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Minding the body

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Abstract

As we continue to elucidate relationships between neural structures and cognitive functioning in this Decade of the Brain, it is important not to lose sight of the larger context. The brain is but one component of the complex system that is the body. We take in information and interact with the world through our bodies, and our bodies change with—and in some cases change—cognitive and emotional processing. In this introductory paper, we present an overview of a broad range of psychophysiological techniques: electroencephalography, event-related potentials, magnetoencephalography, positron emission tomography, optical imaging, functional magnetic resonance imaging, electromyograms, eye tracking, pupillometry, cardiovascular measures, and electrodermal activity. These techniques not only differ in their temporal and spatial resolutions but also in the physiological and psychological processes to which they are sensitive. With respect to the system as a whole, these techniques are thus complementary. Combining measures—old and new, central and peripheral—ultimately provides the most inferential power for attacking the questions we hope to answer with all psychophysiological measures in our quest to understand the nature of the relationship between the mind and the body.

Descriptors: Psychophysiological techniques, Neuroimaging, Combining methodologies, Mind–brain–body system, Cognitive inference drawing

Congress has called this the Decade of the Brain, and indeed much has been learned about brain functioning in the 1990s. We now routinely hear that the frontal lobe is involved in personality, planning, and working memory and that the temporal lobe is involved in object recognition, auditory processing, and language. In textbooks we can read about a frontal–parietal system responsible for different aspects of attention and about the many different types of memory, only some of which are compromised following damage to medial temporal lobe structures. At times, however, it is important to step back and ask what is really meant by these types of statements that link a brain region to a particular perceptual, motor, affective, or cognitive act. In other words, what is the question to which such structure–function relationships are an answer? When we ask this, we find that we are confronted by the mind–body problem.

Throughout human history, people in many cultures have sought to more fully understand the mind by understanding its relationship to the body. In so doing, philosophers and scientists have associated the mind with nearly every major internal organ (e.g., Blakemore, 1976). Modern science now recognizes the brain and the other structures making up the nervous system as the most direct substrate for sensory, cognitive, affective, and motor processing. In the process of landing the mind in the brain, however, we sometimes appear to have forgotten that the brain is both responsive to and responsible for the body in which it is housed. As cognitive neuroscientists, we tend to underestimate how much the brain must do to keep the various structures of the body going.

In our everyday lives as well, it is all too easy to be unaware of bodily homeostasis because it is maintained for us routinely—until, of course, our corporeal bliss is rudely interrupted by a pair of roller skates underfoot, the ring of a telephone at 4:00 in the morning, or the sight of a dog in the middle of the freeway. Yet, at some level we are sensitive to the relationship between bodily states and cognitive or affective ones, consciously or unconsciously responding to pupil size, cool looks, clammy handshakes, perspiring brows, or slouching posture, certainly in others and sometimes in ourselves. We recognize cognitive correlates of our own bodily signals, such as a pounding heart and a queasy stomach, albeit not always with accurate attributions. We sense not only the external world with its sights, sounds, smells, tastes, and tactile sensations but also our own internal environments including muscle tension, heartbeats, and perhaps even the rate at which they come. Even without academic degrees, people have theories, based on their experiences, about what a pounding heart or tense brow might mean.

In *Vehicles*, Braitenberg (1984) provided a compelling demonstration of just how readily we may impute thinking and feeling to a mechanical device that consists of nothing but two sensors wired to a motor or two simply because it appears to act like a sentient and emotive being. Indeed, because most of our techniques for understanding the mind rely on measurements/observations of states

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of the body, we have grown accustomed to making inferences about cognition from what can be simple motor acts. But making insightful inferences from these measurements requires careful consideration of the relationship between cognition and physiology not only in the brain but throughout the body. At minimum, we need to distinguish brain activity related to noncognitive operations such as bodily regulation from that related to cognition. The mind/body problem is truly a hard problem, all the more so if we do not consider the whole body.

We begin here by examining the relationships among mind, brain, and body. Cognitive and affective processes and bodily ones are often closely (if not causally) related. Moreover, even when they are neither, some of the same brain areas take part in both bodily regulation and cognitive processes, creating an indirect relationship between mind and body that may bear on how various psychophysiological measures are to be interpreted. We then introduce and assess the various kinds of psychophysiological measures that have been used to study cognition and affect: (a) electroencephalography (EEG), event-related potentials (ERP), and magnetoencephalography (MEG); (b) positron emission tomography (PET); (c) functional magnetic resonance imaging (fMRI) and optical imaging; (d) electromyography (EMG) and eye tracking; and (e) pupillometry, electrodermal activity (EDA), and cardiovascular measures. These measures are most often contrasted along the dimensions of spatial or temporal resolution; however, in fact, they also crucially differ in what aspect of the brain/body system they tap into. They are thus complementary in the study of mental and behavioral phenomena, and because they are all psychophysiological in nature, they are subject to the same critical inferential problems. Along the way, we also consider the meaning of *activation*, the problem of individual differences, and the difficulties of signal processing. We end with a few comments on the challenges and rewards facing those who attempt to use multiple techniques in their research programs.

A Strong Mind in a Healthy Body . . . and How They Interact

The body is a complex system comprised of many different subsystems serving different functions: nervous, circulatory, respiratory, integumentary (skin), muscular, gastrointestinal, urinary, skeletal, endocrine, immune, and reproductive. One of the primary functions of the nervous system is to carefully coordinate the operation of these mutually interdependent systems over space and time, thereby maintaining bodily homeostasis. The nervous system has a "vested interest" in doing so because, ironically, of all the systems it is perhaps the least resilient to disruptions of homeostasis. The brain is one of the first organs to be damaged by lack of oxygen or glucose, pH imbalance, and overheating (Clarke & Sokoloff, 1994). The brain is thus, in the truest sense, embodied, overseeing the functioning of the body and being crucially dependent upon the very systems that it controls to maintain its own functions.

To coordinate the body, the brain must communicate with it, and it does so through interoceptors, receptors that measure bodily states such as acceleration, muscle contraction, pain, vibration, temperature, blood pressure, and blood chemistry (Reed, Harver, & Katkin, 1990). The brain must process this sensory information from within the world of the body together with what is picked up about the external world by visual, auditory, haptic, gustatory, and olfactory sensory receptors. At least in some cases, interoceptive and exteroceptive signals are processed in overlapping neural systems, especially at the level of the brain stem but also at higher levels. The limbic system, for instance, is concerned with location in space and memory-related processes but also with the control of hunger, thirst, and temperature, and the primary somatosensory cortex maps interoceptive information from the stomach and intestines alongside sensory information from the external surface of the body (Reed et al., 1990). As many as 17 different brain regions, including the frontal lobes, thalamus, hippocampus, amygdala, and midbrain, have been implicated in the skin conductance orienting response (Dawson, 1990). Bodily processes thus naturally impact the functioning of the brain, even when they do not have cognitive consequences.

More often than not, however, bodily processes and cognitive processes are related quite directly. A bodily condition, such as hunger or overall physical fitness, can significantly alter how we think and what we think about, what we do and what we can do. For example, elderly individuals who exercise regularly show many gains in a variety of mental, and not simply motor, tasks (e.g., Bashore & Goddard, 1993). Cognitive processing, in turn, certainly can affect the body. The same external circumstances can lead to very different patterns of bodily changes in individuals, depending on whether or not they are seen as stressful (e.g., Cacioppo, 1994). Viewing pictures can elicit arousal or fear and their accompanying physiological correlates (e.g., Fredrikson, 1981; LaBerg et al., 1992). And simply imaging pleasant stimuli while listening to music can lead to physiological changes such as decreased blood beta-endorphin levels (McKinney, Tims, Kumar, & Kumar, 1997). Even when no obviously causal relationship holds, cognitive and bodily functioning often covary: we smile when we are happy, and, according to the facial feedback hypothesis (e.g., McIntosh, 1996), the reverse may also hold. Moreover, we are disconcerted if we find that one of these expected relationships does not hold. The mind thus emerges from a brain functioning within a body whose demands for producing energy, maintaining the heartbeat, and fueling muscle contractions are likely to constrain the mind's functioning (see Jennings, 1992). An understanding of cognitive processing, therefore, would seem to entail an understanding not only of the brain but also of the body and the brain's relationship to it.

Nearly every bodily system has been monitored by psychophysiologists with the aim of gaining some insight into the workings of human cognition (see Cacioppo & Tassinary, 1990a, for review). Brain functioning, for example, is observed directly at multiple levels of analysis via measurements of its electrical, magnetic, and chemical activity and indirectly via measurements of its glucose metabolism, blood volume, blood perfusion, and blood oxygenation. Bodily responses regulated by the autonomic and motor systems are monitored by measurements of the electrical activity associated with muscle contraction (EMG), gaze direction, pupil diameter (long said to be used by Chinese merchants to gauge a customer's interest), circulatory system parameters (e.g., heart rate), and the electrical properties of the skin (EDA), which change with activity of sweat glands, among others. Less routinely employed for the purposes of understanding cognition are measures derived from gastrointestinal, endocrine, immune, or reproductive system activity.

Resolving Some Issues

All body measurements can provide some valuable information about the mind, but because each is related to cognitive processes in a slightly different way, phenomena that may be easy to capture

with one method may be difficult to observe with another. Psychophysiological techniques, those that rely on changes in physiological signals to make inferences about psychological states or processes in response to endogenous or environmental events, are most often contrasted in terms of their spatial and temporal resolutions, especially with regard to central nervous system (CNS) measurements. However, because these methods also crucially differ in what aspect(s) of cognitive processing and what aspect(s) of physiology they measure, it may make more sense to assess their potential contribution to theories of cognition taking all three dimensions—when, where, and what—into consideration.

