Bridging Psychology and Biology

The Analysis of Individuals in Groups

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Biological systems are particularly prone to variation, and the authors argue that such variation must be regarded as important data in its own right. The authors describe a method in which individual differences are studied within the framework of a general theory of the population as a whole and illustrate how this method can be used to address three types of issues: the nature of the mechanisms that give rise to a specific ability, such as mental imagery; the role of psychological or biological mediators of environmental challenges, such as the biological bases for differences in dispositional mood; and the existence of processes that have nonadditive effects with behavioral and physiological variables, such as factors that modulate the response to stress and its effects on the immune response.

Variation occurs around every central tendency, but in most studies of the biological foundations of mental processes such variation is treated as noise—something to be minimized as much as possible and ideally eliminated altogether (cf. Plomin & Kosslyn, 2001). However, there is good reason not to ignore such variation but rather to use it to gain leverage in formulating and testing theory. Indeed, in his seminal article, Benton Underwood (1975) argued that individual differences provide a unique opportunity to test a wide range of psychological theories (see also Lamiell, 1981). Underwood argued that naturally occurring individual differences reveal the structure of psychological function and in fact may provide more robust insights than many conventional group-based methods. In this article, we extend and modify Underwood's argument to show how individual differences can play a crucial role in understanding the connections between psychology and biology.

We argue here that bridges between psychology and biology will be easier to forge if researchers treat each participant as an individual but conceive of individual differences within the framework of a general characterization of the population as a whole. The key to this orientation is to relate naturally occurring variation in a particular ability or characteristic to variation in the functioning of an underlying mechanism that characterizes the species in general. We note that although all members of the same species share the same fundamental mechanisms, biological systems are notoriously redundant and complex, affording many different ways to accomplish the same goal. Thus, people (or other animals) may differ not only in the efficacy of specific mechanisms but also in the frequency with which particular mechanisms are recruited (which in turn would make some more salient than others). If some people tend to rely on one "strategy" (i.e., combination of processes), whereas others habitually rely on alternative strategies, pooling data from both groups may be uninformative at best and outright misleading at worst. Appropriately collected, group data can provide a good starting point, but individual differences need to be respected if researchers are to understand the nature of the alternative mechanisms. These mechanisms can be characterized at many levels of analysis, ranging from information processing (which may or may not include aspects of phenomenological experience) to the neural structures that underlie such processing to the neuropharmacological, hormonal, and immune systems that regulate events in the body and brain.

The research method advocated here rests on a confluence of correlational and experimental designs. This method avoids the worst criticism of correlational studies,

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namely, that they merely establish a relation between variables and do not implicate causal mechanisms. It does so by using a theory of the general mechanism to produce alternative accounts and then examining the variables associated with these accounts in their own right. That is, instead of simply demonstrating a correlation between the strength of a psychological characteristic or behavior and variation in the workings of a biological mechanism, theories are used to generate alternative accounts of the correlation—which are then considered and compared. Just as control groups can be used to eliminate alternative accounts in group studies, documenting the effects (or lack thereof) of variables associated with alternative accounts can be used to narrow the range of interpretation.

In this article, we use results from our laboratories to illustrate how individual differences can be exploited to address three types of issues: (a) the nature of the neural mechanisms that give rise to a specific type of cognitive ability, (b) the role of psychological or biological mediators of environmental challenges, and (c) the existence of biological processes that have nonadditive effects with behavioral and physiological variables.

Insight Into Mechanisms

Rather than simply being noise that obscures underlying causes of regularities in data, individual differences can actually help to reveal the nature of underlying mechanisms. We illustrate this point with an example of research in a controversial area, mental imagery, where the additional leverage gained from this approach is particularly important. Galton's (1883) famous studies in the latter part of the 19th century put the investigation of individual differences in mental imagery at the core of experimental psychology, and thus, it is fitting that studies of individual differences should play an important role in this field today.

Cognitive and Brain Mechanisms in Mental Imagery

In this section, we use mental imagery to illustrate how investigating individual differences in the context of a theory of general mechanisms can illuminate the nature of internal representations. Mental imagery is the ability to represent perceptual states in the absence of the appropriate sensory input. Imagery can occur in any sensory modality, including visual (as signaled by the experience of "seeing in the mind's eye"), auditory (accompanied by the experience of "hearing with the mind's ear"), and motor (accompanied by the experience of "feeling the mind's limb move"). Mental images are in many respects surrogates for percepts. For example, images can induce illusions like those seen in perception (see, e.g., Finke & Schmidt, 1977, 1978; Kosslyn et al., 1999), visualizing an aversive object can cause skin conductance increases like those found when one actually views the object (see, e.g., Cuthbert, Vrana, & Bradley, 1991; Lang, Cuthbert, & Bradley, 1998), and people may incorrectly remember having seen an object when they in fact only visualized it (see, e.g., Johnson & Raye, 1981). None of these results is surprising given that visual mental imagery and visual perception activate about two thirds of the same brain areas (Kosslyn, Thompson, & Alpert, 1997) and that memories of images are crucial for the interpretation of perceptual input (see, e.g., Ullman, 1996).

