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Editorial

The new field of Brain–Body Medicine: What have we learned and where are we headed?

New evidence that the brain's influence on systemic medical disorders is coherent and important

To our knowledge, this is the first time that neuroimaging findings from a variety of different areas of Brain–Body Medicine have been published together. Certainly there have been a number of such findings presented in a variety of journals in recent years. For example, there is a growing brain imaging literature on pain (Davis et al., 1997; Coghill et al., 1999), placebo effects in pain (Petrovic et al., 2002; Wager et al., 2004) (and in other medical settings, Benedetti 2008), autonomic regulation (Critchley et al., 2000; Milad et al., 2007), neuro-cardiology (Critchley et al., 2005), brain–gut disorders such as irritable bowel syndrome (Mertz et al., 2000), and other functional somatic syndromes such as fibromyalgia (Gracely et al., 2002). There have also been a few neuroimaging papers on asthma (Rosenkranz et al., 2005), bladder function (Fowler et al., 2008), conversion disorder (Marshall et al., 1997), immune function (Ohira et al., 2008), and endocrine regulation (Kirsch et al., 2005). However, these papers have as a rule been pioneering efforts in uncharted territory, published in isolation.

Part of what is unique about the Special Issue is that papers on all of these (as well as other) topics have been published together in a single volume, along with integrative commentaries, reviews and methods papers. Perhaps more importantly, what this juxtaposition reveals is that there is a remarkable commonality of brain areas and brain mechanisms that appear again and again in these papers. This commonality, which exceeded our expectations, suggests that there is a coherent field of neurobiology that relates emotion, emotion regulation and stress on the one hand to systemic medical disorders and peripheral physiological processes on the other. This commonality was presaged by early theorists such as Walter Cannon (1932) and William James (1890), who helped to establish an "integrative physiology" perspective on studying both emotion and disease. The array of approaches and methods now available, however, allows the mechanisms of integrative physiology to be explored in the living human brain with a specificity that these early writers could not have foreseen.

As noted in the editorial that introduced this Special Issue (Lane and Wager, 2009), the field of Brain–Body Medicine has emerged from a foundation of empirical research that in recent decades has unequivocally demonstrated that negative emotional states such as depression and stress have deleterious effects on physical health (Glaser and Kiecolt-Glaser, 2005; McEwen 1998; Scheier and Carver, 1992; Lesperance et al., 2002; Lane 2008). Moreover, researchers are beginning to identify the peripheral mediators of these relationships. In this issue, we have seen how concepts related to negative emotion, stress and pain have been operationalized in specific ways within the context of neuroimaging studies. For example, studies in the Special Issue investigate the brain and bodily effects of social exclusion (Eisenberger et al., 2009), social evaluative threat (Wager et al., 2009a,b; Åhs et al., 2009), grief (O'Connor et al., 2009), uncertainty (Ohira et al., 2009), recall of past trauma (King et al., 2009), and acute (Derbyshire and Osborn, 2009; Vanhaudenhuyse et al., 2009) and chronic (Harris et al., 2009) pain. A number of papers also focus on the effects of psychological interventions, including compassion-focused meditation (Lutz et al., 2009), hypnosis (Vanhaudenhuyse et al., 2009), placebo (and related expectancy manipulations) (Kong et al., 2009), and intentional use of cognitive strategies (Urry et al., 2009). These intervention studies document, in diverse ways, salubrious effects on the same brain and peripheral outcomes implicated in the studies of aversive emotional states.

What is truly new in this Special Issue is the overlap in brain mechanisms revealed by concurrent consideration of the findings in these different research areas. This overlap is apparent in a number of brain regions, including medial, lateral and ventrolateral prefrontal cortices, paralimbic areas including the insular, anterior cingulate, posterior cingulate and orbitofrontal cortices, subcortical structures such as the amygdala, ventral striatum and hippocampus, brainstem nuclei such as the periaqueductal gray, and autonomic and neuroendocrine effectors. As these structures execute their functions in evaluating stimuli for emotional significance, generating emotional responses and regulating these responses, there are concomitant mechanisms at work that alter peripheral physiology and end-organ function. Since these mechanisms related to emotion are in continuous operation, their integrated influences across months or years are likely to have clinically important effects on disease processes and outcome. Indeed, that is what the epidemiological evidence indicates (Glaser and Kiecolt-Glaser, 2005; McEwen 1998; Scheier and Carver, 1992; Lesperance et al., 2002; Lane 2008). What is new is that we are now beginning to identify the neural basis for these observations, which can establish links between specific psychological states, brain processes, and health-related outcomes. These mechanistic links are crucially needed for the integration of mind–body techniques and other psychological and behavioral interventions into mainstream medicine (Lane et al., 2009b).

