An Embodied Neurocomputational Framework for Organically Integrating Biopsychosocial Processes: An Application to the Role of Social Support in Health and Disease

Ryan Smith, PhD, Karen L. Weihs, MD, Anna Alkozei, PhD, William D.S. Killgore, PhD, and Richard D. Lane, MD, PhD

ABSTRACT

Objective: Two distinct perspectives—typically referred to as the biopsychosocial and biomedical models—currently guide clinical practice. Although the role of psychosocial factors in contributing to physical and mental health outcomes is widely recognized, the biomedical model remains dominant. This is due in part to (*a*) the largely nonmechanistic focus of biopsychosocial research and (*b*) the lack of specificity it currently offers in guiding clinicians to focus on social, psychological, and/or biological factors in individual cases. In this article, our objective is to provide an evidence-based and theoretically sophisticated mechanistic model capable of organically integrating biopsychosocial processes.

Methods: To construct this model, we provide a narrative review of recent advances in embodied cognition and predictive processing within computational neuroscience, which offer mechanisms for understanding individual differences in social perceptions, visceral responses, health-related behaviors, and their interactions. We also review current evidence for bidirectional influences between social support and health as a detailed illustration of the novel conceptual resources offered by our model.

Results: When integrated, these advances highlight multiple mechanistic causal pathways between psychosocial and biological variables.

Conclusions: By highlighting these pathways, the resulting model has important implications motivating a more psychologically sophisticated, person-specific approach to future research and clinical application in the biopsychosocial domain. It also highlights the potential for quantitative computational modeling and the design of novel interventions. Finally, it should aid in guiding future research in a manner capable of addressing the current criticisms/limitations of the biopsychosocial model and may therefore represent an important step in bridging the gap between it and the biomedical perspective.

Key words: active inference, biopsychosocial model, biomedical model, computational neuroscience, embodied cognition, predictive coding.

INTRODUCTION

Forty years ago, the biopsychosocial model was proposed by Engel (1) as an attempt to improve upon limitations within the prevailing biomedical model for understanding and treating physical and mental illness. In particular, Engel's model served to draw the attention of clinicians to the important role of psychological, social, and other environmental variables in facilitating, sustaining, and/or modifying the course of illness (i.e., via interaction with the molecular, cellular, and systemic variables of the traditional biomedical model). Although there is now a large body of research supporting aspects of the biopsychosocial model, the fact remains that within most medical domains (with the exception of psychiatry and some primary care settings), the dominant model remains biomedical, and clinical observation of psychological and social/environmental variables has progressively declined (2). These trends are exacerbated by the current medical-economic climate in many industrialized countries, where a premium is placed on profitability of health care and minimization of encounter time with patients. However, another important factor is the mindset of those who adhere strongly to the biomedical model. Clearly, the biomedical model is simpler in the sense that it assumes fewer explanatory elements than the biopsychosocial model (i.e., the biopsychosocial model assumes all of the same mechanistic biological pathways assumed within the biomedical model, but it incorporates psychosocial factors in addition).[1] The biomedical model is, therefore, preferable, all else being equal. Importantly, this view is often accompanied by the belief that the role of psychological and social

[1]Although there is another sense in which higher-level (interventionist) psychosocial explanations are simpler, in that less mechanistic detail is necessary to provide a causal explanation (e.g., "increasing social support reduces stress levels, and reduced levels of stress promote healthier immune functioning"). This type of simplicity can be better in the sense that it can have greater pragmatic utility in certain contexts.

PP = predictive processing, **SES** = socioeconomic status, **SNS** = sympathetic nervous system

From the Department of Psychiatry (Smith, Weihs, Alkozei, Killgore, Lane), University of Arizona, Tucson, Arizona; and the Laureate Institute for Brain Research (Smith), Tulsa, Oklahoma.

Address correspondence to Ryan Smith, PhD, Laureate Institute for Brain Research, 6655 South Yale Ave, Tulsa, OK 74136. E-mail: rsmith@laureateinstitute.org

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factors has not been proven, coupled with the acknowledged challenge of explaining *how* such factors *actually come to influence* medical outcomes in a concrete mechanistic sense. This is particularly challenging for social variables that exist outside the individual. In a recent editorial, one of us proposed that a possible solution to the nonacceptance of the biopsychosocial model within biomedicine would be to express the biopsychosocial model in mechanistic biomedical terms (3). The goal of this article is to provide such a model based on the integrative nature of brain function and new computational approaches that make it possible to specify mechanistic links between neurobiology, peripheral physiology, psychology, behavior, and social variables.

Many examples can be provided that demonstrate the impact of social, psychological, and behavioral factors on medical outcome. Behavioral factors (such as smoking and obesity) are the single leading cause of premature death (i.e., greater than other major factors, such as genetics, healthcare, etc. (4)). Low socioeconomic status (SES) also has a major adverse impact on health, as does physical, sexual, and emotional abuse in childhood (5,6). A great deal of evidence also suggests that vulnerability to illness can be modulated by stressful life events and other chronic social/environmental challenges (7) and that positive emotions have beneficial effects on health (8).

Many other examples could be cited (e.g., regarding doctor-patient relationships, health behaviors, adherence to treatment, etc.). The key point, however, is that many of these findings are correlational and have taken an approach in which biological, psychological, and social variables are assessed independently of one another and then related to medical outcome statistically. Furthermore, although some studies have provided evidence for causal relationships between psychosocial variables and health outcomes (e.g., using randomized controlled trials and natural experiments (9–14)), such findings have not yielded many insights regarding the underlying mechanisms that account for those relationships (i.e., they lead to interventionist causal models but not necessarily to mechanistic causal models, see (15))—where understanding such mechanisms can often highlight further possible targets for effective intervention (16,17). More generally, the biopsychosocial model has also been criticized clinically within psychiatry as too vague to guide the systematic evaluation of (and intervention upon) the relevant biological, psychological, and social factors that a clinician should prioritize in a given individual case (18).

In the recent editorial mentioned previously, Lane (3) proposed that if a mechanistic causal model of both brain-body interactions and brain-behavior-environment interactions was constructed, and combined with a theory linking brain processes to psychological processes, this would be one primary way of bringing the biomedical and biopsychosocial perspectives closer together. By illustrating how psychological and social variables are realized by and/or mechanistically interact with biological variables, such a model would demonstrate how psychosocial variables can be seen as necessary elements of a fully articulated biomedical perspective (also see (19,20)).

In the present article, we draw on current theory and evidence within cognitive science, cognitive and computational neuroscience, and physiology to propose and articulate this kind of mechanistic model. Our hope is that this proposal will represent an important new step toward integrating the biopsychosocial and biomedical perspectives on health and disease and reduce the vagueness of the biopsychosocial model. Important goals are to outline plausible mechanisms that could underlie psychosocial causes, to more precisely guide clinical thinking/practice, to facilitate progress toward the ability to identify individual cases in which the biomedical model may be too simple (e.g., in which it may miss relevant factors, such as treatment adherence, patient-provider interactions, other relationship issues, treatment access, end-of-life issues, etc.) and to aid in the design of effective clinical interventions; in so doing, we aim to demonstrate *mechanistic* relationships between psychosocial variables and medical outcomes that will organically integrate them into biomedical models.

However, because the purview of the biopsychosocial model is exceptionally broad, to provide a concrete presentation of our model, we will first narrow our focus onto a particular example topic: the relationship between social support and health outcomes. We have selected this example topic for three reasons. First, social support is a powerful predictor of health outcomes relative to other psychosocial variables (21–25); therefore, it is plausibly one of the most important examples within the purview of the biopsychosocial model to articulate in concrete detail. Second, there is already a large empirical/theoretical literature to draw on regarding this relationship (the variable of social support/isolation also has the benefit of allowing for the use of animal models with strong face validity for studying health outcomes, e.g., see (26)). Third, social variables create the greatest challenge in explaining *how* psychosocial factors seemingly traverse from extracorporeal reality to bodily physiology and biochemistry.

Therefore, in what follows we will first review current models (and supporting evidence) seeking to explain the relationship between social support and health. Next, we will illustrate how the incorporation of recent embodied neurocomputational perspectives can add to and clarify such models and how the integration of this work can provide support for a more precisely articulated multilevel mechanistic/causal model capable of explaining this relationship in a domain-general manner. Finally, we will explore the implications of this proposal for understanding social support and health and illustrate how—because of the domain-general nature of our model—it can also be generalized to account for a wide range of other phenomena that pertain to the biopsychosocial perspective.

SOCIAL SUPPORT AND HEALTH

Empirical research on the connection between social support and physical/mental health has made considerable progress in recent decades (e.g., (27,28)). Relationships between social support and many health-related variables are firmly established, and plausible factors and pathways to explain these relationships have begun to be identified. These include genetic, environmental, autonomic, endocrine, immune, neural, affective, cognitive, behavioral, and social factors—all plausibly overlapping and/or interacting over time in highly complex ways (29). Understanding these complex interactions remains a daunting challenge for multiple reasons, including the presently limited scientific understanding of each factor, the equal or greater limitations in present scientific understanding of their interactions, as well as the many theoretical/conceptual difficulties that arise when attempting to characterize interacting processes that involve different levels of description (e.g., processes that can be described at neural/biological, psychological, and social levels; for a thorough discussion of multilevel medical research, see (30)). However, it is of potentially great importance to researchers,

health professionals, and the public that these underlying mechanisms are understood—as such, information could potentially be harnessed to promote better health outcomes in a wide range of contexts.

In this section, we will provide a concise summary of major themes in the study of social support and health. Subsequently, we will outline a set of theoretical (embodied neurocomputational) perspectives yet to be fully incorporated into social support research and illustrate how, by incorporating these perspectives, a model of interactions between brain, body, and external world can be constructed that is both sufficiently general to extend to other biopsychosocial phenomena and sufficiently powerful to explain current findings on social support and health in a unified manner.

One initially important observation is that social isolation is associated with both shorter life span and greater vulnerability to a range of somatic diseases (31,32). Furthermore, these associations have most consistently been observed with respect to *perceived* (as opposed to *received*) social support, suggesting the importance of mediating psychological/behavioral variables (27). Specifically, "perceived" social support can be thought of as one's general belief that social support is present, whereas "received" social support involves the receipt of particular supportive actions by others (i.e., which an individual might interpret in a number of ways). Thus, if a person believes that they are generally supported by others, this reliably predicts better health outcomes; on the other hand, an individual might interpret particular supportive acts as indicative of a range of positive or negative evaluations of others (e.g., as a sign of "care" versus "pity"), potentially explaining why the relationship between health and "received" social support appears less robust. This idea is also consistent with multiple reviews (27,28), which suggest that perceived social support plausibly influences health via associations with several personality/individual difference variables (i.e., secure attachment, high optimism, low neuroticism, low hostility, low loneliness) and several cognitive/behavioral variables (e.g., more adaptive interpretations of social transactions, greater appraisals of control and self-efficacy, more flexible/proactive coping strategies, healthier life-style choices) that would plausibly influence the way an individual interprets, and what they learn from, the receipt of supportive/unsupportive actions of others (i.e., in addition to other influences, such as those of cultural norms). Individuals' behaviors in response to the actions of others could also subsequently influence the availability of social support, where less objectively available support can also have adverse influences on health (33).