Nevertheless, studies of imagery remain controversial (see, e.g., Denis & Kosslyn, 1999). Combining group and individual differences approaches has proven useful for addressing a key aspect of the controversy, namely, whether a picturelike representation exists when one has the experience of visualization. In an effort to support the theory that visual mental images do in fact rely on a depictive representation, Kosslyn and his colleagues (e.g., Kosslyn et al., 1993, 1999; Kosslyn, Thompson, Kim, & Alpert, 1995) have reported that visual mental imagery relies in part on the earliest visual cortices, Areas 17 and 18. These findings are important in part because these areas are topographically organized—the pattern of light falling on the retina is preserved by the pattern of activation on the surface of the cortex. Distance across cortex is used to represent distance across the object (or, more precisely, across the planar projection of the perceptual image of the object). However, activation of such areas does not always occur during imagery (see, e.g., Mellet et al., 2000; Roland & Gulyas, 1994; Thompson & Kosslyn, 2000).

Kosslyn, Thompson, Kim, Rauch, and Alpert (1996) used individual differences in performance to provide converging evidence that Area 17 plays a role in visual mental imagery. In this study, participants closed their eyes and received a series of auditory cues. Each trial had two events: First, the participants heard the name of a letter of the alphabet, at which point they were to visualize a standard uppercase version of the letter. Second, they held this image for four seconds and then heard a cue, such as "curved lines," which named a possible property of the letter. Their task was to decide, as quickly and accurately as possible, whether the named property was present in the letter being visualized. For example, they might hear "A . . . curved lines." In this case, the answer is no; in contrast, for "B . . . curved lines," the answer is yes. The response times and accuracy were recorded. The participants were tested in a positron emission tomography (PET) scanner, which assessed cerebral blood flow throughout their brains as they performed the task. The more vigorously a part of the brain worked during the task, the more blood was present in that part.

In Kosslyn et al.'s (1996) study, the data were analyzed in an unusual way. Kosslyn et al. first normalized the blood-flow data from all 16 participants, so that the mean flow was the same for each brain. For each participant, they then calculated the blood flow (relative to the normalized mean) in a set of brain areas that, in previous group studies, had been found to be activated during imagery. Finally, they simply regressed the mean response time for each person onto these measures of blood flow. That is, data from previous group studies were used to identify the brain areas that are typically activated in common across participants. Individual differences in the amount of such activation were then considered. Three findings are of interest.

First, the amount of blood flow in Area 17 was in fact correlated with response times: The slowest people also had the least amount of blood flow (relative to their own mean flow) in Area 17. This finding is as expected if Area 17 is in fact involved in imagery, but that is merely a correlation. Thus, the real strength of the finding comes from the second result: It was possible to rule out a potential counterexplanation for the activation in Area 17 during imagery—and perhaps to do so more effectively than would have been possible with a standard group design. Specifically, one could argue that this correlational result is an artifact of a third variable, namely, blood flow in another brain area that was indirectly affecting blood flow in Area 17. To rule out such an account, the amount of blood flow was measured in all areas of the brain that previously had been found to be activated in the task, and the values for all other areas were entered first into a hierarchical multiple regression analysis. The question is whether variations in blood flow in Area 17 still accounted for variations in performance even after the contribution of these other areas was statistically removed. In fact, individual differences in blood flow in Area 17 did continue to account for significant amounts of the variance in response times, which is good evidence that the correlation between blood flow in Area 17 and performance was not an artifact of input from the other brain areas. Thus, these findings provide strong support for the view that Area 17 plays a functional role in visual mental imagery. The combination of group and individual differences approaches proved more powerful than either would have alone.

Finally, only variation in blood flow in certain brain areas was correlated with performance; the correlations picked out a set of areas that apparently are used in performing the task. Indeed, perhaps the most remarkable result is that the multiple correlation between blood flow in three areas and response time was $r = .93$; monitoring individual differences in blood flow in relevant brain areas provides enormous power in predicting behavior. As discussed in the next section, individual differences not only can be used to establish that a particular type of representation is used during a task (e.g., that which occurs in Area 17) but also can help identify the neural underpinnings of such processing.