While a goal of this editorial is to call attention to important commonalities in the findings rather than to provide a detailed integrative synthesis, we highlight one particular area of convergence in Figs. 1 and 2. These figures show a sample of overlapping results from studies in the Special Issue in the medial prefrontal cortex (mPFC) and brainstem. Collectively, these results illustrate

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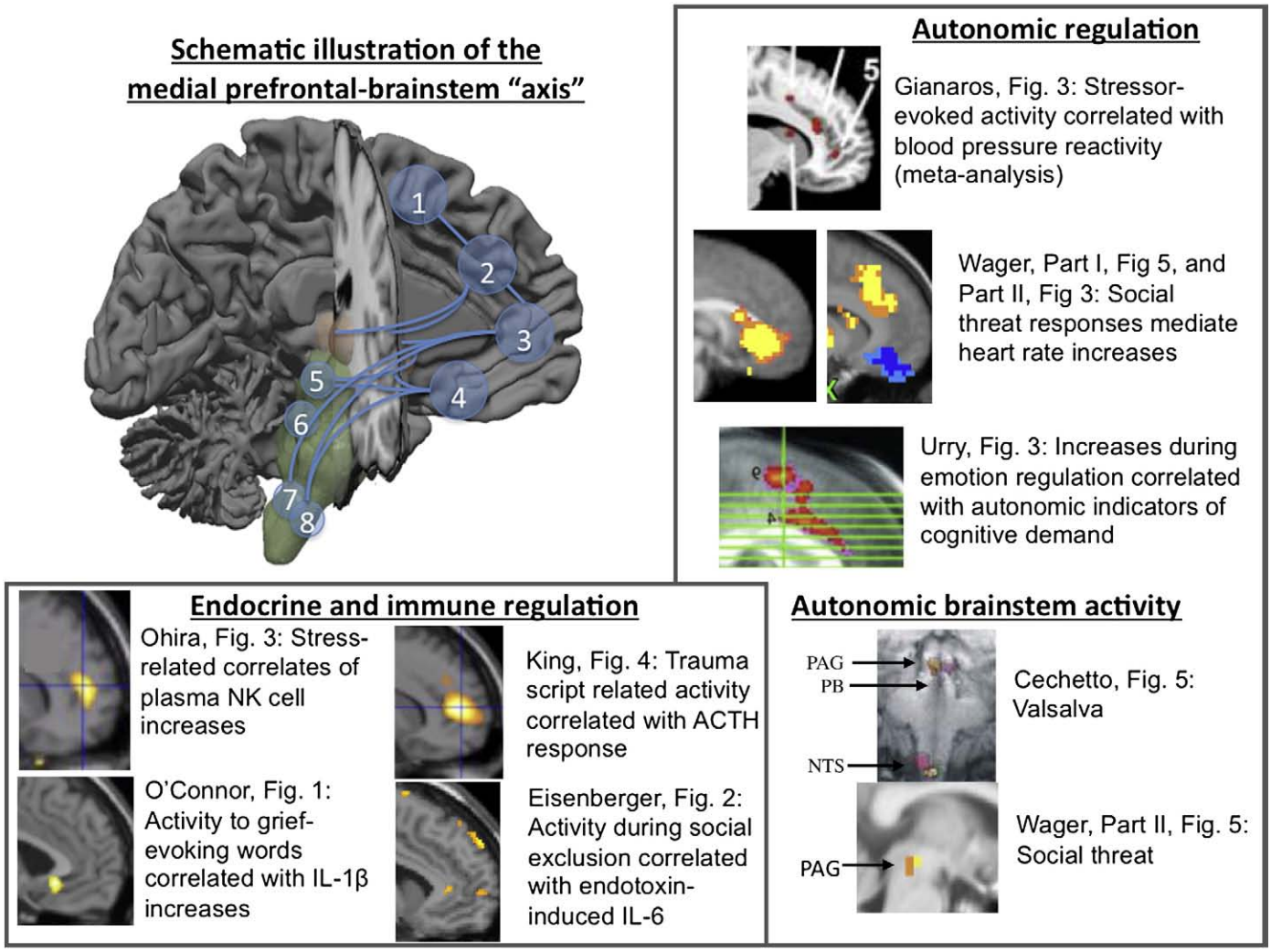