By adding *what* into the equation, we discover that no single technique nor any single bodily response can ever reveal all the answers we seek about why and how humans think, feel, and behave as they do. Even "simple" bodily processes and behaviors entail complex physiological changes throughout the entire body. Ultimately, both how and how skillfully we pick up a glass, for instance, are a function of the entire machine that implements the movement, including, but not limited to, parts of the brain. Even this basic act requires electrical and chemical changes in the brain, adjustments in the position of limbs, changes in the body's metabolism, and perhaps changes in the direction of gaze, heart rate, and respiration. Now consider the physiological changes involved in merely thinking about picking up a glass (full of water or a shot of tequila) versus in actually picking it up, by choice versus on command, with the nondominant as opposed to dominant hand, as an infant, a waiter, a glass-blower, or someone with multiple sclerosis, Parkinson's disease, visual agnosia, anomia, or hemineglect. Understanding how the brain and body act together as a single system to carry out even routine activities clearly requires the information and constraints provided by multiple techniques, even if combining them in any meaningful way raises a whole new set of problems.

Alone or in combination, all psychophysiological approaches are limited by the nature of the inferences that can justifiably be made about a cognitive function or state from a physiological measurement, regardless of its spatial or temporal resolution (see Cacioppo & Tassinary, 1990b; Miller, 1996; Sarter, Berntson, & Cacioppo, 1996). Impressive technical advances in recent years have led to increasingly detailed maps of the internal workings (electrical, magnetic, metabolic, hemodynamic) of the brain on the order of millimeters or in the range of milliseconds, and it is likely that the upcoming years will bring measures with even greater resolution. In our excitement, however, we cannot afford to forget that these are finer and finer maps of physiological—not cognitive—processes. We are still faced with the problem of accounting for the mind. Cognition is a moving target (and as demonstrated by neural plasticity studies showing dynamic functional reorganization of the brain with experience, so is the brain; e.g., Merzenich & deCharms, 1996). Cognitive acts do not necessarily have a location and, even if they do, the site of a measure is not necessarily the site of the action. Nor is it logical to equate a physiological mechanism with the concept it implements (Miller, 1996). Cognitive functions and neural processes are not isomorphic.

In a typical psychophysiological investigation, recordings are taken during two or more experimental conditions, and inferences about the relevant mental processes are drawn from the nature of the changes in the recorded activity. The inferential limits, however, are obvious. As typical of any attempt to reject the null hypothesis, little can be inferred from the lack of a reliable difference between physiological recordings in different conditions and certainly not that the mental processes in the two are identical. Likewise, the presence of a difference does not unequivocally reveal the identity of its cognitive or physiological generator nor offer proof of the generator's sufficiency or necessity for the cognitive process under study. The inferential problem in going from the correlation between a psychological phenomenon and a physiological measure to a meaningful statement about markers, much less causes, is thus far from trivial. As discussed in detail by Sarter et al. (1996), all psychophysiological methods examine the probability of a physiological event given an "psychological" experimental manipulation and not the probability of a psychological event given a physiological change (which is implicit in the argument that some observed physiological change underlies, i.e., causes, the psychological change in question). These probabilities are interchangeable if and only if there is a one-to-one correspondence between physiological events and cognitive functions under all conditions. But given the infinity of psychological and physiological states that would have to be experimentally tested, psychophysiological data alone cannot definitively prove that all the observed physiological changes are in fact relevant to the psychological manipulation. Choosing the wrong measure or from a biased sample, having an inadequate model of the noise or inadequate statistical power, and buying into the wrong theory are but some of the ways that a critical physiological event might go unnoticed. These inferential leaps can be narrowed, however, by employing multiple and complementary measures within a single experiment, the same materials and methods across different participants, or at minimum by making scholarly reference to the relevant literatures including all the available techniques. A single irrelevant variable is significantly more unlikely to affect all measures, and physiological events missed with one technique may be detectable with another. Moreover, we are less likely to over- or underinterpret findings if they can be linked to multiple aspects of the system functioning as a whole.

Combining multiple techniques in practice requires substantial financial and personnel resources. But equally as important for effectively addressing the inferential problem by combining techniques, whether in practice or in principle, is some familiarity with the range of techniques available, including what aspect of the body a particular technique measures, how that aspect of the body functions in relation to other systems, particularly the nervous system, and how this functioning can vary across and within individuals. It may also be informative to know what aspect of "psychology" a technique has, historically, proven useful for studying and what the technique's resolution—spatial, temporal, and inferential—is for a particular domain. Naturally, it is not possible to address these issues for all psychophysiological techniques in any depth here; however, we review a variety of commonly used psychophysiological techniques, indicating the niche each might fill in the space of all methodologies. Although much of the material we cover will be familiar to many of our readers, such an overview is important for three reasons. First, recently developed neuroimaging techniques have been only incompletely related to other, more "traditional" psychophysiological techniques. This situation is both surprising and unfortunate, because the techniques have complementary strengths and weaknesses. Furthermore, these newer brain imaging techniques share inferential, if not methodological and analytic, problems with the older peripheral and central techniques and can thus benefit from the long history of psychophysiology as a discipline. Second, an overview of the many techniques—and many aspects of the body—used to study the mind should instill in the reader a real sense of the extent to which the mind affects and is affected by the body. Finally, we hope to

emphasize the possibilities afforded by combining techniques for obtaining a more thorough understanding of the cognitive system and the physiological one from which it emerges and that it controls.

All Charged Up . . .

When we describe someone as "all charged up," we are in a sense speaking literally; the increased movement and emotional and cognitive expression we observe in that person are the result of an increased flow of electrical current in various parts of the nervous system. When channels in the neural membrane open, either during an action potential or during a postsynaptic potential, a flow of ions results. The currents in the action potential have a very short time course and a quadrupolar current pattern. Those in a postsynaptic potential last for hundreds of milliseconds and are dipolar. Because the electromagnetic field of a quadrupole falls off more rapidly with distance than does that of a dipole, it is thought that the EEG and MEG are mostly measures of postsynaptic currents (Ilmoniemi, 1993).

Viewed from outside the neuron, each region of membrane acts as a tiny current source (out) or sink (in), depending on the direction of the net local current flow. A small region of brain tissue produces an externally observable electric potential or magnetic field if and only if the average distribution of sources and sinks within the neurons in that region is distributed in a nonradially symmetric fashion and if the neurons are systematically aligned and activated in synchrony. Activity of cells that does not satisfy these constraints ("closed" fields) cannot be seen at the scalp. However, these constraints are generally satisfied by the pyramidal cells in the neocortex, which have apical dendrites extending from the soma towards the surface of the cortical sheet. A cortical region containing hundreds of thousands of such cells produces a signal strong enough to be detected at the scalp (for more detail, see Kutas & Dale, 1997).

There are many ways to look at this electrical and magnetic activity in both the temporal and spatial domains, and these techniques are among the most direct, noninvasive methods available for the study of cognitive neuroscience issues. EEG measures the spontaneous activity of the brain; it is characterized by rhythmic electrical activity occurring in multiple frequency bands. Many investigators focus on localized and transient blocking or attenuation of rhythmic EEG activity (e.g., in the alpha band, 8–12 Hz) in the form of event-related desynchronizations to make inferences about the fine structure of neural processing (e.g., Krause et al., 1996; Pfurtscheller, Neuper, & Berger, 1994). In another approach, the average ERPs elicited in response to specific events are examined (where *event* is loosely defined and in some cases represents preparation for movement or the absence of a stimulus). These ERPs are generally measured as a series of positive and negative deflections ("components"), which can be characterized with respect to their amplitude and latency across the scalp, although in principle every time point can provide valuable information about the ongoing brain activity. ERPs (and their averaged magnetic counterparts) have been used to investigate issues in attention, memory, neural plasticity, and language, among others (e.g., Rugg & Coles, 1995).

Although EEG and MEG signals are both weighted integrals of source currents in the brain, they provide different, albeit complementary, views of the underlying activity. The distribution of the normal magnetic field component is orthogonal to the corresponding pattern of the electrical potential produced by a current dipole. Because of the nature of magnetic and electrical signals, the EEG and MEG are affected differently by head shape, dipole location, and dipole orientation. First, it is easier to measure the lead fields of the MEG because they are largely unaffected by skull and conductive inhomogeneities in intervening tissue (Hämäläinen, 1995), whereas the EEG is affected by these variables. Second, magnetic field strength falls off more rapidly with the depth of a dipole than does the electric potential strength; the magnetic pattern is more compact than the electrical one. Finally, and perhaps most importantly, MEG is insensitive to radial sources regardless of their depth (Mosher, Spencer, Leahy, & Lewis, 1993). In practical terms, the MEG is thus mostly sensitive to activity in the superficial parts of the sulci and is much less sensitive to activity in the depths of sulci or on the crowns of gyri. The EEG is sensitive to both tangential and radial sources, although the electric field due to tangential sources in the fissures may be masked by superficial radial sources (Ilmoniemi, 1993).