The Structure of Processing

Combining group and individual differences studies can also provide insights into the nature of the system of processes that gives rise to an ability. For example, studies of individual differences have revealed that mental imagery arises from a set of distinct processes working together. In one such study, Kosslyn, Brunn, Cave, and Wallach (1984) tested 50 people on 13 different imagery tasks. These tasks were designed within the context of a theory that posited a set of distinct processes, such as those underlying mental rotation (visualizing objects changing orientation), image scanning (shifting attention over an imaged object), image generation (the ability to form images), and image resolution (how sharp objects appear in images). When performance on the different tasks was correlated across participants, the correlations were found to vary from $-.44$ to .79, clearly showing that imagery is not a single, undifferentiated ability; if it were, the correlations should have been consistent across tasks (Kosslyn, 1994). Instead, individual differences in imagery are best understood in terms of a set of underlying processes, which are common to all people but which vary for any given individual. Indeed, the precise pattern of correlations was nicely explained by models that specified particular processes used in each task (see, e.g., Kosslyn, Van Kleeck, & Kirby, 1990). Thus, group studies provided the basis for the theory, which then led to models for specific tasks. The theory could then be tested by fitting the models to patterns of individual differences. Unlike previous purely individual differences studies, the tasks were designed and the results analyzed in the context of the overarching theory; the participants were not simply given a set of tests and the results analyzed post hoc. Studying the underlying bases of individual differences in this way provides insights into the common structure of processing shared by all people—which in turn provides insights into the precise ways in which people differ.

If individual differences in brain activity can be used to discover the underlying structure of processing, then one might expect that variations in the activation of different brain areas should predict behavior for different types of tasks. In fact, Alexander et al. (1999) found a linear relationship between increased cerebral blood flow in portions of the occipital cortex plus the thalamus and accuracy in a face-matching task. Nyberg, McIntosh, Houle, Nilsson, and Tulving (1996) reported that the amount of activation a participant had in the medial temporal lobe was correlated with subsequent word-recognition performance. Cahill et al. (1996) recorded activation while participants watched emotional films and found that the participants who had stronger activation of the right amygdala later had better memory for the films. In short, variations in different representations or processes underlie variations in the performance of different tasks.

It is clear, then, that individual differences are not a single, unitary factor. Moreover, they can be understood in terms of variations in the efficacy of representations and processes that are shared by all members of a species. Individual differences thus can be used in the context of general theories of processing to help researchers discover not only the nature of the representations and processes that underlie an ability but also how specific representations and processes are realized in the brain.

Mediators of Environmental Challenges

Studying individual differences in the context of general theories can also be exploited to understand why the same stimuli evoke different responses in different people. In this section, we illustrate this point by considering emotion, one of the most salient characteristics of which is the fact that the same emotional stimulus elicits a wide range of responses across individuals (Ekman & Davidson, 1994;

Frijda, 1986; Scherer, 1999). For affect, individual differences in both the quality and the magnitude of the response are the rule rather than the exception. Although many studies have used self-report measures to probe such individual differences, studies of the neural bases of individual differences have provided crucial information about why people react differently to the same emotion-inducing situation.

Approach Versus Withdrawal

In this section, we illustrate how individual differences in the activation of specific brain circuitry can define general psychological dimensions that underlie emotion. Thus, individual differences are not studied for their own sake but rather as a way to characterize species-general characteristics—which, for emotion, Davidson and his colleagues referred to as *affective style.* These general dimensions are then used to explain why the same stimuli have different effects for different individuals.

For example, Davidson and his colleagues (e.g., Davidson, Ekman, Saron, Senulis, & Friesen, 1990) showed that when participants received stimuli that provoked withdrawal-related negative affect, such as fear and disgust, the right prefrontal regions of the brain became more activated than the left (as measured by electroencephalography). In contrast, when participants received stimuli that evoked approach-related positive affect, the left prefrontal regions became more activated. Moreover, these effects are present within the first year of life (Davidson & Fox, 1982). On the basis of these and related findings, researchers reasoned that individual differences in the baseline amounts of activation in the left versus right prefrontal regions could mediate the effects of environmental stimuli. To test this prediction, the researchers first had to establish that baseline measures of prefrontal activation asymmetry are stable over time and exhibit adequate statistical reliability. Such tests are rarely conducted with biological measures but are crucial: It is not obvious which biological measures are reliable enough to be used to assess individual differences. In the most comprehensive study, Tomarken, Davidson, Wheeler, and Kinney (1992) examined both the internal consistency reliability and test–retest stability (over approximately one month) in a large number of participants ($N = 90$). They found excellent internal consistency reliability ($> .9$) and adequate test–retest stability (intraclass correlations between .65 and .75) for brain electrical activity measures of prefrontal activation asymmetry. If, in fact, the left prefrontal regions mediate approach emotions and the right prefrontal regions mediate withdrawal emotions, then participants with greater baseline right-sided prefrontal activation should report greater dispositional negative affect on a standard paper-and-pencil measure. The data supported the prediction (Tomarken, Davidson, Wheeler, & Doss, 1992; see also Sutton & Davidson, 1997).

