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A Contemporary Perspective on Multilevel Analyses and Social Neuroscience

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The nervous system is organized in a heterarchical fashion, with multiple but interactive levels of processing that may differentially manifest at divergent levels of analysis. Consequently, a comprehensive understanding of neurobiological mechanisms, and their health implications, will require interdisciplinary approaches that entail integrative multilevel analyses. This chapter overviews a collaborative interdisciplinary effort to elucidate the links and underlying mechanisms of psychophysiological relations and their implications for health.

A fundamental organizational feature of the nervous system lies in the basic hierarchical structure of multiple processing levels. This is not a strict hierarchy in the formal sense, but a more complex set of interacting levels, with parallel and serial processing elements, and with both direct and indirect interactions between proximate as well as remote levels—what has been referred to as a *heterarchy* (see Berntson, Boysen, and Cacioppo, 1993). Although distinguishable levels and components of this system can be identified, they are highly interactive. Consequently, an understanding of a given level of functional organization, as gleaned from a single level of analysis, may be accurate but is likely to be incomplete.

Our collaborative program has fostered integrative analyses across levels of organization that range from the social to the neural, and this emphasis on diversity has been critical to the progress we have made on brain-behavior relationships and health. Before we began this collaboration, each of us had established programs that entailed multiple levels of analysis. For one of us (Cacioppo) that extended from the social to the psychophysiological level; and for the other

(Berntson), from the psychophysiological to the psychobiological/neural level. Consequently, we had a common perspective and approach, and the overlap in psychophysiology afforded a grounding for a broader joint effort that would extend from the social to the neural levels of analysis. Important in this venture has been a deep mutual intellectual respect, mirrored in the quality of the collaboration, which has driven perspectives from different levels equally, without one level of analysis being subservient to another.

Multiple Levels of Organization and Processing

The nineteenth-century neurologist John Hughlings Jackson, in his essay "Evolution and Dissolution of the Nervous System," emphasized the hierarchical structure of the brain and the *re-representation* of functions at multiple levels within this neural hierarchy (Jackson, 1884). Implicit in his message was the fact that information is processed at multiple levels of organization within the nervous system. Primitive protective responses to aversive stimuli are organized at the level of the spinal cord, as is apparent in flexor (pain) withdrawal reflexes to noxious stimuli. These primitive protective reactions are expanded and embellished at higher levels of the nervous system (see Berntson et al., 1993). The evolutionary development of higher neural systems, such as the limbic system, endowed organisms with an expanded behavioral repertoire, including escape reactions, aggressive responses, and even the ability to anticipate and avoid aversive encounters. Evolution not only endowed us with primitive, lower-level adaptive reactions, but also it sculpted the awesome information-processing capacities of the highest levels of the brain. At progressively higher levels of organization, there is a general expansion in the range and relational complexity of contextual controls and in the breadth and flexibility of discriminative and adaptive responses (Berntson et al., 1993).

Adaptive flexibility of higher-level systems has costs, however, given the finite information-processing capacity of neural circuits. Greater flexibility implies a less rigid relationship between inputs and outputs, a greater range of information that must be integrated, and a slower serial-like mode of processing. Consequently, the evolutionary layering of higher processing levels onto lower substrates has adaptive advantage in that lower and more efficient processing levels may continue to be expressed. For example, pain withdrawal reflexes, mediated by inherent spinal circuits, can manifest in rapid protective responses to pain stimuli. At the same time, however, ascending pain pathways convey information to higher levels of the brain that mediate more complex affective, cognitive, and behavioral reactions such as fear, anxiety, avoidance, and aggression.

Although reflex responses provide a rather rigidly organized prepotent response, they are not immutable, as higher neurobehavioral processes can come to suppress or bypass pain withdrawal reflexes (e.g., self-injecting insulin or recovering a billfold from a fire). These multilevel organizational features are not limited to somatic systems but apply to the autonomic nervous system as well (Berntson, Sarter, and Cacioppo, 1998). Thus, brainstem baroreceptor reflexes represent fundamental mechanisms for the regulation of blood pressure, but they also can be inhibited, modulated, or bypassed by higher neurobehavioral substrates during stress (see Berntson et al., 1998). This has important implications for cardiovascular control and cardiovascular disorders, and a common theme of our collaborative work has been the links between behavioral processes and cardiovascular functions and health.

Affect, stress, and autonomic control

The multiplicity of processing levels does not reflect a simple redundancy. Because the capacity for stimulus processing differs across levels of the neuraxis, these mechanisms may be sensitive to distinct or only partially overlapping features of the behavioral context and may have differential access to response systems. Pain stimuli can evoke a spinally mediated withdrawal reflex and may also trigger higher-level reactions such as anger or aggression, or acquired anticipatory reactions that may permit avoidance or control of the aversive stimulus. Even associative processes, however, are represented at multiple levels of the neuraxis. Research by LeDoux (1995) and colleagues on conditioned fear reactions to acoustic stimuli, for example, indicates that projections from the auditory thalamus to the amygdala constitute a sufficient subcortical route for simple fear conditioning. In contrast, less-specific contextual conditioning, or pseudoconditioning, which is more akin to anxiety, appears to be critically dependent on the cortex (see Berntson et al., 1998; LeDoux, 1995).

Although the multiple levels of organization entail partially independent processing substrates, they are typically integrated, with systems at one level able to control, modulate, or bias processing at other levels of organization. An important thesis of our research program is that the heterarchical structure of the brain permits both top-down and bottom-up biases and, in some cases, the complete bypassing of other levels. This is a concept of consequence, because it implies that a comprehensive understanding of neurobehavioral processes and their relation to health will require multilevel analyses. This is illustrated by our studies on stress, anxiety, and autonomic control of the heart (see "Key Findings and Perspectives" below).