The spatial resolution of conventional EEG methods is especially poor in large part because of (a) limited spatial sampling, (b) smearing of cortical potentials by volume conduction (from cerebrospinal fluid [CSF], skull, and separation of sensors from sources), and (c) contamination by the reference electrode. Over the past 10 years, however, a number of high resolution EEG (HR-EEG) methods have been developed to deal with these problems and have dramatically improved the spatial resolution of scalp recorded EEG data (e.g., Gevins, 1996; Nunez & Westdorp, 1994). In some laboratories, interelectrode distances have been decreased from the traditional 6 cm in the International 10-20 system to the recommended 2.5–3 cm (125 evenly spaced electrodes), although not all questions require so many electrodes. Regardless of the number of electrodes, however, the high resistivity of the skull blurs the potential distribution at the scalp. This distortion can be reduced by applying the surface Laplacian (e.g., current source density [CSD]) or finite element deblurring (Le & Gevins, 1993; Nunez, 1981; Perrin, Bertrand, & Pernier, 1987). The CSD is computed as the second spatial derivative of the potential field at each electrode; it provides estimates of local current density (averaged over 1–2 cm) flowing perpendicular to the skull and is more sensitive to local sources than are raw potential maps. This derivative is independent of the reference electrode.[1]

These HR-EEG methods provide much better estimates of cortical potential distributions, but they still cannot be used to directly infer the underlying sources. Although it is, in principle, possible to calculate the electrical potential or magnetic field anywhere inside or outside the head for any arbitrary distribution of neural membrane currents (the "forward" solution), the inverse problem of determining the locations, orientations, and time courses of the set of dipoles producing the electromagnetic field has no unique solution. Additional constraints are needed. Most of the approaches to this source problem are based on some explicit model with a small number of free parameters. The most popular model is the current dipole, which has an accuracy of about 3 mm (for MEG) when it can be assumed that only one localized source is active at a particular time (deMunck, 1990). More often than not, however, this assumption cannot be made because the activity is known to be spread over a large cortical area or to be occurring in distinct brain areas. Under these circumstances, multiple current dipoles

[1] Nonetheless, its interpretation in terms of underlying sources is still not straightforward, because a maximum and minimum of the Laplacian map may be due to radially oriented primary currents under the extremes or tangential current between them; this ambiguity, however, can be resolved by the MEG.

must be modeled, and these require yet further constraints. To explain the waveshapes recorded across the scalp during a time interval, the fixed dipole model (e.g., brain electric source analysis) assumes that dipole position and orientation are fixed, while dipole strength is allowed to vary (Scherg & Ebersole, 1993; Scherg & von Cramon, 1986); locations and orientations are informed by other sources of data, including other neuroimaging techniques. Other approaches assume a continuous dipole distribution (e.g., Dale & Sereno, 1993), which, in combination with a careful determination of the three-dimensional folding of the cortex from structural MRI images, can improve spatial resolution considerably. For the moment, the effective spatial resolution of EEG measurements for psychological issues remains an open question, although it is clearly better than has generally been assumed.

Most importantly, both EEG and MEG are not only direct measures but are very much real time when it comes to cognitive processes. The temporal and spatial resolution of these techniques is limited primarily by the method itself and not, for example, by the time necessary for some other physiological variable to change in response to the activity of interest. The temporal precision of EEG and MEG is therefore quite high, with an upper limit at the submillisecond level; both the electric potential and the magnetic field at time *t* depend on the membrane current at time *t* only. Thus, if *t* is the earliest time at which ERPs from the two conditions differ significantly, then it can be concluded that the brain activity differs between the two conditions at that time. The onset of the latency of the ERP difference between two conditions can then be taken as an upper limit on the time by which the brain must have processed the stimuli sufficiently to distinguish them (although, of course, the converse does not hold; there are many reasons why one might fail to detect a difference between two conditions). From a methodological point of view, the temporal precision of these techniques is limited only by the speed with which the potentials travel to the sensors and are transduced and by the measurement sampling rate. The temporal resolution of these techniques is essential for monitoring processes where small differences in timing can have large consequences, such as attentional switching, lexical access, and updating working memory. Because the activity of independent generators is additive, these methods can also be used to determine the extent of functional independence between different brain mechanisms. Thus, in general, direct measurements of brain electrical/magnetic activity seem to have a lot of potential to tell us when, what, and even where.

Exciting . . . Or Is It?

Typically, neuroimaging investigations depict their results in a brain map of activated areas (pixels, clusters, regions of interest, whole brain). But what do these activations mean? Direct (electric and magnetic) and indirect (metabolism, blood flow) measures of central nervous system processing both record changes in the level of activity of particular populations of neurons. However, the neurobiological consequences of increased activation (excitation vs. inhibition) are not directly represented in such measures.

Increased activity in a population of neurons can have either an excitatory or an inhibitory effect on the cells with which they synapse, depending upon the type of synapses involved. An increase of excitatory activity will lead to greater activation of structures downstream, whereas an increase in inhibitory activity has the reverse effect. Likewise, decreases in excitatory activity result in relatively less excitation of downstream structures, whereas decreases in inhibitory activity can have the opposite effect, increasing activity downstream due to a release from inhibition. In fact, the output of any given structure could even remain constant as different patterns of excitation and inhibition impinge upon it under different circumstances. Thus, activation is not synonymous with excitation, just as decreases in activation are not always telltale signs of inhibition. Positive and negative ERP components at the scalp do not necessarily signify excitation and inhibition, respectively. From electrical activity measured at a distance (sensors at the scalp), it is not possible to determine whether the current flow is due to excitatory input onto a distal dendrite or to inhibitory input onto a cell body (of a cortical pyramidal cell). A similar uncertainty dogs the interpretation of the "activations" reflecting increased blood flow in PET and fMRI studies; the "activated" brain structures may, in fact, be either excited or inhibited by the increased synaptic activity responsible for the increased blood flow. Furthermore, failure to observe increased electrical activity in or blood flow to an area (in one condition relative to another) does not allow the inference that the area is definitely not involved in the cognitive act under study. This seemingly "inactivated" brain area may simply be invisible to the chosen CNS measure because the different sets of excitatory and inhibitory input it receives under two task conditions add to yield the same overall activity level. These different patterns of input, however, may have radically different consequences for neurobiology—the amount of synaptic efficacy change, the movement of microtubules mediating morphological change, and the upregulation or downregulation of enzymes and expression of particular genes—as well as for cognition.

Thus, the more information we have about all the various body and brain measures, the more likely we are to figure out whether activity recorded from any one brain measure at any given moment or at any given location is excitatory or inhibitory. And, ultimately, the functional significances of the various patterns of all the measures are most easily interpreted within the context of a physiological and cognitive theory, ideally one that could account for electric, magnetic, and blood flow changes, muscle activity, heart rate, EDA, and pupil diameter, as well as the decision rendered, the speed with which it is given, and the consequences for the system of having had this experience. Brain functions arise out of neural circuits, not just single brain regions, and functional accounts of activity in a particular brain region will undoubtedly differ depending on what the inputs are, what neural circuits are involved (and what aspect of the circuit this particular region is involved in), and what the outputs are observed to be. Thus, the more we know about the state of the brain and the body during some psychological state, the more constrained the possible solution to any particular instance of the mind/body problem and the more likely we are to be theorizing at the right level of analysis. Our interpretation of the meaning of activity derived from CNS measures such as ERPs, PET, or fMRI will thus often require knowledge gleaned not only from neuroanatomy and neurophysiology but also from psychophysiological measures of bodily function and behavior.

Receptive and Reactionary

Electrical activity is only a part of the story on neural information transmission. Information carried by electrical signals within a neuron is transferred between neurons at synapses via the release of neurotransmitters from the presynaptic cell. These chemical compounds bind to receptors on the postsynaptic cell and cause cascades of chemical reactions and electrical changes in the postsynaptic neuron. Neurochemical processes not only allow the transfer of electrical impulses, they also modulate the responsiveness of

neurons to stimulation and mediate structural changes and even genetic expression in neurons. These neurochemical processes play an important role in determining how we feel and therefore what we are most likely to think about and perhaps to remember; this is why, in part, some people drink alcohol to relax, imbibe caffeine to wake up, or take melatonin to put themselves to sleep after cross-continental travel. Brain functioning is crucially chemical, as well as electrical, in nature.

Historically, neurochemical processes in humans have been studied indirectly, for example, by measuring the chemical composition of blood, urine, or CSF in different individuals or in the same individual under different conditions. More recently, however, PET has offered a noninvasive means of directly measuring neurochemical activity in the human brain. It is currently one of few techniques that can be applied to study neurotransmitter receptor affinity and density in vivo and to examine the effects of pharmaca (pharmacologically active agents) on neurotransmitter and receptor systems. PET is based upon the coincidence detection of paired 511 keV annihilation photons arising from the collision between an electron and a positron emitted from a radionucleotide. The collision results in the release of two high-energy photons that travel in opposite directions (180°) and can be measured at detectors spaced around the head. The (near) simultaneous detection of the two photons (and in some cases the time difference between their detection) allows localization of the point of collision at or near the radioactively labeled substance.

