving social support because it primarily focused on the benefits of receiving social support. There may also be gender differences.

The above discussions led to consideration of the range of approaches to measuring wellbeing and then evaluating how such measures are linked to biology. Instruments exist to capture global or domain-specific evaluative assessments of wellbeing, as well as assessments of momentary or “experienced” wellbeing. Both can be valuable depending on the particular research question being investigated. Nielsen noted that survey measures exist for both purposes. Unlike global evaluations, which assess broader cognitive judgments of life satisfaction or meaning and purpose, momentary measures may be capable of capturing dynamic reactions to perturbations in real time. These may be differentially linked to biology. The NIA encourages research that bridges approaches from laboratory and survey science, including the addition of biomeasures or challenge paradigms to surveys, to shed light on these issues. Such questions can be explored using publicly available data from studies (e.g., MIDUS) that already include rich assessments of basal and dynamic measures of biomarkers related to health and wellbeing. It is also possible to add modules to existing studies to further explore these questions, though this approach is not always feasible. Participants further noted the importance of ancillary studies, program project (P01) interdisciplinary funding mechanisms, and broad studies of integrative mechanisms.

Thayer clarified that HRV has trait and state-like characteristics. Those who have a higher resting HRV also have a greater amplitude of adaptations (i.e., they can occupy more possible states) than those with a low resting HRV. This broader dynamic range provides them with greater adaptivity. In response to a question about whether interventions should target HRV directly, he noted that it should be considered a sensitive indicator of adaptability, but the primary changes are in brain activity and connectivity.

Participants observed a common theme of immobilization across the presentations so far. Pause and plan, bonding, and the inhibitory quality of increased vagal tone are all ways to hold on to a resource that will be deployed later. PPWB can thus be viewed as facilitating the acquisition or retention of resources that can be deployed when needed later on.

Kubzansky noted that much still needs to be learned about developmental changes in these systems, critical or sensitive periods, malleability, and ideal intervention strategies. Furthermore, for many of the biomarkers, there is still no established normal range. Some distributions may be linearly associated with beneficial outcomes whereas others could have non-linear associations such as a U-shaped curve. Access to quality longitudinal data will be paramount to disentangling causes and effect.
SESSION 3: RESEARCH AREAS THAT MAY SUGGEST NOVEL BIOLOGICAL FACTORS

SETTING THE STAGE FOR NOVEL BIOLOGICAL FACTORS

*Suzanne C. Segerstrom, Ph.D., University of Kentucky*

Introducing a very diverse and seemingly unconnected set of topics for this session, Segerstrom indicated that the selection of speakers for the third session was intended to inspire participants to look beyond their usual research domains. Each of the research areas covered in this session might hold processes with positive or restorative features, but there has not been any formal investigation of these yet. Segerstrom encouraged participants to consider the following questions:

- Why might this research area be a good candidate for identifying novel and restorative biological processes?
- What biological processes might indicate restoration or something other than deterioration?
- Have these biological processes been linked with other psychosocial factors or even PPF?

She provided a brief explanation of catabolic versus anabolic processes and noted that most of the participants come from the tradition of stress medicine and catabolic processes. Wellbeing, however, is more than the absence of deterioration. This session will, therefore, focus on anabolic processes, which contribute to growth and put the products of catabolism to good use. Anabolic pathways may differ from catabolic pathways and may include insulin, anabolic steroids, and other factors. The challenge for the participants is thus to evaluate if the biomarkers from this field should be incorporated in the psychobiology of wellbeing.

SLEEP AS A SOURCE OF RESILIENCE AND RESTORATION

*Orfeu M. Buxton, Ph.D., Harvard Medical School*

Sleep is a health behavior under homeostatic control by the brain. It is restorative and recuperative and contributes to resilience. Sleep is sensitive to internal (e.g., psychological, physiological) and external (e.g., context, environment, work) factors, and constitutes one of three pillars of health: diet, sleep, and exercise.\(^91\)

Orfeu Buxton reviewed the nightly sleep cycle of alternating cycles of non-rapid eye movement (REM) and REM sleep. Over the course of the night the deepest stages of nonREM or slow-wave sleep are associated with restorative processes marked by, for example, GH release. Slow wave sleep wanes with each successive nonREM and REM cycle. GH makes children grow, but in

\(^91\) In response to a comment from a workshop participant, these three pillars later became four to include sexual activity.
adults has many diverse physiologic functions. Therefore, GH may be thought of as a restorative “infrastructure maintenance hormone.” Although GH has traditionally received the most attention, many other hormones and neuromodulators are secreted along with it, and other restorative processes occur. New synapses are formed during deep sleep. These are then pruned during light, REM sleep. This is important, because space is limited in the brain, and this mechanism is thought to ensure that important memories are kept. Emotion processing appears to occur during REM periods. Any breakdown in natural sleep can be disruptive to the restorative capacity of sleep.