Fig. 1. A midline frontal-brainstem axis plays a prominent role in studies in the Special Issue. Top left: A schematic depiction of the approximate locations of several areas involved in brain–body information transfer, including 1) Pre-supplementary motor area (SMA)/mid-cingulate cortex (MCC); 2) anterior MCC/rostral dorsal cingulate; 3) anterior cingulate/pregenual cingulate; 4) subgenual cingulate/ventromedial prefrontal cortex/medial orbitofrontal cortex; 5) periaqueductal gray (PAG); 6) parabrachial complex (PB); 7) nucleus of the solitary tract (NTS); 8) rostral ventral medulla (RVM). The surrounding panels show images from studies in the Special Issue showing brain activity measures related to autonomic, endocrine, and immune function. Each study's first author, figure number, and topic are listed next to an image of the results.

the diverse functions of a medial brain "axis" that connects the mPFC, a system of cortical structures thought to be central for emotional appraisal and regulation, among other functions (Amodio and Frith, 2006), with brainstem centers that coordinate behavioral and physiological responses to emotionally relevant stimuli. This "axis," also known as the "medial visceromotor network," has an established neuroanatomical basis (Price, 1999). It is now becoming appreciated that meaningful signals in both mPFC and brainstem (and their functional relationships) can be obtained using contemporary neuroimaging methods, and that peripheral physiological measures can be reliably obtained in the fMRI and PET environments and linked to brain activity. As illustrated by the papers in the Special Issue, this paves the way for an integrative analysis of cortical, subcortical, and peripheral systems in emotion as well as disorders that involve emotion dysregulation, e.g. depression. In addition, the convergence highlights the need to compare across different kinds of studies when developing theories of brain function. As might have been predicted by James (1890), Cannon (1932), MacLean (1949) and many other theorists, regions of the mPFC linked to emotional appraisal or regulation in some studies are remarkably similar to those that appear to drive psychosocial influences on autonomic, endocrine, and immune changes in others. Theories relating brain activity to each of these functions are incomplete without a consideration of the other functions as well.

Bringing these diverse research topics together provides many new opportunities for cross-fertilization. The fields of affective, social and cognitive neuroscience have flourished in recent years, in part by mutually enriching one another; but they have not generally linked their research to systemic medical disorders. The papers in this Special Issue establish that these fields, which have been predominantly brain-focused, can be extended by incorporating peripheral measures, end-organ function and disease outcomes into these research paradigms in a more systematic way. In addition, scientists who are focused on bodily disease outcomes can import methods and approaches from these better-established brain-focused disciplines. Moreover, by juxtaposing diverse research topics as we have in this Special Issue, researchers who focus on different organ systems may be more likely to share conceptual frameworks, rating scales, experimental paradigms, imaging techniques, peripheral measures and data analytic approaches.

Highlights and future directions

The original findings and integrative reviews in this Special Issue have a number of implications for promising directions for future research. We discuss these briefly immediately below.