In addition to examining relations between brain electrical measures of prefrontal activation and self-report measures of affective traits, Davidson and his colleagues have also explored whether such individual differences in baseline measures of brain function predict reactivity to emotion-charged stimuli. In several studies, they found that measures of baseline prefrontal activation predicted how strongly individuals reacted to emotional film clips (Henriques & Davidson, 1990; Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993); as expected, participants with greater right-sided prefrontal activation reported stronger negative affect in response to negative affective film clips, even after the statistical removal of variance associated with trait levels of negative affect. Indeed, measures of baseline prefrontal function even predicted how strongly 10-month-old infants reacted to a brief episode of maternal separation: Infants with greater right-sided prefrontal activation at baseline were more likely to cry in response to maternal separation compared with their left-activated counterparts (Davidson & Fox, 1982).

Davidson and colleagues have extended this research program by examining individual differences in brain electrical measures of prefrontal activation and emotional responses in rhesus monkeys (Davidson, Jackson, & Kalin, 2000; Davidson, Kalin, & Shelton, 1992, 1993; Kalin, Larson, Shelton, & Davidson, 1998). These researchers found that the test–retest stability of their measures of prefrontal function is comparable in monkeys and humans. Moreover, monkeys with greater right-sided prefrontal activation had higher levels of cortisol (Kalin, Shelton, Rickman, & Davidson, 1998). Cortisol is a stress hormone that readies the body to engage in fight or flight; it stimulates secretion of intracellular glucose into the blood, which allows one to respond vigorously over a longer period of time. Indeed, animals with greater right-sided prefrontal activation also had higher cerebrospinal fluid levels of corticotropin-releasing hormone, a key molecule produced in the hypothalamus in the series of events that ultimately releases cortisol (Kalin, Shelton, & Davidson, 2000). The fact that chronic differences in prefrontal activation predict levels of cortisol is important for a number reasons—not the least of which is that long-term elevation of cortisol can kill hippocampal neurons (see, e.g., Sapolsky, 1992, 1996).

The results from studies of monkeys almost certainly generalize to humans. For example, Lovallo and colleagues found that participants whose heart rates changed dramatically during a painful cold-pressor test also had large cardiovascular and cortisol responses in a threatening reaction-time task 2 weeks to 13 months earlier (Lovallo, Pincomb, & Wilson, 1986). One might question whether such differences in reactivity arise from central or peripheral mechanisms. Lovallo and colleagues next measured adrenocorticotropic hormone (ACTH), the physiological precursor of cortisol secreted by the pituitary gland and triggered by corticotropin-releasing hormone. They found that people who had the highest heart rate responses to a social stressor, public speaking, also had greater negative affect along with elevated sympathetic reactivity, ACTH, and cortisol responses (al'Absi et al., 1997). The relations among these individual differences are good evidence for a common mediator, and the brain is the only candidate for such a mechanism. These studies suggest that emotional

dispositions, more than external circumstances, are crucial players in this biological response tendency.

The examination of individual differences within the context of theories of general mechanisms has also revealed another important mediator of the effects of emotional stimuli: amygdala function, both at baseline and in response to affective stimuli. Previous studies have shown that the amygdala is activated by aversive stimuli, and thus, a framework has been established for asking whether individual differences in such activation are related to differences in behavior. Using PET with fluro-deoxyglucose, in conjunction with magnetic resonance imaging coregistration and anatomically defined regions of interest, researchers have assessed the metabolic rate in the amygdala and several related subcortical structures. For most, but not all, regions examined, test–retest stability was good (Schaefer et al., 2000). In a study of depressed patients (all of whom were off medication at the time of testing; Abercrombie et al., 1998), those patients who had greater metabolic rates in the right amygdala also reported more dispositional negative affect (with the values of the correlations between .40 and .55). It is possible, as Davidson, Pizzagalli, Nitschke, and Putnam (2002) suggested, that the amygdala activation in depressed patients could arise from comorbid anxiety and related negative affect instead of depression per se. Although the depressed patients in the Abercrombie et al. (1998) study were specifically screened to eliminate concurrent anxiety disorders, with the exception of social phobia, such patients are still likely to have considerable comorbid anxiety. In a series of studies, Drevets and coworkers found that depressed patients had elevated baseline blood flow and metabolism in the amygdala (Drevets, 2001; Drevets et al., 1992). However, these participants all were patients with familial major depressive disorder (i.e., all had first-degree relatives with the disorder) or were patients with melancholic features.

More recently, Irwin et al. (2001) asked a conceptually similar question using functional magnetic resonance imaging in normal participants. They examined the signal in the right amygdala elicited by negative versus neutral pictures. When averaged over participants, negative pictures did indeed produce a significant increase in the amygdala signal compared with neutral pictures. However, the magnitude of this response differed considerably across participants. When such variation was considered in its own right, instead of being considered noise and ignored, the researchers found that participants who had a larger amygdala signal in response to the negative pictures reported higher levels of dispositional negative affect (r = .61).