Buxton noted that an individual’s need for sleep can vary, but that 7 to 9 hours are an appropriate range for most adults. The circadian timing system is synchronized to the external light-dark cycles through light/dark input via the eyes. The circadian system controls 24-hr variations in physiology, including body temperature, autonomic function, and the release of hormones.92

Buxton showed the striking similarity between a U.S. national map from the Centers of Disease Control and Prevention (CDC) showing the prevalence of sleep insufficiency and a similarly patterned map of diabetes prevalence. Sleep is related to diabetes risk. Risk is increased for those who have trouble falling asleep and greatest for those who cannot maintain sleep. A similar pattern is seen for stroke, cardiovascular disease and obesity, but also low educational attainment and poverty. Sleep is a public health priority,93 and increasing the amount of sleep individuals obtain is a federal public health goal included in Healthy People 2020.94

The NHLBI Sleep Disorders Research Advisory Board has recently defined sleep deficiency as “insufficient quantity or inadequate quality of sleep obtained to that needed for optimal health, performance, and wellbeing.”95

Commonly agreed upon definitions of “insufficient,” “inadequate,” and “optimal health” are not yet available, but Buxton emphasized that this is an active area of research.

He further noted that people usually think that they are more resistant to sleep deprivation than they really are. Several studies have shown that sleep restriction strongly impairs

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In a sleep restriction study in the lab, Buxton and colleagues showed that sleep restriction for 1 week increases cortisol levels, reduces insulin sensitivity, and increases diabetes risk.

Parallel experimental and epidemiological studies further support the notion that short sleep may lead to weight gain. Leptin levels are decreased and ghrelin levels are increased in those who sleep less. The body appears to interpret a lack of sleep as hunger. Not only the duration, but also the timing of sleep is important for health. In an experiment of combined sleep restriction and circadian disruption, Buxton and colleagues showed that sleep restriction and circadian disruption (while controlling for the current circadian phase of the standardized test meal response) led to significantly decreased post-prandial insulin levels. This suggests that prior circadian disruption leaves the pancreas unprepared to secrete enough insulin.

Sleep duration has also been associated with heart disease. The risk appears to follow a U-shaped curve such that both too little and too much sleep increases risk. However, the mechanisms underlying these associations are likely different for the short and long sleep portions of the curve.

Buxton noted the importance of sleep for learning and summarized the maladaptive responses to sleep deficiency as follows: impaired alertness and attention, degraded cognitive function and emotional responses, degraded communication, increased risk-taking and substance abuse, increased pain and functional limitations, decreased physical activity, increased hunger, increased snacking, increased cortisol levels, increased inflammation, increased SNS activation, and increased pain and functional limitations.

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altered glucose metabolism, and increased likelihood of infections.\textsuperscript{102} To the extent that sleep is a volitional behavior, the physiology of sleep homeostasis can maintain adequate sleep duration, but to the extent that control of our sleep behavior is not under our physiologic homeostatic control, whether due to work pressures, family demands, excessive screen use in the evening instead of sleep or other factors, sleep duration may not be adequate for optimal functioning or long-term health.

Buxton then briefly mentioned two sleep disorders: sleep-disordered breathing (i.e., sleep apnea) and insomnia. Sleep apnea is caused by obstruction of the upper airway. Known risk factors are male sex, age over 40, and family history. It is a serious condition that can shorten duration and quality of life. A diagnosis of insomnia is made when the subject has adequate opportunity and circumstances for sleep, but still complains about severely disturbed sleep. Insomnia can be transient, co-morbid with other conditions, or chronic.\textsuperscript{103} Several studies have suggested that hyperarousal may play an important role in the pathogenesis of insomnia.\textsuperscript{104}

Buxton noted that the Division of Sleep Medicine at Harvard University, in collaboration with the WGBH Educational Foundation, created and maintains the website healthy.sleep.med.harvard.edu.\textsuperscript{105} The goal is to increase public health through public education.