Historically, the sympathetic and parasympathetic controls of the heart have been viewed as reciprocally organized, with increases in activity of one branch associated with decreases in the other (Berntson, Cacioppo and Quigley, 1991). This concept arose largely through work on basic autonomic reflexes, however, and does not adequately reflect the greater range of autonomic control that can be exerted by rostral neural systems. Our collaborative work has documented that higher neurobehavioral systems are far more flexible in their pattern of autonomic control over the cardiovascular system and may be evidence of notable individual differences (Berntson et al., 1994). This is important because distinct

patterns of autonomic control may have important health implications (Berntson et al., 1998; Bigger and Schwartz, 1994; Cacioppo, 1994). As we and others (e.g., see chapters 3 and 4 in this volume) have shown, sympathetic activation in response to psychological stressors may be associated with the development of disease, and we have found relatively stable individual differences in modes of autonomic cardiac control that vary with the type of stressor (e.g., active vs. passive coping tasks or orthostatic stressors; e.g., Berntson et al., 1994; Berntson, Cacioppo, and Fieldstone, 1996). In this regard, sympathetically driven increases in heart rate, but not similar cardiac responses associated with vagal withdrawal, were found to predict reduced immune responses to influenza vaccine (Cacioppo, 1994).

Of relevance to these psychophysiological relationships is our emerging neurobiological model of the brain systems that underlie fear and anxiety, which emphasizes potential ascending routes by which sympathetic outflow and associated visceral feedback may bias or color processing by rostral systems, including cortical systems that mediate the higher-level cognitive functions. The further elucidation of these systems is important because they represent fundamental links between behavioral processes, autonomic control, and health outcomes. For example, further understanding of these systems and their ascending influences may clarify the physiological and cognitive/attentional bases for the vicious cycle between sympathetic outflow and anxiety in panic attacks and may suggest meaningful treatment strategies.

Personal ties and well-being

Our research program takes an interdisciplinary, multilevel approach to elucidating psychophysiological processes and their relations to health. This ranges from psychophysiological studies in humans to neural and physiological investigations in animals. As outlined in this chapter, some of this work focuses on lower-level neural, physiological, and immune processes. These efforts, however, are seen in the service of explicating more complex psychobiological relations. Work on basic patterns of autonomic control has helped clarify psychophysiological relationships, their links to multiple levels of functional organization, and their implications for health. Additional studies of brain mechanisms have revealed important neural systems and processes that likely underlie cognitive contributions to anxiety and autonomic control. But our collaborative efforts do not stop there, as understanding the mediating and moderating effects of social processes and personal ties on mental and physical functioning is equally important if we are to elucidate fully the mechanisms that underlie health and disease.

The social world has tended to be ignored in the neurosciences because it is complex, falls outside the physical bounds of the body, and operates on biological processes through multifarious and to date poorly specified mechanisms. Personal ties, however, are a ubiquitous part of life, serving important social, psychological, and behavioral functions across the lifespan (e.g., Gardner, Gabriel, and Dickman, 2000). People form personal ties with others from the moment they are born, as the very survival of newborns depends on their attachment to and nurturance by others over an extended period of time (cf. Baumeister and Leary, 1995). Indeed, evolution has heavily sculpted the human genome to be sensitive to and succoring of contact and relationships with others (Cacioppo, Berntson, Sheridan, and McClinock, 2000). The need to belong does not stop at infancy; rather; affiliation and nurturant social relationships are essential for physical and for psychological well-being across the lifespan (see Gardner et al., 2000). People who report having contact with five or more intimate friends in the prior six months are 60% more likely to report that their lives are "very happy," as compared to those who do not report such contact (Burt, 1986). Disruptions of personal ties—whether through ridicule, discrimination, separation, divorce, or bereavement—are among the most stressful events people must endure (Gardner et al., 2000). The restriction of social contact during infancy and childhood has dramatic effects on psychopathology across the lifespan. For instance, blood pressure tends to increase with age in America; this trend is evident in individuals with low levels of social support but is weakened or absent in individuals with high levels of social support (Uchino, Cacioppo, Malarkey, Glaser, and Kiecolt-Glaser, 1995; Uchino, Kiecolt-Glaser, and Cacioppo, 1992).

Epidemiological research has further found that social isolation is a major risk factor for morbidity and mortality from widely varying causes, including cardiovascular diseases. This relationship is evident even after statistically controlling for known biological risk factors, social status, and baseline measures of health. The negative health consequences of social isolation are particularly strong among some of the fastest growing segments of the population: the elderly, the poor, and minorities. Astonishingly, the strength of social isolation as a risk factor is comparable to high blood pressure, obesity, sedentary lifestyles, and possibly even smoking (for review, see House, Landis, and Umberson, 1988).

Our collaborative program is actively exploring the effect of social factors on autonomic, cardiovascular, and immune functions. The autonomic and immune systems have traditionally been viewed as distinct functional domains, with only remote or tangential links and associations. This view is rapidly changing. It is now apparent that substantial two-way communications exist between the brain and immune tissues, and that this reciprocal interaction impacts substantially on behavior and autonomic control (see Maier and Watkins, 1998). Consequently, a comprehensive understanding of cardiovascular health and disease will require an understanding of the heterarchical structure of the brain (Berntson and Cacioppo, 2000), including the integral and reciprocal contributions of the immune system. The effect of social factors on cardiovascular and immune functions, along with the potential links and mediators of these relations, represents an important component of our current research focus (see the following section, "Key Findings and Perspectives").

Interim summary

The overarching perspective of our collaborative program is that the links between psychological and biological processes, and their implications for health, cannot be comprehended fully by a single level of analysis or by investigations at a single level of organization. An integrative, interdisciplinary approach across levels of organization and analysis can add unique perspectives because different levels of analysis can reveal distinct patterns of order in data, and because different levels of organization are known to interact. There remains a need for research with a more restricted focus, and it is not necessary that all researchers pursue multilevel analyses. It is important, however, to include a multilevel perspective if we are to understand the various mechanisms by which the social world gets under the skin.