In short, the prefrontal cortex and the amygdala each have been implicated in mediating specific aspects of emotion. These findings characterize people in general, but armed with such results, one can now turn to the individual—and by studying individual differences, one can in turn garner additional evidence for the fundamental distinctions. Specifically, participants with greater right-sided prefrontal activation at baseline have reported more dispositional negative affect, have reacted more negatively to aversive stimuli, and have had the biological hallmarks of greater stress. Similar findings have been obtained with the amygdala: When the right amygdala has had a high baseline metabolic rate and has been highly reactive to unpleasant pictures, participants have reported higher levels of dispositional negative affect. However, we note that the issue of asymmetries in amygdala activation has proven complicated and is not yet fully understood (see Davidson & Irwin, 1999; LeDoux, 2002, for reviews). The approach advocated here clearly can be used to discover the bases of asymmetries, and we fully expect that additional studies will iron out wrinkles that have appeared in the literature (with some studies reporting asymmetries in amygdala activation and some not).

Dispositional Mood

Considering individual differences within the context of a general theory can also help forge the connection from psychology to biology for another aspect of emotion, which has been called *dispositional mood.* For example, Hugdahl, Beneventi, and Halvorsen (2002) investigated the possibility that dispositional mood reflects how easily one can be negatively conditioned. Classical conditioning affects all animals, but—like everything else—there is interindividual variation in its effectiveness. This variation can be exploited to help understand the nature of dispositional mood.

First, to assess dispositional mood, Hugdahl et al. (2002) obtained scores on the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS consists of statements about negative (e.g., "agitated") and positive (e.g., "enthusiastic") feelings, and the participants indicate the extent to which each statement is characteristic of their dispositional mood. Although the PANAS measures types of activated mood, Hugdahl and colleagues focused on the positive and negative affect dimension, which reflects robust properties of self-rated affect (Watson, Wiese, Vaidya, & Tellegen, 1999). Next, Hugdahl et al. (2002) asked people to complete the PANAS scale and then to participate in a conditioning experiment in which a neutral tone was given affective value by pairing it with aversive pictures several times. The researchers recorded psychophysiological responses to the tone from the sweat glands in the skin of the palms. The participants heard two different tones, one at 500 Hz and the other at 1000 Hz. Half the participants received the 500-Hz tone as the conditioned stimulus and the 1000-Hz tone as an unconditioned stimulus, and vice versa for the other half of the participants. Conditioning was thus measured as the difference in skin response to the conditioned tone versus the unconditioned tone.

The hypothesis was that if people who have more negative dispositional mood are more easily negatively conditioned, then participants who rated themselves more negatively should also be more strongly conditioned in this procedure. By the same token, the correlation should be attenuated (or even reversed) for those who rated themselves as more positive. In fact, participants who rated themselves as having negative dispositional mood, as indicated by the negative PANAS items, had larger skin con-

ductance responses to the conditioned tone (Pearson's $r = .55$, $p < .03$); the corresponding correlation for the positive PANAS items was not significant. Thus, using individual differences within the context of species-general mechanisms, researchers can link aspects of personality and temperament to psychophysiology. In fact, perhaps surprisingly, people can accurately report aspects of their temperaments that reflect the state of their nervous systems (see Hugdahl, 1995, for a review of psychophysiological studies of emotions).

In sum, the study of individual differences within the context of knowledge of general mechanisms has further shown how those mechanisms may mediate one's emotional response to environmental events. Studying the interplay between group-based research and individual differences research has proven to be a particularly powerful way to connect emotional phenomena to their underlying biological substrata.

Nonadditive Effects

Studying individual differences within the context of theories of general mechanisms may also provide a handle on one of the knottier problems in psychology: understanding nonadditive effects of different variables. That is, not only may the effects of one variable alter the effects of another but also the precise degree to which the variables interact may depend on their values. Instead of considering how individual differences mediate the effects of a stimulus, we now consider how individual differences in one process in turn affect the operation of another process.

Modulating the Stress Response

In this section, we consider individual differences that modulate the brain and bodily responses to stress. As noted earlier, cortisol rises in response to stress, readying the body to engage in fight or flight (Lovallo, 1997; Sapolsky, 1992, 1996). Yet cortisol does not always increase in response to a threat, and when it does increase, it may increase to different degrees. In this section, we illustrate how group analyses have obscured the nature of biological responses to stress and how the actual nature of these responses becomes apparent only when individual differences are also considered. In the present approach, the link from psychology to biology depends critically on characterizing individual differences in the functioning of mechanisms shared by all human beings.

An initial wave of studies showed that acute psychological stressors activate the autonomic nervous system and the sympathetic adrenomedullary system axis but not the hypothalamic–pituitary–adrenocortical axis (Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991; see reviews by Benschop et al., 1998; Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992). Cacioppo, Berntson, and colleagues (see, e.g., Berntson et al., 1994; Cacioppo, 1994; Cacioppo et al., 1995, 1998) asked whether the methodologies used previously had led researchers to overlook the role of the hypothalamic–pituitary–adrenocortical system in response to stress. They combined group and individual differences approaches to address this question. For example, in one study, researchers identified individuals who were high or low in sympathetic cardiac activation (Sgoutas-Emch et al., 1994). The researchers first monitored heart rate and blood pressure while participants performed a brief public-speaking task (Saab, Matthews, Stoney, & McDonald, 1989); after confirming the internal consistency of the cardiovascular measures and the fact that the speech stressor significantly elevated cardiovascular activity, the researchers identified individuals in the top or bottom quartiles in heart rate reactivity during the speech task. To control for possible confounds, the researchers conducted ancillary analyses to ensure that high and low reactors had similar basal heart rates and health behaviors.