Buxton concluded his presentation with a brief review of his own research on factors that cause sleep deficiency and that lie outside of an individual’s control.\textsuperscript{106} In the workplace, beneficial factors were supervisor support, higher rank, and ergonomic practices, while harmful factors included harassment at work. Sleep deficiency, job demands, and psychological distress were further associated with outcomes of pain, work limitation, and functional limitation of daily living.\textsuperscript{107} Actigraphy (i.e., wearing a wrist device that measures activity from which sleep


\textsuperscript{105} See: http://healthysleep.med.harvard.edu


patterns can be assessed) is one way of better measuring daily sleep, among other biomarkers useful for multi-level studies. In one actigraphy study, Buxton and colleagues found a strong positive relationship between a manager’s openness and flexibility toward employee work-family needs and sleep duration. Furthermore, the same manager work-family score was also highly correlated with reduced CVD risk.

Buxton noted that in a framework of sleep and disease, sleep can be a modifier, mediator, outcome, and intervention target, depending on the context. Sleep deficiency can be caused by many reasons. Through yet to be fully understood mechanisms, sleep deficiency leads to near-term changes and proximal outcomes. If left unchanged, distal outcomes and risk for chronic disease may follow.

**PHYSICAL ACTIVITY: IMPLICATIONS FOR BRAIN AND COGNITIVE HEALTH**

*Art Kramer, Ph.D., Beckman Institute, University of Illinois*

Art Kramer endorsed Buxton’s notion of the importance of objective measures (e.g., actigraphy, pedometer); people often misreport their amount of activity and sleep. An important challenge for the field of physical activity will be to establish a reliable connection between the more process-pure measurements obtained in the laboratory and measurement in the real world. Kramer explained the cognitive enrichment hypothesis, according to which levels of performance are malleable and open to enhancement throughout the human lifespan. The upper levels of performance are, however, constrained by the boundaries of biological aging.

He also provided a brief review of the state of the art regarding molecular and cellular brain mechanisms of physical activity; most of this work has been carried out in animal models. Researchers usually assess the effects of exercise by comparing animals with access to running wheels to those with no access. The experimental paradigms often contain a learning task (e.g., perceived pain and functional limitations in hospital patient care workers. J. Occup. Environ. Med. 54, 851–858.


Morris water maze) and electrophysiological and histological measurements. Results suggest that exercise increases the number of neurons being born from stem cells in the dentate gyrus of the hippocampus. Other observed changes include an increase in neurotrophins, enhanced synaptogenesis, enhanced angiogenesis, increased production of various neurotransmitters, reduced beta-amyloid protein in mouse knock-out models, increased telomere length, increased expression of genes associated with plasticity and mitochondrial function, downregulation of genes associated with oxidative stress, and enhanced learning and memory.

Kramer then focused on the effects of exercise and physical activity on older human minds and brains. An epidemiological study of 349 subjects ages 55 years and older who were followed for 5.5 years used maximal oxygen consumption (VO2max), oxygen uptake, and stamina as objective measures of cardiorespiratory fitness. Exercise and higher cardiorespiratory fitness showed significant benefits for many cognitive measures (e.g., attention, verbal memory, verbal fluency). Kramer noted that the increasing use of objective measures has helped to achieve significant findings for measures that previously showed non-significant trends or ambiguous results when physical activity was only measured through retrospective self-report measures and questionnaires.

Kramer indicated that there is still a dearth of knowledge of fitness training effects on brain function in humans. In a 6-month fitness training intervention, Kramer’s group found a significant increase in brain volume in older participants engaged in aerobic training. The observed increase in brain size was likely restorative, pushing the individual toward a younger trajectory. Since that study was published, imaging techniques with better resolution have become available. A more recent study found increased hippocampal volume after exercise.

Even more recently, diffusion tensor imaging was able to identify a dose–response relationship between changes in fitness and the integrity of white matter tracts.\textsuperscript{118}

Kramer then reviewed approaches that use networks and graph theory to understand complex changes in brain connectivity.\textsuperscript{119} Assortative networks are resilient to disturbances; malfunction of any individual node does not affect overall network layout and function. Assortativity thus can be considered a measure of network resilience. Disassortative networks break down more easily when central hubs are disturbed.\textsuperscript{120} Kramer’s research group used these paradigms to study the influence of exercise on network resilience. They found a significant correlation between aerobic fitness and age-corrected assortivity. Increased connectivity was, furthermore, associated with increased serum brain-derived neurotrophic factor (BDNF) levels.\textsuperscript{121} In a study using magnetic resonance spectroscopy, Kramer’s group found an association between N-acetylaspartate (NAA), aerobic fitness, and working memory.\textsuperscript{122}