It is also widely recognized that these mediating psychological/behavioral variables have an underlying biological basis in the brain and body (including significant genetic contributions, e.g., for work supporting the heritability of personality variables, see (34,35)). To date, empirical work on these biological underpinnings has focused on characterizing a set of mechanistic, causal, and potentially explanatory links between (*a*) the neural basis of perception of social support (or the lack thereof), (*b*) the causal influence of these systems on the subsequent initiation of adjustments to the endocrine and autonomic nervous system, and (*c*) the causal influence of these endocrine/autonomic systems on peripheral organ systems and inflammatory processes known to contribute to a wide range of disease states (and to mortality generally (32,36,37)).

Such work has first argued that social support is important for survival in humans and other social species (e.g., historically, social rejection may have promoted exposure to predators, hostile conspecifics, and foreign pathogens). Based on this premise, it has then been predicted, and supporting evidence has subsequently been found for, the idea that the brain interprets social exclusion/rejection as a survival threat—engaging the same set of threat-sensitive regions (i.e., amygdala, anterior insula, dorsal anterior cingulate, and periacqueductal gray) activated by pain and other types of perceived dangers (29,38–41). Along these same lines, this work has also demonstrated that perceived social connection/caregiving is rewarding—engaging a set of reward-sensitive brain regions (ventromedial prefrontal cortex, posterior cingulate cortex, ventral striatum, septal area—regions linked to "default mode" and "limbic" networks that are also implicated in visceromotor control, see (42)) and neuromodulatory responses (involving oxytocin, endogenous opioids) that inhibit the previously mentioned threat-sensitive regions (43,44). There also seems to be both developmental and genetic influences on the function of these brain systems (45,46).

This body of work has next demonstrated that the activation of threat-sensitive brain regions (whether by physical or social threats) promotes increases in sympathetic nervous system (SNS) activation, which in turn upregulates gene expression for multiple proinflammatory cytokines (e.g., *IL6* and *IL1B*) in circulating immune cells (29,44,47–55). Activation of threat-sensitive regions also leads to activation of the hypothalamic-pituitary-adrenal axis, which releases glucocorticoids that suppress the expression of these same genes (56–58); however, when threat detection becomes chronic, it appears that the glucocorticoid response becomes desensitized/ineffective, whereas the SNS response becomes sensitized—leading to an overall increase in basal levels of inflammatory gene expression (59–61) (certain gene variants also appear to moderate the afferent influence of these upregulated inflammatory processes, e.g., see (62)). In contrast, activation of reward-sensitive regions (whether by perceived social support or other cues) has been shown to inhibit threat-sensitive regions, to reduce the previously described SNS/endocrine responses, to increase parasympathetic tone, and to decrease inflammatory activity and other related influences on peripheral organ systems (reviewed in (29)).[2]

In summary, current work suggests that a range of individual differences in personality, cognition, and behavior (themselves the joint product of innate/genetic factors and learning from earlier experience) may promote different tendencies to (*a*) perceive events as cases of social support or social rejection and (*b*) act in ways that promote increases in social support or social rejection (also see (63,64)). The perception of social rejection will activate threat-sensitive regions, whereas the perception of social support will activate reward-sensitive regions and inhibit threat-sensitive regions. Greater chronic activation within threat-sensitive regions will in turn promote autonomic/endocrine responses, which in turn increase chronic levels of circulating proinflammatory cytokines in the body. The resulting bodily state indexed by chronic SNS/endocrine/immune activation may directly contribute to poorer physical health outcomes, and via afferent feedback to the brain, it may also promote behavior patterns (e.g., "sickness behaviors") that also lead to worse physical (and emotional) health.

[2]It should be highlighted, however, that experimental work in this area has focused primarily on demonstrating acute, short-term effects of social support manipulations. Future empirical work will be necessary to better demonstrate how these short-term effects relate to longer-term health outcomes.

A MORE INTEGRATED MODEL: INCORPORATING AN EMBODIED NEUROCOMPUTATIONAL PERSPECTIVE

Although previous theoretical/empirical work in this area has clearly begun to incorporate more interdisciplinary perspectives, the field would currently benefit from further integration of conceptual resources and empirical findings in other research areas. For example, the utility of computational perspectives on the brain has recently been recognized as of potentially great importance to psychiatry (65) and to psychosomatic medicine (66); however, limited work to date has attempted to draw on this perspective to understand the link between social support and health or for clarifying the biopsychosocial model more generally (for a recent computational model of interactions between social support and mood, see (67)). Relatedly, there is a large body of work in cognitive science on embodied cognition, which provides important insights regarding the nature of health-relevant brain-body interactions; however, to our knowledge, the conceptual resources provided by such work have yet to be fully applied to the biopsychosocial model as a whole. One notable exception is recent work on social baseline theory (41,68), which has begun to highlight the potential utility of a broadly embodied, Bayesian perspective in social support research. Some aspects of the framework we illustrate hereinafter can therefore be seen as adding concrete detail to, and a broader application of, these recent suggestions.

We will now outline how these (and related) bodies of work, by building on previous attempts to create an embodied computational theory of brain function (e.g., (69,70)), may help provide a broader and more complete perspective on the links between social support and health. We will first review relevant work supporting these perspectives generally. Then, we will illustrate how they can be added to, and integrated with, the work on social support and health described previously. In later sections, we will then demonstrate how the resulting integrated model can be generalized to other biopsychosocial phenomena.

Embodied Cognition

Within cognitive science, a large body of work has illustrated the strong relationship between cognition and the body and specifically how perception, cognition, and behavior seem to be much more overlapping and intertwined than previously assumed (69,71,72). As a whole, it is beyond the scope of this article to thoroughly review this literature. Instead, we will focus on one set of findings regarding the perception of "affordances" (or opportunities for action) that shed light on how representations of current and predicted future states of the body implicitly influence perception and how this in turn may function to optimize decision-making and behavior.

Affordances refer to the properties of objects that indicate how they can and should be used, acted upon, or interacted with in a given situation. The work on perception of affordances, broadly construed, suggests that humans do not actually perceive mind-independent properties of the world, such as steepness, height, weight, and distance. Instead, we perceive opportunities for action (i.e., affordances) that differ depending on the current state of the body and available resources/demands in the current context. For example, people with longer arms (and people given reach-extending tools) reliably perceive target objects as closer, suggesting their conscious perception actually tracks how "reachable" the object is (73–75). As another example, recent work on the size-weight illusion (i.e., where one object is incorrectly perceived to be heavier than another because of its size) similarly suggests that the property being perceived is better described, not as weight, but as "throwability" (76). Furthermore, feeling fatigued, wearing a heavy backpack, being in worse cardiovascular shape, and experiencing chronic pain have each been associated with perception of longer path distances (i.e., perception of "walkability") (77–79); distance perception has also been shown to interact with affective approach/avoidance tendencies (80). Other examples abound: baseball players with better batting averages perceive the ball to be larger (81); golfers who are better at putting perceive the hole to be bigger (82); individuals with larger hands perceive graspable objects to be smaller (83); and individuals feeling greater fear perceive declining slopes to be steeper (84). Thus, in these contexts, humans are better described as perceiving affordances such as how throwable, graspable, walkable, and climbable something is, given the state of the body and contextual task demands. This in itself provides currently underappreciated links between social/psychosomatic medicine and everyday cognition.

Of direct relevance to the current topic of social support, one study in this literature found that a hill was reliably perceived as less steep when an individual was accompanied by a friend versus alone (or if they simply imagined a supportive versus unsupportive individual) and that this effect was moderated by relationship quality (85). This suggests that perceived social support alters neural estimates of the physiological resources required to deal with challenge. When combined with other work illustrating that affordance perception effects are mediated by internal motor simulations (73), it is plausible to suggest the following account. First, to estimate steepness, the brain simulates attempts at climbing the hill, including a comparison of available physiological resources to those required for success in these simulations. Second, the reason social support reduces the perceived steepness is that in the presence of social support, the brain predicts/simulates the need for fewer physiological resources to succeed. The brain does not predict the need to tax the body's physiological resources as much when external sources of support are also available. This therefore has direct implications for how perceived social support can alter (*a*) conscious perception/appraisal of the demands of a situation, (*b*) how the brain regulates the viscera, and (*c*) decisions regarding how to act.

Computational Neuroscience

Recent work in computational neuroscience has provided biologically plausible process models that are capable of accounting for, and providing insights regarding, the findings in the embodied cognition literature described previously. Specifically, these models naturally account for the motor simulation process described previously, as well as the processes that allow the brain to predict required physiological resources within a particular interoceptive/exteroceptive context (e.g., (86–88)). Such models also span various levels of organization of the nervous system, including both large-scale network functions and smaller-scale cellular/synaptic interactions.

Thorough reviews of computational neuroscience and its growing role in understanding pathology within cognition-, emotion-, and interoception-related functions have been recently provided by others (e.g., (65,88–91)). Here, we will focus mainly on one class of proposals in this area, here referred to as the predictive

processing (PP) perspective (i.e., this perspective more specifically includes "predictive coding" for perception and "active inference" for visceral/skeletomotor control; described hereinafter). These models have recently shown considerable promise in their ability to account for interactions between exteroceptive perception, visceral regulation, skeletomotor action, and cognition (e.g., see (86–88,92–96)). The PP perspective suggests that the brain implements a hierarchical generative model of what is happening, both inside the body and out in the world, across various spatial and temporal scales. At hierarchically low levels of processing (i.e., primary sensory cortices), the brain is envisioned to continuously use this model to generate predictions about sensory input for each modality separately (e.g., vision, audition, interoception, proprioception, etc.); this is referred to as "predictive coding" (94). When these predictions are incorrect, prediction-error signals are generated that drive changes to the internal model until prediction-error is minimized—leading to updated internal representations of the most likely causes of sensory input (i.e., perception/recognition). Higher levels in the brain (e.g., secondary sensory cortices, association cortices) also attempt to predict how the lower-level representations will change, and a similar prediction-error minimization process also leads to revision of these higher-level representations. Many levels of representation are envisioned to exist within the brain and operate in this fashion—each sending predictions to their own level and to the level below (mediated by layer 5/6 cortical pyramidal neurons) and each sending prediction-error signals to their own level and to the level above (mediated by layer 2/3 cortical pyramidal neurons).

This message-passing scheme allows for a biologically plausible implementation of algorithms that approximate hierarchical Bayesian inference. Specifically, the mathematics of the PP framework approximate the hierarchical application of Bayes' theorem to probability distributions (i.e., with means and variances) over possible states of the body/world (i.e., at different levels of description) within a generative model. When used in perception/recognition processes, a generative model (m) can be thought of as combining a probabilistic mapping from possible states of the body/world (x) to patterns of sensory input (y), the so-called "likelihood function" $P(y \mid x, m)$, with an a priori probability distribution over possible states of the body/world, the so-called "prior" $P(x \mid m)$—allowing the model to generate (or "simulate") sensory data (i.e., by sampling a value from the prior distribution and inserting it into the likelihood function). Then, given a pattern of sensory input, this process can be inverted to infer the possible state of the world that most likely caused that pattern of input (i.e., the "posterior" $P(x \mid y, m)$) using Bayes' theorem:

$$\mathrm{P}(x \mid y, m) = (\mathrm{P}(x \mid m) \times \mathrm{P}(y \mid x, m))/\mathrm{P}(y \mid m).$$

The most probable state of the body/world under the posterior at a given level of description then corresponds to what is perceived/recognized. This process can then be iterated hierarchically, where estimates at higher levels of a generative model can be used to inform/constrain estimates at lower levels (e.g., inferring the probability of the visual perceptual property "white" at a lower level, given the probability of the conceptualized object "baseball" estimated at a higher level). Thus, the PP framework addresses with mathematical precision how the mind/brain interprets current sensory input based on prior knowledge and provides a mechanism for updating those preexisting beliefs, given that it is impossible to know for sure what is happening in the external world (including what is happening in the body; i.e., because sensory input is noisy/ambiguous, and always consistent with multiple interpretations). For a primer on the detailed mathematics, and its proposed algorithmic/physiological implementation using prediction and prediction-error signals, see (97).