These individuals then were recruited to participate in a follow-up study. The participants relaxed for 5 minutes (the baseline) and then performed mental arithmetic for 12 minutes (the stressor task). During the last 6 minutes of the stressor task, the participants heard random 100-dB noise bursts, which they were told were presented "to make the task more challenging." The researchers collected cardiovascular measures throughout and drew blood prior to and following the stressor. Preliminary analyses confirmed that individual differences in cardiovascular reactivity were maintained across the two testing sessions and that high heart rate reactors in the screening session also had larger heart rate increases to the mental arithmetic stressor. In addition, the researchers replicated prior research showing that the brief psychological stressor increased circulating catecholamine levels but not cortisol levels. This was the finding that had led others to suggest that brief psychological stressors activated the sympathetic adrenomedullary system but not the hypothalamic–pituitary–adrenocortical system.

However, for present purposes, the important point is that when the high and low heart rate reactors' neuroendocrine responses to stressors were compared, a different pattern emerged. Specifically, the mental arithmetic task elevated catecholamine levels comparably for low and high heart rate reactors whereas the high heart rate reactors had higher stress-related levels of plasma cortisol than did the low reactors. In short, the effects of stress were modulated by the participants' level of reactivity—which was only apparent when individual differences were taken into account (Berntson et al., 1994).

Having documented this interaction, the researchers then exploited individual differences to study the mechanisms responsible for the observed findings. Specifically, these researchers examined the neural substrates of heart rate responses to a nonpsychological (i.e., orthostatic) stressor and to three active coping (i.e., mental arithmetic, speech, reaction time) stressors. The same high and low reactors were tested under sympathetic blockade, parasympathetic blockade, double blockade, and placebo. Group analyses revealed that the psychological and nonpsychological stressors produced comparable sympathetic activation and reciprocal vagal withdrawal. Examining individual differences within this framework, in contrast, revealed that the orthostatic stressor operated differently on the brain and

body than did the active coping stressors. The orthostatic stressor, which acts through the baroreceptor reflex to maintain blood pressure when one changes posture, produced sympathetic activation and vagal withdrawal in all of the participants. In contrast, the three active coping stressors elicited consistent patterns of sympathetic and vagal changes within individuals but had very different patterns for different people. The different responses to the two types of stressors are good evidence that different mechanisms are at work. In fact, psychological stressors are modulated by more rostral brain systems, which are not used in other forms of cardiac control.

An important implication of this work is that sympathetic cardiac activation, and not heart rate reactivity per se, may predict whether the hypothalamic–pituitary–adrenocortical system reacts in response to stress (cf. al'Absi et al., 1997; al'Absi, Hugdahl, & Lovallo, in press; Cacioppo, 1994; Cacioppo et al., 1995; Lovallo, Pincomb, Brackett, & Wilson, 1990; Uchino, Cacioppo, Malarkey, & Glaser, 1995). This idea has been pursued in additional research. For example, in one study, 22 elderly women relaxed for 30 minutes, then participated in a 5-minute baseline period, a 6-minute mental arithmetic task, and a 6-minute speech task. Cacioppo and colleagues recorded autonomic activity during the baseline and stressor periods and drew blood at baseline, midstressor, and poststressor (Cacioppo et al., 1995). Replicating prior studies, group analyses indicated that the psychological stressor not only elevated heart rate but also elevated catecholamine (epinephrine and norepinephrine) plasma levels—but did not alter circulating cortisol levels. In contrast, individual differences analyses revealed that the higher a participant's sympathetic cardiac reactivity, the greater the stress-induced changes in plasma cortisol concentrations ($r = -.62$). In contrast, vagal cardiac reactivity was unrelated to cortisol responses ($r = .18$). This is precisely the pattern of results one would expect if sympathetic reactivity were underlying the relationship between heart rate reactivity and cortisol. Moreover, hierarchical regression analyses revealed that brief psychological stressors have an impact on the hypothalamic–pituitary–adrenocortical system not only in some situations but in some situations for some individuals—specifically, those in whom sympathetic cardiac reactivity is also high.

This research not only illustrates the conditions in which the hypothalamic–pituitary–adrenocortical system is involved in stress, and thus illuminates the nature of the fundamental system, but also helps explain relations among systems. When individual differences were added to a standard design, key relations emerged that otherwise would have been masked.