In a 6-month intervention, Kramer and colleagues also examined the role of physical activity and social support for subjective wellbeing.\textsuperscript{123} Frequency of exercise participation was a significant predictor of improvement in satisfaction with life, whereas social relations were related to increases in satisfaction with life and reductions in loneliness. They also studied adherence to exercise interventions by structural equation modeling and found that higher levels of executive function and use of self-regulatory strategies led to increased adherence with exercise interventions.\textsuperscript{124}

Kramer then addressed whether or not there may be a point of no return for human cognitive decline such that people no longer benefit from exercise interventions. Several studies in patients with different types of neurodegenerative diseases have shown persistent beneficial


\textsuperscript{121} See Voss et al. above.


effects of exercise.\textsuperscript{125} Moreover, similar positive effects of exercise on hippocampal volume and memory have been identified in children ages 7 to 10 years.\textsuperscript{126}

Regarding the relevance of this research for the real world, Kramer pointed to findings from path analyses suggesting that older adults with higher levels of fitness indeed show greater preservation of hippocampal volume, which, in turn, is associated with more accurate and faster spatial memory and fewer self-reported episodes of forgetting.\textsuperscript{127} He also reviewed recent studies in his laboratory and elsewhere showing that children who exercise improve in math achievement\textsuperscript{128} and do better in a virtual reality test of multitasking (e.g., during the crossing of busy streets).

Kramer summarized his findings by noting that even relatively brief fitness interventions can improve a variety of perceptual and cognitive abilities. Future efforts should focus on interdisciplinary team science and aim at combining interventions and understanding underlying mechanisms. Stratification of individuals based on biomarkers should also be a priority.

**DOPAMINE (DA), MOTIVATION, AND THE DECISION TO EXPEND EFFORT**

*David Zald, Ph.D., Departments of Psychology and Psychiatry, Vanderbilt University*

People often view happiness as a goal of positive psychology, but joy is a fleeting emotion; being interested in what is going on is a much longer lasting state. David Zald therefore finds measures of positive engagement more useful for his work than measures of happiness. He focused his talk on the correlation between positive affect and approach motivation. He defines motivation as the general desire or willingness to perform a task. His main goal is to find the

\begin{itemize}
  \item \textsuperscript{128} Davis, C.L., Tomporowski, P.D., McDowell, J.E., Austin, B.P., Miller, P.H., Yanasak, N.E., Allison, J.D., and Naglieri, J.A. (2011). Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol 30, 91–98.
\end{itemize}
neural substrates of motivation and to use the models that he has developed to study the effects of manipulations on positive affect. He uses a fairly specific conceptualization of positive affect based on David Watson and Auke Tellegen’s work, according to which positive affect is a dominant factor of mood that can be distinguished from happiness.

Zald reviewed research in rats that used a simple T-maze to test motivation and the willingness to expend effort. The animals get a larger reward if they are willing to expend effort to climb over a barrier. Healthy rats will choose the larger reward at least 80 percent of the time. Using this paradigm, the VS and the mPFC have been identified as two critical nodes of an effort-based decision-making circuit. In humans, research on the neurobiology of effort expenditure for rewards has focused on the mesolimbic DA system. Zald reviewed neural projections involving the mPFC, the ventral tegmental area (VTA), and the nucleus accumbens (NAcc), which are all hypothesized to constitute a behavioral activation system that pushes behavior toward rewards.

Decreasing DA concentrations in these regions or blocking DA receptors with haloperidol decreased the willingness for rats to expend effort. Conversely, rats given amphetamine to increase DA levels will seek the larger reward more frequently. These observations are independent of whether or not the animal likes the food, suggesting a role for DA in motivation for rewards rather than short-term hedonic experiences.

In order to use willingness to work as a measure of motivation in humans, alternative approaches to climbing walls had to be developed. One implementation developed by Zald and colleagues is the EEfRT, which involves a simple lever pressing paradigm. Across multiple trials, research subjects must make repeated cost-benefit analyses regarding whether or not a specific monetary reward is worth additional effort relative to a smaller reward that requires less effort. Researchers assess individual differences in the sensitivity to reward magnitude and probability by varying the reward value of the harder task and the probability of reward for

either task across trials. Depressed individuals prefer the easy, less rewarding task and appear less sensitive to reward magnitude relative to healthy controls.\textsuperscript{134}

Zald and colleagues recently demonstrated in humans that dopaminergic manipulations indeed alter willingness to exert effort for rewards.\textsuperscript{135} In these experiments, administration of amphetamine to research subjects increased effort selectively on low probability trials. This means that increased DA release by amphetamine increases pursuit of unlikely potential rewards. In parallel functional magnetic resonance imaging (fMRI) studies, the mPFC, dACC, and preSMA regions were activated during decisions to expend effort.