Key Findings and Perspectives

Multiple levels of processing and bottom-up influences

Multiple levels of processing in neurobehavioral systems are inherent in the heterarchical structure of the brain and help clarify aspects of cognition and behavior. The cerebral cortex is a crucial neural substrate for higher-level social and cognitive processes, and it is tempting to consider lower levels of the neuraxis as fundamentally subservient to higher-level influences. It is clear that higher-level systems can powerfully modulate lower-level regulation of autonomic, neuroendocrine, and immune functions. An important feature of the heterarchical pattern of neural organization, however, is that there are ample routes by which lower systems may modulate or bias processing of the highest levels of the nervous system. It is increasingly recognized that central and peripheral processes constitute reciprocally linked dimensions of neurobehavioral function. One aspect of our research program examines the role of ascending neural systems in anxiety and autonomic control. Anxiogenic or fear-eliciting contexts are often associated with robust autonomic responses, and abnormal autonomic control and visceral reactivity is a common feature of anxiety disorders. These are important issues because anxiety represents a clear risk factor for cardiovascular disease and sudden cardiac death (Hayward, 1995; Kawachi et al., 1994) and because they bear on the fundamental nature of anxiety and the underlying neural mechanisms that link behavioral processes and autonomic function.

As mentioned earlier in this chapter, research by LeDoux (1975) and colleagues on conditioned fear reactions reveals at least two circuits through which affective learning can occur. Simple fear conditioning to an acoustic stimulus can be mediated by a subcortical circuit that is composed of a direct projection from the auditory thalamus to the amygdala, which, in turn, projects to lower mechanisms for behavioral, autonomic, and neuroendocrine expression. Although an adequate subcortical mechanism exists for simple fear conditioning, more complex contextual conditioning and pseudoconditioning appear to depend on a cortical link (Berntson et al., 1998; LeDoux, 1995). In this regard, cortical and cognitive processes are increasingly recognized to contribute to anxiety states in humans. Figure 2.1 illustrates some interconnected components of the descending systems that have been implicated in fear and anxiety (see Berntson et al., 1998). One likely contribution of cortical systems is in the attentional and evaluative processing of anxiety-related stimuli and associations.

Cortical processing is modulated by ascending neural circuits. Among these is cholinergic projection from the basal forebrain to the cerebral cortex, which appears to generally enhance cortical processing (Figure 2.1; Berntson et al., 1998). Consequently, the degree and efficiency of cortical processing of anxiety-related stimuli and associations would be expected to be a function of activity of this basal forebrain cholinergic system (Sarter and Bruno, 1997). Consistent with this view are the cognitive deficits and dementia associated with the degeneration of this system in Alzheimer's disease. Findings from our collaborative research program (with Martin Sarter) suggest that the basal forebrain cholinergic system also is an important site of action for the antianxiety actions of benzodiazepine receptor (BZR) agonists, such as chlordiazepoxide (Librium) and diazepam (Valium). By enhancing inhibitory actions on basal forebrain cholinergic neurons, BZR agonists can reduce cortical acetylcholine release. The resulting attenuation of cortical processing likely underlies in part the known cognitive-impairing effects of these agents and, we have hypothesized, also mediates the antianxiety actions of these compounds (see Berntson et al., 1998). That is, it appears that the antianxiety actions of compounds like Librium and Valium are due at least in part to the reduction in the attentional focus on, and cognitive processing of, anxiety-related stimuli.

An important feature of the ascending pathways of Figure 2.1 is that they provide relatively direct routes through which sympathetic activation and the associated visceral afferent activity can drive the basal forebrain cholinergic system and thereby potentiate cortical processing. A major excitatory input to the basal forebrain cholinergic system is the noradrenergic projection from the locus coeruleus, which is highly sensitive to emotional states and sympathetic activation (Aston-Jones, Rajkowski, Kubiak, Valentino, and Shipley, 1996; Berntson et al., 1998). A major input to the locus coeruleus originates from a region in the medullary reticular formation (the nucleus paragigantocellularis, or PGi), a region that directly innervates sympathetic motor neurons and receives input from a variety of sources, including visceral afferent activity. Collectively, these considerations suggest that PGi projections to the locus coeruleus transmit information that reflects the state of sympathetic control and associated visceral afference (see Aston-Jones et al., 1996; Berntson et al., 1998). Because PGi neurons activate both the locus coeruleus and sympathetic motor neurons, they appear to modulate both the autonomic and cognitive aspects of emotional activation.