Cognitive Effects of Stress

Individual differences in stress-related elevations of cortisol are important for a variety of reasons, one of which is that cortisol may affect cognitive functioning. In this section, we illustrate such interactions by considering the effect of acutely elevated levels of cortisol on dichotic listening (al'Absi et al., in press). Again, we consider how individual differences in one system in turn affect the functioning of another. Participants who had large cortisol responses during mental arithmetic and a public-speaking task were better 30 minutes later at dichotic listening in comparison with those who had low cortisol responses. Dichotic listening requires sustained focused attention to external stimuli, which is usually considered the purview of executive processes in working memory. Thus, it is of great interest that working memory depends on adequate functioning of the dorsolateral prefrontal cortex (Smith & Jonides, 1999), an area richly supplied with corticosteroid receptors and corticotropin-releasing factor terminals.

If only group data had been considered, the effects of stress on cognitive function would have appeared negligible. By respecting individual differences, not only were systematic effects documented but also their implications for theories of processing in general became clear. The combination of both sorts of factors, considering individual differences but doing so within the context of general mechanisms, allowed the researchers to build a bridge from the psychological effect to the underlying biological substrate.

Modulating the Immune Response

We have seen that studying individual differences can illuminate links from psychological events to three sorts of biological events: central nervous system activity (both cortical and subcortical), autonomic nervous system activity, and neuroendocrine activity. In addition, in this section, we show how this approach can illuminate key facts about the link between psychological events and the immune system. For example, dispositional differences in the effects of stress on the immune system rely in part on the presence of social support (Cacioppo, 1994; Cacioppo et al., 2000). Much of the research on the effect of stress on the immune system has focused on natural killer (NK) cells. This special class of lymphocytes attacks and kills target cells, such as tumor cells (Herberman & Ortaldo, 1981; Roder & Pross, 1982). In normal, healthy humans, NK cells represent from 5% to 15% of circulating lymphocytes (Whiteside & Herberman, 1994). Both the number of circulating NK cells in the blood and the efficiency with which the cells actually kill target cells (NK cell cytotoxic activity [NKCA]) are important indicators of a healthy immune system and tend to be relatively stable within an individual over time (Whiteside & Herberman, 1989, 1994). Persistently low numbers of NK cells and low NKCA can be associated with chronic stress or disease, such as the progression or recurrence of cancer (Ben-Eliyahu, Yirmiya, Liebeskind, Taylor, & Gale, 1991; Levy, Herberman, Lippman, D'Angelo, & Lee, 1991; Whiteside & Herberman, 1995). However, NK levels can also change quickly in response to a particular challenge, such as a cold virus or an acute stressor (Whiteside & Herberman, 1989).

In a laboratory study of the effects of uncontrollable noise (Sieber et al., 1992), participants who perceived themselves as having no control over a stressful noise had suppressed NK activity, both immediately following the task and 72 hours later. On the other hand, participants who believed they had control over the noise (although they did

not) and participants who were not subjected to noise did not show immune suppression. However, participants who reported a high desire for control, as assessed by a personality questionnaire, showed the largest drop in NKCA in the no-control condition. Thus, personality variables may accentuate a participant's response to an uncontrollable stressor, thereby influencing the effect on NKCA.

In addition, stress induced by examinations decreases NK cell number and activity (Glaser et al., 1985; Kiecolt-Glaser et al., 1984, 1986). In one study, researchers assessed first-year medical students one month before and immediately after taking final exams. NK cell number and NKCA dropped following the exams. However, these effects were even worse for students who reported more loneliness and higher subjective stress ratings; these students had lower NKCA (Kiecolt-Glaser et al., 1984), suggesting again that stress-induced suppression of NKCA is modulated by the person's emotional reaction to a stressor and is buffered by the presence of social support. In a related study, students who had greater levels of right prefrontal activation at baseline had lower NKCA following final exams (Davidson, Coe, Dolski, & Donzella, 1999).

Researchers have obtained converging evidence by studying the effects of separation and divorce, which have emotional and immunological consequences (cf. Bloom, Asher, & White, 1978). For example, Kiecolt-Glaser et al. (1987) compared a group of separated and divorced women with a group of married women who were sociodemographically matched. Women who were tested within a year of being separated or divorced had the greatest immune deficiency, having lower percentages of helper T lymphocytes and NK cells and higher Epstein-Barr virus antibody titers. The largest decreases in immune responses were for women who had been separated most recently and who remained emotionally attached to their former mates. However, women who had been separated or divorced for up to six years continued to show evidence of immunosuppression. Furthermore, poorer marital quality in the married group was associated with decreased immune function. These results suggest that the different phases in the disruption of a marital relationship can lead to long-term immunosuppression.

In addition, the clinical salience of disruption of marital support is illustrated by a study of metastatic breast-cancer patients, which found that those who were divorced, separated, or widowed had disrupted cortisol secretion; these patients no longer had normal diurnal variation in cortisol and instead had increased rather than the usual decreased amounts throughout the course of the day. This pattern predicted significantly earlier subsequent mortality in the ensuing seven years (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). Thus, variability in social support may contribute to immune and endocrine effects of acute and chronic stress that play important roles in health.