Zald then went on to relate EEfRT measures to individual differences in DA functions in humans. He used Fallypride, a DA-D2 receptor binding ligand, to measure DA release by a two-scan protocol. After amphetamine administration, fewer D2 receptors are available, leading to decreased Fallypride binding. With this paradigm, DA release can be used as a trait measure of DA system reactivity. Zald and colleagues found that subjects with high striatal DA release have greater motivation to pursue rewards and novelty. There was a dose–response relationship; the more DA subjects released, the more likely they were to select the high-reward task.

Zald discussed the utility of this operationalization of motivation for studies of PPWB. Intensive fMRI studies cannot be easily integrated into large epidemiological studies, but they may be realistic when conducted in smaller, targeted investigations. There, they may fulfill an important role in capturing motivational aspects of wellbeing. He emphasized that this work mainly aims at measuring the eudaimonic side of wellbeing. While there are no data yet on health outcomes, Zald provided examples of possible future uses. These include studies of the willingness to expend effort for health. He speculated that willingness to exercise would correlate with conscientiousness, which is linked to a large number of health outcomes. It may be difficult to assess physical effort in some populations using this paradigm, but cognitive effort (e.g., math tasks) is much easier to implement. Furthermore, the exact contributions of reward seeking versus cost valuation should be examined in greater detail in the future. Another possible limitation of the EEfRT paradigm was also noted; the use of fiscal rewards might show large variability in different age groups or individuals with differing socioeconomic status (SES), limiting its usefulness in larger efforts.

Zald concluded his presentation by noting ongoing efforts to connect these studies to the real world by investigating possible correlations between changes in decision making and changes in measured DA function during aging, and by examining the relationship between EEfRT performance and time spent studying and exercising in college students.


ROLE OF MICROBIOME GUT BRAIN INTERACTIONS IN RESILIENCE

Emeran Mayer, M.D., University of California at Los Angeles

In reviewing the bidirectional interactions of the microbiome-gut-brain axis, Emeran Mayer stated that this axis can be viewed as a link between three “supersystems”: the brain, the enteric nervous system (ENS) with its closely related endocrine and immune components, and the gut microbiome. As such, it links our largest surface with the environment made up by the gut with our brain and the external environment, and has to be assumed to be an important component of the organism’s resilience to internal or external perturbations.

The ENS constitutes the largest accumulation of neurons outside of the CNS. Because of its size and complexity, it also has been called the “little brain” or “second brain.” It comprises 200 to 600 million neurons, some of which have similar morphological, electrophysiological and signaling properties as brain cells. The ENS is considered the third branch of the ANS in addition to the sympathetic and parasympathetic branches. If the connections from the brain to the enteric nervous system are interrupted, then the ENS assures the autonomic functioning of the gut, but the ENS is no longer able to provide important feedback to the brain. The enteric nervous system and the gut microbiome receive sympathetic and parasympathetic signals from the CNS and modulatory influences from the hypothalamic pituitary adrenal axis.

Mayer reviewed various “intestinal target cells” or “transducer cells,” including enterochromaffin cells, immune cells, smooth muscle, and enteric neurons. Under steady state, these cells signal to visceral afferent fibers to constantly inform the brain about events in the gut. The brain, via the branches of the autonomic nervous system, can adjust their sensitivity acutely and change their properties during chronic stimulation. By this latter mechanism, chronic stress is likely to change our interactions with the gut and the gut microbiome. Similarly, neuroplastic changes, which are likely to occur at all levels of the gut-brain axis in patients with chronic abdominal pain, can lead to increased afferent signaling to the brain and influence mood, affect, and cognition. In summary, the gut-brain axis is a highly plastic system of high relevance for health and chronic disease.

Enteroendocrine (EE) cells in the gut form the largest endocrine organ of the body and use 20 different hormones and signaling molecules. Ten discrete EE cells have been described; those secreting serotonin (i.e., enterochromaffin cells, ECs) have received the most attention because they produce 95 percent of the body’s serotonin. They can sense nutrients, bile salts, short chain fatty acids, bitter and sweet taste, bacterial products, and quorum-sensing molecules via specialized receptors on their luminal surface.