Although the precise role of these ascending pathways in anxiety and car-

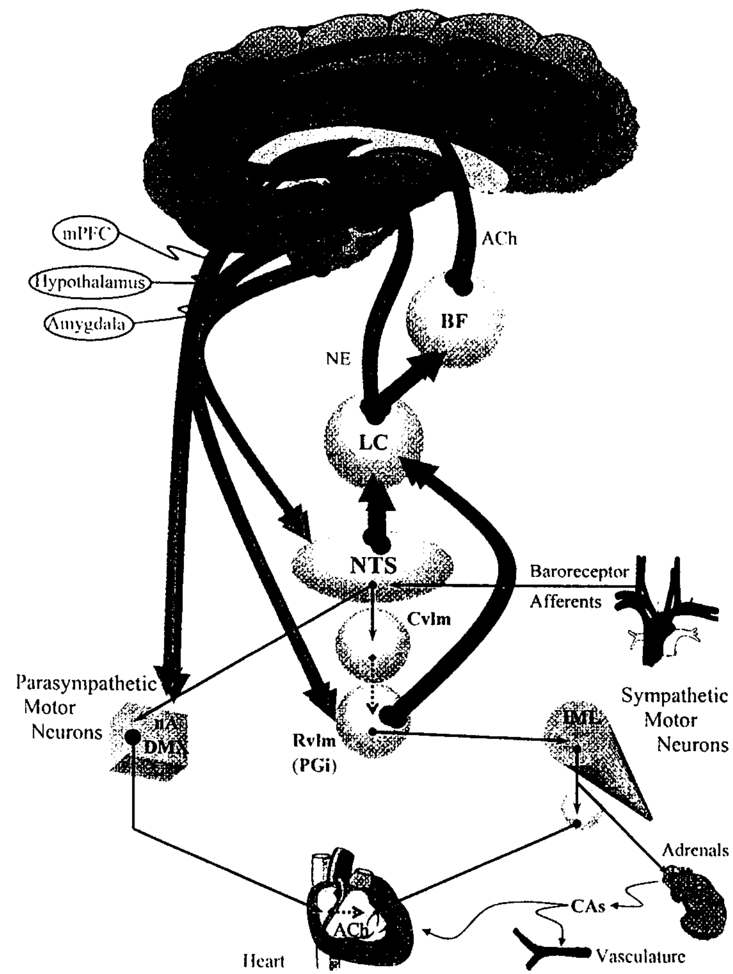

Figure 2.1. Ascending and descending branches of the anatomical model of neuronal substrates by which cortical and cognitive processes may contribute to the development and expression of anxiety and its autonomic features. The model is not intended to present an anatomically complete description of relevant circuits and transmitters; rather, it is conceptually driven and focuses on hypotheses derived in part from experimental evidence (see Berntson et al., 1998). Abbreviations: ACh, acetylcholine; BF, basal forebrain cortical cholinergic system; CAs, catecholamines; Cvlm, caudal ventrolateral medulla; DMX, dorsal motor nucleus of the vagus; IML, sympathetic preganglionic neurons of the intermediolateral cell column; LC, locus coeruleus; mPFC, medial prefrontal cortex; nA, nucleus ambiguous; NE, norepinephrine; NTS, nucleus tractus solitarius; PGi, nucleus paragigantocellularis; Rvlm, rostral ventrolateral medullary "pressor" area. Adapted from Berntson and Cacioppo (2000), with permission of Cambridge University Press.

diovascular control remains to be clarified, they generally appear to enhance or prime cortical processing of anxiogenic stimuli. Consistent with this suggestion is the finding that visceral afference can enhance emotional memories in both humans and animals (see Clark, Naritoku, Smith, Browning, and Jensen, 1999). The latter finding may underlie the vivid and seemingly indelible traumatic memories of posttraumatic stress disorder, as well as the exaggerated autonomic reactivity and feedback that prime and underlie the "vicious cycle" of visceral and emotional responses in panic disorder. In any event, the available findings suggest an important modulatory role for visceral afferent information on central information processing. There is an emerging recognition of a symmetry in the reciprocal interplay among levels of organization, entailing both direct and indirect mutual interactions (top-down and bottom-up) that impact both biological and psychological processes. This interplay could not be appreciated from approaches that focus on a single level of organization or a single level of analysis.

Top-down influences on autonomic, neuroendocrine, and immune functions

Important in the further integration of the biological and the social psychological perspectives in the study of cardiovascular disease is the ability to relate constructs at one level of analysis to those of another. This is not a one-way process, as the scientific value of multilevel efforts accrues to both higher and lower levels of analysis. Illustrative of this issue is the traditional view of the sympathetic and parasympathetic branches of the autonomic nervous system as being subject to reciprocal central control, with activation of one branch associated with inhibition of the other. This is a conception that arose from the early physiological literature and continues to the present, although qualifications are increasingly recognized (see Berntson et al., 1991). Although lower autonomic reflexes, such as the baroreceptor-heart rate reflex, display this reciprocal pattern of organization, our collaborative work has documented that autonomic control arising from higher neurobehavioral systems is not so tightly obligated (Berntson et al., 1991, 1994). In behavioral contexts, activities of the two autonomic branches may show reciprocal, concordant (coactive), or independent changes. These findings, arising from the psychophysiological literature, mandate an expansion and calibration of biological conceptions of autonomic control. This is important because it illustrates how organizational principles derived from lower levels of analysis may not be applicable to higher-level behavioral systems and, in fact, may obscure psychophysiological relations that are crucial in understanding cardiovascular control in health and disease.

An illustration comes from our study of the autonomic responses of human subjects to orthostatic stress (assumption of an upright posture) and to social and cognitive stressors (Berntson et al., 1994; Cacioppo et al., 1994). Quantitative estimates of the sympathetic and parasympathetic contributions to cardiac responses were derived from single and dual autonomic blockade studies. At the

group level, the orthostatic and psychological stressors yielded an essentially equivalent pattern of heart rate increase, associated with sympathetic activation and parasympathetic withdrawal. For the orthostatic stressor, the cardiac response reflected a relatively tight reciprocal central control of autonomic outflows, as evidenced by the significant negative correlation between the responses of the autonomic branches across subjects. Although the overall group response to psychological stressors was similar, there were considerable individual differences in the pattern of autonomic reaction, and there was no significant correlation between responses of the two branches across subjects. Although the individual modes of response were highly reliable over different psychological stressors, subjects differed considerably in their pattern of response (Figure 2.2). Some subjects showed primarily sympathetic activation, some showed reciprocal sympathetic activation together with parasympathetic withdrawal, and still others displayed primarily parasympathetic withdrawal. These are significant findings because individual patterns of response are likely to reflect distinct psychological states and have differential implications for health.