In short, studies of individual differences have allowed researchers to understand not only which biological mechanisms are called into play during psychological events but also how such mechanisms interact. By averaging data from different types of people, key aspects of how psychology is linked to biology have been obscured. Without question, studying individual differences can clarify what previously have been muddy waters.

General Discussion

We have advocated combining group-based research and individual differences research as a powerful method for linking psychology to biology. In the present approach, unlike most group-based research, individual differences are not treated as noise. Moreover, unlike much individual differences research, the measures are tightly linked to mechanisms that characterize the group as a whole. The examples presented here serve to underline the strengths and weaknesses of the two traditional methods. First, we have seen numerous examples where a strictly group-based approach failed to reveal aspects of the underlying biological mechanisms. For example, a main effect, documenting the existence of a phenomenon, may not be revealed if there is considerable variation within a population in the tendency or ability to use it. Thus, a Type II error can occur if individual variance is not taken into account.

Second, we must note that studying individual differences without considering a species-general mechanism or theoretical framework is not adequate. Consider the neuroimaging studies noted throughout this article. In every case, the researchers knew in advance which brain areas to examine (such as the amygdala or Area 17). They knew this on the basis of prior group studies. Such studies provide the framework within which one can ask about individual differences. In addition and perhaps more important, correlations with performance reflect only a subset of the processes used in a given task. By analogy, consider individual differences in typing speed. Variation in performance of this task reflects individual differences in the speed with which one can set up and execute motor programs but does not reflect individual differences in the strength of one's fingers (assuming that the keyboard is properly designed). If one has a certain threshold level of strength, that is sufficient—any additional strength is irrelevant. Similarly, for many mental processes, if one can accomplish the process at all, that is good enough to perform the task well—and thus, individual differences in the efficacy of that process are not correlated with individual differences in performance. Correlations reveal only processes that are rate limiting, that is, for which improvements in the efficacy of the process are reflected by improvements in performance (see Kosslyn & Plomin, 2001).

Neither group nor individual differences research alone is sufficient; researchers need to combine the two. Indeed, by combining the two, one may discover that the group results reflect the combination of several strategies, each of which draws on a different (or partially different) system. Thus, the group and individual differences findings mutually inform each other, with the synergy between them illuminating the complex relations between psychology and biology.

Our aim has been to illustrate three ways that the combined approach can help illuminate the link between

psychology and biology (the nature of mechanisms, the role of psychological or biological mediators of a situational factor, and the ways systems interact to produce nonadditive effects among variables). Thus, we have selected our examples to address the four basic biological systems that are relevant for psychology: the central nervous system, the autonomic nervous system, the neuroendocrine system, and the neuroimmune system. Consider each in turn: First and foremost, consider the central nervous system. It is clear that neuroimaging offers the promise of discovering how mental events arise in the brain. We hope to have shown here that the combination of group and individual differences methods can play a key role in helping fulfill that promise. Second, the autonomic nervous system plays a key role in survival. We have shown how individual differences provide a tool for studying autonomic reactivity (as reflected in the ease of being conditioned), which in turn allows an understanding of the general psychological construct of dispositional mood in greater depth. Third, the neuroendocrine system is crucial for regulating the body, which both is regulated by the brain and in turn affects the brain; this system is key in allowing human beings to cope with stress. The hybrid approach we suggest here not only has allowed researchers to illuminate how this system works but also underscores important limitations of a strictly group-based approach. Finally, the neuroimmune system plays a central role in allowing the mind to affect health. It is clear that personal characteristics modulate the effects of stressors on the immune system.

With the completion of the Human Genome Project, the time is particularly ripe for research of the sort we advocate here. The study of individual differences affords an opportunity to link psychological characteristics to genetics. Most research in behavioral genetics has focused on similarities and differences in some characteristic or ability among people who share different percentages of common genes (Plomin, DeFries, McClearn, & Rutter, 1997). With the advent of the Human Genome Project, it has become increasingly practical to link the presence or absence of particular genes to specific characteristics. Such research rests on prior characterization of individual differences among people.

In addition, linking psychology to biology in a way that respects individual differences may have profound implications for psychotherapy. Different treatments may be more or less appropriate for different people. For example, some people may—perhaps because of their genetics—resist some types of conditioning, be particularly vulnerable to lack of social support, or have difficulty forming vivid imagery, and so on. By discovering the proclivities of a given person, it is even possible that psychologists can customize interventions to help a patient gain control over his or her health. Mental events clearly affect the systems—autonomic, endocrine, and immune—that underlie health. This goal is admittedly barely in sight, but the path to it is becoming clearer. A key aspect of this journey will be to characterize individual differences rigorously, in ways presaged by the examples offered here.

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