Mayer reviewed research from the past 10 years on gut-brain interactions and neuronal correlates of gut-induced changes in brain signaling. He noted a long-standing interest in common chronic visceral pain conditions, such as irritable bowel syndrome (IBS) and often

comorbid syndromes involving the esophagus and upper GI tract. In spite of the large prevalence and frequent supposed breakthroughs in the understanding of the causes of IBS, no effective therapy has yet been developed.

Mayer’s research group focuses on readouts in the brain of abnormal signals from the gut. In a recent study of cortical thickness, they compared 83 individuals with IBS to 194 controls. They saw increased cortical thickness in somatosensory cortex areas and decreased thickness in regions of emotion regulation circuits. Further studies revealed corresponding changes in white matter connectivity. Overall, the IBS brain is characterized by extensive structural remodeling and altered function, including enhanced sensory perception, compromised prefrontal inhibition (including altered prefrontal-limbic-pontine input to endogenous pain modulation systems), and enhanced emotional arousal.

In the future, Mayer’s group plans to extend this approach to study gut brain interactions in health and various disease states. They will explore the relationship between brain signatures (i.e., structural and functional brain changes) and other –omics datasets to create distinct signatures or biomarkers of chronic disease and wellness.

Mayer also briefly reviewed the human gut microbiome. By cell count, humans are 90 percent bacterial. Individuals differ in the composition of their microbial enterotypes. Emerging findings suggest a significant role of the bacteria in gut-brain communication; furthermore, microbiome diversity has been suggested to predict resilience and protect against obesity. Bacteria produce metabolites homologous to catecholamines, gamma-aminobutyric acid (GABA), tryptophan, histamine and serotonin, and many other substances. To understand whether and how these signals act as communication signals between microbial communities and signals to the brain, affecting its structure and function, remains a future challenge.

Mayer concluded his talk by emphasizing the emerging role of bidirectional microbiome-gut-brain interactions in wellness and disease. Distinct signatures of these closely connected systems may become as relevant as biomarkers.

137 Jiang et al., under review.
GENOMIC APPROACHES

Steve Cole, Ph.D., School of Medicine, University of California at Los Angeles

Gene expression studies have become powerful tools to study the molecular changes leading to increased risk of morbidity and death. An expression study of social isolation, one of the most robust environmental risk factors for disease and mortality in humans, revealed a non-random signature of up- and down-regulated genes that were associated with isolation. Pro-inflammatory genes that are known to be involved in disease processes of CVD, cancer, and neurodegeneration were particularly relevant. The same general pattern of increased inflammatory gene expression and reduced activity of interferon and antibody genes has been observed across a wide variety of adverse life circumstances (e.g., low SES in childhood and adulthood, social loss, post-traumatic stress, cancer diagnosis, social threat, loneliness, social instability, chronic stress, low social rank, caregiving for seriously ill people, and depression). Experiments in macaques have provided converging evidence for these profiles. Because of its consistent emergence, this pattern has been called conserved transcriptional response to adversity (CTRA). According to Steve Cole, the challenge for the field now lies in the identification of higher-order correlates in this pattern.

Cole noted that details of current endeavors to understand the origin of these patterns were beyond the scope of the current presentation, but that white blood cells of the monocyte type appear to account for most of the transcriptional reprogramming. Recent research has also started to identify some of the key biological pathways (e.g., HPA- and SNS-regulated gene transcription) mediating these cellular effects, answering questions about which particular hormonal pathway is connected to which particular gene profile. This knowledge will enable researchers to then search for upstream causes of these events.

Cole summarized that the results presented so far can tell us about how not to live. But can genetic expression profiles also be used to answer more positive questions about true happiness? Does the genome prioritize one type of wellbeing over another (e.g., hedonic wellbeing over eudaimonic wellbeing)?

Cole recently had a unique chance to study this question by collaborating with Barbara Fredrickson and her group at the University of North Carolina, Chapel Hill. They recruited 80

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healthy adults, brought them into the laboratory, assessed hedonic and eudaimonic wellbeing and depressive symptoms, and extracted DNA from their white blood cells. They then simultaneously assessed expression of all 21,000 human genes.