Importantly, because high-level representations are multimodal, in that they attempt to predict the way lower-level representations in different sensory modalities will change together (and over time), this allows the brain to learn about the cross-modal relationships between interoception and exteroception. Thus, if minimization of a visually induced prediction-error signal led to changes in high-level representations, this could also activate a change in high-level predictions about interoception (i.e., visually perceiving something could lead to changes in the way the body is perceived as well). In symmetric fashion, changes in the body (conveyed by interoceptive prediction errors) could also influence high-level visual predictions (i.e., visual perception could be influenced by one's current visceral state). Thus, this aspect of the PP perspective is capable of capturing the empirical phenomena described previously, in which exteroceptive perceptions of social support can influence interoceptive predictions, and visceral states can in turn influence exteroceptive perception. Consistent with this perspective, some of the threat-sensitive cortical regions described previously (e.g., anterior insula and anterior cingulate; sometimes referred to as central hubs of the "salience network") represent examples of high-level, multimodal regions that are believed to serve the function of directing cognition/attention toward information relevant to visceral regulation (42).

Beyond unimodal and multimodal perception/recognition, the PP perspective has also been extended to account for both motor control and context-dependent neuromodulatory function. Briefly, this extension of the PP perspective—termed "active inference"—suggests that downward prediction signals to skeletomotor and visceromotor reflex arcs (i.e., proprioceptive and interoceptive predictions, respectively) can act to modify the set points for those reflex arcs, which can subsequently lead the relevant effectors (i.e., muscles, organs, etc.) to change their activity to match the updated set points (86,91,98). Essentially, this allows proprioceptive predictions to control skeletomotor actions and it allows interoceptive predictions to regulate visceral activity. Furthermore, the balance between perception and action in these models is under the dynamic control of neuromodulatory processes that regulate postsynaptic gain (i.e., the "weight" of prediction and prediction-error signals exchanged between brain regions) in a context-dependent manner. For example, when these processes amplify the strength of proprioceptive/interoceptive *prediction* signals, this will favor bodily action. In contrast, when these processes amplify the strength of low-level proprioceptive/interoceptive *prediction-error* signals, this will favor internal model revision and changes in bodily perception. This neuromodulatory process—termed "precision weighting"—is theorized to modulate postsynaptic gain based on estimates of signal reliability (via a diverse set of mechanisms involving the norepinephrine, dopamine, and acetylcholine systems, and local GABAergic inputs, among others—and their interactions with high-level regions that represent current goals and other relevant aspects of the current context), such that prediction-error signals expected to have higher reliability (i.e., a higher signal-to-noise ratio,

termed higher precision) in a given context are amplified, whereas those with low reliability estimates are attenuated (95,96,99). This is based on the following generic belief update rule (100):

$$\Delta\mu_i \propto (\pi_{i-1}/\pi_i) \times PE_{i-1}$$

Which can be read as "the change in the belief at the higher level, $\Delta\mu_i$, is proportional ($\propto$) to the ratio of the estimated precision at the lower level, π_{i-1}, to the precision of the current belief at the higher level, π_i, multiplied by the prediction-error signal passed upward from the lower level to the higher level, PE_{i-1}." Thus, prediction errors lead to substantial revisions of an internal model when they have high estimated precision (i.e., the postsynaptic gain of the synapses communicating these prediction-error signals will be upwardly modulated), but have very little effect when they have low estimated precision (i.e., or when the higher level prior has very high precision). To now reiterate the description in the previous paragraph, in active inference, it is when high precision is assigned to the previous predictions for interoceptive/proprioceptive states that are passed downward that this has a strong top-down effect on the set points of skeletomotor and visceromotor reflex arcs, leading to changes in body states/behaviors.

This extension of the PP perspective provides plausible mechanisms by which the brain can perceive something exteroceptively, leading to updated multimodal predictions that also include interoception and proprioception, and how these updated multimodal predictions can then be used to regulate the viscera and control behavior. For example, it provides a mechanism allowing visual perception/recognition of social support to engage interoceptive predictions pertaining to decreased metabolic demand; these predictions (when given high-precision weightings) would then induce a low-arousal visceral state. The same mechanism also allows visual perception/recognition of social threat to engage interoceptive predictions pertaining to increased metabolic demand; these predictions (when given high-precision weightings) would then induce a more high-arousal visceral state. As another example, such mechanisms would also allow perception/recognition of social support or social threat to engage different proprioceptive predictions (i.e., emanating from the somatomotor network (42,101)), which (when given high-precision weightings) would lead to different behavioral responses (e.g., smiling versus frowning, approaching versus avoiding, etc.).

To illustrate how this approach has the potential to offer quantitative modeling advances in biopsychosocial research (Figure 1), we will now offer one simplified example (i.e., using single probability values instead of probability distributions with means and precisions) to provide an intuition about the kind of probabilistic mathematical precision that Bayesian computation can allow (i.e., which PP algorithms approximate). In this context, Bayes' theorem can be formulated as follows:

$$P(H|E) = (P(H) \times P(E|H))/((P(H) \times P(E|H) + P(\neg H) \times P(E|\neg H))$$

This is read as "The probability of a hypothesis given some evidence, P(H | E), is equal to the product of the prior probability of that hypothesis, P(H), and the likelihood of getting that evidence if the hypothesis were true, P(E | H), divided by the sum of (*a*) the product of the prior probability of that hypothesis, P(H), and the likelihood of getting that evidence if the hypothesis were true, P(E | H) and (*b*) the product of the prior probability of that hypothesis being false, P(¬H), and the likelihood of getting that evidence if the hypothesis were false, P(E |¬H)."

To see how this applies to the type of hierarchical model shown in Figure 1, consider a case in which an individual has just perceived an ambiguous facial expression (a cryptic smile) from a co-worker and is trying to infer whether the co-worker likes them (i.e., the presence of SOCIAL SUPPORT) or dislikes them (i.e., the presence of SOCIAL THREAT). For the sake of this example, assume that these are the only two relevant concepts that the individual has acquired in their internal model (i.e., SOCIAL SUPPORT and SOCIAL THREAT). Next assume that the individual has two pieces of information: (*a*) an abstract expectation that "people tend to be unsupportive" and (*b*) the cryptic smile. Further assume that (*a*) given the previously stated abstract expectation, P(SOCIAL SUPPORT) = .3 and P(SOCIAL THREAT) = .7 within their internal model (i.e., SOCIAL THREAT is more likely when this higher-level expectation is active) and that P("cryptic smile" | SOCIAL SUPPORT) = .6 and P("cryptic smile" | SOCIAL THREAT) = .4 (i.e., this ambiguous smile is slightly more consistent with SOCIAL SUPPORT than with SOCIAL THREAT in their internal model, but it could still indicate ridicule, etc.). Thus, if an individual's brain were using an algorithm that approximates Bayes' theorem (i.e., as in the PP framework), the inference would look as follows:

$$P(\text{SOCIAL SUPPORT} \mid \text{"cryptic smile"}) = (.3 \times .6)/((.3 \times .6) + (.7 \times .4)) = .18/.46 = \mathbf{.39}$$

$$P(\text{SOCIAL THREAT} \mid \text{"cryptic smile"}) = (.7 \times .4)/((.7 \times .4) + (.3 \times .6)) = .28/.46 = \mathbf{.61}$$

Thus, the individual's brain would infer that SOCIAL THREAT is more likely—corresponding to the conscious belief that the other individual is acting in an unfriendly manner. Similar computations one level below could then be used to derive probabilistic predictions about physiological/behavioral demands in a particular context given the belief that the person dislikes them, and, if these interoceptive/proprioceptive predictions were assigned high-precision weightings, they would subsequently lead to a specific amount of increased autonomic arousal and avoidance behavior. Importantly, if the individual instead entered the previously described situation with a stronger (i.e., higher probability) abstract expectation that "people tend to be supportive" within their model, it should be clear that the person would infer SOCIAL SUPPORT and subsequently react with a very different physiological/behavioral response (i.e., a low-arousal state and approach behavior in Figure 1). It should be highlighted, however, that this example refers to the perception of a single event and its link to physiological and behavioral responses. The link between such events and more stable, long-term differences in perception, physiology, and behavior would require further explanation, and as discussed further hereinafter, it may involve feedback loops that maintain prior probability estimates favoring perception of threat versus support throughout life more generally.

Example Neural Implementation

To provide an intuition about how this type of mathematical modeling can relate to neurobiology, consider the simplified example in Figure 2 (based on (97)). In Figure 2A, a network of four cortical pyramidal neurons (blue triangles) connected by a set of axons/synapses