These studies point to the need for more sophisticated conceptualizations of stress. Mason (1972) and Selye (1973) and made seminal contributions to the scientific study of stress by demonstrating that physical and psychological stressors serve similarly to activate the sympathetic adrenomedullary (SAM) and hypothalamic pituitary adrenocortical (HPA) axis. In our own research, nomethetic (group) analyses have indeed revealed very similar levels of SAM and HPA activation as a function of physical (e.g., orthostatic) and psychological (e.g., mental arithmetic) stressors. Idiographic (individual) analyses, however, have revealed very different organizations in these data. Importantly, individual differences in the pattern of autonomic response to psychological stress were distinct from responses to physical stressors, and it was the former (but not the latter) that were predictive of immunological status (Berntson et al., 1994; Cacioppo et al., 1998). Similarly, the clinical outcome after myocardial infarction appears to be a function in part of the specific pattern of autonomic cardiac autonomic control (Bigger and Schwartz, 1994). Stress has often been recognized as a contributor to disease. Current findings, however, suggest that identification of the underlying mechanisms of stress effects, their clinical implications, and the development of meaningful treatment strategies may all benefit from a differentiation of subtypes of stress and somatovisceral response.

In sum, researchers often seek general laws, universal patterns, and common mechanisms, with individual differences treated as error variance. The health implications of individual differences may be important to consider as well, however. Accordingly, reliable individual differences should be treated more as a crucible for refining conceptual models, and for theory construction and testing, than as error variance per se. Toward this end, multilevel research on stress that considers both the heterarchical organization of the brain and individual differences in the construal of the social world is clearly needed (Berntson et al., 1998).

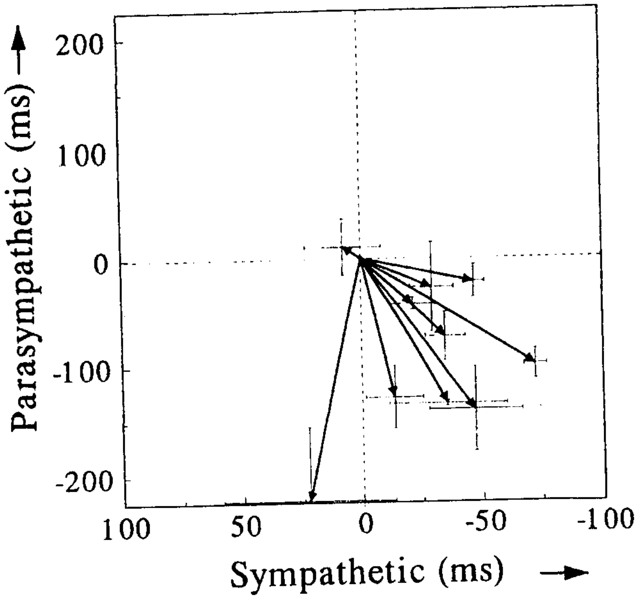

Figure 2.2. Cardiac responses of individual subjects to social or psychological stressors, depicted as changes in sympathetic and parasympathetic control derived from autonomic blockades. The arrows represent individual autonomic responses (from baseline) along the sympathetic and parasympathetic axes, expressed in ms of heart period. Each arrow vector represents the mean response of a given subject, across three separate tasks. The horizontal and vertical error bars at each arrowhead depict the standard errors of the sympathetic and parasympathetic responses, respectively, across the three tasks for that subject. As is apparent, there were large and stable individual differences in the amplitude and direction of the response vectors. Adapted from Berntson et al. (1994), with permission of Cambridge University Press.

Social factors in health

Our interdisciplinary research (which has involved psychologists, immunologists, endocrinologists, and molecular biologists) indicates that social factors mediated by higher neurobehavioral systems can exert especially potent modulatory effects on cardiovascular, neuroendocrine, and immune functions. A meta-analytic review of the extant human literature revealed that perceived social isolation is associated with a variety of altered physiological functions, such as blood pressure regulation, catecholamine levels, and immune reactions (Uchino, Cacioppo, and Kiecolt-Glaser, 1996). A causal link in these relations is suggested by findings of

improved physiological functioning after interventions that served to reduce social isolation (Uchino et al., 1996). The role of psychological variables in these relations is indicated by the fact that subjective indices of social isolation are often better predictors of stress and health than are objective indices (Seeman, 1996; Uchino et al., 1996). These findings in humans are supported by studies on animals, which document the important of social factors in cardiovascular and immune function (see Cacioppo et al., 2002).

Kaplan and Manuck (this volume) review evidence that social reorganization contributes to cardiovascular disease in primates, and Padgett et al. (1998) found that social reorganization can reactivate herpes-simplex virus in mice. Importantly, social reorganization has effects above and beyond what might be expected from traditional models of stress and disease. For example, Padgett et al. (1998) demonstrated that physical stressors yielded comparable elevations in glucocorticoid levels but had much less potent effects on disease; thus, psychosocial stress was selectively transduced into physiological signals that modulated the expression and effect of virally transmitted host/pathogen genes. Importantly, the immunological consequences of social stress also appear to be modulated by individual differences in social relations, as dominant mice were more likely to show reactivation than submissive mice—a finding that again is mirrored in research on social reorganization and cardiovascular disease in primates (Kaplan and Manuck, this volume).

The influence of social factors on cardiovascular and immune functions is not limited to animals. Parallel findings of stress effects on cardiovascular function (e.g., Uchino et al., 1996) and susceptibility to viral infections and other markers of immune function have also been reported for humans, with social stressors being particularly potent (Cohen, Frank, Doyle, Skoner, Rabin, and Gwaltney, 1998; Kiecolt-Glaser, Malarkey, Cacioppo, and Glaser, 1994). These examples demonstrate the potent influence of social relations on autonomic and immunological function, and they illustrate how the order in physiological, pharmacological, or immunological data may not be fully understandable from the vantage of a single level of analysis. Rather, comprehensive accounts of psychophysiological relations will likely require multiple analyses across distinct levels of functional organization. As described in this chapter, we have found that autonomic response patterns can predict immune reactions. An obvious question arises as to the mechanism of this association. Some insights into these mechanisms are beginning to emerge from the literature, but their ultimate elucidation will require even more integrative, interdisciplinary research.