They found that eudaimonic and hedonic affects had very similar inverse relationships with depression, which means that individuals with greater levels of hedonic and eudaimonic wellbeing had lower levels of depression. They then looked at the biology and the clusters of antibody-related genes, antiviral interferon genes, and inflammation. Eudaimonic wellbeing was associated with a “healthy” profile of high levels of interferon- and antibody-related gene transcripts and reduction of pro-inflammatory gene transcripts. Hedonic wellbeing, although fairly highly correlated with eudaimonic wellbeing, produced an adverse expression vector containing greater expression of inflammation-related genes and lesser expression of genes involved in interferon antiviral responses and antibodies. The study controlled for many behavioral confounders, such as substance abuse and other unhealthy behaviors. Cole noted that the human genome has had a long time to evolve, and the apparent preference of eudaimonic wellbeing may teach us something about what it has historically meant to “live well” over the course of human evolution.

Cole concluded his presentation with a brief review of additional studies showing similar changes in gene expression profiles resulting from experimental interventions such as cognitive-behavioral stress management, mindfulness-based stress reduction, and yogic meditation.

DISCUSSION

Participants noted that the resolution with which tools such as the Mental Health Continuum Short Form (MHC-SF) or Center for Epidemiologic Studies Depression (CES-D) Scale measure hedonic or eudaimonic wellbeing and depression may be insufficient to draw detailed conclusions about these concepts. These tools also have limited power to differentiate between affective and somatic components, each of which contains a large number of individual concepts. The field must pay more attention to the adequacy of the measurement tools used; much information can be lost when these constructs are not sufficiently detailed. Hedonic and

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eudaimonic wellbeing can be highly correlated (Pearson’s r has ranged from 0.25 to 0.73)\(^{148}\) and separating their effects will require sophisticated methods in large samples.

Mayer noted that the gut research field has not yet discovered a poor-health associated transcriptional response profile similar to the CTRA pattern seen in lymphocytes. Roughly three different enterotypes are seen around the world, and each can produce several different profiles. Decreased diversity in gut gene expression was found to be associated with reduced resilience to several diseases. These expression patterns may correlate with altered networks at brain levels. Mayer further believes that microbiome shotgun sequencing might become a routine clinical test in the near future at a cost of as little as $500 per test.

When asked what the best biomarkers for anabolic and restorative processes might be, participants generally agreed that there was no magic bullet. Glycosylated hemoglobin, blood pressure, sleep, lipids, BDNF, OT, connectivity, and networks may all prove useful in carefully defined contexts. A “barcode of health” is, however, unlikely to be found. Rather, concepts such as assortivity may provide guidance on how to look at multiple systems at once and see which systems are most robust and which are likely to break down. Mayer noted a recent trend of the field to move toward system biology, which suggests that changes in individual hormones taken out of context have essentially no predictive power. Carter replied that there might, however, be important hierarchies where some components may be more critical than others.

Although none of the presentations focused specifically on endorphins, they certainly play a role in the pain suppression paradigm discussed by Eisenberger. Participants further noted that the role of sex hormones in PPF was not discussed during this meeting.

**BRAINSTORMING**

The workshop covered broad research areas, provided an informative tour of novel biological systems, and opened new windows for the understanding of how the human body functions. The diverse background has been very inspiring for further discussions. Nielsen encouraged participants to think about the different constructs and their utility, and to think about the most important questions that must be answered to move the field forward.

To illustrate the kinds of questions that may be relevant, Nielsen offered a number of examples that were developed by members of the organizing committee at the end of the first day:

1) **There is a significant need for rich and well-defined measures of positive psychological functioning and related biological processes.** Are there measures that can be obtained

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with relatively little effort? Which measures are necessary to address questions of causality?

2) **Investigators must consider the possible bidirectionality of associations.** For example, the weight of the current evidence suggests that exercise causes positive emotions, but could there be significant effects in the opposite direction?

3) **The field must get better clarity on the role of positive psychological states in health.** Individual research programs need to clarify the extent to which positive states are considered ends in themselves, i.e., as target outcomes for health promotion, or the extent to which they are important as means to other ends, for example as potential motivators of behavior change, or as aids in self-management of disease.

4) **Knowledge gained in this field has great implications for intervention design.** What are the best targets for interventions? When are systems malleable? Are there sensitive periods and windows of plasticity? Are there individual differences in responsiveness to interventions? If biological embedding is too strong for reversal of trajectories, then can compensatory systems provide improvements?

5) **The nature of the psychological phenomena under study must be better understood.** When talking about experience, motivation, dispositions, etc., are we looking to increase or decrease, or do we seek an optimal adaptive state?