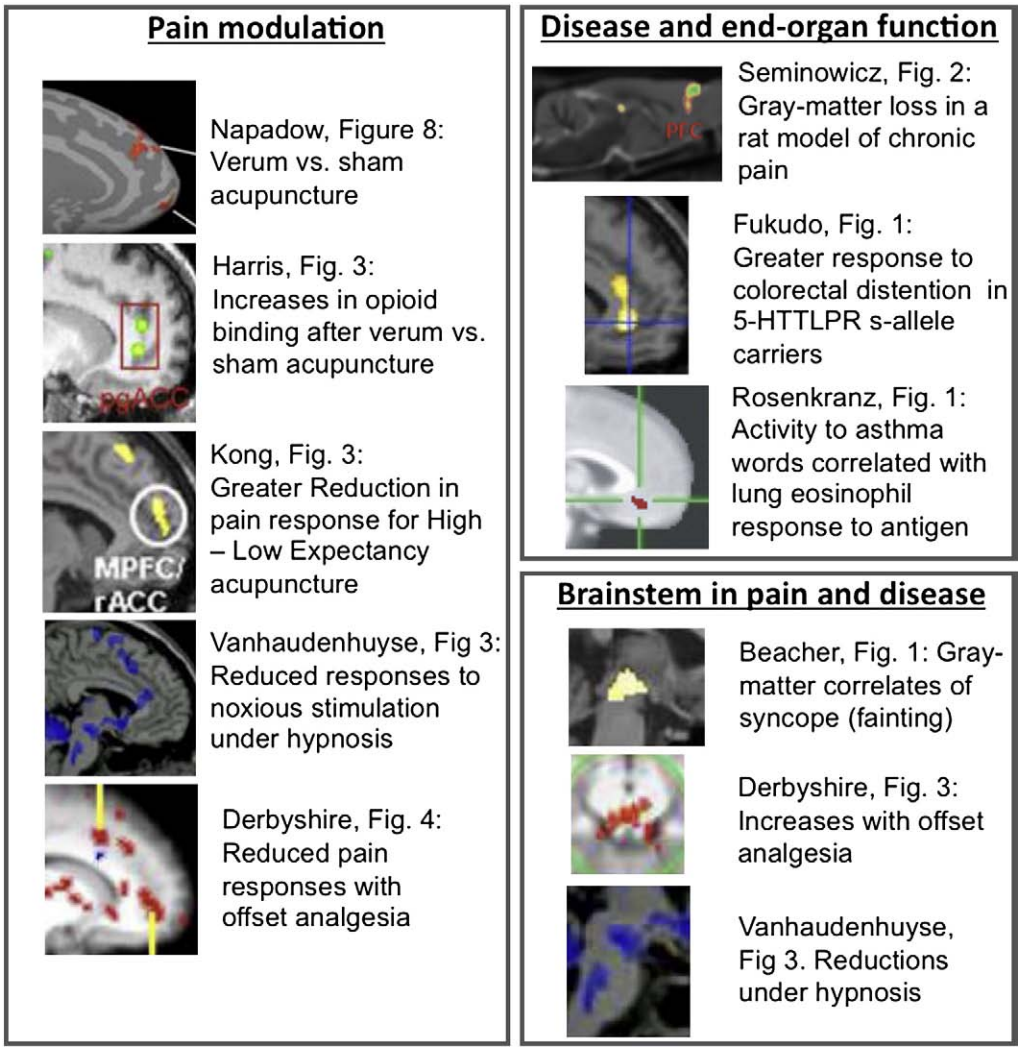

Fig. 2. Images from studies in the Special Issue showing brain activity measures related to pain, other disease processes, and end-organ function. Each study's first author, figure number, and topic are listed next to an image of the results.

Integration of human and animal work

An important area for future work is increasing integration of theory and observations across species. As in the field of neuroimaging generally, human research in Brain–Body Medicine is enriched and informed by animal work. Generally speaking, animal research on brain–peripheral interactions has tended to focus on the brainstem and "lower" subcortical systems in the diencephalon. Our understanding of how brainstem mechanisms of visceral regulation such as vagal nuclei operate is still poor (Hallett and Cruccu 2006; Mifflin 2007) despite the fact that a wide range of new neuroscientific tools are now available to study such mechanisms, e.g. ensemble and field potential recordings from multiple neurons. Human research, on the other hand, has tended to focus on cortical and forebrain subcortical structures. **A unifying framework that links many of the papers in this Special Issue is that brainstem mechanisms directly regulate vital bodily functions, and that cortical–subcortical interactions modulate the function of these brainstem mechanisms** (Lane et al., 2009a). From this perspective, a synthesis of animal and human work appears necessary.