As discussed here, a particularly significant insight has recently emerged concerning the bidirectional interactions between the brain and the immune system, and the associated links between immune, autonomic, neuroendocrine, and behavioral mechanisms (Maier and Watkins, 1998). It is now clear that cardiovascular regulation is not isolated from immune function. Indeed, an infection (or an injection of lipopolysaccaride—a component of bacterial membranes) triggers a centrally orchestrated sickness response, mediated in part by vagal afferents, and entailing behavioral (e.g., inactivity and a decrease in appetite and food intake), as well as autonomic and neuroendocrine, components (Maier and Watkins, 1998). The immune system cannot be viewed as a functional domain independent of the brain or autonomic nervous system. Indeed, it would be most surprising if the immune system was functionally isolated from behavioral and autonomic mechanisms, given the early evolutionary emergence of immunological functions and the adaptive significance of these processes. Clearly, a comprehensive understanding of cardiovascular health and disease will require an understanding of the heterarchical structure of the brain, as well as the contributions of the immune system to this heterarchical regulation. An important aspect of our collaborative research is directed toward the identification of the critical signaling mechanisms and molecules that mediate the interactions between the immune systems and autonomic control. This research represents a particularly important emerging focus that will likely contribute to the understanding of relations between behavioral, autonomic, neuroendocrine, and immune processes.

As noted, social isolation and loneliness have been shown to be major risk factors for morbidity and mortality from widely varying causes and are comparable to smoking, hypertension, and obesity (House et al., 1988). Differences in health behaviors represent a partial but incomplete explanation of these relations. Our recent work in humans, therefore, sought to identify pathways and signals that link higher neurobehavioral processes to immune functions and health. In a recent laboratory and ambulatory study, chronically lonely college students (matched on other factors) were found to have altered sympathoadrenal and hypothalamic-pituitary-adrenal (HPA) functions. The enhanced HPA activity and elevated adrenal corticosteroid levels of lonely subjects may represent one mechanism by which social factors, including the stress of social isolation, can affect immune functions. A potentially related pathway may be via lymphocyte growth hormone (L-GH), which is secreted by peripheral blood lymphocytes. The social isolation of caregiving spouses of Alzheimer's patients was associated with markedly suppressed L-GH levels, which were negatively correlated with ACTH and norepinephrine (Wu et al., 1999). Moreover, lymphocytes from caregivers displayed a blunted L-GH response to an influenza vaccine, and this attenuated response may contribute to a reduced lymphocyte proliferation and cytokine production (Wu et al, 1999). Thus, it appears that L-GH may enhance immune reactions to a foreign antigen and that the L-GH response may be diminished by social stress.

Finally, lonely and nonlonely college students were found to engage in generally comparable health behaviors, but the salubrity of restorative behaviors such as sleep was found to be less in lonely individuals. Although these studies are still in early stages, they offer promise for the ultimate elucidation of the routes by which higher neurobehavioral processes can affect the autonomic, neuroendocrine, and immune systems, and they may suggest important approaches to intervention.

Life History of the Program

Our interdisciplinary research effort was enabled by the availability and efforts of a large number of highly competent researchers with broad vision and profound dedication. The rapidly advancing state of knowledge within specialized disciplines, and their distinct levels and methods of analysis, impose limits on the ability of a single investigator to pursue multilevel research, except across relatively proximate levels of analysis. A broad, integrative, multilevel approach increasingly requires an interdisciplinary team of researchers with specialized knowledge of the methods, data, and concepts of their respective fields. The composition of our research group has often been dynamic, being reshaped based on the issues at hand. In fact, it is not composed of a single coherent group but of various consortia. The crucial feature of our collaborative venture lies not in the particular set of individuals who make up the research group but in key principals who share a common recognition of the need for multilevel analyses.

The important feature of our interdisciplinary research has been the continued involvement of two individuals, the authors of this chapter, Bernston and Cacioppo, who constitute the "glue" for the effort, who maintain the overall focus, and who organize the disparate and often changing constituents of the program. Our collaborative effort began in 1989, when Cacioppo joined the faculty at Ohio State. There was an immediate compatibility between us, both personally and professionally. Both of us had a long history of efforts to bridge at least proximate levels of analysis. Cacioppo was formally trained as a social psychologist but had also emerged as a leading contributor to the field of psychophysiology. Berntson was trained in psychobiology and behavioral neuroscience, with an abiding interest in basic neurobiological mechanisms and their implications for psychophysiological processes. The fit was natural, as each of us bridged distinct levels, and the confluence afforded the opportunity for a broader bridge—that between social psychology and neurobiological mechanisms.

The resulting collaboration, although initially limited primarily to the two of us, proved to be a highly synergistic and productive intersection. In part, the success of our effort lies in the dissatisfaction and frustration each of us had felt (independently) over the limitations of single levels of analysis. An additional cohering force was the mutual respect that we shared over each other's prior multilevel research efforts. This led to a natural intellectual synergy, rather than an instrumentality, in the collaboration. That is, neither of the principals was overly concerned about personal benefits from a joint venture, and both saw the opportunity to continue individual efforts with the added intellectual and scientific benefits accrued from the collaborative component. Indeed, in addition to the ongoing collaborative effort, each of us continued to pursue independent links to higher and lower levels of analysis, and these partially independent efforts ultimately led to the broader interdisciplinary program of research. But that broader effort would take additional time to fully develop.

Further development involved a gradual coalescence of our mutual program with our other, relatively independent collaborative ventures. Those included the work of Cacioppo with the psychoneuroimmunology group at Ohio State, and the collaborative work of Berntson with neuroscientists in examining neural and neurochemical systems involved in anxiety and autonomic control. Initially, that coalescence was at the conceptual level, which ultimately developed into an integrated research program. There were impediments to this effort, including a degree of disciplinary isolationism that existed even within the subdisciplines of psychology.