In a PET experiment, volunteers are injected with a radiolabeled substance (e.g., one containing ^{15}O, ^{13}N, ^{11}C, ^{18}F, ^{68}Ga, or ^{62}Cu; Hartshorne, 1995), nanomolar concentrations of which can be detected after it has been taken up by and, in some cases, begun to be used by the brain. Inferences then are made about the locus of activity and/or changes in uptake or distribution of these substances under different conditions. [^{18}F]deoxyglucose has been used to study cerebral metabolism, and ^{15}O-labeled water has been used to follow blood flow changes associated with transient physiological increases in neuronal activity. However, theoretically, any chemical compound that can be synthesized with one of these radiolabeled tracers can be followed with PET to investigate receptor parameters or the distribution of various pharmacologically active compounds in the brain. This approach requires a detailed model of the biochemical processes affecting the tracer-containing compound, including an understanding of where a labeled substance will go, how fast it will get there, and how long it will remain and of whether it will be broken down and, if so, which of its parts will retain the radioactive label and where those parts will ultimately end up (excreted or stored, in water or in fat) (e.g., Holcomb, Links, Smith, & Wong, 1989). Answers to these questions rely in large part on autoradiographic analyses performed in animals. For a strong enough signal to be measured, the compound should also have a high specific activity for the receptor of interest (when the equilibrium model is used, a low-specific activity preparation is also required) (Ring, 1995). Although many compounds are still imperfectly understood, progress has been made in synthesizing radiolabeled versions of neurotransmitters or pharmaca known to affect particular neurotransmitter systems, and these have been used to examine receptor density and affinity across groups and within individuals over time. For example, [^{11}C]-raclopride, a compound with selective affinity for D2 (dopamine) receptors, has been used to examine dopaminergic functioning in normal and schizophrenic individuals, [^{18}F]-methylspiroperidol has been used to examine D2 receptors following chronic cocaine abuse and detoxification, 6-^{18}F-DOPA has been used to examine Parkinson's disease, [^{11}C]-flumazenil has been used to image benzodiazepine receptor functioning in normal and epileptic individuals, and ligands for histamine receptors and muscarinic receptors have recently been described (for review, see Ring, 1995).

These approaches allow for an examination of the number and distribution of neuromodulatory receptors under various conditions, but they do not provide a direct look at their functions. Inferences about the effects of pharmaca on neural function can be drawn by combining their administration with PET measurements of metabolic activity or blood flow (for an example of such a study, see Friston et al., 1991c). However, these physiological parameters are indirect measurements of neuronal activity and are nonspecific with regard to neurotransmitter type. Moreover, neuromodulatory synapses are typically distributed sparsely in the brain and may constitute only a small percentage of the synapses in any particular area, thus making it likely that the pharmacologically induced activity will fall below threshold and be missed. PET methods, however, are sensitive to fluctuations in the level of endogenous chemicals (see Fisher, Morris, Alpert, & Fischman, 1995, for review), which can be measured as a result of competition between them and externally administered radiolabeled compounds at the receptors of interest. An increase in the concentration of an endogenous compound results in a concomitant decrease in the binding of the radiolabeled tracer. Under the right model, this observation may allow the functioning of neuromodulatory systems during cognitive and affective processing to be monitored in much the same way that blood flow or cerebral metabolism has been followed (Fisher et al., 1995).

Under the right methodological circumstances, PET techniques can have fairly good spatial and temporal resolutions. The temporal resolution of PET is limited primarily by the half-life of the radionucleotide, which can range from about 2 min for ^{15}O to more than 1 hr for ^{18}F (Hartshorne, 1995). The upper limit spatial resolution of PET is controlled, ultimately, by the distance traveled by the positron before it collides with an electron, which is typically no more than a few millimeters, depending on the tracer. The number and spacing of detectors can make the practical resolution slightly lower (on the order of centimeters), although the most recent generation of scanners approaches the theoretical upper limit (with resolutions of 5–6 mm). Ultimately, though, the use of PET to trace neurochemical activity is an excellent example of a case in which when and where the temporal and spatial resolutions of the technique are less important than what it can measure. PET techniques provide the only available window into the living human brain's neurochemistry and the relationship between neurochemistry and cognition and disease, and, as such, should be especially valued for their unique potential in this area of psychophysiology.

Blood Rushing in Her Ears . . .

Anyone who has ever felt her face grow hot with anger or shame or has stood up too fast and passed out knows only too well that there is a relationships among blood flow, the brain, and the mind. The brain depends upon a constant blood supply to meet its metabolic demands, which in turn change with neuronal activity. Concentrations of various ions inside and outside a neuron are maintained within bounds by several energy-consuming pumps, particularly the sodium–potassium pump. Because the brain stores little glucose, it requires a continuous supply via the blood to meet its energy demands (Clarke & Sokoloff, 1994). Whatever the cause—a light, a laugh, or a thought—ionic concentrations deviate from

their resting levels with increased neuronal activity, and glucose consumption goes up. Thus, under normal conditions, an increase in neuronal activity is expected to be accompanied by an increase in glucose metabolism.

This relationship between neuronal activity and glucose metabolism has been exploited by PET studies using [^{18}F]deoxyglucose, a glucose analog that is partially metabolized and then trapped in the cells (reviewed by Herscovitch, 1994). By using PET to measure radioactivity levels after injection of [^{18}F]deoxyglucose, it is possible to determine which populations of neurons were metabolically (and presumably electrically) active during the time period between the injection and the detection of the radioactive decay. These metabolic changes can be followed during normal development and aging, after pharmaca administration, and in association with movement disorders, epilepsy, dementia, schizophrenia, and other psychiatric conditions. The half-life of ^{18}F, however, is nearly 2 hr. Although this long half-life can increase reliability for inferences about changes in, for example, disease states, it is quite long relative to psychological phenomena that take place on the order of seconds or milliseconds. It can therefore lead to subject fatigue and response habituation and generally precludes the measurement of multiple experimental conditions within the same individual. To gain better temporal precision, researchers have turned to examining circulatory system correlates of glucose metabolism rather than the metabolism itself as an index of neuronal activity.

Until recently, it was assumed that neural activity requires glucose, glucose metabolism requires oxygen (although nonoxidative glycolysis is possible), and both rely on a continuous flow of fresh blood to supply the substrates. From this view, functionally induced increases in neural activity should thus be associated with local increases in both blood flow and oxygen extraction. As expected, at rest the regional rates of cerebral blood flow, oxygen extraction, and glucose metabolism do show a strong spatial correlation (Fox & Raichle, 1986). However, the precise nature of the link between energy metabolism and local blood flow becomes controversial during physiological increases in neuronal activity. Although both blood flow and glucose uptake are closely correlated with neuronal activity, they are all less closely correlated with oxygen extraction. In many cases, blood flow increases appreciably more than oxygen consumption (Fox, Raichle, Minton, & Dence, 1988b), reflecting a true uncoupling or, alternatively, that disproportionately large changes in blood flow are needed to support small changes in oxygen metabolism, as predicted in a model developed by Buxton and Frank (1997). Future research will need to elucidate what the metabolic needs of active neurons are, how this activity triggers changes in blood flow, and how and with what time course those changes meet energy demands so as to better understand the physiological signals from which inferences about sensory, motor, and cognitive processes are drawn.

Despite the relatively long (and still loose) inferential chain between, for example, the sight of a snake, increased blood flow in the amygdala, and fear, regional neuronal activity seems to be reliably accompanied by both local circulatory and metabolic changes. In fact, such psychophysiological data have already led to many claims about word recognition, verb generation, selective attention, the effects of practice, and other sensory, motor, and cognitive processes. PET, which has been fairly extensively used to examine blood flow changes during cognitive processing, has recently been joined by newer, less invasive techniques (not requiring the ingestion of radioactive material) such as optical imaging and fMRI.

Although optical imaging with voltage-sensitive dyes has allowed the visualization of neuronal activity in nonhumans for some time, the use of intrinsic optical signals to measure neuronal activity in humans noninvasively is a very recent development (see Fabiani, Gralton, & Corballis, 1996, for review). In this technique, light from a near-infrared source is used to illuminate a point on the surface of the skin and is recorded at a distance by a detector, also located on the skin. The amount of photon migration (which determines the amount of light recorded by the detector) is a function of the scattering and absorption properties of the tissue through which the light passes. These scattering and absorption properties are believed to change with the concentration of metabolically significant substances, with changes in blood volume due to local capillary recruitment or dilation of venules, and as some have suggested with electrical activation. The measurement of slow effects (2–10 s poststimulation), presumably due to metabolic and circulatory factors, is a fairly well established technique in the animal literature and recently has begun to be used in humans as well. Preliminary studies suggest that fast effects (50–500 ms poststimulus activation) due to neural activation may also be reliably detected (Fabiani et al., 1996). If optical imaging techniques live up to their promise, they could provide a direct measure of neural activity with millisecond temporal resolution and millimeter spatial resolution. Moreover, because both fast and slow effects could be observed in the same individual, optical imaging could prove to be an important tool for examining the relationship between electrical activity and microvascular changes. Already the ability of optical imaging to assess the oxygenation state of hemoglobin has been used to assess the temporal characteristics of certain fMRI findings (Hu, Le, & Ugurbil, 1997).