Participants then discussed the most important ingredients and designs of future efforts. Results from these discussions are summarized in the “Critical Issues” section of the Executive Summary of this report.
## APPENDIX 1 – WORKSHOP AGENDA

### Tuesday, March 12

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>11:00 am</td>
<td>Registration</td>
<td>Symphony IV Foyer</td>
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<tr>
<td>12:30 pm</td>
<td>Lunch</td>
<td>Symphony III</td>
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<tr>
<td>1:00 pm</td>
<td>Welcome</td>
<td>Symphony IV</td>
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  Lis Nielsen, National Institute on Aging  
  Arthur Stone, Stony Brook University and Princeton University

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1: Psychological factors and health</th>
<th>Location</th>
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<tbody>
<tr>
<td>1:20 pm</td>
<td>Introduction to psychological factors and health: Julia Boehm</td>
<td>Symphony IV Foyer</td>
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<tr>
<td>1:30 pm</td>
<td>Positive psychological wellbeing: Laura Kubzansky</td>
<td>Symphony IV Foyer</td>
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<td>1:50 pm</td>
<td>Salubrious social connections: Tara Gruenewald</td>
<td>Symphony IV Foyer</td>
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<td>2:10 pm</td>
<td>Self-regulation: Suzanne Segerstrom</td>
<td>Symphony IV Foyer</td>
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<tr>
<td>2:30 pm</td>
<td>Question and discussion period</td>
<td>Symphony IV Foyer</td>
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<tr>
<td>2:45 pm</td>
<td>Coffee break</td>
<td>Symphony IV Foyer</td>
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3:00 pm  Session 2:  Symphony IV

**Known biological factors**

*This session will describe key biological processes that have been identified as being relevant to or indicative of positive physiological functioning. The first speaker will define the characteristics of restorative biological processes and indicate how they differ from deteriorative biological processes such as atherosclerosis. Subsequent speakers will present brief overviews of each known restorative biological process, indicate how or why the biological process can be considered restorative, and demonstrate links between the biological process and positive psychological functioning.*

*Primary questions for the speakers to address:*

- What characterizes a restorative process?
- What restorative characteristics do each of the known biological factors have?
- Are the biological processes associated with positive factors from which we could extrapolate (e.g., depression)?

3:00 pm  Restorative biological processes and health: A useful concept?: Ted Robles
3:20 pm  The healing power of love: An oxytocin hypothesis: Sue Carter
3:40 pm  Heart rate variability as an integrative index of resilience: Julian Thayer
4:00 pm  Immunity and positive psychobiology: Marian Kohut
4:20 pm  Exploring the neural correlates of receiving and giving social support: Naomi Eisenberger
4:40 pm  Question and discussion period
5:00 pm  Adjourn
Wednesday, March 13

8:00 am  Continental breakfast  Symphony III

8:30 am  Session 3:  Symphony IV

Research areas that may suggest novel biological factors
This session will explore research areas that may suggest novel biological processes with positive or restorative features, but that have not yet been formally investigated as such. Speakers will present brief overviews of each research area, describe known associations between psychosocial factors and relevant biological processes, and assess whether the biological process could be considered restorative or could be linked with positive psychological functioning.

Primary questions for the speakers to address:
- Why might this research area be a good candidate for identifying novel and restorative biological processes?
- What biological processes might indicate restoration or something other than deterioration?
- Have biological processes been linked with other psychosocial factors or even positive psychological functioning?

8:30 am  Setting the stage for novel biological factors: Suzanne Segerstrom

8:50 am  Sleep as a source of resilience and restoration: Orfeu Buxton

9:10 am  Physical activity: Implications for psychosocial function, cognition, and brain: Art Kramer

9:30 am  Dopamine, motivation, and decision to expend effort: David Zald

9:50 am  Coffee Break  Symphony IV Foyer

10:05 am  Session 3 (Continued)  Symphony IV

10:05 am  Role of brain-gut interactions in resilience: Emeran Mayer

10:25 am  Genomic approaches: Steve Cole

10:45 am  Question and discussion period

11:00 am  Coffee Break

11:15 am  Session 4: Brainstorming  Symphony 4

Introduction: Lis Nielsen

12:15 pm  Closing Remarks

12:30 pm  Adjourn
APPENDIX 2 – LIST OF PARTICIPANTS

Workshop Planning Committee:

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APPENDIX 3 - LIST OF SUGGESTED READINGS