The few animal studies in this Special Issue, including papers by Seminowicz et al. (2009) and Rowny et al. (2009), were notable in adopting an approach that is more whole-brain oriented. Human brainstem function is represented in this Special Issue in the review by Cechetto and Shoemaker (2009) on the neural basis of autonomic regulation, the companion papers by Wager et al. that identified cortical-brainstem pathways involved in the regulation of heart rate (2009a) and anxiety (2009b), the paper by Beacher et al. (2009) on vaso-vagal syncope, the paper by Derbyshire and Osborn (2009) on offset analgesia, the paper by Kong et al. (2009) on acupuncture, and the paper by Vanhaudenhuyse et al. (2009) on hypnosis in the context of experimental heat pain. Since brainstem mechanisms are fairly well conserved across the evolutionary timescale (Sarnat and Netsky, 1974), a key ingredient of the brain–body agenda will be to conduct studies in rodents and other animals examining brainstem regulation of cardiovascular, pulmonary, renal, hematopoietic and musculoskeletal function, in addition to autonomic, endocrine and immune function. The translation to human conditions will be facilitated by parallel study designs in humans and animals in which cortical–subcortical interactions, particularly in midline structures (Northoff and Panksepp, 2008), can be studied with functional brain imaging. While animal research provides unparalleled opportunities for invasive manipulations, as well as exquisite control and manipulation of genetic and environmental factors, the findings in this Special Issue regarding neocortical and paralimbic involvement indicate that there is no fully adequate substitute for the human brain, that both human and non-human animal work will play an

essential role, and that the tools are now available to carry this work forward.

An important reason for doing this work is to further our understanding of the pathogenesis of physical disease, and to develop a more complete understanding of mechanisms that will inform new clinical interventions. In two recent review papers published elsewhere (Lane et al., 2009a,b), it was pointed out that a complete mechanistic account will involve concurrent assessment of a) psychological states, traits or behaviors; b) brain activity; c) information transfer system(s) including autonomic, endocrine and/or immune systems; and d) disease outcomes and/or end-organ function. Research to date, including that published in this Special Issue, typically presents evidence from two or three of these domains, but none has involved all four simultaneously. The use of connectivity analyses in neuroimaging studies to assess the organization of cortical and subcortical systems, and path analyses and related techniques to connect brain and peripheral processes, is a promising direction. Some of the studies in the Special Issue, such as those by Wager et al. (2009a, b) and Labus et al. (2009), take promising steps in this direction. A goal for the future is to implement such a comprehensive approach across all four domains, and to do so in a way that coordinates animal and human research.

Integration of neuroimaging and genetics

Another area that will be important for future work is the integration of neuroimaging and genetics. Any comprehensive attempt to understand the pathogenesis of physical diseases will require inclusion of genetic variables. Two studies in this Special Issue by Williams et al. (2009) and Fukudo et al, (2009) feature a specific genetic marker, the variants of the serotonin transporter linked promoter region (5-HTT-LPR) polymorphism. These two papers, which were written independently, show a remarkable convergence of findings across diverse settings. No doubt this is the tip of the iceberg in relating genetics and brain science to physical disease, as a variety of genetic markers have been used in brain imaging studies in other contexts (Hariri and Weinberger, 2003). As of yet, however, their application to brain imaging in relation to systemic medical disorders has been limited.

This reality raises several issues for future research. First, studies of polygenetic influence will progressively increase our ability to quantify genetic vulnerability to a wide variety of human diseases (Wallis 1999). Second, research to date has demonstrated that gene-by-environment interactions are the rule rather than the exception (Weaver et al., 2004). These interactions will be particularly important in studies that directly assess brain activity, especially as related to the functions of information transfer systems with which the brain interacts. Third, the pathogenesis of physical disease can be subdivided into etiology, onset, and course following onset. Papers in this Special Issue that involved clinical disorders almost uniformly used cross-sectional designs. Future research should include longitudinal studies in which structural or functional brain imaging findings, as well as genetic markers, are used as predictors of future development of disease. Developmental studies that begin in childhood and relate brain structure and function to genetic predisposition, environmental variables, and psychological constructs as they interactively affect disease expression will be another important research area in Brain–Body Medicine.