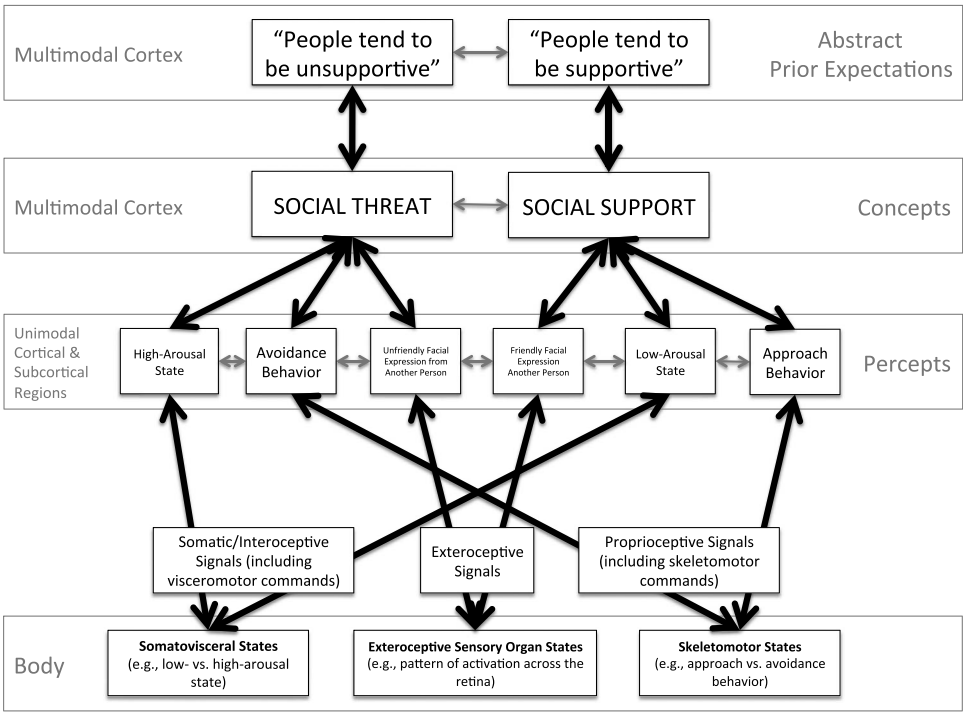

FIGURE 1. Hierarchical basis of PP. At the highest level, the brain represents the probability of a set of abstract, long timescale expectations about the world (in this case, whether or not people tend to be supportive); these act as Bayesian Prior Probability estimates, which directly influence concept-level interpretations of multimodal sensory input. Based on these innate and/or learned expectations, certain conceptual descriptions of perceived events are predicted to be more likely (in this case, the presence of SOCIAL THREAT or SOCIAL SUPPORT). When activated, each of these concepts in turn predicts the co-occurrence of different percepts across different sensory modalities. Here, SOCIAL THREAT predicts the co-occurrence of the exteroceptive percept of "Unfriendly Facial Expression from Another Person," the somatic/interoceptive percepts associated with a "high-arousal state," as well as proprioceptive percepts associated with skeletomotor actions involving "avoidance behavior." SOCIAL SUPPORT instead predicts the co-occurrence of the exteroceptive percept of "Friendly Facial Expression from Another Person," the somatic/interoceptive percepts associated with a "low-arousal state," as well as proprioceptive percepts associated with skeletomotor actions involving "approach behavior." Active inference models suggest that interoceptive and proprioceptive predictions can, when assigned high precision, be fulfilled by (and therefore act as) visceromotor and skeletomotor commands, respectively. In the context of an ambiguous facial expression from another person (cryptic smile), this example indicates how abstract expectations about whether or not people tend to be supportive will determine whether that facial expression is perceived as friendly or unfriendly, whether the individual will recognize social support or social threat, and whether they will respond with a low- versus high-arousal state and with approach versus avoidance behavior. Black arrows indicate the exchange of mutually reinforcing top-down predictions and bottom-up prediction-error signals between hierarchical levels (e.g., SOCIAL THREAT predicts a "high-arousal state," and prediction-error signals due to the unpredicted perception of a high-arousal state would drive bottom-up increases in the probability of SOCIAL THREAT). Signals exchanged between inconsistent representations at different levels are omitted for clarity (e.g., between SOCIAL SUPPORT and "Unfriendly Facial Expression from Another Person"). Smaller gray arrows indicate lateral (within-layer) excitatory and inhibitory signaling, allowing, for example, the activation of SOCIAL THREAT representations to inhibit the activation of SOCIAL SUPPORT representations, or allowing "Unfriendly Facial Expression from Another Person" representations to directly prime predictions about avoidance behavior (e.g., if these were consistently activated together in past experience).

(black lines) is displayed (those ending in arrows are excitatory; those ending in filled circles are inhibitory). The higher-level neuron marked "SS" estimates the level of social support (i.e., higher levels of activity indicate higher levels of perceived social support). The lower-level neuron marked "SM" estimates the degree of smiling in another person's facial expression (i.e., high levels of activity indicate smiling and low levels indicate frowning). The two neurons "PE_{SS}" and "PE_{SM}" indicate prediction errors for the higher and lower levels, respectively. The SM neuron receives information about sensory input from below, whereas the SS neuron receives prior prediction signals (Pr_{SS}) from higher levels (stored in the strength of the descending axon's synapse). The precision/reliability estimates of prediction errors at each level (π_{SS} and π_{SM}) are stored in the synaptic strengths of the looping axons that both leave from and return to each PE neuron (which, although not explicitly modeled in this example, can also be further modulated by higher-level expectations; dashed arrows). The relationship between level of smiling and level of social support is assumed to be positive and linear (i.e., all else being equal, more smiling indicates more social support). As thoroughly explained elsewhere (97), under Gaussian assumptions, this type of network can approximate Bayesian inference.

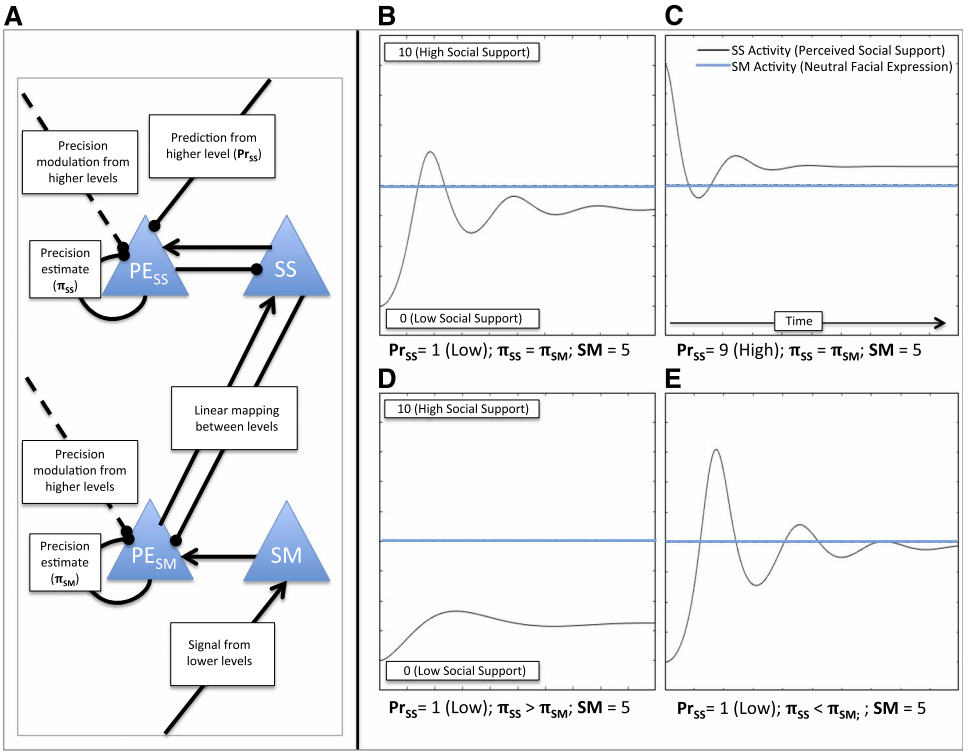

FIGURE 2. Panel A provides a simplified example of a possible neural implementation of an internal model guiding perception of social support (described more thoroughly in the text, section 3.3). Blue triangles indicate cortical pyramidal neurons, and black lines indicate axons terminating in synaptic connections. Arrows indicate excitatory synaptic influences, and circles indicate inhibitory synaptic influences (dashed arrows are not modeled but indicate additional context-specific modulatory influences that would be present in a more complete model). Activity of the SS neuron estimates level of social support, and SM neuron activity represents level of smiling in the perceived facial expression of another person (i.e., low activity indicates a clear frown and high activity indicates clear smile). The two PE neurons reflect prediction errors associated with expected social support (higher level) and with SM activation (lower level). The strength of the two looping axons' synapses (connecting each PE neuron to itself) estimates the precision (reliability) of prior expectations (π_{SS}, higher level) and SM activity (π_{SM}, lower level). Expected social support (Pr_{SS}) is conveyed through the strength of the top-down inhibitory synapse on the higher-level PE neuron. Although not modeled here, PP models also include quantitative synaptic learning mechanisms (i.e., update equations) allowing the strengths of the Pr_{SS}, π_{SS}, and π_{SM} synapses (i.e., prior expectations and precision estimates) to be altered over time to better match patterns in experience. Panels B to E illustrate changes in SS neuron activity (i.e., perceived social support; black lines) over time when presented with a neutral facial expression (i.e., moderate SM activity, most consistent with a neutral amount of social support, all else being equal; blue lines) under different model parameter values. These different parameter values reflect (*a*) prior expectations of low (B) versus high (C) levels of social support and (*b*) high (D) versus low (E) reliability estimates for expectations of low social support. As can be seen, after SS neuron activity stabilizes, lower levels of social support are perceived in B compared with C (reflecting the influence of prior predictions) and in D compared with E (reflecting the influence of higher reliability estimates for prior predictions of low social support). For the detailed mathematics on which this example is based, see (97). Color image is available only in online version (www.psychosomaticmedicine.org).

In Figures 2B to E, simulations of network activity are shown when a neutral facial expression is observed (i.e., SM neuron activity at a level of 5 on a scale from 0 to 10) given different prior expectations and precision/reliability estimates. In Figures 2B and C, the individual has a prior expectation of low versus high social support (1 and 9, respectively). As can be seen, after neural activity levels stabilize, the estimated level of social support (i.e., level of activity in the SS neuron) is lower than 5 in the first case and higher than 5 in the second case, although the sensory input (represented by SM activity) is identical. In Figures 2D and E, the precision estimate for prior expectations indicates high versus low reliability levels, respectively (i.e., where the prior for social support is 1 in each case). As can be seen, sensory input has a much weaker influence on perceived social support when an individual implicitly believes that their expected level of social support is highly reliable (i.e., in Figure 2D). This example concretely illustrates how precise mathematical simulations of brain function could be used to model individual differences in perceived social support. Other elements of these types of models also allow prior expectations and precision estimates to be modified through repeated experience over time (i.e., by altering synaptic strengths (97)), but the mathematical details of these model elements are beyond the scope of the present manuscript.

It is worth noting that almost all of what occurs in such networks is implicit (e.g., priors, precision estimates, changing levels of prediction error, etc.). Only the final estimate of a perceived quantity (e.g., the stable level of activity in the SS neuron above) is typically treated as a candidate for conscious experience. Thus,

a person could experience perceiving lower versus higher levels of social support, but they need not be aware of why or how that percept was generated. It is also worth noting that the previously mentioned simulation used a continuous representation of social support (i.e., from low to high levels), whereas our earlier example used discrete representations (i.e., the binary presence of either SOCIAL SUPPORT or SOCIAL THREAT). The PP perspective offers approaches for modeling both continuous and discrete representations (and ways in which they can interact, see (102,103)), because each approach can be useful in different contexts (e.g., low-level perception versus conceptualization and decision-making). The biopsychosocial phenomena we describe here are somewhat general in that there are ways they could be modeled in both a discrete and continuous (or mixed) fashion.

Further Theoretical Advantages of Integrating Predictive Processing and Embodied Cognition to Understand the Social Support-Health Relationship

The explicitly hierarchical nature of the extended PP perspective also offers two additional advantages. First, it offers a direct means of implementing the motor simulation process that mediates affordance perception in the presence/absence of social support. Second, it offers a broader perspective on the contribution of different cortical and subcortical structures in mediating the link between perceived social support and visceral/behavioral responses (and their associated health consequences). The first advantage, regarding motor simulation, has been previously discussed in the context of cognitive control and decision-making (86,104). Essentially, by temporarily attenuating the postsynaptic gain (precision) of low-level predictions and prediction errors (i.e., preventing belief updating and the efficacy of efferent influence on skeletal muscle), higher-level brain regions can launch predictions about the selection of different actions in the current context, and allow the brain's internal model to simulate the expected outcome across cortical sensory and motor systems, without these predictions affecting actual behavior. The multimodal predictions engaged during this process (which would take perceived social support into account) would therefore be expected to influence exteroceptive perception and would ultimately contribute to the final action chosen.

The second advantage, regarding understanding the distinct contribution of cortical and subcortical structures, has been previously elaborated within recent extensions of the neurovisceral integration model (87) and recent explicitly mathematical Bayesian models of homeostasis and allostasis (88). As reviewed in detail there, specific subcortical structures (e.g., amygdala, periacqueductal gray, several hypothalamic and brainstem nuclei) can be understood as issuing the low-level interoceptive/proprioceptive predictions that initiate, maintain, and regulate visceral/skeletomotor responses; many of these nuclei also influence neuromodulatory functions and can therefore further adjust information processing (i.e., precision-/reliability-based weighting via adjusting patterns of postsynaptic gain) across cortex (e.g., altering biases in attention and memory retrieval). As long as the low-level predictions of these subcortical regions remain stable, a given pattern of bodily states and cognitive modulation can therefore be maintained. We refer to these bidirectional interactions between subcortical systems and the body (and its upward modulatory influence on cortical information processing), in which low-level predictions (regarding expected physiological/behavioral demands in a situation) maintain particular bodily response patterns (i.e., minimizing afferent prediction-error signals from the body), as the "Subcortical Response Generation/Maintenance Loop" (depicted by red arrows in Figure 3).