Although the discrepancy between cerebral blood flow and oxygen extraction remains puzzling, it presents another intrinsic variable that can be linked to neuronal activity. Because the increase in local blood flow (and hence oxygen delivery) far exceeds cerebral blood volume changes and the slight increase in local oxygen extraction, blood near a region of local activity will eventually have a higher concentration of oxygenated hemoglobin than will blood in locally inactive areas.[2] These differences can be detected using fMRI because as hemoglobin becomes deoxygenated it becomes more paramagnetic than the surrounding tissue, thereby creating an inhomogeneous environment. The basis for fMRI is the fact that certain nuclei—hydrogen, for example—have an intrinsic magnetic moment. These nuclei behave like small magnets, and when placed in a magnetic field, a small percentage of them aligns with that field. When a second field (oscillating at the right frequency) is transiently introduced, perturbing these nuclei, their magnetic moments will be caused to precess (rotate) around the direction of the stable large field, thereby creating a signal that can be detected. Because of local inhomogeneities in the magnetic field, the moments of the nuclei become realigned with the larger field and this signal decays. The rate at which the signal decays depends upon certain physical and physiological factors. For example, the signal decays more rapidly in the presence of deoxyhemoglobin than in the presence of oxygenated hemoglobin, so fMRI can detect the increased local levels of oxygenated hemoglobin that seem to result from functionally in-

[2] The increase in the concentration of oxygenated hemoglobin may be preceded by an initial decrease in oxyhemoglobin concentration caused by activity-induced oxygen extraction that takes place before hemodynamic changes have begun (see Hu, Le, & Ugurbil, 1997, for discussion). This earlier negative signal may also be detectable with fMRI in single individuals under the right circumstances.

duced increases in neuronal activity. The signal changes are quite small—1–5% at 1.5 Tesla and 2–15% at 4 Tesla—yet adequate signal-to-noise ratios can be achieved to detect them (Cohen & Bookheimer, 1994), assuming contamination from physiological fluctuations (cardiac, respiratory) and motion artifacts have been eliminated (the lower field fMRI is more sensitive to motion-related artifacts) (e.g., Biswal, DeYoe, & Hyde, 1996; Le & Hu, 1996).

Currently, fMRI methods are capable of localizing oxygenation differences (using blood oxygenation level dependent [BOLD] contrast) or, in some cases, blood flow differences (with spin "tagging" sequences or EPISTAR techniques) with high spatial resolution. Insofar as these changes actually reflect neuronal activity, fMRI is capable of localizing that activity to approximately the level of a cortical column. However, as for other psychophysiological measures, the true spatial resolution of fMRI is a property not just of the methodology but of the physiological relationship between what is being measured and what is being inferred from that measure. For example, veins draining relatively large areas of the brain are known to contribute much of the signal with some fMRI pulse sequences (e.g., gradient echo BOLD experiments); these oxygenation changes cannot as easily be localized to activity in specific brain areas as changes in smaller capillaries could be (Boxerman et al., 1995). Spin-echo techniques (in which a 180° radiofrequency refocusing pulse is included in the sequence) shift the balance toward capillary changes, albeit at the expense of the size of the signal change. It has been suggested that the initial negative signal (1–2% decrease at 4 Tesla) is more spatially specific than the later positive phase (Hu et al., 1997) although also more likely to be contaminated by respiration, which has comparable temporal characteristics.

When making inferences about the spatial localization of neuronal activity from fMRI measurements, it is also important to consider that changes in blood flow and metabolism seem to reflect activity at synapses and not cell bodies. Thus, increased activity of neurons with distant projections may be reflected in increased metabolism in their projection zones even if little activity is ultimately elicited in those zones (Nadeau & Crosson, 1995). Under certain conditions, therefore, evidence of increased synaptic activity may extend one synapse beyond the area primarily involved in the computation of interest; as a specific example, activity in the globus pallidus could be detected as a metabolic increase in the thalamus (one of its distant projection zones). The spatial resolution of fMRI is therefore ultimately limited by the spatial relationship between the signal changes measured and the neural activity those signal changes represent, although it is currently the best among the neuroimaging techniques.

The fMRI technique of choice for studying the time course of signal intensity changes in the brain is echo planar imaging, which can generate a complete two-dimensional image in as little as 40 ms following a single excitation of the spin system (Jezzard & Song, 1996); it is, however, sensitive to a number of artifacts, including image ghosting and geometric distortion. Until quite recently, the temporal resolution of fMRI, like that of PET, has been limited by the need to block experimental conditions. In the case of PET, a cumulative period of at least 40 s is necessary to derive a clean map of regional cerebral blood flow in the brain, and the choice of addressable experimental issues is limited to those that are unaffected by multiple exposures (e.g., repetition or practice effects). By contrast, in the case of fMRI, the recently demonstrated feasibility of selective averaging techniques has obviated the blocking requirement (Buckner et al., 1996). Ultimately, the temporal resolution of fMRI is limited, not as much by the method itself as by the fact that the blood flow response typically lags behind the actual electrical signal by 1–2 s and does not track activity on a millisecond-by-millisecond basis. That is, because the blood flow response seems to be influenced by activity levels averaged over some time interval (a few hundred milliseconds or more), it is less temporally specific than the activity with which it is associated.

Nonetheless, there are certain real advantages afforded by this class of techniques. Appropriately used, fMRI offers excellent, uniform spatial resolution and the potential to map activity in the human brain, whose exploration was previously limited to highly invasive techniques in animals. For example, fMRI has been used successfully to map the visual field in intact human visual cortex with a specificity that allows cross-species comparisons (e.g., Sereno et al., 1995). Unlike PET (with its radionucleotides), fMRI measurements apparently can be made multiple times in the same individual and can be easily combined with information about that individual's brain (from structural MRI). In fact, the analysis of individual data in fMRI studies signifies a virtual paradigm shift in cognitive neuroscience from the more dominant approach of reporting group means (based on averaging).

Individuality

For experimental purposes, individuals can be studied on a case-by-case basis or as a group, in which case inferences are based on group means. Psychophysical and some neuropsychological research is based on extensive study of one or a few single individuals. However, historically, research in the cognitive neurosciences has been conducted on the "average person," the result derived from averaging across a homogeneous group (number determined by effect size) of individuals. If the assumptions behind averaging are met, then its application increases the signal-to-noise ratio, which is especially important when measuring small signals. This approach, however, requires not only that the signal be invariant from trial to trial but that the statistical properties of the noise and its relation to the signal are known, and these conditions are rarely met in cognitive neuroscience studies. Averaging can also provide a picture of what is common, as opposed to idiosyncratic, across individuals and, given appropriate sampling techniques, it can afford better generalization to a population of interest.

However, psychophysiological studies require averaging across both the psychological and the physiological dimensions of the participants. Even in a presumably homogeneous experimental group, participants can differ considerably in their psychological and emotional traits and abilities—their attentional and working memory capacities, their prior language experience (what languages they know, what books they have read), their emotionality and response to stressful situations—and these differences can all affect both their processing strategies and their task performance. The difficulty of selecting homogenous groups of participants for study is more than doubled if physiological and anatomical differences among the participants must also be considered. Physiology (and anatomy) differs across individuals matched for age, gender, socioeconomic status, and IQ. Even if the cognitive consequences are minor, there can be significant physiological differences between and within individuals as a function of their eating, sleeping, and drug history and position in the circadian or lunar cycles (e.g., Polich & Kok, 1995). Heterogeneous groups are likely to produce heterogeneous physiological responses in the face of similar cognitive demands (although the extent to which cognitive processing can be said to be identical under different physiological conditions is an open question).

These issues are especially acute when comparing groups of individuals, as in experiments concerned with effects of variables such as age, brain damage, and disease states, that impact both physiological and cognitive processes. Development and aging, for example, are complex constellations of changes that are undeniably distributed across both the body and the mind. Likewise, brain damage affects not only the functioning of neurons but also the transport of blood, the allocation of energy resources, and so forth. Although both physiology and cognition are affected, however, the relation between the changes need not be causal. In such cases, then, accurate interpretation of the psychophysiological differences observed between groups requires that physiological differences with consequences for the psychological process of interest be distinguished from those without.

Thus, a distinct advantage of fMRI techniques for brain structure/function mapping is the ability to reliably detect blood flow and blood oxygenation changes throughout the brain of a single individual. Substantial variability has been reported in the amplitude and in the temporal response of the fMRI signal, which would have been distorted by averaging across individuals (e.g., Hu et al., 1997). Moreover, the same individual can be scanned repeatedly in a whole host of paradigms, and these functional scans can easily be coregistered with a structural MRI scan of the same individual's brain. Ultimately, it will be possible to map an individual's entire brain across the whole space of its mental functions. Clearly, this ability to localize physiological changes within an individual's particular anatomy significantly increases the spatial resolution of fMRI in neuroimaging, where the current standard for reporting localizations of activated foci is with reference to a stereotactic atlas, such as that of Talairach and Tournoux (1988), which is based on sparsely sampled sections of a single postmortem brain and is not accurate to within closer than a centimeter.

Improved signal processing techniques and methodological advances have also made it more feasible to study single individuals (and in some cases single trials) with other psychophysiological methods (ERPs, MEG, PET). Although this shift in focus alleviates some of the problems with group studies mentioned above, it comes with its own set of inferential issues. Most obvious, perhaps, are concerns about statistical power, which is not always easy to calculate for the designs used in neuroimaging studies. When the use of individuals or only small groups of subjects causes insufficient power, it becomes problematic to interpret the meaning of "inactive" regions or the reasons for variability across subjects. Moreover, measurements made on a single individual or a small number of individuals may not be representative of a population of interest, especially if they are not chosen randomly. For example, the repeated use of "good activators" in fMRI or those with large N1 effects in ERP attention experiments may reduce the generalizability of inferences made about human cognition. These concerns underscore the even greater need to collect all sorts of background information about the individuals under study. When studying blood flow, for example, it may be useful to know if a participant has high blood pressure or is taking aspirin. Indeed, the study of physiological differences between individuals and the predictive value for cognitive processing differences is an interesting question in its own right. One benefit of examining single individuals is that the effects of physiological variables on cognition can be examined using individuals as their own controls, such as when comparing performance before and after some kind of treatment, during different phases of the circadian cycle, or over development. Naturally, the inferential problem posed by the study of individuals can also be alleviated by continuing to examine group data while focusing on the individual. In this way, we may be able to better understand not only the generic but the idiosyncratic mind . . . at the same time maintaining our individuality and membership in the human race.