Historical impediments

Social psychology and psychobiology have shared a richly intertwined history. The Darwinian revolution had immense impact on psychology, as it focused attention on the biological origins of behavior and emphasized the continuity between the human and the animal mind. This perspective fostered a view of psychology as a biological science, despite its historical roots in philosophy, and promoted a conceptual evolution toward biological models of psychological processes. Among the benefactors of the Darwinian movement were instinct theorists, who consequently had a mechanism for their views on the nature and origins of "purposive" behavior. Instinct models struck an intellectual chord with both social psychologists and psychobiologists and held out the promise of an integrated psychology. Instinct theories collapsed, however: in part, because of their teleological focus, but also because of their devolution into massive instinct "lists" and their failure to mature into predictive, explanatory, and hypothesis-generating theoretical systems.

The instinct adventure was a failure for both social psychology and for psychobiology, and both disciplines sought alternative paradigms, models, and theories. Behaviorism, with its emphasis on learning, offered some hope for a conceptual link between the subdisciplines, and learning models continue as salient features of both areas. But there developed a growing chasm between the areas. Both psychobiology and social psychology were hampered by the straitjacket of behaviorism. Especially pernicious was the radical behaviorism of Skinner, which eschewed scientific explanations of behavior that appeal to "something going on in another universe, such as the mind or the nervous system" (Skinner, 1968, p. 88). This perspective effectively excluded meaningful accounts of behavior in terms of biology, and it failed to admit emerging concepts from social and cognitive psychology. Psychobiology and social psychology pursued separate paths. Social psychology increasingly focused on the cognitive bases of behavior, whereas

psychobiology increasingly embraced the emerging neuroscience perspective. For many, these were seen as incompatible, or at best inharmonious, directions (Scott, 1991).

Contemporary impediments

There remain impediments to the initiation of interdisciplinary research. There are residual disciplinary boundaries between departments and programs, often including those of physical location, administrative structure, and differences in language and perspectives. Biopsychology often focuses on neural substrates and production mechanisms for behavior, whereas social psychology generally emphasizes multivariate systems and situational influences in studies of the effect of human association on mind and behavior. Human biology is anchored in concrete anatomy and genetics, providing fundamental elements from which to draw interconnections and with which to construct theory. In contrast, the social world is a complex set of abstractions, representing the actions and influences of the relationships among individuals, groups, societies, and cultures. The differences in levels of analysis have resulted in distinct histories, research traditions, and technical demands, which constitute an impediment to truly integrative research across social and biological levels of analysis. An additional impediment arises in grant review. Even when programs are interested in supporting interdisciplinary research, the gateway to these programs is the initial review process, which may involve review panels that "represent" more traditional disciplines and perspectives. Consequently, the initial stages of the collaborative effort were maintained by grant support to each of the principles for more limited and focused research. Ultimately, broader support for aspects of the interdisciplinary program were obtained in the form of program project grants, center grants, and funding from private foundations.

Positive developments

Current developments in both social psychology and neuroscience, however, are shifting the paths of these disciplines toward an intersection that is based on a more solid scientific foundation in both disciplines. That intersection, which has been termed *social neuroscience*, is based on integrative multilevel analyses that seek to integrate information derived from levels of analysis ranging from social psychology to molecular biology. This perspective is now increasingly embraced by the rapidly developing fields of behavioral neuroscience, cognitive neuroscience, behavioral neurology, behavioral medicine, behavior genetics, and psychoneuroimmunology. The explosive developments in these fields are attributable to the recognition of the value of multilevel analyses and the inclusion of both social and biological perspectives.

Conclusions and Implications

Changes in medical science, worldwide health problems (e.g., AIDS, chronic disease), and U.S. demographics have helped fuel basic social and biological research on societal problems. Many of the most pressing contemporary health problems—cardiovascular disease, drug or alcohol abuse, HIV/AIDS, chronic obstructive pulmonary disease, cancer, diabetes, sleep disorders, and affective disorders—are social as well as biological phenomena. The etiology and course of these chronic health conditions have biological substrates, but these biological substrates and the efficacy of treatments are influenced profoundly by the social world. The complementarity of biological and social approaches to human behavior were not readily apparent when research methods were limited primarily to descriptions of the behavior of animals, to observations of patients with localized disorders of the brain, and to postmortem examinations. As a consequence, biological approaches tended to be viewed by social psychologists as uselessly reductionistic, while social approaches tended to be viewed by biopsychologists as more literary than scientific.

The complementarity of biological and social approaches also was not readily apparent from either traditional or contemporary training programs. The collaboration between the coauthors, for instance, began by accident rather than by design and was accompanied by skepticism and a certain amount of suspicion by colleagues in our respective programs. Multiple factors led the collaboration to flourish, however: foremost among them were personal factors, such as a deep respect for and trust in one another; institutional factors, such as the freedom to explore new ground without preconceptions about what the collaboration had to yield or become; and intellectual factors, such as the order in the data that emerged when working collaboratively on theoretical analyses, experimental designs, and empirical data. These factors promoted interdisciplinary research representing the union rather than the intersection of our respective fields.

Although serendipity and personal dispositions will likely play a large role in the establishment of successful interdisciplinary collaborations, their establishment need not be left completely to chance. Our own experiences suggest that support for the following would promote interdisciplinary work on health:

1. Most laboratories and funding opportunities support single or limited levels of analysis. Investigations of individual mechanisms (e.g., social, neural) in isolation, however, can hinder discovery of associations and interactions among these mechanisms. Because health outcomes across the lifespan tend to be multiply determined, research would ideally be multivariate and multilevel (cutting across multiple levels of organization). Initiatives that foster integrative interdisciplinary analyses (e.g., centers, PO_1s) are therefore important if the diverse expertise required in research that cuts across multiple levels of organization is to coalesce.