In the previously mentioned models (87,88), these low-level predictions in turn depend on higher-level cortical predictions that represent (*a*) current perceptions and (*b*) their inferred conceptual meaning (e.g., perceiving an increase in heart palpitations, and inferring that this means you are having a heart attack; or perceiving those same heart palpitations, but inferring that they instead indicate anxiety). In the context of new sensory input, ambiguities in perception and conceptualization will further be resolved via the influence of even higher-level (and goal-/context-specific) predictions/expectations emanating from long-term memory systems (i.e., based on patterns in one's own past experience, and [possibly innate] differences in personality and cognitive style). Thus, for example, if a person has learned from past experience to expect that cardiac conditions run in their family, then they may also be more likely to perceive/recognize them as evidence of a heart attack. Such perceptions/conceptualizations may predict the need for greater physiological resources to deal with the demands of the situation, leading subcortical regions to then alter set points in homeostatic reflexes and generate an even higher arousal visceral state. These higher-level cortical processes and the prediction/prediction-error signals they exchange with subcortical regions are depicted by the blue arrows in Figure 3. We refer to the combination of the red and blue arrows in Figure 3 as the "Intrapersonal Loop" (i.e., with the first loop nested inside of it), because it allows the generation, maintenance, and regulation of bodily/cognitive reactions in response to the activation of self-related percepts, concepts, and memories.

Finally, the green arrows in Figure 3 depict one's own externally perceptible actions/behaviors, and the exteroceptively detectable consequences of those actions/behaviors. For example, you may smile at someone, subsequently perceive that person smiling back at you in response, and you may infer that this means that they are supportive, or you might perceive a neutral facial expression in response and infer that they are hostile and unsupportive. This "social loop" (with the other two loops nested inside of it) illustrates how the externally perceptible aspects of one's own bodily responses/behaviors can causally influence the state of the world around us (including the state of other individuals) and how this can affect the subsequent sensory inputs we receive. Just as described previously, and drawing on the same multimodal cortical systems described previously, subsequent ambiguities in perception and conceptualization will be resolved via the influence of higher-level predictions/expectations. Thus, for example, if one has learned from past experience to expect that a certain individual will act in an unfriendly manner, then one may be more likely to perceive a neutral/ambiguous expression from that individual as negative and be more likely to conceptualize that individual as unsupportive. Such perceptions/conceptualizations would likely also predict the need for greater physiological resources to deal with the demands of the situation, leading subcortical regions to generate a high-arousal visceral state, changes in one's own facial expression, and other changes in behavior (i.e., some of which the other individual may perceive and respond to, leading the loop to continue).

The role of a wide range of cortical regions/systems in these second and third loops is supported by recent evidence of a

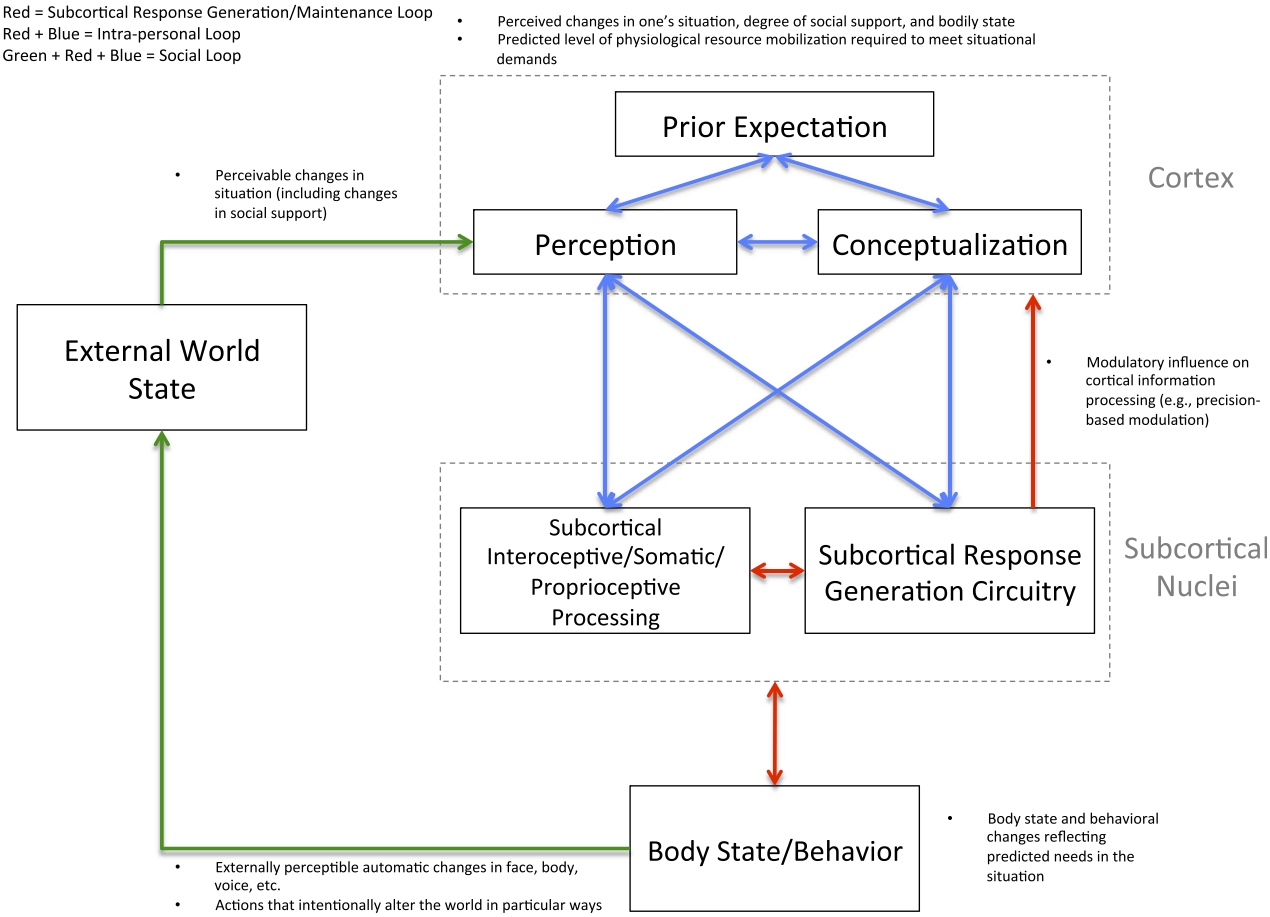

FIGURE 3. Three nested loop model. In this model, the red "Subcortical Response Generation/Maintenance Loop" is involved in activating and maintaining particular somatic/visceral states (or patterns of evolving states) and in upwardly modulating higher-level cortical processing (e.g., adjusting patterns of postsynaptic gain). This loop is nested within a larger "Intra-personal Loop" that also contains the blue arrows. This loop allows the cortical perception and conceptualization of afferent bodily sensations (biased by higher-level prior expectations; e.g., inferring that bodily sensations are due to SADNESS, given prior expectations in the context of a funeral), and it allows these cortical representations to drive changes in subcortical activity and to the responses they generate/maintain. This loop is in turn nested within a larger "social loop" that also contains the green arrows. This loop allows body state changes (e.g., facial expressions, overt behaviors) to be perceived by others and to influence the external environment more generally. The subsequent consequences (e.g., the reactions of others, other changes in the environment) are subsequently perceived and conceptualized in light of prior expectations. This can similarly alter subcortical responses and subsequent changes in body states (i.e., visceromotor and skeletomotor actions/behaviors). In this model, a wide range of subcortical nuclei are expected to contribute to the processes described previously, including the amygdala, basal ganglia, hypothalamus, thalamus, periacqueductal gray, a range of autonomic brainstem nuclei, and neuromodulatory system nuclei (e.g., the noradrenergic locus coeruleus, serotonergic raphe nuclei, acetylcholinergic basal forebrain nuclei, and dopaminergic midbrain nuclei). Relevant cortical regions could plausibly include unimodal sensory cortices (perception), default mode network cortices (conceptualization), medial temporal lobe cortices (prior expectations from long-term memory), executive control network cortices (goal-based prior expectations), salience network cortices (prior expectations based on current body state), and limbic network cortices (visceromotor predictions influencing subcortical nuclei; for greater discussion of these networks/functions, see (42,101)). Although not an explicit focus of the present model, genetic factors are expected to influence all of the processes discussed previously in complex ways (e.g., by predisposing individuals toward developing different top-down expectations, biasing attention and decision-making, promoting stronger/weaker visceral/inflammatory responses, etc.). Color image is available only in online version (www.psychosomaticmedicine.org).

large-scale brain system supporting emotion, interoception, and visceral regulation (also termed allostasis (92,105)). This evidence supports a model in which the dorsal mid/posterior insula computes prediction-error signals between afferent visceral signals (i.e., conveyed by the subcortical nuclei described previously) and higher-level prediction signals emanating from the ventral anterior insula and anterior cingulate cortex (hubs of the salience network) and from surrounding medial prefrontal cortex regions that participate in multimodal conceptualization processes as part of the default mode network ((105–108), e.g., for evidence supporting the role of prediction signals in these regions in regulating stressor-evoked cardiovascular reactions in particular, see (47,109)). Default mode network regions (e.g., medial prefrontal cortex, posterior cingulate cortex, lateral temporal cortex, medial temporal lobe) seem to play an important role in conceptualizing interoceptive/exteroceptive perceptual representations in light of past

experience and subsequently initiating high-level influences over the Subcortical Response Generation/Maintenance Loop. For example, recent studies have found that inflammatory markers are linked to functional connectivity in the default mode network (110) and that altered top-down influences of medial prefrontal regions on the amygdala are associated with real-world avoidance behavior (111). Of particular relevance to the example illustrated in Figure 1, another study has shown that during the perception of social exclusion, altered medial prefrontal activation is associated with nonsuicidal self-injury (112), which is a type of avoidance behavior (i.e., acting as a distraction from emotional distress (113,114)). Thus, default mode network and salience network regions may play an especially important role in the processes assigned to cortical function in Figure 3, although other regions/networks are also expected to make relevant contributions (see the Figure 3 legend for a brief list of other candidate brain regions/networks that may be associated with these processes).

IMPLICATIONS FOR UNDERSTANDING THE LINK BETWEEN SOCIAL SUPPORT AND HEALTH

One primary benefit of the embodied neurocomputational perspective advocated here is that it *organically integrates* the different elements in the chain of mechanistic causation from social support to medical outcome. This could help advance biopsychosocial science in some important ways, including (*a*) potentially generating novel hypotheses regarding plausible mechanistic explanations for previously observed correlational and causal relationships and (*b*) potentially highlighting novel therapeutic intervention strategies targeting, for example, the mechanistic "points of contact" between psychosocial and biological variables highlighted within the model. As illustrated by the examples in the previous section, the model depicted in Figure 3 (i.e., which is just a more general way of depicting the structure shown in Figure 1 and its interactions with the outside world) can incorporate all major aspects of the previous work on social support and health in a fairly simple set of three nested causal loops; however, it can also provide unifying insights allowing previous findings to be understood in terms of domain-general embodied computational processes. For example, relevant individual differences in personality and cognitive style identified in previous work are accounted for primarily by the domain-general top-down influence of prior expectations on perception and conceptualization (e.g., abstract expectations reflecting optimism versus pessimism, one's level of self-efficacy, the ability to control the environment, etc.), which are in turn understood as reflecting the combined contribution of innate/genetic factors and differences in previous experience. These differences moderate the degree to which individuals will perceive/recognize external events as indicative of the presence of social support versus social threat; high-level representations mediating expectation and conceptualization are also multimodal, allowing changes in body state to update these representations and subsequently influence external perception (and vice versa). The threat- and reward-sensitive regions in previous models can also be identified as either (*a*) cortical regions that mediate perception, conceptualization, and high-level prior expectation (e.g., default mode network and executive control network regions are likely especially important for conceptualization and high-level expectation-related processes (42,87,115)) or (*b*) subcortical regions that contribute to lower-level control of skeletomotor/visceromotor responding.