Slouching and Shifty Eyed

Ultimately, we study CNS activity or its physiological correlates because this activity has behavioral consequences, and only by understanding the relation between them can we assign functional interpretations to the physiological changes we measure. Therefore, making sense of functional brain images, whether electrical, chemical, or hemodynamic, requires knowledge of the functions those images purport to capture. Psychophysiological measurements of (concomitant or associated) bodily responses can provide some important clues to what those functions might be.

Motor outputs constitute the majority of the most readily observable changes in bodily activity. Most psychological experiments use motor activity of some kind as their primary dependent measure (e.g., manual reaction times, naming latency). Psychophysiological measures provide more sensitive indexes of motor activity, especially motor preparation, and can register covert activity, changes in muscle tension that may have cognitive consequences even if no actual movement occurs. Furthermore, these measures allow motor activity to be monitored naturally without the imposition of any extraneous task. Common psychophysiological measures of motor activity include the measurement of the electrical activity leading to muscle contraction (EMG), and the measurement of the electrical field changes that occur as the eyes move (electrooculogram EOG) or pupil movements tracked with video or laser techniques (reviewed by Stern & Dunham, 1990).

The temporal and spatial resolutions of these techniques can be quite good, although in this case these resolutions are defined for various peripheral physiological measures and not for CNS neuronal activity. Surface EMG techniques can be used to follow activity in underlying muscle clusters with millisecond temporal resolution, and spatial resolution is limited only in practice by the impossibility of measuring muscle activity over the entire body. Inasmuch as many actions are multiply determined, partial information from only one of several relevant muscle groups can limit the inferences that can be drawn. When considering the spatial resolution of EMG, however, it is important to distinguish between inferences about movements and inferences about mechanisms. Because similar limb displacements can be achieved by very different muscle activity, of which only a limited subset is sampled by EMG, comparing muscle output in two or more conditions may be complicated. However, if movements in two conditions are associated with different patterns of muscle activity, it is likely that different mechanisms are responsible. Eye movement monitoring techniques also attain temporal resolutions on the order of milliseconds and afford an upper limit spatial resolution of $<1^\circ$ of visual angle.

EMG techniques have been used to great advantage to study motor preparation, intention, and the time course of information processing (Rugg & Coles, 1995), and the study of saccadic eye movements has contributed to our understanding of reading and visual scene/object processing (e.g., Eberhard, Spivey-Knowlton, Sediry, & Tanenhaus, 1995; Rayner, 1995; Rayner & Sereno, 1994). These techniques can be combined with CNS measures to provide crucial information about the nature of brain activations observed during cognitive and affective processes. Areas involved in the control of motor activity often also are engaged by cognitive and

emotional processing. Thus, it is not surprising that the tension in particular muscle groups increases not only with the physical and motor demands of a task but also with factors such as the stress or anxiety brought about by task demands, the intensity of concentration required by the task, the emotional response to it, and so forth (Cacioppo, Tassinary, & Fridlund, 1990). Furthermore, changes in muscle activity may accompany cognitive acts that do not explicitly require motor output. Likely loci of such changes are areas of the body that would be involved if the response were acted out, as has been noted in the face and jaw muscles associated with speech even during silent reading or language processing (e.g., Cacioppo & Petty, 1979). Because this covert EMG activity is mediated by the CNS, it may well be the source for the activity measured by CNS imaging techniques in some cases. Perhaps, for example, covert speech accounts for some of the activity observed in motor areas during various PET studies of verbal processing (e.g., Fiez et al., 1996); this hypothesis could easily be tested by recording facial EMG during the same conditions if not during the actual PET recordings.

Eyes Wide, Heart Pounding, Hands Clammy . . .

Although we often think of behavior in terms of overt movements—eye movements, speech, and manual responses—the body behaves in many other ways as well. At times, in response to both internal and external stimulation, the skin sweats, the heart pumps harder, the eyes take in more light. These autonomic nervous system responses, bodily changes controlled by the sympathetic and parasympathetic systems, can have a cognitive or emotional origin and may themselves affect cognitive and emotional processing. Measures of pupillary size, cardiovascular activity, and the electrical properties of the skin have revealed that cognitive processing and autonomic influences on body states are linked and have begun to reveal where and how these links arise.

The parasympathetic system serves to reduce pupil size and to decrease heart rate, and the sympathetic system increases pupil size and heart rate and causes changes in the activity of sweat glands, which can be recorded as changes in the electrical resistance of the skin.[3] Many peripheral measures are also known to be influenced via more direct CNS pathways. Pupil size, for example, can be regulated by the reticular activating system (Beatty, 1986); the baroreceptor reflex, a negative feedback loop responsible for rapidly adjusting cardiovascular output if blood pressure to the head is not maintained, is influenced by a number of higher level brain structures, including the thalamus, the hypothalamus, and the forebrain (Hugdahl, 1995); and EDA is influenced by one pathway through hypothalamic and limbic structures and another through premotor structures via the pyramidal tract (Dawson, Schell, & Filion, 1990).

These measures change consistently with several kinds of cognitive manipulations. For example, pupil size varies with cognitive load (Beatty, 1982), although some have suggested that the size reflects amount of processing actually accomplished rather than the load per se (Stern & Dunham, 1990). Task-evoked changes in pupil size, known as the task-evoked pupillary response, can be observed within the first several hundred milliseconds after stimulus presentation (e.g., Beatty, 1982) and have been correlated with emotional processing and degrees of alertness. Similar correlations (with similar temporal resolutions) can also be observed between attentional and affective processes and various aspects of cardiovascular functioning, including heart rate, morphological characteristics of the electrocardiogram, blood pressure, and peripheral blood flow. Heart rate acceleration, for instance, often accompanies tasks requiring cognitive elaboration, whereas heart rate deceleration is often observed during detection tasks or tasks requiring the intake of information (Papillo & Shapiro, 1990). Furthermore, cardiovascular functioning seems to be intimately connected with inhibitory processing (in the behavioral sense); a systematic decrease in heart rate is observed during response inhibition, such as during the interval between a stimulus and a response. This relationship between inhibition of motor activity and cardiovascular functioning seems to be mutual; response inhibition appears to be effective only when it falls within particular phases of the heart cycle (e.g., Jennings, 1992). Changes in electrodermal activity can be reliably detected within <1 s of stimulus presentation, often following a single event. These changes, which may be linked to slightly different aspects of behavior than cardiovascular changes (e.g., Fowles, 1988), have been used successfully to study implicit aspects of cognitive processing. For example, Tranel and Damasio (1988) found that prosopagnosic individuals (who have difficulty identifying faces) show normal changes in their electrodermal responses to familiar faces despite claiming at a conscious level to have never seen the face before.

The neural circuits mediating autonomic responses are in many cases less thoroughly understood than those mediating motor activity. Nonetheless, these kinds of autonomic techniques can be combined fruitfully with CNS activity measures. They are especially well suited for tapping into aspects of cognitive and emotional processing that may be difficult or impossible for individuals to describe overtly. Investigations of emotion using a CNS measure, for example, could benefit from the reported physiological specificity of feelings (e.g., Davidson et al., 1994) by pretesting the materials with a combination of EMG and autonomic measures. Autonomic measures can be reliable indices of the kinds and intensities of emotions evoked by stimuli and can also provide independent estimates of factors such as task difficulty and attentional states that are known to affect measures of CNS activity. Peripheral techniques in general, therefore, are an essential part of the inferential chain linking brain to body and mind to brain.

Mind Observed . . . Mind Inferred

Here, we have reviewed a number of well-studied measures of the brain and the body. We have shown that no two measures detect exactly the same physiological process and that each measure has its strengths, which should be preserved whenever possible, and some limitations. Although combining techniques is generally beneficial, whether or not it makes sense to do so (or which ones to combine) is a matter of the question under investigation. One does not use a screw driver to thread a needle. Combining measures with different strengths and weaknesses may at times necessitate yet further compromises in the experimental procedure, making the inferential leap even larger, if not more costly. Effective integration requires improved techniques for image fusion, including anatomical standardization, model-based synthetic analyses by means of cross-methodological constraints, collective databases for neural system modeling, and principled ways of evaluating the consequences of procedural differences on cognitive inferences (see Fox & Woldorff, 1994; Grabowski et al., 1996).

[3] In fact, the electrical resistivity of all mammalian tissue varies with use, such that its measurement via electrical impedance tomography offers a means of imaging the internal conductivity distribution of the human body, including the brain (Metherall, Barber, Smallwood, & Brown, 1996).