Brain-based research on clinical interventions

This Special Issue explores the domain of negative emotional states in some depth and addresses their attenuation with interventions such as compassion-focused meditation (Lutz et al., 2009), hypnosis (Vanhaudenhuyse et al., 2009), placebo (Kong et al., 2009), and intentional decreases in negative emotion (Urry et al., 2009). A topic that is not addressed in the Special Issue but is ripe for further study is the neural basis of positive emotion and its effects on health — particularly whether positive emotional interventions primarily reverse the effects of negative emotion or have independent and concurrent influences on disease.

The section of this Special Issue on interventions includes a wide range of both psychological and brain-based interventions, but the implications of this research for treatment are far more extensive. Methods for stimulating the brain, including electroconvulsive therapy and magnetic stimulation therapy, were represented in this Special Issue (Rowny et al., 2009), whereas deep brain stimulation, vagus nerve stimulation and transcranial magnetic stimulation therapy were not. The modern field of deep brain stimulation, made possible in part by high-resolution structural MRI (Sedrak et al., 2008), is in its infancy. Brain imaging findings may be used to identify new targets for direct brain interventions; this direction is being actively pursued in several fields, most notably in neurology (Troster 2009) and psychiatry (Mayberg 2009; Greenberg et al., 2006). Moreover, imaging research can also be used to examine the mechanisms of action of established interventions, and can be used to explain heterogeneity in treatment outcome. Such research may in turn be used to identify predictors of treatment success and may eventually be used in the selection of treatments for individual patients (Kemp et al., 2008).

A critical and as-yet unanswered question in mind–body medicine generally is whether interventions that alter risk factors for disease, such as the treatment of depression as a risk factor for cardiac mortality (Angermann et al., 2007), actually influence disease outcomes. Should it be found that that is the case, brain imaging will play a key role in this research in determining who responds to such intervention, who does not, and the mechanisms of these effects.

The use of diverse, converging methods in self-regulation and health

This Special Issue highlights exciting new findings using PET and fMRI, but methods with greater temporal resolution, such as EEG/ERP, MEG, optical imaging and single unit and field recordings with depth electrodes were less well represented. These methods can potentially be applied to the important goal in mind–body medicine of enabling individuals to "heal themselves" by using mind-based techniques that promote self-regulation (Harrington 2008). In combination with autonomic, endocrine and immune measures, the use of brain imaging methods with high temporal and spatial resolution have the capacity to capture feed-forward and feedback loops that play a critical role in perpetuating/exacerbating or down-regulating/alleviating certain systemic medical disorders. The paper by Urry et al. (2009) in this volume, in which the brain and autonomic consequences of increasing, maintaining or decreasing negative emotion were reported, illustrates the potential for studying the brain–body dynamics of self-regulation. In this era of personalized medicine, it may become possible one day to use brain imaging to enable individuals to alter their own regional brain activity, using techniques such as biofeedback with real-time fMRI (deCharms 2008), in such a way as to alter or reverse dynamic processes that contribute to the perpetuation or exacerbation of disease. This research, should it be successful, will also serve the important functions of demonstrating in what contexts mind/brain interventions influence disease physiology, how they do so, and in what contexts they do not.

Conclusion

These research directions represent goals that from our current vantage point are visible on the horizon. Successful research along

these lines will help to establish Brain–Body Medicine and the incorporation of a personalized approach, in the psychological and social as well as the biological domains, into mainstream medical practice. This new interdisciplinary focus will serve the dual function of advancing basic knowledge and promoting health. As we move forward, we believe that many of the goals that are merely glimmers on the horizon now will be catalysts for the achievement of significant advances, and that new opportunities will be afforded that we cannot as yet envision.

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Richard D. Lane
Department of Psychiatry, University of Arizona, P. O. Box 245002, Tucson, AZ 85724-5002, USA
E-mail address: lane@email.arizona.edu.
Corresponding author. Fax: +1 520 626 6050.

Tor D. Wager
Department of Psychology, Columbia University, New York, NY, USA