Differences in the state of the autonomic/endocrine/immune system, which are suggested to proximally lead to differences in physical health outcomes in previous work, are accounted for by chronic subcortical predictions regarding high physiological demands—leading to increases in physiological arousal—which may remain chronic because of the continued perception/recognition of threat. In our model, this chronic perception of threat may in turn be biased by bottom-up modulatory influences on cognition (e.g., increased attention to the possibility of threat due to afferent feedback indicating high levels of inflammation; i.e., acting as probabilistic evidence that threat is more likely) as well as learned top-down expectations (62,64). The role of differences in behavior in promoting differences in social support and health is also accounted for by the outermost loop of our model. For example, this allows some patterns of behavior to garner additional perceived social support, while allowing others to promote perceived social rejection instead. This further allows for virtuous and vicious cycles in which the perception of social support leads others to provide more social support, whereas the perception of social rejection leads others to act in a more rejecting manner in the future. One important example of such phenomena is the considerable body of work showing that higher hostility/cynicism (i.e., not liking others and believing that others are selfish and only interested in themselves) is associated with poor cardiac outcomes (e.g., (116–118)). For example, this could be explained (at least in part) by the fact that, all else being equal, the prior expectations associated with hostility/cynicism would promote (*a*) perceptions of selfishness in others, (*b*) interactions that would promote more hostile responses from others (and subsequently greater social isolation), and (*c*) chronically higher autonomic arousal within such social interactions (reduced vagal tone, increased inflammation).

This model is also fairly general in its ability to account for related phenomena. As another example, consider the relationship between low SES (especially during childhood) and worse health outcomes (9,119,120). One hypothesis that could be generated by our model pertains to the influence of learned expectations in a low SES environment—such as expectations for unpredictability, unhealthy living conditions, and unhealthy behaviors. In PP models, learned expectations for social/environmental unpredictability would promote lower reliability estimates for expected long-term outcomes, potentially leading to greater perceptions of challenge and associated metabolic demands, increased impulsivity, reduced applications of cognitive control, reductions in expected support, and a general tendency not to invest in the future (i.e., because distant future outcomes cannot be reliably predicted within their models of the world; e.g., maintaining long-term relationships, attaining a college education, etc.). Many of these predictions are already supported by studies of "fast life history strategy" in low SES environments and by studies of children who have been raised in other socially impoverished environments (e.g., (121,122)). Unhealthy models of behavior and living conditions could also lead to the acquisition of more reliable predictive models of those behaviors and conditions, reducing the tendency to engage in healthier behaviors or to seek out healthier conditions for which they have impoverished models.

Low SES in childhood is also associated with higher levels of inflammation in adulthood, and a recent study found that the

presence of social support reduced inflammatory responses to stressors to a greater degree in those who experienced a low SES childhood (123). Such findings could be explained from the PP perspective by highlighting that (*a*) low SES in childhood would plausibly lead one to learn generic expectations of low social support and greater physiological demands in situations on average and (*b*) the perception of social support would then induce larger prediction errors (and larger subsequent revisions to visceral predictions) in individuals who grew up in low SES conditions. Our model therefore highlights the important role of learned expectations during development in contributing to differences in physiological wear and tear at baseline and in how this would interact with new experience/learning later in life. This adds a great deal of psychological complexity and sophistication to what might otherwise be thought of as straightforwardly social variables (i.e., SES and social support).

IMPLICATIONS FOR THE BIOPSYCHOSOCIAL MODEL

Domain-General Explanation and the Potential for Quantitative Modeling

As illustrated in Figure 4 (which is a generalization of the PP hierarchy depicted in Figure 1), because of the domain generality of the processes in our model, it also has the ability to organically integrate the different elements in the chain of mechanistic causation from essentially any relevant psychosocial variable to its influence on medical outcomes. Therefore, the mechanisms described previously can also (as promised in the introduction) be generalized to the larger biopsychosocial model as a whole. In Figure 3, the depicted cortical processes can apply to the perception and conceptualization of any social, environmental, or bodily variable (e.g., those associated with personal health, self-esteem, perceived discrimination, etc., (124)), as well as to any innate/learned prior expectations about anything social/environmental, psychological, or biological in one's own life. The depicted subcortical processes can then trigger changes in one's peripheral physiological state and behavior in response to any of the resulting cortical representations (based on whatever they happen to predict). The "social loop" then further allows any resulting behavior (e.g., choosing to follow a medical regimen or not, choosing to maintain contact with family or not, etc.) to influence the subsequent social/environmental and health-related events that one perceives.

As one concrete example of this type of generalizability, consider the role of the clinician-patient relationship, where a more positive relationship may promote better health outcomes (125). There are many interrelated hypotheses about this relationship that could be generated by our model. Given space constraints, however, we will focus on one for illustrative purposes: inference about a clinician's trustworthiness and motivations. In the context

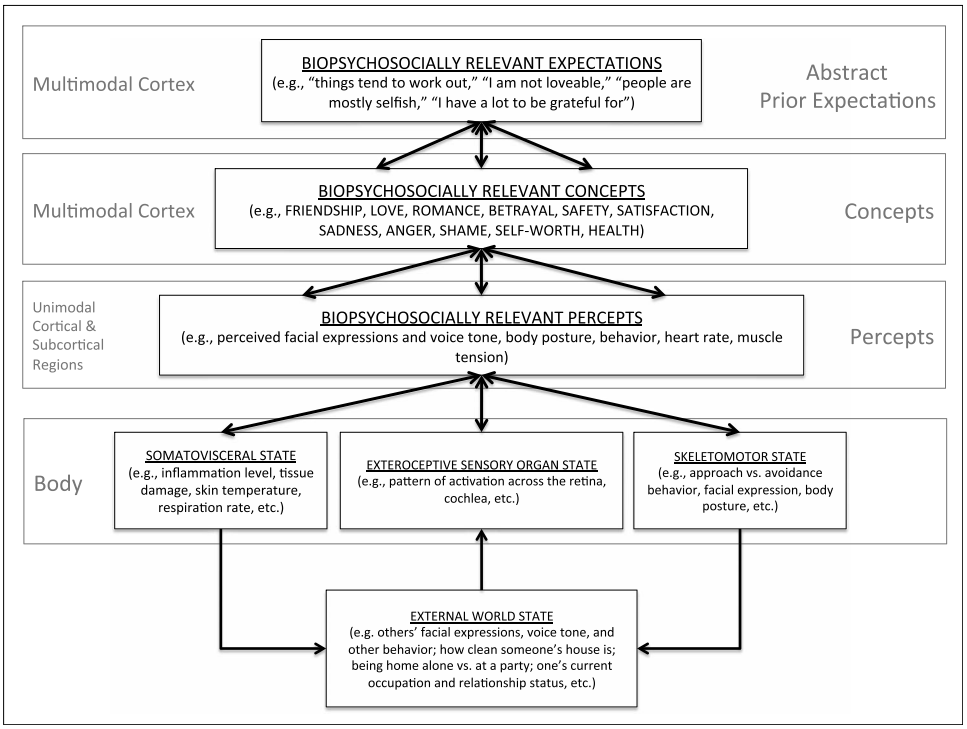

FIGURE 4. Generalization of the PP hierarchy depicted in Figure 1. This figure illustrates the domain generality of hierarchical processing, allowing its application to a wide range of biopsychosocial phenomena. Bidirectional black arrows indicate the exchange of top-down predictions and bottom-up prediction-error signals between hierarchical levels (i.e., maintaining consistency between the representations at each level with high estimated probabilities; e.g., the expectation "things tend to work out" would increase the represented probability of SAFETY but not SADNESS and vice versa). Unidirectional black arrows indicate causal interaction between bodily reactions and the external world and between the external world and exteroceptive sensory organ states. The lateral (within-level) interactions depicted in Figure 1 are not explicitly shown here; however, these would also play a role in maintaining consistency between representations (e.g., the concept of LONELINESS may activate the concept of SADNESS but inhibit the concept of CONTENTMENT).

of a warm, mutually respectful relationship, a patient's prior expectations would likely promote the inference that a clinician's treatment recommendations are reliable and reflect genuine care and concern; in contrast, in a poorer relationship (e.g., colder, less open communication, etc.), these same treatment recommendations might be perceived as less reliable/genuine (e.g., "they don't care what I'm going through, they just want my money"). In the latter case, the patient would likely arrive at more pessimistic expectations about treatment outcomes, simulate the task of following treatment recommendations as more challenging, and perceive their support system for doing so as weak or nonexistent. According to our model, this cascade of inferences would lead a patient to engage greater physiological resources when contemplating following a treatment regimen and less motivation to do so. Failure to do so could in turn promote avoidance of follow-up appointments, perceptions of disappointment and judgment, and self-perceptions of failure. This could further worsen the perceived and actual relationship with the clinician, leading to a vicious cycle.

As a second example, consider the comorbidity between major depression and poor cardiovascular health. In a previous article, we reviewed a large body of evidence supporting the existence of four nested positive feedback loops that can promote the maintenance of depressive symptoms (64), which is highly consistent with the neurocomputational framework we defend here. Briefly, this article highlighted ways in which the influence of priors for depressive schemas (i.e., from multimodal association cortices) and associated precision estimates (e.g., altered neuromodulatory influences) would promote biased inferences in perceptual systems consistent with those schemas, leading to perceptions of social rejection, an increased tendency to simulate negative possible futures in decision-making, reduced vagal tone and chronically elevated inflammation (proximally mediated by multiple subcortical nuclei), reduced motivation and increased sickness behaviors, and reduced sleep quality. We also reviewed evidence suggesting that these effects would in turn maintain depressive schemas and promote social isolation and vulnerability to diseases—including cardiovascular diseases—that are known to be promoted by autonomically mediated increases in inflammation and by reduced physical activity (also see (62)). This dovetails well with previous work demonstrating the further role of altered autonomic balance (favoring sympathetic influence) in promoting altered lipids, increased blood glucose, and increased blood coagulation (126). It is also consistent with biobehavioral frameworks that have been proposed to account for multimorbidity more generally (127).

In addition to offering this kind of generalizability to many biopsychosocial phenomena, it is also worth highlighting that, as illustrated by the simplified quantitative examples previously presented (in relation to Figures 1 and 2), PP models have a precise mathematical (i.e., Bayesian, information-theoretic) basis. This mathematical basis could in principle allow for rigorous, quantitative, testable predictions regarding how particular types of new experiences (new evidence) would lead to changes in the probabilistic beliefs regarding biopsychosocial variables that are held within an individual's mind (e.g., how likely they believe that they are to feel better in the long term if they start exercising). Thus, if quantitative estimates could be gathered about (*a*) an individual's abstract expectations and (*b*) the structure of the biopsychosocially relevant concepts that an individual has learned (i.e., what interoceptive/exteroceptive percepts are represented as more/less consistent with them), then quantitative modeling of biopsychosocial processes may become possible. This could perhaps be done by designing psychosocial tasks in which individual subject parameter estimates can be inferred from trial-by-trial behavioral responses (for examples of such tasks used outside the social domain, see (128,129)). In the context of social support research, for example, tasks might be designed in which participants are asked to predict how likely different individuals are to engage in a future socially supportive act (or predict how supportive they will be), after being exposed to images of those individuals and information about a few of their previous behaviors. In principle, participants' predictions could be used to derive subject-specific probability distributions, indicating quantitative differences in their prior expectations about social support (e.g., similar to previous work on optimism (130)).

A further point worth considering is how the present model builds off of constructs introduced by earlier models, which have provided useful but less comprehensive explanations of psychosocial phenomena. Two relevant examples are the qualitative constructs of "person schemas" and "internal working models" that have been discussed, for example, within the literature on psychodynamic theory and attachment theory (131–133). Both of these constructs reflect the broad idea that, beginning in childhood, individuals develop mental structures that provide guiding expectations regarding the self, social relationships, and the typical motivations and behaviors of others. It is then through the lens of these mental structures that objective life events are perceived and interpreted and to which they are responded. These constructs could be seen as forerunners of the hierarchical probabilistic (generative) internal models described in this article. This updated conception of an internal model can be seen as building on these earlier constructs by (*a*) providing a quantitative mathematical formalism and (*b*) providing plausible neural process models for their biological implementation. Figure 2, for example, provides a possible neural basis for a very simple internal model, consisting of synaptic connection strengths that specify (*a*) expected levels of social support and (*b*) a learned relationship between social support and a particular lower-level signal derived from sensory input (i.e., a more intense smile indicates more social support). Realistic neural implementations of plausibly human internal models would be massively more complex (i.e., requiring a massively larger number of neurons/synapses; e.g., the human brain contains billions/trillions), but this illustrates how the framework offered here can be seen as extending previous theoretical constructs and advancing their scope and explanatory power to incorporate a quantitative biological level of description.

A Shift in Perspective Within Biopsychosocial Research

Despite the previous considerations, one might wonder why the more complicated model we have proposed is necessary for biopsychosocial research. After all, some current experimental designs already provide useful causal information, even without elucidating underlying mechanisms (e.g., demonstrating that experimentally increasing either social skills or emotion regulation skills leads to better cardiovascular health outcomes, but without examining why such causal relationships hold (12–14)). In addition, behavioral scientists may not perceive major difficulties in explaining currently observed relationships between psychosocial and biological variables at particular levels of description. For example, explanations

such as "social support buffers stress," "being socially integrated adds meaning to life," and "social support can help take the load off of an individual by sharing the burden" all seem to be informative. Social baseline theory has also pointed out that humans arose as interdependent creatures, helping explain why the absence of this is stressful and painful (41,68). Given observed peripheral physiological correlates in the autonomic, endocrine, and immune systems associated with social variables, the idea that such "information transfer systems" plausibly affect medical outcomes, and the ease with which psychological variables can be incorporated as mediating/moderating factors, it could be argued that a coherent biopsychosocial model does not require further complexity.

The embodied neurocomputational perspective we have outlined here suggests at least six, and likely many more, important shifts away from the traditional perspective characterized previously. First, although traditional approaches have tended to focus on social, psychological, and biological variables separately, our model highlights the central role of mechanisms underlying causal interactions between these variables and their mediation by the brain, both of which have received much less attention. Furthermore, to be accepted in biomedicine, biopsychosocial explanations must conform to traditional standards, which require a more complete account of pathogenic mechanisms. Because the traditional perspective has not emphasized mediating brain processes, it is unable at present to provide such an account. This is the groundwork our model seeks to lay. That is, by providing a characterization of biopsychosocial processes at a similar level of mechanistic description/detail as other biomedical processes, this type of model may allow practitioners from both perspectives to "share the same language," allowing discussion of biopsychosocial processes to occur at whatever level of characterization happens to be most pragmatic/informative in a given medical context (i.e., social, psychological, or biological levels).

A second, related point pertains to the need to uncover pathogenic mechanisms. As highlighted previously, although causality can be demonstrated through interventions (e.g., randomized controlled trials), this need not provide any mechanistic information. If underlying biological mechanisms explaining observations in such clinical trials are to be delineated, one will first need a mechanistic model. The presently proposed model can therefore be seen as an important step toward fulfilling that need. For example, one trial in patients with coronary bypass surgery showed that psychosocial skills training increased indices of interpersonal wellbeing (i.e., greater satisfaction with life and social support, reduced anger and depression) and that it also decreased heart rate and blood pressure (i.e., both at rest and in response to an anger recall stressor (12)). If a pre- and posttraining neuroimaging study were conducted to investigate the mechanisms of these effects, our proposed model would generate specific testable hypotheses. In particular, our model would suggest that this psychosocial skills training would (both directly and through behavioral change) alter high-level prior predictions about the mental states of others, leading to altered default mode network activity. The influence of these altered top-down predictions would also be reflected in functional connectivity changes between default mode network structures (medial prefrontal cortex in particular) and cortical/subcortical regions that regulate autonomic influences on the cardiovascular system (e.g., insula, amygdala, periacqueductal gray). If neuroimaging could be performed during a psychosocial skills training task, our model could also be used to generate specific tests of computational dynamics, such as modeling neural responses linked to changing predictions and prediction errors during learning. Findings of other randomized controlled trials offer similar opportunities to uncover biological mechanisms (e.g., examining other behavioral interventions that reduce mortality in cardiovascular disease (13,14)), but the present example illustrates how the results of such causal findings could be better understood by drawing on the resources offered by our proposed framework.

Third, although there are a large number of disparate findings in the field of biopsychosocial research, less work to date has focused on providing a general, unifying model that would make this body of knowledge more useful/digestible to clinicians, other health care providers, and other health care systems. Our model can be seen as unifying in this way; furthermore, although some neurocomputational aspects of our model are complex, the broader elements and their interactions (Figure 3) are fairly simple and intuitive for health care professionals. For example, a clinician could use our model to reason as follows. "Are this patient's complaints linked to problems in actual social circumstances or simply in perceived social circumstances? If the latter, is this causing the patient to act in ways that reduce the quality of actual social circumstances as well? Is there an identifiable top-down expectation that is driving these perceived social problems? Given the physiological fatigue resulting from this patient's illness, might their perception of the demands of maintaining relationships be increased? How might I intervene to motivate increased social engagement in this context?" Such possible reasoning illustrates how the basic elements of our model, such as top-down expectation, perception, conceptualization, physiological demands, and affordances, could inform straightforward clinical reasoning with respect to how one might (*a*) alter psychosocial variables to improve the course of an illness and/or (*b*) treat an illness as a way of promoting improved psychosocial functioning.

A fourth shift in thinking afforded by our model strongly emphasizes why brain mechanisms are relevant to linking social and biological variables. One major reason is that variables such as social support seem to largely influence biology and health based on the way they influence perception and belief, which is mediated by the neurocomputational mechanisms we have described. Thus, for example, although two individuals may receive the same amount of objective social support, it will be the individual who ends up perceiving/believing that social support is available to them that will obtain the greater health benefit. To understand why one individual ends up with different perceptions/beliefs than another individual, when both are in objectively similar social circumstances (leading to different health outcomes), neurocomputational process theories become highly relevant. They also have the added benefit of being able to integrate not only mind/brain processes but also regulation of peripheral physiology and the perception of, and interaction with, the outside world.

Fifth, our model's incorporation of work on embodied cognition further highlights ways in which perception of social variables is not based on a stable external reality; instead, such perceptions are influenced by a person's current physiological state (e.g., social/occupational tasks may be perceived as more challenging when in a state, such as that of chronic illness, in which represented metabolic resources are low). There are related concepts in the literature; for example, people who are depressed have a

negativity bias, they may think they are not supported when they are, and perhaps they induce a lower level of support because they engage in social isolation behaviors (for a recent review, see (64)). Affordance-related aspects of perception in our model, and how those influence behavior, provide a rational structure to account for the way such individuals inadvertently shape the level of social support they have.

Sixth, and most broadly, it is important to draw attention to the fairly dramatic shift in thinking the PP and embodied cognition perspectives jointly entail about both the way neurocognitive processes operate and their functional separability from the body and the environment. Perception has traditionally been understood passively, in that the brain has been seen as simply detecting and responding to signals out in the world. In contrast, the updated perspective described here conceives of perception as active in multiple senses. First, perceptual experience primarily represents the brain's active attempt to build an internal model that successfully predicts sensory input. As such, perception is much more strongly shaped by expectation, past experience, and physiological/environmental context than previously assumed. Perhaps most surprisingly, exteroceptive perception and its influence on behavior can be actively shaped by interoceptive predictions about the physiological state of the body, such that objects/events will be perceived differently (and responded to differently) given different predicted metabolic demands. Second, behavior can be seen as an active (or "enactive") process of selecting the sensory input being sampled in perception (e.g., shifting one's gaze to the left because that is where reliable information is expected to be). Thus, behavior also sculpts perception of the world, in that our behavior is targeted toward producing the percepts that we expect/desire (e.g., eating food because we expect/desire the percept of fullness/satiation). These considerations first highlight how looping interactions with the body can be understood as central to cognition, in that interactions between the brain and body are necessary to accomplish both perception and effective action selection. Furthermore, the brain-body system cannot be fully understood without knowledge of its interactions with the external (sociocultural) environment in which it is embedded, because these interactions shape the individual's further expectations, percepts, bodily regulation processes, and behaviors (for further discussion, see (69,134)). In contexts of both treatment and prevention, this shift in perspective therefore strongly emphasizes the need for practitioners to consider these highly individual, complex, bidirectional interactions in shaping health outcomes.

These six unique aspects of the embodied neurocomputational model combine to illustrate the importance of an individualistic perspective. That is, it is the individual who perceives the level of a social or task-related variable (whether or not this corresponds to objective reality), and it is the individual's perception that leads to physiological responses that influence health outcomes (e.g., for a review of studies showing the stronger relationship between health and perceived versus received social support, see (27)); the individual's perceptions/expectations also lead to behaviors that either directly (e.g., exercise) or indirectly influence health outcomes via altering the objective social/environmental circumstances they are in. From this perspective, it appears somewhat less relevant to characterize objective social/environmental circumstances in isolation and more relevant to characterize the individual's interpretation of those circumstances, as well as the way these interpretations influence subsequent physiological responses, health-relevant behaviors, and the perceived and actual changes in circumstances those behaviors produce. This is also consistent with recent behavioral genetics studies, which have demonstrated that despite shared genes and overlapping environmental factors, nonshared aspects of perception/experience can account for significant differences in health-relevant outcomes (e.g., see (135–141)). This personalized perspective focusing on the uniqueness of each person is the essence of Engel's biopsychosocial model. It can also be easily extended to include the unique relationship that exists between any given physician and any given patient, and the potentially beneficial or deleterious effects of this interaction.

Broader Relevance to Research and Clinical Practice

Aside from the broad theoretical points highlighted previously, it is important to consider the relevance of our model for future research. Table 1 highlights current theoretical/empirical evidence in support of our model. This table illustrates how nearly all of the domain-general elements listed currently have considerable support (i.e., with the exception of applications of the PP framework to interoception and visceral regulation, which has only begun to receive empirical support). What remains to be done is to confirm that many of these domain-general elements are fully applicable to biopsychosocial processes in particular. Important experimental tests of this model will therefore primarily involve adapting currently used paradigms to examine perception and behavior in biopsychosocially relevant contexts. This could be done, for example, by testing applications of computational modeling to currently used social threat/exclusion tasks (e.g., (39)) or by testing for neural/behavioral/physiological evidence of probabilistic/Bayesian information processing with respect to a variety of other relevant variables (e.g., social perception, mentalization, intensity of autonomic responses, etc.). If such evidence can be found, it would confirm the validity (and potential usefulness) of our proposed application of these domain-general processes to the biopsychosocial context in particular. This would represent important progress in biopsychosocial science.

It is also important to consider some particular clinical domains and relevant interventions for which our model may be useful. One such domain is that of somatoform pain. First, current developmental theories of somatoform pain have suggested that nonoptimal early-life experiences and especially the lack of interpersonal affect regulation between infant and caregiver may lead to aberrant development of the threat-related neural circuits that activate in response to both physical and emotional pain (183); this aberrant development is suggested to lead to increased sensitivity to both kinds of pain in adulthood and to related deficits in effective emotion regulation. However, the neural basis of this learning process has not been thoroughly elaborated. The present model extends such previous proposals by illustrating how repeated nonoptimal experiences of this kind would lead to repeated internal model revisions at multiple hierarchical levels (driven by iterative prediction-error minimization processes). The resulting internal model would come to predict the absence of interpersonal resources for affect regulation in general (i.e., a high-level prior expectation), which would jointly amplify perceived situational/physiological demands and perceived pain (e.g., via increased inflammation, etc., (184,185)); this internal model would also have failed to learn adaptive ways to conceptualize and respond to pain (i.e., due to the absence of anyone modeling such responses during development).

TABLE 1. Current Work Supporting Different Elements of the Proposed Neurocomputational Biopsychosocial Model

Model Elements	Supportive Evidence
Predictive processing	
Presence/importance of hierarchical neuroanatomical structure	(86,87,94,142–145)
Consistent physiological/neural/behavioral activity – exteroception/skeletomotor behavior*	(41,68,128,129,146–160)
Consistent physiological/neural activity – interoception/visceral regulation*	(88,91,92,105,161–164)
Role of neural networks	
Default mode network regions (including hippocampus) – abstract expectations and conceptualization*	(42,106,165,166)
Salience network and subcortical regions – interoception, social threat detection, and visceral regulation	(29,42,101)
Limbic network and subcortical regions – rewardingness of social connection and visceral regulation	(29,42,101)
Executive control network regions – goal-related abstract expectations*	(42,101,167)
Somatosensory, auditory, and visual cortices – unimodal perception	(101,168)
Somatomotor network – cortical control of skeletomotor action	(72,101)
Interactions between neural percept and concept representations*	(169–174)
Hierarchical neurovisceral integration within/between networks	(87,175–182)
Embodied cognition	
General	(69,73–76,81–84)
Biopsychosocially relevant variables	(77–79,84,85)

* Although there is substantial support for these model elements in general, further work is required to thoroughly support their role in biopsychosocial processes in particular.

Another relevant clinical domain is that of the maintenance of maladaptive social behavior. Current models of repetitive maladaptive behaviors suggest that this phenomenon may be driven by the production of vicious cycles in which such behaviors promote reactions from others (as well as the maintenance of other environmental conditions) that effectively reinforce those behaviors and a perspective on the world that justifies them (186); such cycles are often observed in clients by psychiatrists/psychotherapists. The present model offers a way of understanding the embodied neurocomputational basis for such vicious cycles and also suggests the types of new experiences that may be necessary to disrupt them. For example, consider a case in which an individual's past experiences have been most consistent with the abstract expectation that "personal relationships normally end in pain and rejection." When such expectations bias current perception/conceptualization of the behaviors of others, a large range of behaviors could be interpreted in a manner consistent with that expectation (e.g., "she will only date me until she finds somebody better"). This would likely lead to negative affective responses and defensive, standoffish behavior that would appear prejudgmental, ungrateful, and "assuming the worst," which would deter further affectionate or helpful behavior from others (i.e., acting as evidence confirming the previously mentioned abstract expectations). It is also easy to imagine how different abstract expectations could lead to different interpretations and to more affectionate/grateful responses, which would instead promote further affectionate/supportive behavior from others in the future (for an explicit model of such cyclical processes in relation to gratitude specifically, see (63)). This phenomenon could also help explain why, according to our model, the stronger relationship found between health and "perceived" versus "received" social support described previously would be expected (i.e., because received support can be interpreted in many ways and lead to response patterns that either promote or hinder health).

Aside from providing these clarifying insights about the way previously observed clinical phenomena can be understood within a unified, domain-general computational framework, the present model also makes predictions about interventions that could be tested in future research. For example, it predicts that for a given individual, the relationship between received social support and health should increase if they were provided with a psychotherapeutic intervention designed to increase particular expectations about the nature of others. For example, if an individual were repeatedly exposed to experiential evidence that people tend to be more altruistic on average (i.e., relative to their previously learned expectations), then future acts of support from others would be more likely to be conceptualized as true support and therefore be more likely to reduce inflammation, related estimates of metabolic demand, and promote long-term health. Simpler interventions may also be effective for altering certain maladaptive social expectations. For example, a recent study demonstrated that (*a*) many people believe that others lead more rich/active social lives than they do and (*b*) reducing the cognitive availability of memories of highly social people (i.e., trendsetters/socialites that come easily to mind as an automatic standard of comparison) can reduce/eliminate this bias (187). This illustrates how even short-term interventions that alter biases in attention and memory retrieval could be successful at altering activated prior expectations and the influence they have on perception, action, and overall wellbeing.

Yet another prediction is that particular behavioral interventions could be designed to disrupt vicious cycles that maintain low levels of perceived support from others. For example, if individuals were taught to respond to all instances of *received* support in an authentic, grateful manner (i.e., independent of how they interpret the intentions of such acts), then this would be expected to promote further support from others over time. This could eventually flood the individual with sufficient evidence that was inconsistent with their prior "unsupportive" expectations and therefore change these expectations. This would then increase the probability that future instances of received social support would be interpreted as genuine and in turn promote physiological responses beneficial to long-term health.

CONCLUSIONS

In this article, we have articulated how incorporating an embodied neurocomputational perspective can provide a novel framework with the potential to advance biopsychosocial science. To be clear, this framework is fully consistent with currently proposed nonreductionist explanations within this field (e.g., "better patient-clinician relationships promote recovery," etc., see (188,189)), and it does not seek to replace those (empirically supported) causal explanations with others that appeal only to biology or to render them epiphenomenal (i.e., one can talk informatively about causation and explanation at multiple levels of description—the only requirement being that descriptions at each level must be consistent with one another; e.g., see (190)). Instead, the primary advancement offered by our model is that it allows the multilevel connections and interactions between social, psychological, neural, and bodily processes to be understood in a more precise, detailed, integrative, and coherent (and less eclectic) way (e.g., it offers a multilevel mechanistic explanation for *why* better patient-clinician relationships promote recovery). By further outlining an explicit hierarchical PP model for biopsychosocial phenomena in general, and illustrating how its dynamics can lead to both beneficial and harmful feedback loops with the external world, this also extends previous proposals regarding the potential utility of a Bayesian perspective in social support research (41,68). The perspective we have outlined offers the following specific advancements:

1. It greatly increases the psychological complexity of social phenomena.
2. It emphasizes that a purely social (outside the individual) evaluation of social support is relatively lacking in utility and remains mechanistically disconnected from biology.
3. It highlights that the relevant unit for understanding the bio-behavioral mechanisms of health (including social support) is the individual.
4. It highlights the active nature of perception, and illustrates why an individual's cognition and behavior can only be fully understood through consideration of brain-body interactions and the social/environmental context within which they have been embedded throughout their life.
5. It provides a new way to conceptualize and model the way broad expectations regarding perceptions (some plausibly learned during development), and their influence on social behavior, can themselves bring about the actual ways that one interacts with others, such that those expectations lead to changes in the reality of the social circumstances one subsequently experiences/perceives—potentially leading to both virtuous and vicious perception-action cycles.
6. It demonstrates that biological, psychological, and social processes are regulated through similar, interrelated and integrated algorithmic processes within the individual's brain.

We have also illustrated how this perspective can advance understanding of the specific relationship between social support and health in several ways. First, it can explain, in explicitly probabilistic (and precise, mathematically modelable) terms, why bidirectional relationships exist between interoceptive and exteroceptive perception. Second, it provides a simple, general way of understanding individual differences in personality and cognitive style as reflecting different innate/learned prior expectations about the abstract probabilistic nature of individuals and other aspects of the way the world works. These differences might in turn be influenced by genetic differences in peripheral factors, such as inflammatory cytokine gene variants, that promote stable differences in afferent modulatory influences on the brain (e.g., see (62)). In general, although genetic factors have not been explicitly discussed as part of our model, the likely influence of genetic factors on the processes in our model can be captured (at least in part) by both peripheral influences on disease vulnerability and central influences (e.g., on synaptic receptor subtypes) promoting individual differences in the influence of prior expectations (e.g., perhaps reflected in temperament) and the way those expectations are updated in response to experience (e.g., see (191)). This allows previously identified individual difference variables to have a clear influence on the probability that particular acts of others will be interpreted as socially supportive/accepting or unsupportive/threatening/rejecting and in turn lead to different physiological and behavioral responses (e.g., similar to the way individual differences in optimism have been modeled as reflecting differences in prior expectations about the probability of future reward (130)). Third, our model provides a more precise way of understanding the hierarchical computational role of the "threat-sensitive" and "reward-sensitive" brain regions identified in previous research, and highlights important ways in which yet hierarchically higher brain regions (e.g., default mode network and executive control network regions (42)) and current widespread neuromodulatory influences (i.e., implementing context-specific precision estimates) may act together to modulate whether threat- or reward-related regions will respond more strongly (and inhibit the other) in response to a particular perceived event.

Fourth, this model makes important predictions about the way particular interventions might be designed to increase the amount of social support (or other socially beneficial phenomena) that an individual perceives and therefore indirectly promote better long-term health. Such interventions should be designed and tested in future research. Fifth, the domain generality of our model offers the possibility that it could be extended to a wide range of other phenomena, even outside of the biopsychosocial domain (i.e., to any other domain where abstract expectations inform conceptual and perceptual interpretations of internal/external events and where such interpretations subsequently influence cognitive, skeletomotor, and visceromotor responses). Thus, future work should therefore also examine the potential insights that this general framework could provide in other domains (e.g., research on interpersonal autonomic physiology, research on the influence of emotion on pain, etc. (192,193)). A detailed application of this framework to animal models (e.g., regarding the role of maternal care on stress reactivity, see (194–198)) or specific adverse health behaviors (e.g., smoking, nonadherence to treatment) could also lead to similar or even stronger conceptual models supporting the utility of a Bayesian perspective. Finally, by illustrating links between neurobiological, computational, and psychological levels of description of brain-body processes, and illustrating how particular mechanistic causal processes plausibly facilitate specific reciprocal interactions between social, neurobiological, physiological, and behavioral phenomena, it is our hope that this can act as a clear demonstration of how all the major elements of the biopsychosocial model are, in a sense, *already present* within any complete biomedical model. In principle, this could facilitate future work that more specifically

guides clinicians in evaluating the degree to which biological, psychological, and social variables are each relevant in individual cases of illness; at present, it represents an important step in bridging the biopsychosocial and biomedical perspectives within clinical practice.

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