In some centers, the coregistration of PET and structural MRI images is an integral part of the analysis of PET data, although there is no agreed-upon standard; some rely on fiducials, and others rely on mathematical algorithms that examine the entire image or on some combination thereof (e.g., Friston, Frith, Liddle, & Frackowiak, 1991a). Combining fMRI and structural MRI for an individual is relatively straightforward, except for some distortions in the lower resolution echo-planar fMRI images, which can be corrected (Reber, Wong, Buxton, & Frank, in press). Anatomical (brain size, size of areas, cortical folding patterns), neurovascular, and functional variability, however, increases the difficulty of combining data across individuals. In the case of PET, where cross-subject averaging has often been used to increase the signal-to-noise ratio, Fox et al. (1997) suggested using the published literature to model functional brain areas as spatial probability distributions from which confidence limits for the functional areas can be determined (functional volume mapping). Progress is also being made on various algorithms for anatomical normalization of either the entire brain or specific structures, with noteworthy advances coming from high resolution volume constructions and associated surface reconstructions that represent the cortical sheet as an explicit surface (Drury & Van Essen, 1997; Drury et al., 1996; Sereno, Dale, Liu, & Tootell, 1996). These cortical flat maps (where the topological relations between neighboring points are preserved) may provide an excellent means of visualizing and comparing activations derived from all neuroimaging techniques. Still other representational and a whole host of analytic problems must be solved.

Part of the difficulty involved in integrating techniques lies in the complicated nature of the signal processing and statistical decisions that must be made simply to analyze data within a given methodology. The neuroimaging literature abounds with polite debates over which is the "best" method for analyzing data. The great majority of analyses are based on the assumption that the variables being measured can be well described by their means, standard deviations, and correlations, although other features of neuroimaging data have been proposed for analysis (e.g., Strother et al., 1995; Votaw & Li, 1995). These analytical decisions are not straightforward because they depend upon the structure of the underlying data (including characteristics of the signal and noise), knowledge about the implications of incorrect assumptions, and the purpose for which the measure is being used (see Ford, 1995, for a discussion of PET analyses). For instance, questions about whole brain differences in one condition/group versus another call for different analyses (e.g., multivariate) than those in which regional or pixel level differences are sought (e.g., multiple univariate). Among the more controversial issues are decisions about methods for reducing noise so as to increase the signal-to-noise ratio, the choice of the test statistic, and methods for determining significance.

One major concern in both pixel and region of interest-based analyses of PET measurements is variability in whole brain metabolic activity between individuals and/or between scans in the same individual; this issue is not uncommon with peripheral psychophysiological measures (Ben-Shakhar, 1985; Levey, 1980). Because such variability can at times overwhelm experimental differences, it has become standard practice to remove global fluctuations in regional cerebral blood flow (rCBF) or PET counts prior to statistical analysis, albeit with a variety of data transformations (e.g., ratio adjustment, analysis of covariance [ANCOVA], *Z*-score transform) (Fox, Minton, Reiman, & Raichle, 1988a; Friston et al., 1990; McIntosh et al., 1996). These adjustments are based on very different assumptions about whether or not regional and global CBF changes are dependent and upon the nature of the relationship (multiplicative, additive) and spatial structure of the dependency, if they are dependent. Moreover, although there is no general consensus on which method is the "best" (Clark & Carson, 1993; Tempel, Snyder, & Raichle, 1991), choice of method seems to make little difference in the outcome of the statistical analysis when regional and global metabolic activity are strongly linear. In fact, a host of other factors can impact the choice, including the experimental paradigm, the population sampled (and whether global CBF changes are a part of the disease process and therefore what information is lost in the transformation), the type of scanner, and the dependent measure (e.g., blood flow or tissue radioactivity counts) (McIntosh et al., 1996). (See also Aguirre, Zarahan, & D'Esposito, 1997, for discussion of global blood flow contributions and their removal in fMRI analyses).

Data processing (filtering, smoothing) is followed by the application of statistical tests; the choice of which of these tests to perform and how to determine significance plays an extremely important role in the nature of inferences that are and should be made about the collected data. Because the underlying structure of neuroimaging data is multivariate, multivariate analyses would seem preferable in that they can take the correlation structure of the data into account and can detect differences in pattern of regional activity across conditions. However, the application of multivariate tests requires that there be more subjects than regional values; this requirement cannot be met if analyses are performed at a pixel level, because a 128×128 image would require more than 10,000 subjects. Thus, most investigators have chosen to perform the appropriate univariate test (assuming a general linear model) at each pixel so as not to lose spatial precision. However, this choice can lead to a reduction in sensitivity in some cases, and it creates a problem of multiple comparisons, potentially leading to a high chance of false positives (Type I errors) when all of the tests are viewed together. Electrical and magnetic techniques also face these multiple comparison problems, especially when large numbers of sensors are used (see Vasey & Thayer, 1987).

In PET studies, the most common method for analyzing activations is to normalize and then subtract two images that differ on one cognitive variable and to then look for values significantly different from zero by setting a threshold. Many investigators have discussed the interpretive errors that arise if the assumptions of the "cognitive subtraction" approach are violated, and several designs have been introduced to deal with these concerns (e.g., Ford, 1995; Friston, 1997). Here, we focus instead on the considerations for setting a decision threshold for a particular level of significance. Once test statistics have been mapped to every pixel, a decision must be made whether to accept or reject the presence of activation. The most common approach has been to set a threshold using some statistical criterion, considering everything above threshold "real" and everything below it "noise." The decision can be made on the basis of signal intensity, spatial extent, or both. Nonparametric thresholding has been proposed (Holmes, Blair, Watson, & Ford, 1996), although most thresholding has been performed at a predetermined alpha level, with correction for multiple comparisons (Friston, Frith, Liddle, & Frackowiak, 1991b; Worsley, Evans, Marrett, & Neelin, 1992). The choice of any particular threshold (often based on modeling involving a *t* or *z* distribution) affects both sensitivity and reliability. Of particular concern is the so-called multiple comparisons problem, that is, how to assess the statistics at all voxels individually and simultaneously while insuring that the probability of false positives (familywise Type I error) is less than the specified alpha level. If the threshold is set

too low, significance will be attributed to nonactive elements, but if threshold is stringent, then signals, especially small ones, are likely to be missed. In the procedures controlling for mapwise error, there is thus a trade-off between sensitivity and regional specificity. A simple approach for reducing the per pixel false-positive probability is to set the alpha level using a Bonferroni correction; this correction, however, assumes that the voxels are independent (which they are not) and is thus overly conservative.

The most common approach has been to create a statistical parametric map (SPM) from the univariate tests performed at each voxel and to interpret this SPM as a spatially extended statistical process that behaves as a smooth Gaussian field under the null hypothesis (Friston, 1995; Friston et al., 1996). This approach assumes that the neuroimaging data have a homogeneous spatial covariance structure. SPM allows the selection of a mapwise significance threshold for an entire multidimensional data set, with corrected *p* values assigned at the level of a voxel, a cluster of contiguous voxels, or a set of clusters (defined by intensity and extent thresholds). Hunton et al. (1996) found that the use of spatial extent rather than intensity thresholding improved sensitivity in small sample sizes. However, some small but reproducible foci are likely to go undetected with spatial extent thresholding, suggesting that the best approach may be the use of a smaller smoothing filter and a combined threshold based on both intensity and extent of activation. In general, thresholding techniques seem to work best for relatively large responses, which can then be accepted as "real" with confidence. Small responses that exceed threshold may better serve as the basis for hypotheses in future studies (sites to look for replication). Note also that the between- and within-subject variability in the size of PET activations is such that although *t* values provide a good estimate of the reliability of a response across individual observations, they do not always provide the best estimate of its location (Hunton et al., 1996).

Opponents of SPM have questioned the assumption of the homogeneity of regional variances across the brain; Votaw and Li (1995), for example, pointed out that the noise in PET images is not uniform across the image because of the attenuation of photons by the head (although this can be corrected). Moreover, even if the variances were uniform in the raw images, there is no reason why they should still be uniform after ratio normalization or ANCOVA adjustment. Others have questioned the assumption that a Gaussian random field is the correct sampling distribution of test statistic images. The independence assumption of the general linear model is violated by BOLD fMRI "noise" data sets. Such fMRI data were found to have a spatially nonstationary temporal autocorrelation structure, with more power at lower frequencies, although the requirement can be met by smoothing the data (including removal of cardiac and respiratory effects). These fMRI noise data sets also show spatial coherence (i.e., dependence between voxel time series; e.g., Aguirre et al., 1997; Zarahn, Aguirre, & D'Esposito, 1997). Failure to accurately model the temporal autocorrelation present within fMRI data under the null hypothesis can result in an unacceptable mapwise false-positive rate, which occurs with application of the standard SPM. Additionally, in fMRI, especially with smaller pixel sizes, there is an increased probability of violating the uniformity assumption as sensitivity to activity in local blood vessels is heightened (Sereno, personal communication, 1997).

Despite the notable differences in the acquisition and tomographic reconstruction of the data, anatomical standardization and methods for noise reduction, and choice of test statistic and thresholds, there appears to be a reasonably high degree of replicability across studies (Gold et al., 1997; Grabowski et al., 1996; Ramsey et al., 1996; but see Poeppel, 1996, for an alternative view). For example, a direct comparison of the change distribution analysis, Worsley's method, the pixelwise general linear model, and a nonparametric analysis of PET images revealed a high degree of specificity and concordance for PET activations detected (Grabowski et al., 1996), with all procedures committing relatively few and about the same number of Type I errors. However, these pixel-based methods differ in their Type II error rates, which are highest for methods that depend on local variance estimates and exacerbated by small sample sizes. As expected, larger sample sizes lead to lower variance and more power. Also of potential interest, however, is the finding that blood flow decreases measured via PET show lower rates of detection, replication, and concordance than blood flow increases even at moderate sample sizes (Grabowski et al., 1996). In general, it clearly behooves investigators to meet minimal standards for reporting statistical results (Gold et al., 1997) and readers to be aware of the methodological and analytical choices that underlie the reported foci of functional activations, of which these are but a few examples.

The current "hard problem" of neuroimaging integration is combining EEG/MEG data with fMRI/PET data. Issues include (a) solutions to the ill-posed nature of the inverse problem and (b) the poorly understood link between electrical activity (responsible for EEG/MEG) and metabolic and hemodynamic processes (responsible for the fMRI/PET). To what extent should we expect local changes in electrical activity to be correlated with local changes in metabolic and/or hemodynamic activity when it is assumed that ERPs reflect primarily postsynaptic activity and the fMRI signal may reflect primarily presynaptic activity? How might hemodynamic and blood flow changes differ in response to the kind of synchronous activity measured with EEG and MEG, as opposed to asynchronous neural activity? Other technical difficulties to overcome include the need to coregister data from different techniques and to find informative ways of depicting the resulting combined data on a few representations if not a single one. These are difficult integrative problems indeed, but progress is being made (e.g., Dale et al., 1995), and there are many types of physiological data that can be used to constrain the integrative problem of the mind and the body. In some cases, different measures can be recorded simultaneously, whereas in other cases it simply makes sense to use different measures to test the efficacy of the stimulus materials or to test the validity of the inference one would like to draw from a particular measure. The domain of language can be used as an example of how different psychophysiological techniques can help elucidate the processes of language comprehension and production.

A "Wordy" Example

In humans, language mediates between acoustic/visual signals and thoughts and between thoughts and motor commands. This mediation takes place in the brain, which also must enervate the muscles and coordinate the movements of the lungs, vocal cords, joints, and lips (and hand/arms in the case of a deaf signer) during language production and must transform acoustic (visual in the case of the deaf) information at the ear (eye) into a meaningful message during language comprehension. Both comprehension and production occur with such amazing speed (word recognition in context occurring within 200 ms and 15 speech sounds produced per second) that it is not surprising to find prominent roles for processing speed and dynamics in current theories of language processing and language dysfunction. Eye movement measures and ERPs/MEG (and perhaps someday fMRI and optical imaging) are particularly

excellent psychophysiological techniques for tracking the fine-grained temporal course of linguistic processes peripherally and centrally, respectively. Furthermore, ongoing efforts to combine these two methods to yield saccade-related electrical brain activity (King, Coulson, Federmeier, & Kutas, 1996), if successful, will permit a real time analysis of natural reading and visual exploration with unparalleled temporal precision. The temporal resolution of these techniques spans the crucial milliseconds that can completely change the identity of a phoneme to the more extended time course needed to determine that *captivatory* is not a word, as well as the hundreds of milliseconds that are required to determine who did what to whom after reading a sentence such as, "The neuroscientist that the psychologist that the preacher questioned questioned questioned the nature of the inference about the soul from those images" (for reviews, see Kutas & King, 1996; Kutas & Van Petten, 1994). Electrical and magnetic recordings can also be used to examine the validity of assertions attributing processing differences between conditions to different anatomical regions, when they might instead result from the engagement of a single process (in the same brain region) at different times relative to the input (for an example, see King & Kutas, 1995). Clearly, for the study of language processing the unquestionable strength of electrical and magnetic techniques lies in their ability to provide exquisite temporal information about brain processes and about the dynamic relations among various brain areas.

Because independent ERP generators have additive effects on the amplitude of scalp electrical activity, these measures can also be used to address the reality of and the interactions among the various proposed levels of linguistic representations (phonological, morphological, syntactic, semantic, pragmatic). The psycholinguistic literature is rife with controversies over when the information types in various linguistic representations come together, if at all; these controversies include questions about the effects of sentential context on word recognition, the effects of semantics on syntactic analyses, the effects of pragmatics on semantic analyses, and the involvement or influence of any nonlinguistic processes (e.g., working memory) on language processing as a whole (Gernsbacher, 1994). These differences can be (and have been) examined in multiple input modalities with ERPs. Replication of such ERP studies with other psychophysiological techniques, when possible, might help account for the different patterns observed, thereby clarifying the mental processes involved. Given that MEG activity represents a substantial subset of the EEG activity (omitting only completely radial sources), repeating ERP language experiments in a magnetometer is a means of assessing the replicability of the temporal information. Combined ERP and MEG studies may also be a way to localize generators of the effects to a general vicinity within a hemisphere, thereby accounting, for example, for changes in the laterality of an effect with age. Moreover, the similarities and the differences in the timing information provided by EEG/MEG recordings can be mutually constraining for the localization of their sources and can aid in the decomposition of an fMRI activation into a series of temporally ordered activation maps.

Clearly, more precise localizations of the areas involved in language comprehension and production can be achieved with techniques of higher spatial resolution, such as PET and fMRI. These techniques, especially in some combination, can reveal which systems are actually affected by the chemical imbalances that lead to language disorders in schizophrenia, Parkinson's disease, Alzheimer's dementia, and other diseases with neurochemical roots. PET can pinpoint the specific chemical system involved, and fMRI can track the consequences of abnormal neurochemical functioning on neural activity to a high degree of spatial resolution in a single individual. Such data might well inform the hypothesis that Parkinson patients make errors in deciding that the past tense of *image* is *imaged* because their rule-based processor is broken. The ability to specify the brain areas involved in language processing also may help us to sort out a number of complicated issues, such as the modality specificity of certain processes or representations, the domain specificity of language processes, and the role of the nondominant hemisphere in the language processing of intact infants, monolingual and bilingual adults, and recovering aphasic patients.

Furthermore, EMG changes associated with the speech apparatus reveal that the body talks, perhaps even to itself, as it deals with structurally complex sentences. EMG recordings from the face and hands, as well as various eye movement measures, may help tighten the links between perception and language and between language and action. The EMG (perhaps combined with ERPs) in such cases can be used as an index of preparation prior to actual vocalization, gesturing, and so forth or to measure any intention to move, including false starts and imagined movements. To what extent is simply (over)hearing a command associated with muscle and brain activity in the areas that would normally carry that command out? Measurements of the eyes can serve to let us see where people look and for how long, that is, how they distribute their attention, during reading or when listening to speech and interacting with their environment. Eye movements and ERPs can be combined to discover how the processing of a word being fixated for the first time differs from that when the word is the target of a refixation at the end of a regressive eye movement. In an fMRI or PET scanner, eye movement patterns can also be monitored and used as an index of task engagement. The use of peripheral measures also might elucidate the relationship between factors such as working memory, attention or emotion, and language. The results of psycholinguistic reaction time studies attest to the slowing of processing in the presence of lexical, semantic, or syntactic ambiguity. When is that slowing due to the presence of too many options (and thus the need to inhibit some) and when does it simply reflect the lack of any viable option? Cardiac and EDA measures, and especially their combination, may help answer these kinds of questions, telling us when inhibition and excitation are taking place. These methods also open up new possibilities for measuring what individuals understand without the need to ask them to articulate it. Does the sentence, "The light flickered and went out, and Pat felt a chill fall over the room," elicit changes in pupil size, heart rate, respiration, and/or facial and skeletal musculature that are predictable from the pragmatics, and if so, under what circumstances? Do people who enjoy reading experience these changes more often and, if so, can people learn to become "reactive readers"?

Conclusion

As we near the end of the Decade of the Brain, therefore, we need to begin exploring new ways to examine the mind–body question. We have learned something about the roles that various brain structures play in perceptual, motor, cognitive, and emotional processing. However, as we uncover, for example, the role of the frontal lobe in determining personality, it is important to keep in mind that personality may also be influenced by a weak heart, tight shoes, an overbearing father, or a full moon. Each neuroimaging and psychophysiological technique provides a window into the mind, specifically a physiological measure that can be used to

make inferences about the questions we seek to answer. However, these techniques, alone or in combinations, do not solve the mind–body problem. Rather, they serve to illuminate the full complexity of the influences that create the states and behaviors we call mind, complexities that cannot be simplified with more precise measurements alone. We need constraints. Luckily, many of the constraints we need are to be found in the biology of the body and the brain, which have served as constraints for one another throughout evolution. The use of multiple techniques, measuring multiple parts of the body (and the discovery of more effective ways to combine them), is thus an important source of constraint for our model building and theorizing. Still other constraints reside in the social, culture, and physical environment in which humans live. However, the complexity problem presented by the mind–brain–body system may require new ways of thinking about the kinds of measures we use and need to use because, in fact, the mind arises in a physical system that is distributed over space and time. Spots in the brain that do not change in a statistically significant way with a particular task are still part of the system and may, indeed, be exerting significant effects on it. Models based in dynamical systems kinds of approaches, for example, call into question the validity of considering only the part of the system that most noticeably changes as somehow responsible for that change; rather, in these models changes arise out of the whole in ways that are often not easy to predict from simply looking at the parts in isolation, no matter how fine the analysis. To leave open such possibilities and others, our inference drawing must respect the limitations of our ability to sample all the variables relevant to understanding the interactions among mind, brain, and body (not to mention environment). We, therefore, must respect the role of the body in cognitive processing and the role of multiple techniques in elucidating that relationship. As we leave the Decade of the Brain, we should remember that the brain minds the body . . . and that the body minds.

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