2. To the extent that accrued stress and the associated allostatic load contribute to the development of disease, cross-sectional and complementary longitudinal studies should be promoted. Longitudinal research that cuts across multiple levels of analysis is especially needed.
3. The effect of social relationships on physiological responses has typically been studied either in animal models or in the laboratory. The extent to which these snapshots generalize to what people do or how they actually respond in their daily lives is an open question. Advances in ambulatory recording procedures and experience in sampling methods now make it possible to address this question. Given the complementing strengths of laboratory and ambulatory research (and the feasibility of now performing ambulatory behavioral along with physiological and endocrinological assessments), it is now possible and fruitful to extend traditional laboratory studies by using the experience in sampling methodologies and the corresponding ambulatory physiological assessments.
4. Identifying associations between concepts in the social sciences and neurosciences is important but does little to illuminate any underlying mechanisms or to advance effective interventions. Unfortunately, much of the prior research has been correlational, leaving open the question of causal factors. Animal studies offer a valuable complement, although significant limits exist here, too, as, for instance, when studying the effects of norms and cultures. One of the greatest challenges is to go beyond correlational data to reveal the psychological and physiological mechanisms and causal (including reciprocal) structures involved.
5. As noted here, nomethetic and idiographic analyses reveal different organizations in the data. The latter is often treated as error variance but more often should be treated as a crucible for theory construction and testing.
6. Finally, scientific inquiries require that individual investigators specialize and focus. Interdisciplinary research teams provide a means of overcoming this limitation, but disciplinary training, departmental reward contingencies, and institutional policies tend to foster parochialism and work against the establishment of such teams. Parochialism, however, ignores the distinction between levels of explanation, the organization in the data that may become evident from research across levels of organization, the theoretical insights about the nature and timing of the relationships among variables that can be derived from descriptions of phenomena from multiple

scales or perspectives, and the economy of thought that can be gained by using the form of representation most appropriate for the task. Parochialism also alienates scientists who are working at a different level of organization and who might otherwise contribute relevant theory and data, and it renders it acceptable to ignore relevant research simply because it was not born from one's own level of analysis. Because there are phenomena that derive from events at one level of analysis that are only or distinctly observable at other or broader levels of analysis, multilevel integrative analyses may contribute to the empirical data and theoretical insight needed for a comprehensive understanding of human behavior.

Recent research has provided growing evidence that multilevel analyses spanning neural and social perspectives can foster more comprehensive accounts of cognition, emotion, behavior, and health. Social and biological approaches are complementary rather than antagonistic. Together, these perspectives are helping to illuminate questions about cardiovascular function and disease by examining how organismic processes are shaped, modulated, and modified by social factors, and vice versa. Rather than viewing social sciences and the neurosciences as alternative approaches to understanding health and disease, we see the potential for more comprehension of these problems and their underlying mechanisms through research that cuts across these distinct but equally important levels of organization.

To summarize, it is increasingly apparent that problems and issues in both the neurosciences and the social sciences will not be fully understood by studies restricted to a single level of analysis, regardless of the specific level selected (Anderson, 1998; Cacioppo and Berntson, 1992). A process or event at one level of organization may have antecedents and determinants both within and across organizational levels, as encapsulated in what has been termed the *principle of multiple determinism* (Cacioppo and Berntson, 1992). Neither social scientists nor neuroscientists can, or should, directly concern themselves with all possible levels of analysis. A corollary to the principle of multiple determinism is that mapping relationships across levels of organization becomes more complex as the number of intervening levels increases. Although it is certainly worthwhile to adopt a broad scientific perspective, specific research programs would probably achieve maximal benefit by attention to more proximate levels of analysis (both higher and lower). If this perspective was embraced generally by those pursing distinct levels of analysis, it may be sufficient to ensure the ultimate integration among disciplines.

An important trend in neuroscience is toward more molecular levels of analysis. There remains a need for higher-level analyses as well, because the properties of more basic elements at lower levels of organization may only become apparent when these elements interact with others, at a higher level of organization. Although the whole may not be greater than the sum of its parts, the properties of its parts may only, or more readily, be knowable by the properties of the whole. This has been articulated as the *principle of nonadditive determinism* (Cacioppo and Berntson, 1992). There are efficiencies in higher-level organizations of information. For example, the essential features of Beethoven's Ninth Symphony may be fully captured by the digital data on a CD, and analysis of that data set may be sufficient to identify the piece; alternatively, it may be easier and more enjoyable to simply play it out acoustically. The esthetic organization of the data is more efficiently processed by auditory perceptual mechanisms, and identification of the relevant digital patterns that correspond to specific perceptual qualities could not be derived readily from the digital data stream alone.

A final principle that characterizes the relations among heterarchical levels of organization is the *principle of reciprocal determinism*, which asserts that there can be mutual influences among higher and lower levels of organization in the determination of behavior. To the extent to which both top-down and bottom-up processes contribute to anxiety and autonomic regulation, for example, an account of these processes based on a single level of analysis is necessarily incomplete.

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3

Risk of Hypertensive Heart Disease

The Joint Influence of Genetic and Behavioral Factors

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Behavioral Contributions to Hypertension Development: Key Hypotheses

The belief that behavioral factors may contribute to the pathogenesis of hypertension is almost as old as the earliest methods of measuring blood pressure (BP). (For reviews, see Henry and Grim, 1990; Light, 2000; Pickering, 1997.) One group of candidates for increasing hypertension risk may be termed "indexes of environmental exposure." In etiologic models of hypertension, the most frequently mentioned environmental exposure factors are high dietary salt intake and high life stress. High salt intake seems like an area where little new research is needed because our public health messages have emphasized that it has well-documented negative health effects, but the story is not nearly as simple as this implies. Laboratory studies indicate that less than half of the population is salt sensitive, and salt restriction has been associated in at least one major investigation with increased rather than decreased risk of morbidity (Alderman et al., 2000). Stress is also something that the lay public is very familiar with, and most people believe it is well established that stress helps "cause" high BP, heart attack, and stroke, yet physicians and scientists continue to debate among themselves about whether and how stress may play any role (see Manuck, 1994; Pickering and Gerin, 1990).

The linchpin for our research group holding together the apparently contradictory findings on behavior and hypertensive heart disease is this: