# Emerging Cognitive Neuroscience and Related Technologies

Committee on Military and Intelligence Methodology for Emergent Neruophysiological and Cognitive/Neural Research in the Next Two Decades, National Research Council

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# Current Cognitive Neuroscience Research and Technology: Selected Areas of Interest

## INTRODUCTION

Cognitive neuroscience and related technologies constitute a multifaceted discipline that is burgeoning on many fronts. Based on the expertise of its members, and realizing that it could not possibly cover the entire range of science within the discipline, the committee chose to discuss three specific areas of interest: (1) challenges to the detection of psychological states and intentions via neurophysiological activity, (2) neuropsychopharmacology, and (3) functional neuroimaging. Even then, the study's timeline makes it impossible to provide an exhaustive review. Despite these limitations, however, the following discussions accurately depict the current state of cognitive neuroscience research in the selected fields.

## CHALLENGES TO THE DETECTION OF PSYCHOLOGICAL STATES AND INTENTIONS VIA NEUROPHYSIOLOGICAL ACTIVITY

### Overview

There is little doubt that great progress has been made over the last quarter century, particularly the last 10 to 15 years, in understanding the physiological and neural bases for psychological processes and behavior. Furthermore, there is a high likelihood that more progress will be made as more sophisticated theoretical models are developed and tested using ever more sophisticated assessment technology. In the applied sector, scientists will probably be better able to identify valid neurophysiological indicators of performance. For example, modeling the human genome will help researchers to index affective, cognitive, and motivational states and evaluate the effectiveness of training techniques or to determine the readiness of combat units.

The vast majority of neuroscientific research has been conducted at the group, or aggregate, level rather than at the individual level, and this trend is likely to continue. To achieve sophisticated and highly sensitive neurophysiological assessment of psychological states at the individual level, many significant challenges must be overcome. At a minimum, the neurophysiological indicators will probably have to be individually "tuned" to each user given the issues of individual variability and plasticity described below.

To accurately assess psychological states using neurophysiological measures, basic neurophysiological work needs to be accomplished over the next two decades. The committee identified and discussed a nonexhaustive list of issues that need to be addressed and questions that need to be answered. These included the nature of psychological states compared to "mind reading," the nature of neurophysiological and neural activity, and barriers to identification of mental states and intentions.

An important qualification about the parameters necessary for determining psychological state became apparent during the committee's deliberations—the end use of information about the inferred psychological state. Because technology to infer a psychological state or intention could be put to a broad range of alternative uses, it is important to recognize that acceptable levels of error depend on the differential consequences of a false positive or a missed identification. The technology being applied to determine psychological state could even be derived from an incomplete model of brain function as long as it had sufficient predictive power to accomplish the desired goal. For instance, one would not need a complete model of brain function to construct a brain–computer interface that could improve the self-piloting capabilities of unmanned air vehicles. But, the tolerance for error will be much less if a technology is used to determine whether an individual is lying about an act of treason, because the consequences of an error will be greater.

The committee believes that it is critical to fully understand the relationship between neurophysiological markers and actual mental states when the application is the detection of deception.

## Mind Reading and Psychological States

It has proven difficult since the beginning of modern psychology 150 years ago to achieve agreement, even among psychologists and other behavioral scientists, on explicit definitions of psychological constructs. Such agreement is important because most psychological constructs bear labels borrowed from common language. Dictionary meanings and usage tempt many scientists to assume that they know the scientific definition of a psychological construct without consulting the scientific literature, where such constructs are explicitly defined.

Typical didactic schemes for organizing psychological constructs imply a more rigid separation between them than actually exists and operates. Today, the main organizing constructs for understanding psychology at the individual level are *affect, cognition,* and *motivation*.[1] However, such organization does not necessarily reflect how affective, cognitive, and motivational processes interact. Indeed, attempting to understand each construct in isolation rather than the three as an interdependent triumvirate is to wander in an epiphenomenal domain rather than a realistic psychological domain. If scientists could, for example, accurately determine how a particular soldier processes information about a member of the enemy force (cognition), that knowledge would do very little to help us understand how the soldier will behave toward that enemy unless scientists also take into account how he or she feels about that enemy (affect) and how both constructs play into motivational processes.

When behavioral scientists ask *why* individuals behave in certain ways, they typically are asking a motivational question. During the first half of the twentieth century, psychologists focused on external environmental factors such as reinforcement to explain motivation. In the latter half of that century, they focused on internal processes to explain affect (moods and emotions) and cognition (information processing, memory) but without knowing details of the causal interconnections among the processes. Today, psychologists understand that behavior occurs between interrelated affective, cognitive, and motivational processes on the one hand and environmental factors and processes on the other. This complex set of interrelated factors must be

[1]Individual psychology is also determined by important factors such as fundamental biological drives and programming of behavior, cognition, and affect by all levels of biology, including genes, proteins, receptors, synapses, and nuclei, among others. In addition, endogenous and genetic drivers dominate cognition, affect, and behavioral capability—for example, in human development, sleep and circadian rhythms of cognition and affect, eating, the need for social affiliation and for salt and water, sexual drive, aggression, and nurturing—and dominate human behavior. This section of the report discusses in some detail environmental factors relating to individual psychology, but this is not meant to de-emphasize the importance of biological factors such as the ones just described.

understood and accounted for to detect a psychological state—that is, to "read" a mind—using any technology.

There has been growing use of the term "mind reading" in the popular press and in a few circumscribed areas of the Department of Defense (DOD). Because the precise meanings of the terms that are used to communicate understanding are critical to the scientific endeavor, the committee believes it is important that the DOD and IC communities understand what is meant in this study by "mind reading" and "psychological state." Mind reading typically refers to the capacity (imparted by an external mechanism—that is, some form of technology) to determine precisely what an individual is thinking or intending, whether or not the individual is willing to communicate that state of mind. As discussed below, to "read" minds scientists must understand how minds really work to come up with a technology that is of real use, and there are several formidable barriers to achieving such an understanding any time in the next two decades. In contrast, "psychological state" sometimes refers to a broad range of mental activities associated with cognition, affect, and motivation, but more often refers to a discrete and definable mental state, for example, sustained attention (cognition), anger (affect), or hunger (motivation). The committee believes that experimentation, with the careful control of any number of possibly confounding variables, will result in important progress toward understanding the nature of psychological states over the next two decades, using current and yet-to-be developed technologies. It must be understood, however, that much neuroscientific research still infers psychological state based on the experimental controls. Barriers to being able to read minds as well as the hurdles that must be overcome to accurately determine psychological state are discussed below.

### The Nature of Neurophysiological Activity

The progress being made by scientific discovery in the field of biology is truly amazing, particularly at the molecular level. At the level of the neural system, however, current knowledge is more speculative. This is understandable given the complexity of the brain. Estimates are that each of the (approximately) 100 billion neurons in the brain synapses—that is, connects—with as many as 50,000 other neurons, making for a large and complicated control network that will likely take decades more of scientific work to map out.

This level of complexity also makes it unnecessary to identify neural centers of activity that are responsible for or associated with specific psychological "modules" of activity. It has been shown that although the neural activity in some brain loci appears to increase or decrease during specified mental activities, these brain loci represent only a small fraction of ongoing neural activity (Raichle, 2007). The rest of the brain is still active, and much more of the operation of the brain system must be understood to develop a firm scientific basis for reliably inferring psychological states.

## Barriers to Identifying Psychological States and Intentions via Neural Activity

> A science of the relations of mind and brain must show how the elementary ingredients of the former correspond to the elementary functions of the latter. (James, 1890)

The hurdles that must be surmounted in order to detect individual psychological states in a scientifically valid way are quite challenging. Here, several of these challenges are identified and discussed.

## Technological Limitations and Advances

The impediment to detection of psychological states via neurophysiological states that is currently the most tractable is availability of technology to monitor and measure putative neurophysiological and neural processes with high spatial and temporal resolution. Although the assessment of peripheral somatic and autonomic systems has been possible for many years (Shapiro and Crider, 1968), advances in the assessment technology have come only recently. Inexpensive, noninvasive endocrine assays (Dickerson and Kemeny, 2004) and noninvasive, high-density electroencephalographic and functional brain imaging technology with high spatial and temporal resolution of brain processes have advanced rapidly. However, scientists must be cautious about what to expect of these technologies in the next quarter century. Technology is yielding new and powerful measurement tools. However, these tools will require sound scientific methods to be of benefit.

## Errors in Logic and the Scientific Method

Given that the challenge set forth in the statement of task is to help the intelligence community (IC) and Department of Defense (DOD) "better understand, and therefore forecast, the international neurophysiological and cognitive/neural science research landscape," members of the committee believe that individuals who are not members of the neuroscientific community tend to make several common errors of logic when they interpret the findings of various technologies that are used to infer psychological states. These errors tend to occur because people misunderstand the relationship between the neurophysiological measurements and the actual mental state that the scientist is attempting to measure. A heightened awareness of the potential for such errors may help the IC and DOD make the best possible decisions when evaluating the scientific claims of researchers in other countries as well as the United States.

Furthermore, because technological innovation is as elemental to certain branches of neuroscientific investigation as the neuroscience itself is, the IC and DOD are likely to encounter two approaches to developing end-user applications of neuroscience, one favored mainly by neural and behavioral scientists, the other by engineers. Both approaches have their strengths, but when evaluating neuroscience, there are important differences. The first approach, as articulated by Cacioppo and Tassinary (1990), places a premium on plausible scientific theory and the causal relationships underlying the psychological construct and the physiological index. This approach emphasizes the discovery of causal relationships so the theory can be refined and more and more precise hypotheses can be posited, helping to avoid misinterpretation of the data—that is, third-variable confounding, as discussed below. The second approach (the "engineering" one) is to propose, demonstrate, or purport that a given device or technology or method works from a signal detection point of view—for example, "with this technology we can tell when a pilot is too tired to fly with 92.3 percent accuracy." Any underlying causal model is secondary to the correlated effects. This approach is appealing, works well for many applications, and fits well with the DOD's proactive approach to problem solving. One significant problem with the largely atheoretical "engineering" approach in neuroscience is that it leaves one open to third-variable confounding because without a model it is not possible to predict potential confounding. Furthermore, if problems do develop in implementation, there is no model from which to predict the next step. In contrast, the theory-based approach is one of successive approximations by which the underlying theory is continually refined and built upon through the use of models describing the underlying causal relationships.

## Relationship Between Neurophysiological Measures and Psychological State

First and foremost, it is important that the reader understand the nature of neuroscientific investigation. When a neuroscientist is studying the biochemistry or the physics involved in brain function—changes in amino acids or the flow of ions, for example—these physiological changes are the phenomenon of interest and the focus of the study. However, when a neuroscientist is studying a psychological state such as attention or anger, changes in brain activity or chemistry are the *correlates*, or the means by which scientists study the mental state, which is the phenomenon of interest. Whereas physiological changes may regularly accompany a shift in mental state, scientists cannot assume that the mental state bears a one-to-one correspondence with the neural changes they are measuring. A discerning reader might argue "But what if (and this is a very large *if*) scientists knew everything about how the brain functions, and knew how to measure it; would they then, in fact, be measuring mental states?" This line of reasoning, which is often followed by the lay community, is actually a philosophy of science known as reductionism. Reductionism, introduced by Descartes in the seventeenth century, argued that complex things can be fully explained and predicted by reducing them to the interactions of their parts, which are simpler or more fundamental things. He said that the world was a machinelike system that could be understood by taking apart its pieces, studying them, and then putting them back together to see the larger picture. Taken to its logical extreme, measuring the biological mechanisms associated with a mental activity would be equivalent to measuring the mental activity itself rather than just a correlate.

Although a reductionist philosophy of science is accepted in many areas of modern science, including much of physics, chemistry, and microbiology, reductionism to these levels of analysis has never taken hold in the behavioral sciences, probably with good reason. Although reductionists (see, for example, Wilson, 1998) believe that behavior can best be explained by genetic biology and/or the operation of neural control mechanisms, most other scientists argue that reductionist assumptions limit scientific understanding of complex systems. If this is true, mental states may be more than the sum of their parts and may not be amenable to measurement even if the underlying neural activity is fully understood. Stated another way, mental states may emerge only at a psychological level of analysis and cannot be described in terms of purely neurophysiological activity even though the mental states are assumed to be caused by the brain. If reductionism is indeed correct, then at the current level of knowledge about the complexity of neural systems, science is indeed a very long way from being able to read minds from genetic or neural information.

This argument is important because neuroscientists realize that they are measuring the correlates of some mental state, not the mental state itself. As such, the issue of how closely the measures of neural activity map on to the mental state of interest (discussed below) becomes important. This point is of less concern to certain applications of technology to infer brain states (such as augmenting cognition to facilitate the piloting of unmanned aircraft), but it becomes critical when aspects of the psychological state can have legal ramifications, as, for example, in the determination of deception or intent to harm. The knowledge that scientists do not *know* that the neural activity corresponds one to one with the actual mental state (deceiving) must be weighed very carefully in these instances.

## Mapping Measurements of Neurophysiological Activity to Psychological States

The most critical barrier to the identification of a psychological state from its neural signature is the fact that the neural activity underlying the psychological state subserves multiple tasks, so there can therefore be no one-to-one correspondence between neural activity and any psychological state. An excellent example of this point is that of deception detection, or credibility assessment. William Marston, the father of the polygraphy technique for deception

detection, believed that there was a unique physiological response during deception. This has proved not to be the case, and few investigators since Marston, including current researchers investigating the use of neural activity measurements to infer deception, believed a unique signature associated with deception would ever be found. Whereas investigators expect to find some consistency in neural response during deception, they do not expect the activated neurons to fire only when the individual is being deceptive and at no other time. Rather, these same neurons are likely to also fire during other types of cognitive and emotional states besides deception (e.g., anxiety, dealing with a heavy cognitive load, inhibiting a prepotent response). Whereas some low-level physiological processes may have a one-to-one correspondence with neural activation, no higher-order phenomenon on the order of a mental state has been found to have this type of neural pattern. Accordingly, researchers investigating the neural correlates of psychological states must control for many other variables, including other mental states, that could account for the neural activity they are measuring to be more certain that their results are indeed due to the construct under investigation (say, anxiety rather than deception or vice versa).

Fortunately, there is a very useful approach to proper inference between indexes and psychological constructs or states originally suggested by Cacioppo and Tassinary (1990), who elucidated four types of neurophysiological index for psychological constructs: outcomes, concomitants, markers, and invariants. Awareness of this typology helps us to recognize important inferential problems associated with putative neurophysiological and neural indices of psychological states. Whereas the goal of a neurophysiological index for a psychological construct may be a symmetric, one-to-one relationship between the index and the variable based on a plausible and verifiable scientific theory, in practice this is rare. [2] To be symmetric, the presence of the variable must always be accompanied by the presence of the index and vice versa, and the two must covary systematically. To be based on a plausible scientific theory, the underlying causal relationships between the psychological construct and the physiological index should be valid ones.

More commonly, neurophysiological indices are outcomes and concomitants. Outcomes and concomitants are merely associations or correlations between a physiological response (or set of responses) and a psychological construct that are context bound or context free, respectively (see Figure 2-1).

Neither enjoys a symmetric one-to-one relationship between the response and the construct. For instance, the sympathetically driven autonomic responses indicative of stress is an outcome within the Cacioppo and Tassinary framework (1990)—that is, it is context dependent and asymmetric. In a different context (the diagnostic one Erasistratus found himself in), such responses could be related to different psychological states (e.g., love or anxiety).

Markers and invariants are associations between a physiological response and a psychological construct that are context-bound or context-free, respectively, but do enjoy a symmetric one-to-one relationship (Figure 2-1). There are few (see below) well-validated symmetric peripheral or central nervous system (CNS) neurophysiological markers of affective, cognitive, and motivational psychological constructs. This paucity is partially due to poor/insufficient understanding of how neurophysiological systems operate and the resulting lack of sophisticated and validated biopsychosocial theory, which have facilitated the development of valid markers and invariants of psychological states.

[2] "Symmetric" means "If A then B *and* if B then A." For example, if there is a symmetric relationship between a lie (A) and a neurophysiological response (B) then every time the lie occurs the specific neurophysiological response occurs *and *every time the neurophysiological response occurs the lie occurs. "Asymmetric" means "If A, then B, but not vice versa." For example, if a lie is accompanied by a neurophysiological response that does not mean every time the neurophysiological response occurs that a lie has occurred.

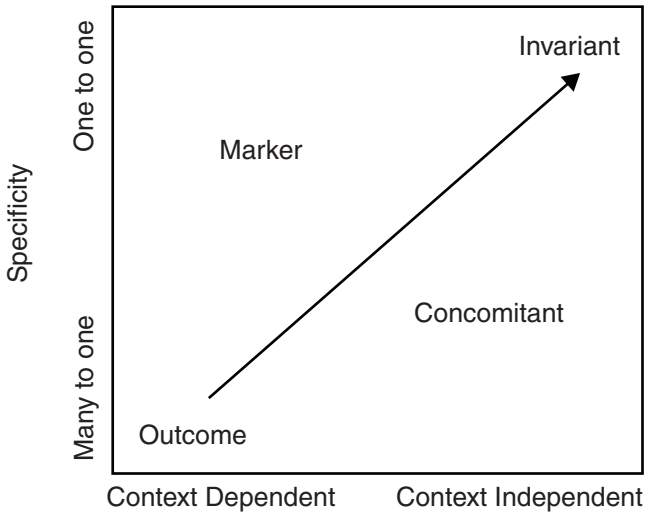



FIGURE 2-1 Associations between a physiological response (or set of responses) and a psychological construct. SOURCE: Cacioppo and Tassinary (1990) ©1990 by the American Psychological Association. Adapted with permission. The use of APA information does not imply endorsement by APA.

Symmetric (one-to-one correspondence) relationships have rarely, if ever, been shown to exist between psychological constructs and their neurophysiological indicators. This lack of a symmetric relationship is a major problem for detecting psychological states from the indicators. Neurophysiological and neural activities are almost always multifunctional when it comes to causing underlying psychological constructs. So, even if every time an individual enters a psychological state (e.g., "love") the same portion of cortex (i.e., the left prefrontal cortex) is activated, does not mean that every time that portion of the cortex is activated the person is in that psychological state—that is to say, neurological measures may be sensitive, but are rarely specific. Good science avoids this logical error known as the "affirmation of the consequent."

These errors of inference can be avoided by precisely specifying the circumstances or "controls" under which the data can be interpreted by limiting the number psychological states. For instance, a brain–computer interface designed to assess attention to an external task and that has been accompanied by individual training for the user may place sufficient limits on both the environment and the user's possible states to allow accurate and useful interpretation of the neural responses. This highly controlled scenario, however, which has controls similar to the experimental controls that are used to interpret neuroimaging data does not amount to mind reading or to determining intent from the raw neural signals. Rather, a cognitive state is inferred based on the controls placed on the situation and is still subject to potential signal detection errors (e.g., false positives, false negatives, misses).

## Avoiding Errors of Inference

Fortunately, a reductionist philosophy of science is not a requisite for drawing valid inferences about psychological states from neurophysiological and neural activity if one accepts the "identity thesis" as a basic metaphysical assumption. This assumption states that all psychological phenomena occur via bodily processes and is widely shared by behavioral scientists and neuroscientists (Cacioppo and Tassinary, 1990; Blascovich, 2000; Blascovich and Seery, 2007). Accordingly, there is nothing ethereal about human behavior, and all psychological states are embodied somehow. If one can associate certain neurophysiological data with certain psychological states, then identifying psychological states from such information is a potentially

tractable, though very difficult, challenge. Several logical and inferential issues, including those associated with the section below on the third variable problem, cause this challenge to be daunting.

*The Third Variable Problem.* When two variables, such as a psychological state and some specified neurophysiological measure, are related probabilistically, even if perfectly so, scientists cannot assume that they are causally related. For example, the correlation between shoe size and reading ability in children might be a spurious correlation. There is no doubt that both increase with age; however, correlation does not imply causality. Correlation is necessary for causality, but two other criteria must be met to imply causality: (1) time ordering (the cause must occur before the effect) and (2) third variables must be ruled out. Whereas an engineering approach can be used to determine time sequencing, a scientific model could allow ruling out third variables as the cause of a correlation; however, a poor or incomplete model will allow for many interpretations of an effect that might have an altogether different cause. This becomes a significant problem, for instance, when one wishes to decide whether a person is lying on a polygraph test; even if there is a high correlation between guilt and strong autonomic reactions to certain questions, it would a mistake to conclude that guilt is causing the stronger reactions if anxiety, not guilt, can produce those same reactions.

The goal of a neurophysiological index of a psychological construct is a symmetric, one-to-one relationship between the index and the variable based on a plausible and verifiable scientific theory. To be symmetric, the variable must always be accompanied by the index and vice versa, and the two must covary systematically. To be based on a plausible scientific theory, the underlying causal relationships between the psychological construct and the physiological index should be valid.

## Brain Plasticity

Brain plasticity refers to changes that occur in brain organization and function as a result of experience. There is now considerable evidence that brain activity associated with a psychological state or process can change throughout life as a function of factors such as sleep, maturation, experience, damage, exogenous (e.g., pharmacological) agents or a combination of these. Indeed, most poststroke rehabilitation therapy (e.g., relearning walking, talking) would be ineffective if such change were not possible.

Brain plasticity is manifested in at least three ways. One involves functional shifts and changes that occur when control of motoric behavior reorganizes itself in a different area of the cortex as a result of experience. A second way, termed synaptic plasticity, involves changes in neuroreceptor production and/or sensitivity that potentiate or antagonize the likelihood of synaptic transmission. A third way, at least speculatively, brain plasticity may manifest itself is changes in brain structure; that is, actual changes in the number of neurons and synapses, the most obvious examples of which are increases occurring early in life and decreases occurring as a result of lesions or aging.

Brain plasticity represents a challenge to those seeking to develop neuronal indexes for psychological states—i.e., outcomes, concomitants, markers, and invariants—on an individual level, because structural, organizational, and functional differences between individuals—and within them over time—will have to be accounted for. It is also possible that a high degree of plasticity-based error in any given index could reduce its sensitivity and specificity and, hence, its practical value for "reading" individual minds. However, this remains an open question, for scientists do not yet know how plasticity might affect any given set of measures across various populations.

### Variability Within and Between Individuals

Two important challenges to using brain states to index psychological states are variability between individuals and also within a single individual. It seems likely that brain plasticity, along with genomic factors, may be one of the underlying causes of such variability, which apparently exists. However, "it is not easy to change the habits of people who are comfortable with traditional ways of doing things, and developers of cognitive models have continued to rely for support mainly on the fitting of functions such as curves of learning, retention, and generalization to averaged data," (Estes, 2002).

Estes has examined the relationships between typical brain scan images aggregated across individuals and those of the individual cases from which aggregated images are derived. Figure 2-2 illustrates the problem of individual variability for location of episodic memory in the brain. The leftmost image is the group or aggregate image. The next three images illustrate some of the individual cases from which the aggregate image was derived. None of the individual images match the group image. Hence, it would be inappropriate to base a neural index of the operation of episodic memory on the aggregate picture without adjustment for individual differences.

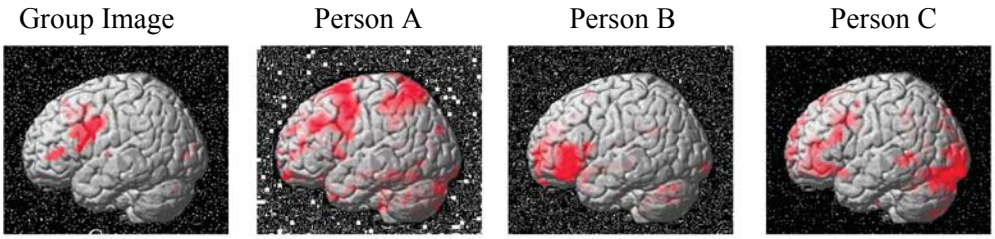



FIGURE 2-2 Individual variability in the case of the putative location of episodic memory in the brain. SOURCE: Figure reprinted with permission from unpublished work (Miller, 2007).

Miller concludes that "investigations into the sources of unique individual brain activity may be necessary in order to understand the dynamic patterns of brain activity that underlie widely distributed, strategy-filled tasks like episodic memory (Miller, 2007). There appears, moreover, to be variability across tasks, with some tasks showing more or less variability of locus than others. Furthermore, Miller reported that with-in subject location appeared to be relatively stable across time, such that the same areas were activated in the same individual by the same task performed 6 months apart (Miller et al., 2002). Individualized approaches to functional mapping, however, are feasible under certain circumstances. For instance, if a government wanted to outfit trained combat pilots flying high-tech aircraft with some type of neural interface, it would make sense to invest in determining individualized neurophysiological markers. Accounting for individual variability is both reasonable and feasible, because within-subject variability across time (after accounting for reorganization due to learning) tends to be low for cognitive tasks (Miller, 2007). This cost-benefit argument is more of a problem when attempting to apply a generic (averaged) algorithm to a given individual without individual tuning.

### Specificity of Psychological States within Contexts

The likelihood of developing valid neurophysiological indexes for inferring psychological states or intentions depends on the required specificity of the state itself and the specificity of the context within which it occurs. It is typically easier to develop an accurate index of a given psychological state if the number of candidate states can be limited by experimental controls. Consider, as an example, a vigilance scenario in the cognitive domain. It would be simpler to

develop a neurophysiological index that marks a person as consciously processing information at a general level (e.g., having or not having the resources to cope with the situation he or she is in) than at a more specific level (e.g., having or not having specific resources). In the affective domain, it would be simpler to develop an index that distinguishes the polarity of a superordinate affective state (e.g., negative vs. positive) than an index that distinguishes between more specific superordinate states (e.g., anger or fear). In the motivational domain, it would be easier to develop an index that distinguishes between fairly general superordinate motivational states (e.g., avoidance or approach) than to develop one that distinguishes more specific states (e.g., take flight or surrender).

Simultaneously indexing superordinate categories of general cognitive, affective, and motivational psychological states based on neurophysiological information can have great practical value because these general categories of psychological states are highly interdependent and simultaneous. Hence, if one could index all three categories simultaneously in a given context (say, warfighting), the resulting combined index would be more useful for drawing inferences and making predictions than any single index. Furthermore, one would be able to make these predictions without asking the warfighter questions and one could refine the predictions to reflect these continuously available indexes.

Indeed, one can probably infer psychological or behavioral intentions more accurately based on the combination index. If the cognitive index revealed that a soldier evaluates his or her resources as sufficient to meet the perceived needs in the particular context (e.g., a battle), if the affective index revealed that the soldier is experiencing positive affect (e.g., challenge) rather than negative affect (e.g., threat), and if the motivational index revealed that the soldier is motivated to approach rather than avoid the situation, one would could reasonably conclude that the soldier was prepared or even intended to do battle. On the other hand, if one index revealed that the soldier cognitively evaluates his or her resources as insufficient, another revealed that he or she is experiencing negative affect, and a third revealed that the soldier is avoidance-oriented, one could reasonably conclude that the individual was ready to retreat.

Existing peripheral neurophysiological measures include the following: (1) hemodynamic markers of cognitive resource/demand evaluations—for example, reciprocal changes in cardiac output and total peripheral resistance (Blascovich and Tomaka, 1996), (2) electromyographic indexes of affect—for example, relative reciprocal increases and decreases in zygomaticus major and corrugator supercillii muscle movements in the face (Cacioppo et al., 1986), and (3) cardiac indexes of approach/avoidance motivation—for example, increases or decreases in cardiac ventricular contractility and heart rate (Dienstbier, 1989; Blascovich and Tomaka, 1996). If one could develop CNS indexes of superordinate categories of cognitive, affective, and motivational state, there would be a useful redundancy.

### Assumptions About Base Rates of Psychological States and Intentions

Just as they like to rely on averaged data (Estes identified this propensity in 2002), many scientists also assume that base rates of dichotomous psychological states are 50/50. Much as scientists know that not everyone or every brain is average, they also realize that the probability that a person will act in one way rather than another is not necessarily 50 percent. This realization notwithstanding, development and even validational work on indexes of psychological states often assumes a base rate of 50 percent.[3]

If base rates of psychological states, such as intentions to commit an act of terrorism or to defect, were 50 percent, individuals with such intentions would be much easier to identify.

[3]In the experimental literature, and especially in the lie detection literature, tacit assumption of 50 percent appears to guide much of the physiological indexing of psychological states. The committee notes this rate may seem otherwise high.

Unfortunately, many important psychological states are infrequent events, with the consequence that indexes validated assuming a 50 percent base rate produce a very large number of mistaken detections. Green and Swets's classic paper on signal detection theory (1966) detailed the logic and mathematics for inferring the existence of target states from signals (or indexes) as a function of base rates.

Mistaken detections can be avoided only when a target signal is in almost perfectly symmetric (i.e., 1 to 1) correspondence with the target event in the biological or other system. Additionally, systems for transmitting and identifying the target signal must be almost perfectly accurate (Imrey, 2007). Imrey further argues that (1) combinations of these two circumstances are rare; (2) intuition on this point is notoriously poor, partly because of the ways accuracy is commonly expressed; (3) known biases in data collection invariably lead to overoptimism; (4) overoptimism means overconfidence in the reliability of results, and (5) this means underestimation of false positives and false negatives. A specific discussion on base rates and the detection of deception is found later in the chapter under the case study of detecting deception.

**Finding 2-1.** Cognitive neuroscientists can identify neurophysiological markers of general psychological states—for example, positive versus negative affect, automatic versus controlled cognitive processing, approach versus avoidance motivation, attention versus inattention—within individuals in specified contexts but are not yet able to identify highly specific psychological states and intentions—that is, exactly what a particular person is thinking, intending, or doing. Given the current state of knowledge about brain neurophysiology, it is highly likely that any advances in collective knowledge about individual psychological states over the next two decades will continue to occur in highly controlled situations where the number of candidate mental states is limited. The ability to determine a person's mental state strictly from neurophysiological markers without environmental controls is unlikely to be gained any time in the next two decades.

## Detection of Deception as an Example of Efforts to Identify Accurate Neurophysiological Indices of Specific Psychological States in Individuals

The concept of the detection of deception was recently broadened and is now known as "credibility assessment," and includes additional factors such as source verification and witness corroboration. The concept is of considerable interest to the IC and DOD. Detection of deception can serve to illustrate the considerations discussed above as barriers to the identification of accurate neurophysiological indices of specific psychological states in individuals (Feinberg and Stern, 2003).

At the societal level, the capacity to detect deception is valued for many social, legal, and medical reasons. At the government level, the capacity to detect deception is valued because those having or seeking authority and/or power need to be able to safeguard the national interest. At the individual level, detection of deception helps to identify individuals who threaten some important value of a social group. In addition, it often makes sense to help determine the reliability of information or witnesses before resources are allocated. As such, technologies for the detection of deception entail identifying a specific kind of psychological state at the individual, or idiographic, level.

Not unlike in the scientific community at large, there was considerable debate among members of the committee about the ability to develop useful neurophysiological markers of deception. The committee believed, however, that it is critical for the IC and DOD to understand where opinions differed. Box 2-1 summarizes the key points of agreement and disagreement on detection of deception.

**Box 2-1**
**Committee Agreements and Disagreements on Detection of Deception**

*Agreement*

The committee agreed that, as outlined in previous NRC reports, traditional measures of deception detection technology have proven to be insufficiently accurate. Second, the committee agreed that the IC and DOD should understand the nature of the relationship between neural/physiological/cognitive measures of brain states and the psychological states they are meant to measure. This derived from the concern that the neural correlates of deception could be construed as incontrovertible evidence of deception and therefore (mistakenly) used as the sole evidence for making critical legal decisions with lasting consequences. Current physiological measurements cannot be taken as direct measures of psychological states. Third, the committee agreed that for large-scale screening, the low-base-rate problem—very few terrorists among millions of travelers—created a significant problem given current rates of reliability. Fourth, the committee agreed that even if a highly reliable deception test were developed, it should be treated as only one element in a Bayesian approach. Fifth, the committee agreed that future research on measures of deception would benefit from a scientific, theory-driven approach in concert with an applied, problem-oriented approach. Lastly, the committee agreed that insufficient high-quality research using an appropriate research model and controls has been conducted on new modalities of credibility assessment to make a firm, data-driven decision on their accuracy.

*Disagreement*

The committee disagreed on whether functional brain measurements would prove to be more reliable for detecting deception than traditional autonomic polygraphy. Detractors cited neural plasticity, individual variability, and low base rates as barriers to developing accurate indices of deception. In contrast, several committee members who conduct functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) imaging research agreed that preliminary studies of deception using these modalities were promising, as they found consistent results across research protocols, technologies, and populations. Second, the committee disagreed on what level of accuracy would be a useful or practical for detecting deception. Some committee members believed that because of the base-rate problem and the legal implications of deception, accuracy rates should be virtually inerrant to be practical, whereas others believed that measurements that kept the error rate to 1 percent or less would be useful if combined with the Bayesian approach. Lastly, the committee disagreed on whether more financial resources should be put into further research on deception detection. Some members strongly believed more research resources were warranted, others strongly disagreed.

## Previous Research on Detection of Deception

No known lie-detection technology has been sufficiently accurate (i.e., virtually inerrant) to be legally acceptable, especially given the relatively low base rates for many types of threats to a social order. As described above, the main technology used during the last 100 years in the United States and a few other countries (e.g., Israel, Canada, and Japan) is the polygraph, the generic name for an instrument that can record multiple physiological measurements which has come to be closely associated with the lie detection technique utilizing it. Conventional polygraphy relies on psychophysiological measures of the sympathetic nervous system response (respiration rate, heart rate, electrodermal activity) to detect anxiety associated with guilt or lying (Office of Technology Assessment, 1990). As determinants of psychological states, however, these autonomic response suffer, in particular, from a lack of specificity and cannot differentiate

guilt from other cognitive/affective states—say anxiety—resulting in an unacceptably high level of false positives (Office of Technology Assessment, 1983; Iacono, 2000).

A report on the polygraph and lie detection (NRC, 2003, p.4) concluded that:

> …in populations of examinees such as those represented in the polygraph research literature, untrained in countermeasures, specific-incident [i.e., criminal] polygraph tests can discriminate lying from truth telling at rates well above chance but below perfection.

However, this should not be understood to be the applied accuracy of polygraph testing in operational field situations. Readers should note that many of the examinees referred to in the quote above are research subjects who, for the most part, are often informed of the nature of the research beforehand and are not typically drawn from the population to whom polygraph tests are typically given (individuals being investigated for criminal activity, those seeking employment in sensitive national security positions, prisoners of war). Often participants are college students or other volunteers and are hardly representative of populations that are likely to threaten the social order. Hence, the NRC report goes on to conclude that "polygraph testing yields an unacceptable choice for. . . employee security screening between too many. . . employees falsely judged as deceptive and too many major security threats left undetected." (NRC, 2003, p. 6).

It is the lack of specificity, in particular, of these autonomic measures to discriminate deception from other affective states that leads to insufficient positive and negative predictive power. That is, autonomic responses, as least as measured by the polygraph, are "outcomes" only, could represent a number of psychological states, and must be interpreted within a highly specified context. It is not surprising, then, that both the IC and the DOD have been interested in more precise (more sensitive and specific) measures of deception detection. As for other deception detection techniques, the report concluded that

> Some potential alternatives to the polygraph show promise, but none has *yet* been shown to outperform even the polygraph. None shows any promise of supplanting the polygraph for screening purposes in the near term. (NRC, 2003, pp. 7-8)

However, the report (NRC, 2003, p. 174) goes on to state that:

> Functional brain imaging techniques have important advantages over the polygraph, in theory, because they examine directly what the brain is doing. . . . Not enough is yet known about the specific cognitive or emotional processes that accompany deception, about their localization in the brain, or about whether imaging signals can differentiate the brain activity associated with these processes from brain activity associated with other processes to make an assessment of the potential validity of these techniques on the grounds of the basic science. Further research with fMRI, coupled with a scientifically based cognitive psychological approach to deception, will be needed to determine if these issues can be addressed. . . . If a research effort is undertaken to find improved scientific techniques for the detection of deception, basic research on brain imaging would be a top candidate for the research agenda.

For illustrative purposes, the committee next discusses deception detection work in light of the challenges described above. As noted, there was considerable debate among the committee members about what would constitute a practical or useful application of technology to the assessment of psychological states.

**Deception and the Nature of Neurophysiological Measures**

Understanding the nature of the relationship between physiological markers and the psychological states that are purportedly assessed by quantifying the markers is critical for several reasons. First, users of the technology must recognize the limitations of the tools they are using. The majority of polygraphers do not make the mistake of believing that they are measuring deception directly via neurophysiological information, avoiding an unwarranted reductionistic approach. Rather, they claim that certain neurophysiological changes (e.g., respiration, heart rate, blood pressure, electrodermal activity), as a set, pattern themselves differently during acts of deception than during acts of truth telling. This places a burden on the methods used to gather the psychophysiological or neurological data, as proper interpretation of the data fundamentally relies on appropriate methodological technique and controls.

While it can be tempting to assume that brain imaging or other neurophysiological measurements allow direct access to the psychological state under investigation, this assumption is not warranted. Based on research to date, it is highly improbable that there is any specific "lie circuit" in the brain that is dedicated to deception. Rather, the neural circuits that respond during deception will respond in other, nondeceptive circumstances, and only appropriate techniques will allow accurate interpretation of the data. The committee agrees that important legal decisions should not be made as if incontrovertible proof of deception existed if they are based only on the correlates of deception.

Unfortunately, the biopsychosocial theory underlying the putative relationships between the autonomic measures that are obtained with a traditional polygraph and their actual value as accurate indices of lying remains unsophisticated and essentially unchanged for nearly a century. Twenty-five years ago (1983), the United States Office of Technology Assessment issued a report prepared by a group of scientists who had evaluated the scientific validity of polygraph testing for lie detection (OTA, 1983). The report concluded that "the basic theory of polygraph testing is only partially developed and researched. . . . A stronger theoretical base is needed for the entire range of polygraph applications" (NRC, 2003, p. 6).

This statement largely reflects the paucity of well-designed and controlled studies for investigating the potential confounds when a strong inference is drawn from polygraphy data collected under a great variety of conditions. From a neuroscientific perspective, theory must be refined through experimentation. The report leveled the same criticism at the theoretical basis of polygraphic lie detection (NRC, 2003). Indeed, a long line of similar reports, including one in the archives of the National Research Council as early as 1917 and another in 1954 (Guertin and Wilhelm, 1954), made the same point.

This may be due to the fact that there are essentially two communities when it comes to judging the utility of the polygraph in determining deception, the polygraph community and the scientific community (Porges, 2006). These two communities base their judgments on different criteria. A critical difference between them has been their approach to research: The polygraph community has long taken an applied, problem-oriented approach, with efficacy as its goal, driven by perceived societal needs. The scientific community, in contrast, takes a basic, theory-driven approach that emphasizes understanding the mechanisms underlying the process of deception, driven by the principles of science as they relate to society. These two approaches are often conceptualized as inherently divergent, which they certainly have been in practice. However, lacking a scientific basis, the applied approach has failed to increase its efficacy or advance its credibility over several decades, as outlined above.

The literature on lie-detection research, which has long focused mostly on measurements of autonomic reactions, appears to value seemingly high correlations between particular neurophysiological responses and the prevarication they identify, independent of sound biopsychosocial theory. Continued reliance on a century-old, outdated physiology-based rationale has resulted in a failure to advance the underlying science. The best that can be said for the

current physiological indexes of lying used in polygraph testing is that they are outcomes, the type of index that provides the logically weakest basis for inference (Cacioppo and Tassinary, 1990). Put even more succintly, the lack of biopsychosocial theoretical sophistication underlying polygraphic lie detection techniques over the past century has led to entropy in the field of lie detection. Because no known physiological or neurophysiological measure enjoys a one-to-one relationship with deception, all correlates of deception have multiple causes, only one of which is deception. This being the case, protocols and uses that rely on very few or even a single response to determine deception will be highly susceptible to false positives, despite which such protocols continue to be used (see, for example, Tsiamyrtzis et al., 2007). This has been demonstrated many times from work in such fields as event-related potentials, where multiple trials have proved much more reliable than single trials. If a marker is a true correlate of the deceptive state, it should survive several response trials, capitalizing on Bayesian probability. (Although it is well known that autonomic responses habituate, they can serve as markers for a few trials.)

The committee agrees that an integration of basic, theory-driven science with an applied, problem-oriented approach could facilitate acceptable solutions to the assessment of credibility. According to Porges (2006), basic science can help delineate the neural processes underlying deception and the theoretical relationships among the psychological state(s), their neural and physiological markers, their measurement, and their application in the field.

## Improvements in Technology

Given that standard polygraph technology is no different in basic measurement principles than it was a century ago and, according to the literature, has failed to produce sufficient reliability, it is not surprising that many lie-detection researchers have turned to newer CNS assessment technologies, including high-density electroencephalography, near-infrared spectroscopy (fNIRS), and functional magnetic resonance imaging (fMRI) to improve the accruracy with which it detects lies. A small formative body of published research on the neural circuitry associated with deception utilizes various neuroimaging techniques. Recent studies using positron emission tomography (PET) and fMRI have provided insights into the neural circuitry associated with deception, with specific areas in the prefrontal cortices and amygdala being the most commonly implicated regions (Abe et al., 2007; Abe et al., 2006; Mohamed et al., 2006; Davatzikos et al., 2005; Kozel et al., 2005; Langleben et al., 2005; Lee et al., 2002; Lee et al., 2005; Nuñez et al., 2005; Phan et al., 2005a; Kozel, et al., 2004a; Kozel et al., 2004b; Ganis et al., 2003; Langleben et al., 2002; Spence et al., 2001). Recent fNIRS studies of deception have also implicated prefrontal brain regions in the neural circuitry associated with deception (Bunce et al., 2005). Consistent with the Bunce et al. (2005) observation, through the end of 2007, all published neuroimaging studies of deception except one (Langleben et al., 2002), including PET, fNIRS and fMRI technologies, studies of well-practiced vs. spontaneous lies (Ganis et al., 2003), studies of malingering, and cultural samples (Lee et al., 2005, with Chinese subjects, Bunce et al., 2005, with East Indian subjects) have found activation in a similar area of the dorsolateral/ventrolateral prefrontal cortex. Another recently published study correlated fMRI images with standard skin conductance measurements during a concealed information paradigm, with interesting results (Gerard et al., 2007). Although some members of the committee believed this preliminary body of work to be quite promising there has not yet been sufficient systematic research to determine if functional neuroimaging can meet the challenges to the neurophysiological detection of psychological states relevant to deception, as described above. Future research is warranted in the brain plasticity and variability; specificity of psychological states; and base rates.

## Brain Plasticity and Individual Variability

An important divergence between traditional polygraphic lie detection and newer lie detection based on newer CNS assessment technologies is the latter's susceptibility to problems created by the brain's plasticity and resultant individual variability in CNS structure and function. For example, if the loci of CNS synaptic transmissions underlying prevarication vary across individuals or within an individual across time, those loci would not be accurate enough to be useful as neurophysiological indexes of lying for individual testing. This is still an open question because to date, no sufficient research on these issues has been published. If individual variability proves to be a significant factor, there will be no scientific basis for using the newer assessment technologies unless theoretical mechanisms relating such variability to the biopsychsocial basis for lying can be specified and validated. This does not mean that a theory could not be developed, and some preliminary models have already been proposed (Porges, 2007; Spence, 2004). However, a great deal of appropriate research needs to be done before a specific conclusion could be drawn about the validity of CNS measures of intentional deception, with an interactive process between the scientific model and the research. While this does not rule out any role for an applied, problem-oriented approach—for example, does the outcome or marker predict at a given level of sensitivity/specificity—a good model would help to avoid serious misinterpretation of the data.

In addition to CNS-based measurement, several other sensing techniques are being investigated for their potential ability to discern deception or concealed knowledge. These techniques may avoid some of the issues surrounding neural plasticity, but they must still meet appropriate criteria for accuracy. Some are remote, noncontact sensing techniques that measure autonomic function and are already in use. For instance, laser Doppler vibrometry is a remote sensing technique for heart rate, blood pressure, and several other physical properties. Although the technique does provide more information about heart function than a polygraph, it typically measures aspects of autonomic function associated with stress in response to threat. Other similar techniques include voice stress analysis, pupilometry, and infrared measures of the periorbital regions.

One measurement that appears to have a largely cognition-based etiology is that of eye-movement-based memory assessment (EMMA) (see, for example Marchak, 2006). This method is based on evidence that people scan faces they have previously seen in a different way than they scan novel faces (Altoff and Cohen, 1999). People reliably use fewer eye fixations, sample fewer regions, and fewer statistical constraints in viewing familiar rather than new faces. By tracking and quantifying these eye movement patterns using the appropriate technology and experimental controls, researchers can identify concealed knowledge. These patterns can also be combined with performance measures such as speed and accuracy, which show increased efficiency in the subject's processing of previously learned materials. The technique has been applied to objects and scene recognition as well as faces. EMMA, which stems from a theory-driven model of memory and adaptive function, appears to be promising. Published levels of correct classification across studies (grand mean = 88.1 percent) are on a par with results from standard polygraphs. More work is needed on the level of positive and negative predictive power across various samples of individuals. In addition, the methodology itself is somewhat constraining because it requires a specific type of knowledge on the part of the subject and a specific set of stimuli.

## Specificity of Psychological States

The specificity of a psychological state should be reflected in the specificity of the neurophysiological index created for it. The neurophysiological index for a more general or superordinate psychological state is likely to be more easily validated than the corresponding index for a more specific psychological state. Deception in everyday matters is not as general a

psychological state as information processing or fear or anxiety, but it is not as specific as lying about something as portentous as, say terrorism. Developers of new technologies must avoid making the same type of error. Turning to measurement of CNS response to deception (may represent) an attempt to develop an appropriate level of analysis for deception.

**Reconsideration of Base Rates**

The challenge posed by base rates can be overcome by applying signal detection theory, as mentioned above. Here is a substantive example. Assume that deception has a base rate of 1 in 1,000, and an index that is 90 percent accurate and that 10,000 individuals are being screened using the index. This assumed base rate is probably high if scientists are attempting to identify spies or terrorists in organizations as large as the military or in the populations of individuals on a given day traveling by air to or within the United States. As Table 2-1 from a report on the polygraph and lie detection illustrates (NRC, 2003), 1,598 people, or 99.5 percent of those who failed the screen and were identified as spies or terrorists, would be false positives and 2 people (20 percent of the actual spies) who passed the screen and were identified as nonspies or nonterrorists would be false negatives. Only 8 people (0.5 percent) of those who failed the screen would actually be spies or terrorists and therefore true positives.

TABLE 2-1 Rates of False Positives and False Negatives from Polygraph Examinations

| | Subject's True Identity | | |
|---|---|---|---|
| Test Result | Spy | Nonspy | Total |
| Fail | 8 | 1,598 | 1,606 |
| Pass | 2 | 8,392 | 8,394 |
| TOTAL | 10 | 9,990 | 10,000 |

SOURCE: Adapted from NRC (2003).

If the detection threshold is lowered to reduce the number of false positives, as Table 2-2 from the NRC report illustrates, the number of spies or terrorists who passed the screen (false negatives) would increase. In this case, 8 people (80 percent) of the spies or terrorists would have passed the screen. This example emphasizes the importance of a highly accurate test when testing large numbers of people for low-base-rate events, and calls attention to the care that must be taken in using the information when a less accurate test is involved.

TABLE 2-2 Increase in the Number of Spies or Terrorists Who Passed the Screen (False Negatives)

| | Subject's True Identity | | |
|---|---|---|---|
| Test Result | Spy | Nonspy | Total |
| Fail | 2 | 39 | 41 |
| Pass | 8 | 9,951 | 9,959 |
| TOTAL | 10 | 9,990 | 10,000 |

SOURCE: Adapted from NRC (2003).

These statistics make evident an important conclusion. When looking for targets in settings with a low-base-rate, such as terrorist screening at an airport, to have high confidence in a positive detection requires a technology with an extremely high discriminating capacity on the order of HIV testing or the even more accurate DNA testing. If such a level of accuracy cannot be achieved using the test technology alone, further information that additionally differentiates true targets, and is external to the test technology, needs to be obtained and brought to bear.

**Finding 2-2.** The committee recognizes the IC's strong interest in improving its ability to detect deception. Consistent with the 2003 NRC study *The Polygraph and Lie Detection*, the committee uniformly agreed that, to date, insufficient, high-quality research has been conducted to provide empirical support for the use of any single neurophysiological technology, including functional neuroimaging, to detect deception.

Opinions differed within the committee concerning the near-term contribution of functional neuroimaging to the development of a system to detect deception in a practical or forensic sense. Committee members who conduct neuroimaging research largely agreed that studies published to date are promising, and that further research is needed on the potential for neuroimaging to provide a more accurate method to determine deception. Importantly, human institutional review board standards require, at minimum, that individuals not be put at any greater risk than they would be in their normal everyday lives. The committee believes certain situations would allow such testing under "normal risk" situations; though the committee strongly endorses the necessity of realistic, but ethical, research in this area, it does not specify the nature of that research in this report.

**Recommendation 2-1.** The committee recommends further research on multimodal methodological approaches for detecting and measuring neurophysiological indicators of psychological states and intentions. This research should combine multiple measures and assessment technologies, such as imaging techniques and the recording of electrophysiological, biochemical, and pharmacological responses. Resources invested in further cognitive neuroscience research should support programs of research based on scientific principles and that avoid the inferential biases inherent in previous research in polygraphy.

## NEUROPSYCHOPHARMACOLOGY

### Overview

Drugs and other mind-altering chemicals can influence all aspects of human psychology, including cognition, emotion, motivation, and performance. For known drugs, predictions of the type, onset, magnitude, and/or duration of effects in individuals or groups can be limited by incomplete knowledge of the interacting processes that govern drug effects. Clinical, field, and research experience reveals that drug effects in individual humans arise from interactions of multiple factors, including (but not limited to) the drug itself; its dose and route of use; the demand characteristics of the current situation; and the individual's health, physiology, and experience with drugs and performance demands. Attempts to predict the effects of new drugs are hampered by the possible surprise in structure, targets, delivery, mechanisms of action, interactions with other drugs, and varying performance conditions.

In the following discussion the committee uses the term "drug" to refer to any chemical agent with the capacity to alter human affect, cognition, motivation, or performance. Agents that can do this include not only pharmaceutical drugs for preventing, treating, or mitigating disease symptoms, but also, include for convenience sake foods, hormones, intoxicants, nutrients, plants, poisons, supplements, toxins, and so on. The porous boundaries among these classifications is exemplified by botulinum toxin type A, available by prescription as Botox. The actions and effects of drugs may change with long-term use or under altered conditions; may interact with medical, occupational, physical and psychological conditions, as well, drugs may affect individuals differently; and may affect human functions other than psychology. Effects may be perceived as beneficial, harmful, or neutral, and such perceptions may change with conditions.

Most discussions of drugs and their effects are organized along the lines of current models of brain and nervous system functioning. This method of organization can help to identify likely

effects of known drugs but probably should not be used to identify potential dual-use threats. Changes in models of brain function may create new and surprising ideas about how, when, where, or why drugs produce their effects; about what those effects are; about the kinds of chemicals that function as drugs to alter human functioning; and about ways to enhance, minimize, or counteract drug effects. It is particularly important to realize that the drugs that changed psychiatry in the mid-twentieth century were not predicted by many pharmacological or psychological models of their time, perhaps especially in the United States (Swazey, 1974). Rather, the brief history of neuropsychopharmacology illustrates how the expectations of a particular cultural, medical, and research climate may cause a failure to predict new drugs, new ways of using drugs, or new drug effects. Recent advances in neuropsychopharmacology that have the potential to be "game changers" include a much improved knowledge of brain function and delivery systems such as are enabled by nanotechnology that would allow substances to cross the blood-brain barrier.

Many current psychotherapeutic drugs—that is, drugs used in treatment and management of psychiatric disorders—and their likely mechanisms of action were not anticipated by prior research or theory (Barrett, 2007). Classic examples of psychotherapeutic drugs with unexpected mechanisms of action and/or unanticipated effects, and called to attention by alert clinicians, include lithium, chlorpromazine, monoamine oxidase (MAO) inhibitors, and tricyclic antidepressants (Cade, 1949; Jarvik, 1970; Swazey, 1974). Another unexpected discovery was lead poisoning, which had long-lasting psychological effects in the employees of a workshop where batteries were made (Hamilton, 1915; International Labour Office, 1934). These examples suggest that new drugs with marked effects on critical psychological functions are "black swans," unanticipated events with effects that could not have been predicted, that may fail to be observed when they happen, or that have large, long-lasting consequences that go unrecognized (Taleb, 2007a; 2007b).[4]

One modern drug with psychological effects that were not predicted by initial descriptions of its clinical pharmacology is ketamine. Developed in the private sector as an anesthetic, then discovered in clinical use to have hallucinogenic effects and co-opted into the club drug scene as Special K, it is now under investigation in the public and private sectors as a rapidly acting antidepressant and for the treatment of chronic pain; the use of ketamine as a rapid acting anti-depressant remains unreplicated and provocative. Other such drugs are opioid antagonists as a treatment for alcoholism and cannabinoids. These examples suggest that current models of neuropsychopharmacological effect account post hoc for psychological effects of drugs and may have poor predictive ability.

In spite of the difficulty of predicting their psychological effects, psychotherapeutic drugs have proven to have greater clinical effectiveness than many other treatments. This has had important consequences for medical and cultural expectations about drugs. First, the discovery and clinical use of drugs for treatment and management of psychiatric disease have had far-reaching effects on research and practice in psychiatry, psychology, cognitive science, and other mental health and behavioral sciences. Demonstration that particular drugs could effectively treat psychiatric illnesses suggested that such illnesses were treatable much like other illnesses and promoted the medicalization of psychiatry. Equally important, the clinical usefulness of the earliest such drugs provided insight into the brain mechanisms that mediate the drugs' therapeutic efficacy and created opportunities for research to understand the chemical and biological bases of their effects. The critical linkage between drug effects and discoveries of brain receptors for neurotransmitters and other endogenous brain chemicals enabled the development of drugs with

[4]The term 'black swan' as defined by Taleb (2007a; 2007b) is an accepted term in the IC for unanticipated consequences. It should be noted that Taleb's 'black swan' is not related to the older term 'white crow' that implies sufficiency to disprove a hypothesis.

fewer side effects and more focused activity as well as a few truly new drugs that could target newly discovered chemical systems in the brain.

The appearance of clinically useful brain drugs occurred as the field of neuroscience coalesced so that medical and behavioral researchers could explore how biology manifests itself in behavior (Barrett, 2007; Dinges, 2007). One marker of the importance of the emerging field of neuroscience is the growth in attendance at the annual meeting of the premier professional association in the field, the Society for Neuroscience, from 1,396 in 1971 to 34,815 in 2005 (Society for Neuroscience, 2007).[5] Discoveries in neuroscience can be exploited to create new cellular or subcellular targets for drugs, new drug delivery systems, and new strategies to direct or control drug effects and achieve desired psychological effects. Novel classes of drugs approved by the Food and Drug Administration (FDA) illustrate the potential surprises of research, including drugs for erectile dysfunction, which arose from chemicals that were targeted at treatment of angina but failed to increase cardiac blood flow while unexpectedly increasing blood flow to the penis, and sleep-inducing drugs that exploit the roles of gamma aminobutyric acid (GABA) and melatonin receptors in brain sleep systems. Recent news stories on topics ranging from brain systems and drugs for memory enhancement (Rovner, 2007; Foer, 2007), appetite control (Bentivoglio and Kristensson, 2007), and sleep drugs (Saul, 2007) reflect the intense public, academic, and commercial interest in neuropsychopharmacology.

This interpretation of neuroscience research carries the additional implication that drugs can achieve or modulate not only abnormal, diseased, or disordered psychology but also normal, healthy, or optimal function. Development and utilization of drugs to treat psychiatric disorders have been accompanied by important changes in expectations of physicians, consumers, and policy makers about how drugs can and should be used (Barrett, 2007; Chatterjee, 2007; Kelly, 2007). These changes include

expectations about the duration of a drug's use by an individual and who drives the choice of whether, when, and which drugs to use; opinions on personal drug use; and ideas about which human functions can, or should, be modulated by drug use. It may be particularly important that many current prescription drugs, and possibly the majority of current prescription drugs with primarily psychological effects, are used widely off-label.[6] Such off-label use and the possibility of important placebo and nocebo effects (Lasagna et al., 1954, Beecher, 1955; Olshansky, 2007) cannot but open analysts' eyes to the probability that drugs have heretofore undiscovered effects.

Drugs that are described and marketed as having disease-specific or diagnosis-specific effects are quite capable of producing striking psychological effects in individuals who do not suffer from the condition identified with the drug's descriptive name or clinical indication. These psychological effects may or may not be similar to the effects in individuals with medical conditions for which the drugs are prescribed. Recent examples discussed in the public press include use of antipsychotic drugs for individuals without psychosis, beta-blockers to modulate performance anxiety in concert musicians, and steroids to enhance athletic performance. Other emerging changes in how drugs are prescribed and used include increased incidences of polypharmacy, of consumer decisions about whether and when to use drugs (as illustrated by erectile dysfunction drugs and Botox), and of consumer decisions to seek out and use available drugs for multiple effects. For example, the use of certain prescription drugs as study aids is not uncommon (White et al. 2006). Of 1,025 U.S. college students surveyed, 16.2 percent reported such use of prescription stimulants. Ninety percent of this group did not hold a legitimate prescription for stimulant drugs; 96 percent of them used Ritalin to improve attention, improve ability to participate in partying, reduce hyperactivity, and improve grades; and 15.5 percent reported using Ritalin at least two or three times per week.

[5] See http://www.sfn.org/index.cfm?pagename=annualMeeting_statistics&section=annualMeeting. Last accessed December 17, 2007.

[6] Under current FDA guidelines, manufacturers are prohibited from marketing approved drugs for off-label use.

Addiction and substance (or drug) abuse presents another area of change. The demarcation between abused drugs and medicines is situation dependent, as demonstrated by recent experience with OxyContin, by nicotine in over-the-counter smoking cessation aids, and by college-student exploitation of prescription stimulants. The illicit market not only provides incentives for novel drugs, manufacturing processes, and delivery systems but also poses novel risks. These factors are illustrated by episodes such as the appearance of permanent symptoms of Parkinson's disease in opiate addicts who used the illicitly manufactured 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin probably produced by improper chemical conditions in illicit manufacture of meperidine, a synthetic opioid (Langston, 1995). The incentives provided by the illicit market are also exemplified by recent U.S. experience with methamphetamine labs and by the emergence of crack cocaine (smoked, minimal manufacturing danger, sold in small quantities) to challenge freebase cocaine (smoked, risks of explosion during manufacture), both of which challenged powdered cocaine (snorted or injected, sold in large quantities) (Kleiman, 1992; Musto, 1987). Epidemiological and clinical research on the natural history of drug abuse also provides information about the long-term effects (often) high doses of at least a subset of performance-altering drugs, which may alert analysts to dual-use possibilities. The same may be true of patterns of drug use in highly competitive industries or markets, such as the steroids, stimulants, and endurance-altering drugs used by athletes or the stimulants used by floor traders.

## Cognition Enhancers

One specific area of neuropsychopharmacology that may be of considerable importance is that of cognition enhancement. Cognition enhancers can be broadly defined as drugs or other agents that have the potential to improve human functions such as attention, learning, and memory (Sarter, 2006; Sahakian and Morein-Samir, 2007 and accompanying online discussion at http://network.nature.com/forums/naturenewsandopinion/). Considerable research investment in the United States and other countries is directed to the discovery and development of pharmacological cognition enhancers. Often, these agents target declines in memory and cognition linked to age, dementia, or neuropsychiatric or neurological disease. It is likely, however, that agents developed for prevention or treatment of disease will alter brain processes in normal individuals. Additionally, agents already in wide medical or social use are known to alter memory and cognition, sometimes by mechanisms shared with disease-related agents and sometimes by mechanisms not so clearly linked to age or pathology. Examples of widely used agents with known or suspected ability to alter and perhaps enhance certain components of human cognition and/or performance include caffeine (found in coffee, tea, soda), nicotine (tobacco products), tacrine (energy drinks), amphetamines and methylphenidate (attention deficit hyperactivity disorder medications and certain abused drugs), propranolol (certain beta-blockers), dextroamphetamine, and modafinil.

A fairly wide range of neuropharmacological or chemical systems have been suggested as possible sources for cognition or performance enhancers (e.g., Sarter, 2006). This expanding list is illustrative of the wide range of brain processes suspected of having potential to enhance normal and/or disordered cognition. Conversely, opposite changes or disruption in such systems might disrupt cognition and/or performance. Specifically, if agonists of a particular system enhance cognition, it is mechanistically plausible that antagonists might disrupt cognition; conversely, if antagonists of a particular neurotransmitter enhance, its agonists might disrupt. Examples of the former might include dopamine agonists, which enhance attention, and dopamine antagonists, which disrupt it; examples of the latter might include the suspected cognitive enhancing effects of cannabinoid antagonists and the disrupting effects of agonists like THC.

Three areas of research in behavioral pharmacology have particular importance for analysis of enhancement and/or disruption of cognition and performance. One identifies the boundaries or limitations of cognition enhancement. Many current models of cognition incorporate ideas of processing resources and their limitations. It is an open question as to whether drug-induced enhancements in one area of cognition have a cost in other areas. Stimulant drugs are known to have rate-dependent effects, such that the same exposure regimen may enhance attentional processes that are initially occurring with low frequency but simultaneously decrease attentional processes that are occurring at high frequency (Dews and Wenger, 1977), which could result in unwanted performance decrements. A cognition enhancer that optimizes performance under a taxing attention condition might not improve performance of a task with lower attention demands (Robbins, 2005) and in fact might disrupt it. As another example, drugs that enhance working memory capacity or operation may impair capacity to simultaneously filter distractors; this could increase false alarms in a detection operation (Lavie, 2005). Public recognition that modafinil, which promotes wakefulness and increases alertness, can have small but valuable cognitive effects is an example of a change that creates opportunities for public discussion of the risks and benefits of potential cognitive enhancers.

A second relevant area of behavioral pharmacology involves efforts to identify which specific neurochemical changes actually covary with cognitive processes. Studies of neurochemistry in cholinergic brain systems, for example, suggest that drug-induced changes in neurotransmitter release activated by attentional processes are vitally different from drug-induced changes in basal release (Sarter and Bruno, 1994; Kozak et al., 2006).

A third, and related, area is research to identify agents that produce specific kinds of cognitive enhancements rather than broadly acting agents (Rovner, 2007). Additionally, the full range of effects of potential cognition- or performance-enhancing drugs warrants attention. For example, stimulants such as amphetamine can increase attention and concentration, but they also exert cardiovascular effects that can be exacerbated by physical exertion and heat, and with prolonged or high dose use, they carry risks of addiction and paranoia.

## Implications for Agents That May Act to Change or Disrupt Various Aspects of Human Psychology

There is currently a widely recognized "translational gap" between preclinical research, clinical research, and development of cognition enhancers, perhaps best articulated in the area of schizophrenia (Hagan and Jones, 2005; Floresco et al., 2005). Similar translational gaps exist in most, if not all, areas of neuropsychopharmacology. Examples of recognized roadblocks to new therapeutic entities include the need for improved clinical models, the rudimentary knowledge of brain neurochemistry and function, the paucity of models to predict side effects, and poor understanding of brain diseases and disorders. One recommendation for closing these translational gaps is to improve the predictive power of animal models so that they map onto operationally defined domains of affective, cognitive, and motivational processes (Robbins, 1998; Sarter, 2006; Barrett, 2007). The neuronal bases of cognitive function are poorly understood, and most animal models that are used to identify potentially useful therapeutics are not based on molecular- or systems-level understanding of brain processes or on functional understanding of human cognition and behavior. Improved animal models for human psychopathology (depression, anxiety, memory decline, cognitive failure) and for normal functioning (learning, affect, motivation, performance) could permit development of novel drugs and/or drugs that can be targeted to effect human cognition and performance. While animal models are useful, many effects on cognitive dimensions cannot really be tested on rats or mice.

The discovery of the probable role of the hypocretins (also called orexins) in human narcolepsy shows that once the chemistry is known and the market drivers are in place, a drug can be developed rapidly. Symptoms of narcolepsy are currently managed with amphetamine-like

CNS stimulants or modafinil (for excessive daytime sleepiness) and antidepressants or sodium oxylate (for cataplexy), but none of these treatments are based on an understanding of how brain chemistry is dysregulated in affected individuals. Recent research, which arose from the discovery of narcolepsy genes in animal models, suggests that a deficiency of hypocretin/orexim is responsible for about 90 percent of human narcolepsy-cataplexy cases (Nishino, 2007a; 2007b). This finding led directly to development of new diagnostic tests for narcolepsy and has led to the search for new therapeutic drugs for narcolepsy caused by a deficiency of hypocretin/orexim. Additionally, novel small-molecule hypocretin/orexim receptor antagonists that can be used to inhibit feeding have been identified.

**Finding 2-3.** Neurochemical systems modulate, and can be used to control, a wide range of human psychology. The number of neuropsychopharmacological drugs increased dramatically after the mid-1900s, along with their availability, and emerging technologies may improve the ability to harness drug effects or to produce targeted changes in human psychology. Cognitive neuroscientists do not have specific understanding of how most drugs produce their effects. Basic research in the public or private sectors that identifies the specific mechanisms of disease and of drug effects might enable rapid development of new drugs. New drugs may have unrecognized effects that emerge owing to variation in individuals, settings, or performance demands.

## Nanotechnology in Medicine

In addition to bringing new drug entities or new uses for existing entities, emerging technologies might allow new pathways for drug delivery. Some observers say it is likely that the paradigm of the pharmaceutical industry will change, from "discovering" drugs by screening many compounds to the purposeful engineering of desired molecules.

Richard Feynman famously said, "There's plenty of room at the bottom," in a lecture in which he outlined the principle of manipulating individual atoms using larger machines to manufacture increasingly smaller machines (Feynman, 1959). Nanotechnology is a rapidly expanding, multidisciplinary field that applies engineering and manufacturing principles at a molecular level. It can be roughly divided into categories that include nanobiotechnology, biological microelectromechanical systems, microfluidics, biosensors, microarrays, and tissue microengineering (Gourley, 2005). In some sense nanotechnology is intuitive, since everything in nature is built upward from the atomic level in order to define limits and structures (Emerich and Thanos, 2006). Understanding and developing nanotechnology, therefore, depends on understanding these limits and pushing against them.

Nanomedicine (the development of effective clinical treatments based on nanotechnology) has had some successes (Freitas, 1999) and depends on several overlapping molecular technologies. These new but progressing technologies include (1) the construction of nanoscale-sized structures for diagnostics, biosensors, and local drug delivery; (2) genomics, proteomics, and nanoengineered microbes; and (3) the creation of molecular machines capable of identifying and eliminating host pathogens by replacing and repairing cells and cellular components in vivo (Emerich and Thanos, 2006). Of particular importance may be nanotechnologies that allow delivery of drugs across the blood-brain barrier in ways now impossible.

### Nanotechnology for Drug Delivery

In the last decade nanotechnology and nanofabrication have significantly impacted the field of drug delivery (Emerich and Thanos, 2006). The continued development of these technologies will probably be in conjunction with the development of pharmaceuticals targeted at the brain (Ellis-Behnke et al., 2007; Jain, 2007; Koo et al., 2006; Silva, 2006, 2007; Suri, Fenniri, and Singh, 2007; Teixido and Giralt, 2008). The development of such neuropharmaceutical

combinations is of great interest to the Department of Defense. Guided by the Statement of Task, the following paragraphs outline nanotechnologies that may become advances for the delivery of CNS drugs.

Techniques have shifted from microfabrication and micromachining (e.g., the osmotic pump) to designs ranging from secondary constructs at the nanometer scale (e.g., microspheres). The engineering of nano delivery systems for small molecules, proteins, and DNA has led to the emergence of entirely new and previously unpredicted fields. Formulation science has linked up with computer technology to create a controlled-release microchip capable of infinite modulation that would allow for the greatly improved controlled release of pharmaceutical agents (Santini et al., 1999; Grayson et al., 2003; Maloney et al., 2005; Prescott et al., 2006). Tissue engineering applications have also moved toward the development and implementation of nanometer-sized components. The creation of artificial cells with appropriate physiologic properties may provide a better understanding of normal physiological processes. Transfection systems on the nanoscale for genetic manipulation and gene delivery are being tailored using different polymers.

Nanotechnology is opening new therapeutic opportunities for agents that could not be used effectively as conventional drug formulations owing to their poor bioavailability or drug instability (Santini et al., 1999). Microsphere formulations are used to protect agents susceptible to degradation or denaturation while prolonging their duration of action by increasing systemic exposure or retention of the formulation (Hillyer and Albrecht, 2001; Hussain et al., 2001; Torche et al., 2000; Van Der Lubben et al., 2001; Varde and Pack, 2004). Nanoparticles are able to cross membrane barriers, particularly in the absorptive epithelium of the small intestine (Hillyer and Albrecht, 2001) and are being used to deliver small molecules, proteins, and other therapeutics (Dunning et al., 2004; Hamaguchi et al., 2005; Koushik et al., 2004; Panyam and Labhasetwar, 2003; Silva, 2006; Weissleder et al., 2005). Biodegradable nanospheres enhance bioavailability through uptake, followed by degradation and disappearance of the vehicle from the system.

Integration of controlled-release drug reservoirs with microchips (Santini et al., 1999) provides unlimited potential for modulating drug release. Nanotubes that have large relative internal volumes also can be functionalized on the inside surface (Martin and Kohli, 2003). One fabrication technique used self-assembling lipid microtubes to deliver testosterone in rats (Goldstein et al., 2001). Testosterone was covalently bound with an ester linkage to a glutamide core lipid, forming nanotubes that possessed an in vivo biphasic release profile characterized by an initial burst followed by a more sustained release. Another method of fabrication involves synthesizing carbon nanotubes using fullerene. These nanotubes range from one nanometer to tens of nanometers in diameter and are from several to hundreds of microns long. Drugs can be covalently attached to functional groups on the external surface of the nanotubes (Chen et al., 2001). Another drug delivery approach uses nanoshells or dielectric-metal (gold-coated silica) nanospheres. When embedded in a drug-containing polymer and then injected into the body, these nanoshells accumulate near tumor cells. When heated with an infrared laser, the polymer melts, releasing the drug at a specific site (Hirsch et al., 2005; Loo et al., 2005). This technology allows delivering drugs at very precise locations in the brain. Growing knowledge about the neural circuits underlying various functions will probably enhance the capacity to target specific effects with fewer side effects.

Improvements in drug-containing nanoparticles are already gaining regulatory approval. Abraxane, a nanoparticle form of albumin and paclitaxel,[7] eliminates the need for toxic solvents in earlier versions of paclitaxel (Taxol) and permits more of the drug to be administered. Similarly, a micellar nanoparticle formulation of paciltaxel (NK105) is being developed to reduce toxicity while enhancing antitumor activity (Hamaguchi et al., 2005). There is broad international interest in research on nanotechnology for drug delivery. Asia, in particular, is active in this area, as evidenced by the published literature (Miyata and Yamakoshi, 1997; Chen et al., 2001; Tabata

[7]For additional information, see http://www.cancer.gov. Last accessed on January 24, 2008.

et al., 1997a; 1997b; Tsao et al., 1999; Hamaguchi et al., 2005), and there is especially strong research in drug delivery to the brain and neuropeptides (Gao et al., 2007a 2007b).[8]

**Finding 2-4.** Technological advances will affect the types of neuropsychopharmacological drugs available and methods for drug delivery. For the IC, nanotechnologies that allow drugs to cross the blood-brain barrier, increase precision of delivery, evade immune system defenses, evade metabolism, or prolong actions at cellular or downstream targets will be of particular importance. These technologies will increase the likelihood that various peptides, or other brain proteins, could ultimately be utilized as drugs. Development of antidotes or protective agents against various classes of drugs that could be used by an enemy force will also be important.

### Neuropeptides and Behavior

Neuropeptides act as messengers in the brain, influencing many neurobehavioral functions (Strand, 1999). Their therapeutic use in humans has been hampered because they do not readily pass the blood-brain barrier (BBB) and they induce potent hormonelike side effects in the blood (Illum, 2000; Pardridge, 1999). To date, the results of intranasal administration testing have been mixed (Born et al., 2002; Heinrichs et al., 2003; Heinrichs et al., 2004; Merkus and van den Berg, 2007). However, nanotechnology may someday allow for quick pharmacological modifications of behaviors. Box 2-2 provides an overview of the function of the BBB.

**Box 2-2**
**The Blood-Brain Barrier as an Obstacle to the Delivery of Therapeutics**

The blood-brain barrier (BBB) remains an obstacle to the delivery of therapeutics to the brain.[1] It comprises an endothelial cell monolayer associated with pericytes and astrocytes. The BBB separates the blood from the cerebral parenchyma and prevents the penetration of drugs into the CNS. The BBB was first noticed by Paul Ehrlich in 1885 and later confirmed by Edwin Goldmann. It protects the brain from substances that can be neurotoxic in physiological concentrations — for example potassium, glycine, and glutamate (Gururangan and Friedman, 2002). This physical barrier is characterized by tight intercellular junctions (zonulae occludens) (Brightman and Reese, 1969) and by the absence of fenestrations, both of which limit the penetration of therapeutic molecules. The deficiency in pinocytic vesicles and the high metabolic capacity of cerebral endothelial cells (Reese and Karnovsky, 1967) also help to limit the exchange of anticancer agents between the plasma and the CNS. Furthermore, the cerebral endothelium has a high level of ATP-binding cassette (ABC) transporters such as P-glycoprotein involved in drug efflux mechanisms (Golden and Pollack, 2003). Thus the BBB prevents the uptake of all large-molecule drugs and more than 98 percent of pharmaceutical small-molecule drugs. Only very small (<5 $KD_a$), lipid-soluble, electrically neutral molecules and weak bases are able to diffuse passively across the BBB (Abraham et al., 1994).

[1]For more information on nanotechnology for neuroscience, neuropeptides, and the blood brain barrier, which is beyond the scope of this report, see (Beduneau et al., 2007; Pardridge, 1999, 2001; Emerich and Thanos, 2006; Strand, 1999).

One neuropeptide of interest is oxytocin, which—in addition to its well-known functions in milk letdown and childbirth—has a central role in positive social behavioral interactions and can increase trust behavior in human experimental subjects. Oxytocin receptors are distributed in

[8]Psivida Ltd. of Austrailia and SkyePharma of Great Britain are two examples of international interest in this area of research. For additional information, see http://www.psivida.com/. Last accessed on April 10, 2008.

brain regions associated with certain behaviors (Huber et al., 2005; Landgraf and Neumann, 2004) such as pair bonding, maternal care, sexual behavior, and the ability to form normal social attachments (Carter, 1998; Carter et al., 2001; Heinrichs et al., 2002; Huber et al., 2005; Insel and Young, 2001; Pedersen, 1997; Uvnäs-Moberg, 1998; Young et al., 2001). Thus oxytocin permits animals to overcome their natural avoidance of proximity and facilitates approach behavior. Given that oxytocin is believed to promote social attachment and affiliation in nonhuman mammals, researchers have hypothesized it might also promote more social behaviors—such as trust—in humans (Kosfeld et al., 2005; Zak et al., 2007; Zak and Fakhar, 2006).

## FUNCTIONAL NEUROIMAGING

### Introduction

Broadly defined, functional neuroimaging is the use of neuroimaging technology to measure aspects of brain function, often with the goal of understanding the relationship between regional brain activity and specific tasks, stimuli, cognition, behaviors or neural processes. Common technologies for functional neuroimaging include multichannel electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), functional transcranial Doppler sonography (fTCDS), and magnetic resonance spectroscopy (MRS). EEG and MEG measure localized electrical or magnetic fluctuations in neuronal activity. PET, fMRI, fNIRS, and fTCDS can measure localized changes in cerebral blood flow related to neural activity. PET and MRS can measure regional modulation of brain metabolism and neurochemistry in response to neural activity or processes. These functional neuroimaging technologies are complementary, and each offers a different window onto complex neural processes. Because of this complementarity, multimodal imaging is an emerging area of great interest for research, clinical, commercial, and defense applications.

Neuroimaging technologies are likely to play an important role in endeavors to enhance cognition as well as affect and motivation over the next two decades. Predictions about future applications of technology are always speculative, but if the issues discussed above come to fruition this emergent technology might provide insight into the following areas, and others, of direct relevance to national defense: the acquisition of intelligence from captured unlawful combatants, enhanced training techniques, augmented cognition and memory enhancement of soldiers and intelligence operatives, the screening of terrorism suspects at checkpoints or ports of entry where there are no constitutional protections (i.e., airports), and soldier-machine interface devices such as are used in remotely piloted vehicles and prosthetics. Indeed, science is already beginning to see contributions of this field to clinical and battlefield medicine.

Over the next two decades, good brain–computer interfaces (BCIs) are likely to be a great of interest to the gaming industry as well as to the rehabilitation, medical, and military sectors, and neuroimaging and neurophysiology will play a central role in those endeavors. BCIs are likely to be used to enhance several areas of cognition, including memory, concentration, and emotional intelligence, among others. Indeed, this has been a focus of the Defense Advance Research Projects Agency's (DARPA's) Augmented Cognition program for several years. Brain prosthetics could become the new input-output devices for memory systems, allowing efficient searching and encyclopedic access to information. Sandberg and Bostrom suggest BCIs may improve better concentration by reducing working memory load and exploiting the broad attention abilities of the visual system.

Similarly, DARPA has been working on EEG and fNIRS-based BCIs that use the human visual system as the input device to a computer system to increase the speed of data processing in visual search mode. The idea is that although current technological capacities with computer vision are not even close to the speed and sophistication of the human eye, there is a lag time

between the visual mental process and a motor output to the computer system. By using EEG or fNIRS to directly measure the brain's response when it detects a target, the search process can occur more quickly than with an operator's motor response. Given the current level of miniaturization of computer memory, a wearable computer with an efficient brain-based input/output device (a "mental mouse") and an efficient search strategy could allow access to huge amounts of stored data in milliseconds, effectively augmenting the user's long-term memory. Such devices could allow military troops to access visual maps and intelligence when they approach a new area or to access medical information in the field.

Sandberg and Bostrom suggest that wearable computers could also enhance emotional intelligence—that is, the ability to perceive emotions in others and respond appropriately. Such capabilities could be useful for gathering intelligence. The current prototype system was designed to help people who have difficulty in accurately assessing the emotions of other people—for example, children with Asperger syndrome—by improving their ability to interact (El Kaliouby and Robinson, 2005). The system consists of a camera to record the facial expressions of a conversational partner, facial and emotion processing software that estimates the most likely emotional state, a readout that displays a cartoon of the emotion, and suggestions for a proper response. Such systems could also help a participant in a high-stakes negotiation or interview to gauge more accurately the emotional intentions of his or her counterpart (see, for example, Ekman and O'Sullivan, 2006). Indeed, Ekman and Mark Frank (Frank and Ekman, 2004), along with others at DARPA, have been using computer-aided analysis of facial responses based on Ekman's theories to study at-a-distance measures of deception.

Owing to their awkward size and shape and their cost, some technologies such as MEG and MRI/fMRI are likely to take a backseat in enabling cognitive enhancement, providing the underlying neuroscience upon which more fieldable technologies, such as EEG and fNIRS, can be based. It is, for example, unlikely that brain–computer interfaces based on fMRI could be loaded onto jets or spaceships in the next two decades, whereas an EEG or fNIRS-based system could very well be so deployed in that timeframe. However, the information about cognitive, affective, and motivational states that accrues from these various kinds of neuroimaging is likely to play a key role in the use of technology-based systems to enhance performance.

Another example is the use of transcranial magnetic stimulation (TMS) to facilitate neural changes that have been identified through neuroimaging. TMS is a noninvasive way to excite neurons in the brain: rapidly changing magnetic fields (electromagnetic induction) are used to induce weak electric currents in neural tissue, allowing the brain to be activated from outside with minimal discomfort. One alternative to using pharmacological agents to influence neural function is to use electrical stimulation such as TMS to excite the neuromodulatory centers that control plasticity. Experiments in the monkey have shown that electrical stimulation can result in faster cortical reorganization. In their review, Sandberg and Bostrom cite evidence that TMS can increase or decrease the excitability of the cortex, in turn changing its level of plasticity. TMS has been used to facilitate the learning of a procedural memory task by stimulating the motor cortex. Sandberg and Bostrom suggest TMS has succeeded in facilitating working memory, classification, learning motor skills such as finger tapping sequences, coordinating visuomotor tasks, and consolidating declarative memory during sleep.

Because TMS is noninvasive and able to improve performance on a variety of cognitive tasks, Sandberg and Bostrom suggest that it could be a very versatile tool for cognitive enhancement. One limitation is the short duration of its effect (minutes to an hour after stimulation), although some results suggest that coupling TMS with pharmacological manipulations of the dopaminergic system could facilitate long-term consolidation or longer effects TMS (Nitsche and Lamp, 2006). It is worthwhile reminding the reader that the considerable interindividual variability in responses to TMS might require individual tuning of dosage, placement, and so on. Neuroimaging tools such as MRI, fMRI, or fNIRS could play a role in providing precise localization for such technology integrations.These functional

neuroimaging technologies, some mature, others emergent, are commonplace in research and clinical environments and are having an impact on defense policy decisions (Peters et al., 2008). Recent advances and developments allow for functional neuroimaging capability with real-time or near-real- time data acquisition and analysis that is becoming cheaper, portable, and more user friendly. Continued refinement of these technologies is likely to lead to increased dissemination of this technology, with applications expanding well beyond the current primary fields of neuroscience research and clinical medicine. Areas where the application of advanced functional neuroimaging technology likely are business (marketing, economics, human resources), human performance, risk assessment, the field of law, and the military, all of them having great relevance to national policy and defense issues. Progress continues to be made in both functional neuroimaging and neurophysiological methods towards the holy grail of neuroimaging; namely, millisecond-level temporal resolution with precise spatial localization. No current technology affords both high temporal resolution and high spatial resolution with access to the full brain. The strengths and limitations of each technology are briefly described below.

## Electroencephalography

The oldest device used to assess brain function in real time is the EEG. Many years ago it became known that electrical activity in the brain could be recorded by placing electrodes on the surface of the scalp (Berger, 1929). Such recordings represent the summated electrical signal from nominally 50,000 local neurons. Early studies focused on the spontaneous rhythmic oscillations in voltage—frequency bands that tended to shift together with changing mental status, such as alpha waves, which have frequencies between 8 and 13 Hz. Early clinical EEG was used primarily to detect and diagnose epilepsy, but today, with advances in computer technology, informative new experimental paradigms and techniques are being developed. EEG recordings are of two main types: continuous and discrete. Continuous recordings are the traditional multitrace waveforms recorded since EEGs began and activity is classified by the frequency of the dominant waveform (0-40 Hz) on any given channel, such as alpha waves. Discrete recordings are triggered by an event, such as an external flash of light, and then the next 1 to 4 seconds of activity are recorded. In discrete recordings, the "normal" EEG waves are considered background.

Discrete, or event-related, recordings were first described by Davis (1939), who noticed that event-related changes could be seen in an ongoing EEG. Event-related potentials (ERPs), currently the focus of EEG research, refer to the measurement of the brain's electrophysiological response to a particular stimulus. The brain's response to discrete stimuli are typically relatively small (a few microvolts) compared with the ongoing background EEG activity (approximately 50 mV), and multiple stimulus presentations are averaged to distinguish the response associated with the stimulus from the background activity. When the brain response is largely automatic and dictated by the physical properties of the stimulus (say, the loudness of a sound or the brightness of a light flash) it is called an evoked potential. Evoked potentials generally occur 15-100 ms after a stimulus is presented. Later responses, which occur as early as 150 ms after a stimulus, are thought to be influenced by cognitive processes and are referred to as ERPs.

Quantitative electroencephalography (QEEG) uses postrecording computer analysis to analyze the relationship between each of the electrodes placed at the scalp. The frequency composition, amplitude, and position of each electrode is compared to the same information taken from a database of individuals without any known neurological disorder. The resulting EEG brain maps are then analyzed with sophisticated statistical techniques to reveal patterns. The results of these analyses can be presented in graphical form as topographical displays of brain electrical activity. Applications include neurofeedback, or neurotherapy, and the identification of responses to medication for certain neurological and psychiatric disorders. Neurotherapy is an experimental technique that uses a QEEG brain map to analyze psychiatric problems from attention deficit

disorder to depression to schizophrenia. Patients are then subjected to a conditioning protocol to "train" the "abnormal" brain activity towards a statistically more "normal" pattern of activity. Neurotherapy can reduce aberrant symptoms of many conditions (Fox et al., 2005).

Interpretation of a scalp EEG often involves speculation as to the location inside the brain of the source of the activity recorded (Brazier, 1949; Shaw and Roth, 1955). While there is substantial PET and fMRI literature on finding the neural sources of the functional network implicated in given mental tasks (Cabeza and Nyberg, 2000), PET and fMRI are temporally limited in their ability to probe discrete neural events. The source localization capability of the EEG has been used to overcome this limitation and solve the inverse problem. Whereas EEG offers millisecond-level time resolution, the signals measured at the scalp do not directly indicate the location of the neurons that are generating the activity. Although the sites at which the scalp potentials are measured at any given point in time are finite, an infinite number of source configurations could account for those measurements (Plonsey, 1963; Fender, 1987). Source localization involves mathematical attempts to solve the inverse problem by introducing a priori assumptions about the generation of the EEG (or MEG) signals. The better these assumptions are, the more trustworthy the source estimations will be, and several different models have been formulated and implemented in algorithms to reach the inverse solution, each using different mathematical, biophysical, statistical, anatomical, or functional constraints (for a recent review, see Michel et al., 2004). Technological advances in the field include noncontact electrodes that use high-gain preamplifiers to mitigate the effects of the high impedence caused by the lack of contact. This arrangement could allow the "application" of a large number of electrodes in a relatively short time, at the cost of a noisier signal. As these models and constraint estimates improve, there is promise for important future developments. EEG has several advantages over other functional neuroimaging techniques, including the relatively low cost of the technology (around $15 million). Also, a single technician can produce reliable recordings with unmatched temporal resolution measured in milliseconds. A number of other countries use high-density EEG with source localization.[9]

## Positron Emission Tomography

The introduction of computed tomography (CT) by Sir Godfrey Hounsfield in 1973 (Petrik et al., 2006) dramatically changed the way scientists and physicians examined the brain. The development of PET (based on prior brain autoradiographic work) quickly followed, creating in vivo autoradioagrams of brain function (Ter-Pogossian et al., 1975; Phelps et al., 1975) and introducing a new era of functional brain mapping. For an excellent historical review of PET and functional neuroimaging the reader is referred to Raichle (1998).

PET can be used to produce a three-dimensional image or map of functional processes in the brain. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radioisotope, which is introduced into the body on a metabolically active molecule. Images of regional metabolic activity or blood flow are then reconstructed by computer analysis. Modern versions of PET scanners are combined with CT scanning and MRI scanning capability to coregister metabolic activity with high- resolution anatomic images of the brain, creating three-dimensional metabolic/anatomic overlays.

The radionuclides utilized in PET scanning typically have short half lives; carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (123), and fluorine-18 (~110 min). They are incorporated into compounds such as glucose and water. These radiotracers distribute in the brain by following the metabolic pathways of their natural analogues or by binding with specificity to the receptor proteins for which they have affinity. Due to the short half lives of most

[9]In Cuba, some scientists are reportedly doing very accurate localization using high-density EEG arrays to locate tumors. Personal communication to committee member Scott Bunce from Roy John.

radioisotopes, the radiotracers must be produced in a cyclotron and a certified medicinal radiochemistry laboratory co-located with the PET facility. Fluorine-18, with a half life long enough to allow commercial manufacture at an offsite location and transport to an imaging center daily, is an exception.

PET has gained widespread utility in clinical medicine, particularly in oncology, where it has become the favored imaging technology for the detection, staging, and monitoring of response to treatment for many neoplasms. Clinical PET is also used in neurology, psychiatry, cardiology, and pharmacology. There is continued widespread use of PET technology to study brain metabolism and receptor ligands. Limitations of PET include its relatively low temporal resolution; spatial resolution limited to approximately 5 mm; relatively expensive equipment; requirement for an injectable, short-lived positron-emitting radioisotope that is usually produced in a cyclotron; and limits on its use for repetitive longitudinal studies and studies in certain populations owing to its emission of ionizing radiation.

However, PET remains a powerful tool for functional neuroimaging, especially with the proliferation of PET/CT and PET/MRI scanners. PET's exquisite ability to elucidate specific receptor binding sites/activity within the brain and its ability to produce images of brain metabolism mean it is not likely to be supplanted by other neuroimaging technologies in the foreseeable future. Indeed molecular neuroimaging via PET is likely to show the most growth in functional neuroimaging research over the next decade (Hammound et al., 2007).

### Functional Magnetic Resonance Imaging

MRI is widely accepted as the gold standard for anatomical neuroimaging. The most common form of functional MRI (fMRI) utilizes a blood-oxygenation-level- dependent (BOLD) contrast mechanism to distinguish areas of neural activity. Other methodologies for fMRI include dynamic contrast techniques and noncontrast techniques (e.g., arterial spin labeling). There has been explosive growth of fMRI research and clinical applications over the past decade, with research applications including brain mapping of task (motor and cognitive) dependent processes. MRI has also been employed for detection of deception, an application that has drawn the interest of various communities (ethics, defense, legal). Under controlled experimental conditions with cooperative subjects, this technology has shown initial promise (Abe et al., 2007; Abe et al., 2006; Mohamed et al., 2006; Davatzikos et al., 2005; Kozel et al., 2005; Langleben et al., 2005; Lee et al., 2005; Nuñez et al., 2005; Phan et al., 2005a; Kozel et al., 2004; Ganis et al., 2003; Langleben et al., 2002; Lee et al., 2002, Spence et al., 2001).

Real-time data acquisition (single-trial fMRI) and near-real-time data analysis (hundreds of milliseconds delay) of complex cognitive tasks have been demonstrated and will expand the applications areas of relevance to the research, clinical, and defense communities (Posse et al., 2003; Phan et al., 2004). Real-time fMRI has been utilized to demonstrate the voluntary suppression of affective state, suggesting that it may provide insight into complex cognitive processes (Phan et al., 2005b). Whether these findings can be generalized to nonexperimental settings remains to be determined. fMRI has many advantages over other functional imaging techniques, including high spatial resolution of the activation patterns (measured in millimeters); temporal resolution (measured in a few seconds); no known risk factors in healthy subjects[10]; and, recently near-real-time analysis. Its key disadvantages include its relatively high cost; problems with data interpretation if the subject moves a few millimeters; a user-unfriendly scanning environment (noisy, small enclosed space); and the requirement for large superconducting magnets

[10]The main injuries during MRI are caused by the magnetic field being attracted by the ferrous (i.e. magnetic) substances within the body. Proper screening of subjects by attending personnel eliminates this risk.

Recent advances in neuroimaging technology, including high-field (3 tesla) and ultrahigh-field (7 tesla) magnetic resonance techniques for MRI, fMRI and MRS, real- time acquisition/processing, and parallel imaging, offer the potential for significant advances in spatial and temporal resolution for structural, functional and neurochemical imaging. In other words, MRI-based imaging technologies are providing faster and more detailed pictures of the human brain and brain function than ever before. These and other related technologies are moving forward rapidly, driven by clinical and research demand, and over the next two decades there are likely to be continuing significant advances in this technology, with unique applications certain to emerge (Dickerson, 2007; Ladd, 2007; Nakada, 2007).

As shown in Table 2-3, a concerted effort at the national level in China to invest in research relating to high-field structural and functional fMRI has led to a network of coordinated laboratories and programs (Cao et al., 2006; Poo and Guo, 2007; Simon, 2007; Alderson, 2007).[11]

TABLE 2-3 Current Neuroimaging Research in the People's Republic of China

| Name | Location | Machines | Known Use of Machines |
|---|---|---|---|
| Xuanwu Hospital | Beijing | 1.5 T, 3 T Siemens TRIO | Clinical and research; 14 Articles published 2007 |
| Beijing Friendship Hospital* | Beijing | 0.5 T Philips Gyroscan T5-NT | Clinical and research |
| Beijing MRI Center for Brain Research* | Beijing | 3 T Siemens TRIO | Research; 7 articles published 2007 |
| Beijing MRI Center for Brain Research* | Beijing | 3 T Siemens Verio | Believed delivered October 2007 two units wide bore PET scanner insert |
| Tsinghua University* | Beijing | Has access to low field, 1.5 T and 3 T | Research |
| Beijing Hospital* | Beijing | 1.5 T, 3 T Philips Achieva | Clinical and research; 8 articles published 2007 |
| Beijing Jishuitan Hospital | Beijing | Unknown | Clinical and research |
| Institute of Biophysics* | Beijing | 1.5 T GE, 3 T Siemens TRIO | Research |
| Tian Tan Hospital | Beijing | Unknown | Clinical and research; 9 articles published 2007 |
| An Zhen Hospital | Beijing | 1.5 T Siemens Sonata | Clinical and research |
| China-Japan Friendship Hospital* | Beijing | 0.5 T | Clinical and research; 13 articles published 2007 |
| Peking University First Hospital* | Beijing | 1.5 T GE and a 3 T GE Signa | Clinical and research; 9 articles published 2007 |
| Peking Union Medical College Hospital | Beijing | Unknown | Clinical and research |
| Peking University Third Hospital* | Beijing | 1.5 T Siemens Magnetom | Clinical and research; 8 articles published 2007 |
| Second Xiangya Hospital* | Changsha | 1.5 T GE | Clinical and research; 9 articles published 2007 |
| Guilin Medical College* | Guilin | 1.5 T | Clinical and research |
| University of Science and Technology of China* | Hefei | Unknown | Research |
| Shanghai Children's Medical Center | Shanghai | 1.5 T | Clinical and research |

[11] Personal communication between committee chair Christopher Green and Amy Kohl of Wayne State School of Medicine.

| | | | |
|---|---|---|---|
| Shanghai 9th People's Hospital* | Shanghai | 0.2 T Siemens Magnetom Open | Clinical and research |
| Xin Hua Hospital | Shanghai | 0.5 T | Clinical and research; 5 articles published 2007 |
| Renji Hospital | Shanghai | 1.5 T Philips, 1.0 T Philips Gyroscan NT | Clinical and Research |
| Ruijin Hospital | Shanghai | 1.5 T GE Signa | Clinical and research: 7 articles published 2007 |
| MR Application Academy* | Shanghai | Unknown | Training |
| Changhai Hospital | Shanghai | 1.5 T Siemens Symphony | Clinical and research; 11 articles published 2007 |
| Anhui Wu Jing Hospital | Shanghai | 0.35 T Siemens C! | Unknown |

* Reported by the National Ministry of Science and Technology. Military funding, requirements, and/or program coordination.

## Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) provides a noninvasive window into brain chemistry. Research clinical applications include the ability to differentiate pathology (e.g., brain neoplasm) from normal or necrotic tissue (Moore, 1998); monitoring brain metabolism (glutamate, glucose levels); and monitoring neuropharmacologic treatment effects (neurotropic/neuroprotective medicines or psychoactive compounds) (Manji et al., 1999; Moore et al., 2000). While spatial resolution is on the order of 1 cc, this methodology has the potential to monitor neurochemical modulation in response to neural processes or neuropharmacologic intervention. Multiple studies have demonstrated the ability of MRS to detect biomarkers of complex neural processes, and rapid (<30 sec) neurochemical imaging becomes possible with high-field magnetic resonance technology (Phan et al., 2005c). Advances in MRS should be followed carefully because its complementarity with respect to the other functional neuroimaging technologies, particularly in the area of monitoring neuropharmacologic response, is likely to make it applicable for defense purposes. For example, as the ability to monitor neurochemistry in vivo and in near real time is developed with advanced high-field MRS and related technologies, the possibility arises of developing state-dependent neurochemical biomarkers for stress and anxiety as well as their pharmacologic modulation in a dose response fashion.

## Magnetoelectroencephalography

Magnetoencephalography (MEG) is a completely noninvasive, nonhazardous technology for functional brain mapping, localizing and characterizing the electrical activity of the CNS by measuring the associated magnetic fields emanating from the brain. Every electrical current generates a magnetic field. However, unlike an electrical signal, magnetic fields are not distorted by traveling through the skull, and the source of the summated magnetic fields can be triangulated within a few millimeters. MEG provides functional mapping information on the working brain.

Modern MEG scanners use as many as 300 superconducting quantum interference device (SQUID)[12] detectors, allowing very fast acquisition and extremely high localization of the source of the electromagnetic signal. The information provided by MEG is entirely different from but complementary to the information provided by structural imaging techniques like CT or MR imaging. While MRI and CT provide excellent anatomical images, MEG measures correlates of neurological function. The advantages of MEG over fMRI and PET include the measurement of brain activity with higher temporal and spatial resolution. Its disadvantages include its greater

[12]SQUID: Superconducting Quantum Interference Device, supercooled electronic component designed to detect extremely small changes in magnetic fields.

cost than fMRI. It also requires a specialized technical team with broad expertise in the acquisition and processing of complex data and requires very precise positioning requirements.

## Transcranial Ultrasonography

While transcranial ultrasonography operates on the same principle as the diagnostic ultrasound imaging of a fetus in utero, it is more difficult to obtain high-quality images of the brain because the propagation of sound waves is impaired by bone. However, the skull is thin enough in a few "monographic windows" (Duscheck and Schandry, 2003) to provide a path for the ultrasonic signal and can provide accurate real-time measurements of blood flow velocity. The transorbital window, located above the zygomatic arch (the "temple"), is used to image the posterior, anterior, and medial cerebral arteries along with a few of the branches that provide blood flow to specific areas of the brain.

Although both rely on blood flow, sonography is very different from fMRI, which measures blood oxygenation level changes with a spatial resolution of a couple of millimeters. In functional transcranial doppler sonography (fTDS), the spatial resolution is determined by the volume of the brain supplied with blood by the vessel under study. These areas can be quite large, making the spatial resolution of fTDS extremely limited. Changes in blood velocity, which are presumed to directly measure changes in resistance of the artery (i.e., the lumen diameter change), occur nearly instantaneously in an event- related experimental paradigm, giving exceptional temporal resolution.

There remain several technical problems with fTDS. Only a limited number of large arteries can be imaged. Even in the arteries that are large enough and located within sight of the few available ultrasonic windows, the angle of the ultrasonic beam can make it very difficult to accurately measure blood flow changes. However, fTDS has several advantages over other functional neuroimaging techniques including cost effectiveness; portability; continuous monitoring of blood flow activity; and excellent temporal resolution.

## Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) is an emerging neuroimaging technology with several characteristics that make it a good candidate for use in military and intelligence applications. fNIRS uses light in the near infrared (700-900 nm), outside the visible spectrum, to measure changes in brain tissue that are associated with neuronal activity—in other words, it provides accurate spatial information about ongoing brain activity. Although fNIRS can measure several parameters associated with neural activity, the most commonly of which is the change in the ratio of oxygenated to deoxygenated hemoglobin in the blood, a measure analogous to fMRI's BOLD signal. The data from Huppert et al. (2006) demonstrate the relationship between the fMRI BOLD signal and fNIRS measures of deoxyhemoglobin (HbR), oxyhemoglobin (HbO), and total hemoglobin (HbT). The design used a short-duration, event-related motor task, finger tapping, during the simultaneous recording of fMRI and fNIRS in five subjects. The results of Huppert et al. indicate that the fMRI-measured BOLD response is more highly correlated with the fNIRS measurement of deoxyhemoglobin than with the fNIRS measurement of oxyhemoglobin or total hemoglobin. This result was predicted from the theoretical basis of the BOLD response (as the BOLD response is based on changes in the concentration of HbR) and from previous publications (Toronov et al., 2001).

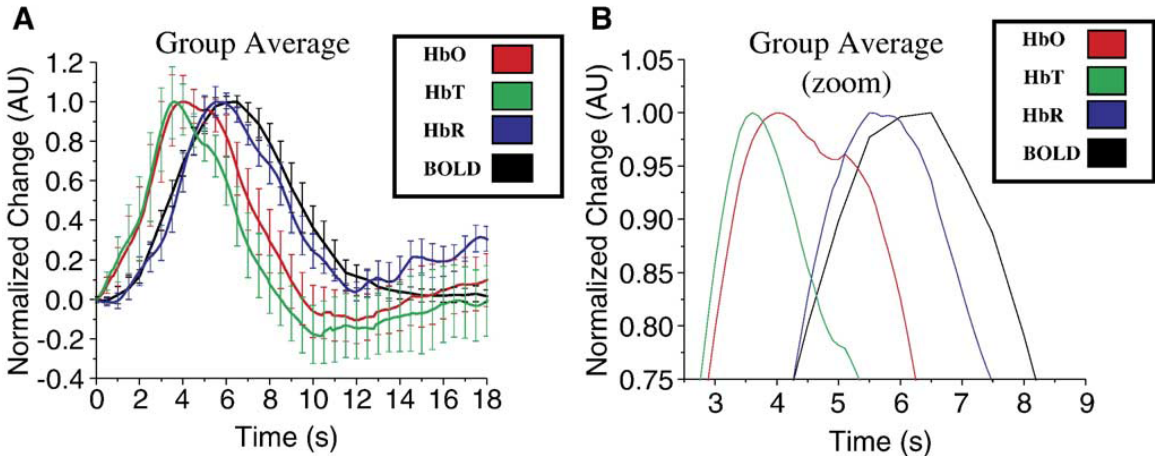
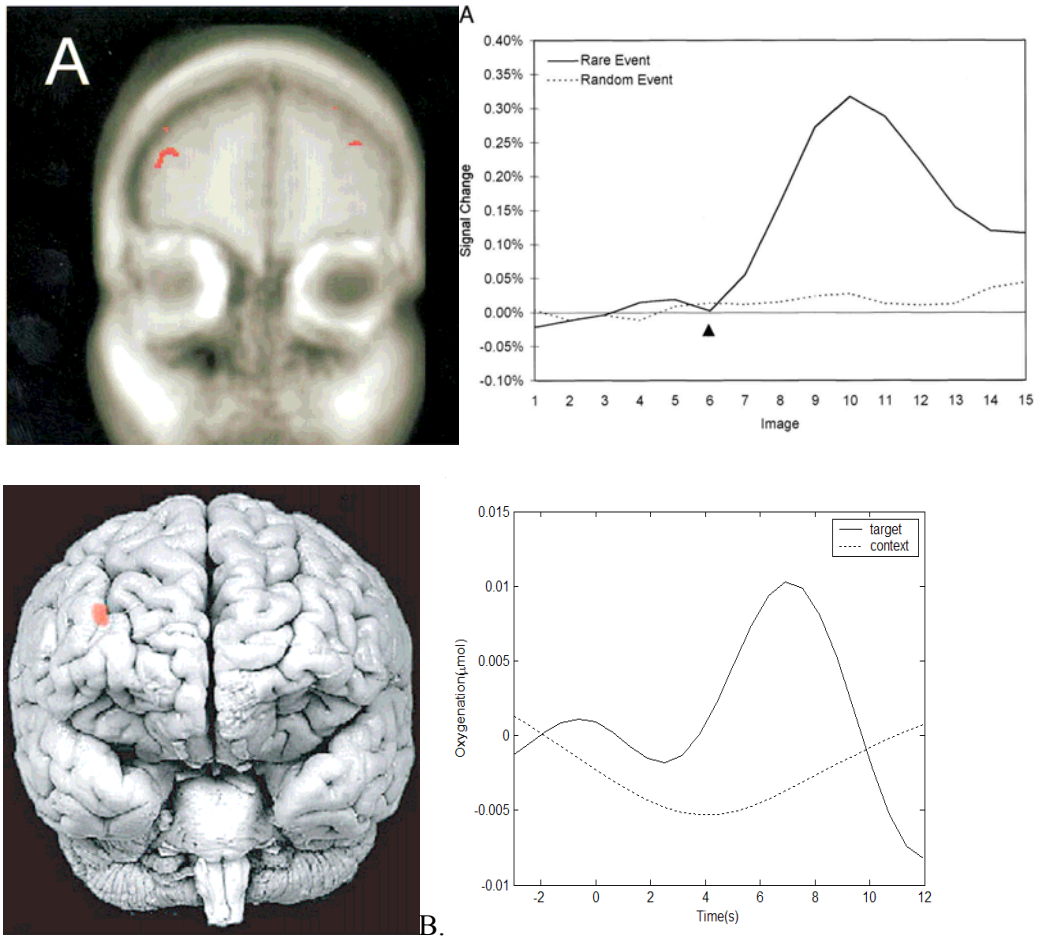



FIGURE 2-3 Averaged hemodynamic response function for simultaneously recorded fNIRS and BOLD responses during finger tapping. Maximum change was normalized to unity, and the HbR response was inverted. The error bars on plot (A) represent the standard error of each time point from the average. Plot (B) presents the first 8 sec of the same data to highlight the response peaks. The BOLD signal closely tracks the HbR measurement. SOURCE: Huppert et al. (2006). ©2006 Reprinted with permission from Elsevier.

Using a more complex cognitive paradigm, target categorization, Bunce et al. (2006) replicated the fMRI protocol of McCarthy et al. (1997) using fNIRS. The results location and time course of McCarthy et al. are displayed in Figure 2-4, Row A. The fNIRS results were quite similar to the fMRI results reported by McCarthy et al.

fNIRS has also been reported to measure changes in the optical properties of the cell membranes themselves that occur when a neuron fires (Gratton et al., 1995), referred to as an event-related optical signal (EROS). Although the signal-to-noise ratio is low in current technological incarnations, this latter measure is particularly interesting as it represents the holy grail of neuroimaging; high spatial resolution coupled to high temporal resolution. (Please see Appendix D for a more thorough discussion of fNIRS technology.)

Of importance in military applications, fNIRS is safe, noninvasive, and highly portable, even wireless. Subjects are able to sit upright, work on computers or perform other tasks, even walk on treadmills (Izzetoglu et al., 2004). With near-zero run-time costs, fNIRS is also inexpensive. Although current systems cost between $25,000 and $300,000, they are still largely bench-made. Continuous-wave systems could be manufactured for a few thousand dollars, and probably for less in volume, especially as the cost of manufacturing lasers and light-emitting diodes continues to fall (see Appendix D for further information on system types). Extant systems operate from a laptop computer and a 2 x 4 x 6 inch control box. Technological advances currently under development include having the entire system on a digital signal processing chip operating from a laptop computer and linked to a wireless sensor. These properties of fNIRS make neuroimaging possible where other neuroimaging technologies are impractical or impossible. Preliminary studies have been conducted with fNIRS in the backpacks of warfighters walking through virtual reality programs. Other advances currently under investigation include closed-loop human brain–computer interfaces and implantable optodes. Implantable optodes could allow realizing the holy grail of neuroimaging, the direct, noninvasive measurement of neuronal activity with millisecond-level time resolution and superior spatial resolution.




FIGRE 2-4. Replication of the fMRI protocol of McCarthy et al. (1997) using fNIRS. SOURCE: A. McCarthy et al. (1997) ©1997 reprinted with permission from the American Physiological Society; B. (Image) Sundsten and Mulligan (2000); (Graph) Bunce et al. (2006) ©2006 IEEE.

fNIRS measures relative changes in HbO and HbR, and total blood flow can be calculated from the differential equation. There are no approved clinical neuroimaging uses for this technique, but there are several advantages for experimental use. fNIRS systems are not as susceptible to movement artifact as fMRI, and algorithms are being refined for the removal of such artifacts (Izzetoglu et al., 2004). fNIRS depends on measurements of energy outside the visible spectrum. fNIRS was first used during World War I to monitor the blood oxygenation of bomber crews, a critical measurement before pressurized cabins were introduced in B-29s. Although fNIRS research has been ongoing since the late 1930s, the recent breakthroughs in both fNIRS and fMRI research have renewed interest in this technology. The capacity to translate findings from fMRI into fieldable, user-friendly, wearable devices is of significant interest. For instance, fNIRS has been shown to have promise in the detection of deception (Bunce et al., 2005), being both affordable and fieldable. The potential experimental uses of this technology are very exciting and include ecologically valid brain–computer interfaces; neurofeedback for guided facilitation of neural plasticity; and wearable neural monitors. Research groups in Japan (Haida et al., 2000), Ireland (Coyle et al., 2007), and the United States are working on brain–computer interfaces that allow locked—in patients (patients with no motor control, such as amyotrophic lateral sclerosis (ALS) patients)—to communicate. In addition, Singapore has asked researchers in the United States to develop a brain fingerprint to identify specific brain signatures using fNIRS. Some advantages of the technology are its moderate cost (between $25,000 and $300,000)

(Duscheck and Schandry, 2003). It is also portable, wireless, and completely noninvasive and its temporal resolution, which is similar although somewhat lower than that of fMRI ($1\ cm^3$).[13]

These attributes allow fNIRS to be used with children and with patients who may find confinement to an fMRI magnet very unpleasant. A number of sensor applications exist, including caps, tension straps, and medical-grade adhesives. fNIRS is quiet and comfortable and therefore amenable to sensitive protocols such as the induction of positive moods and to integration with other technologies, including EEG. Appendix D provides additional information on the cost of the technology. NIRS can theoretically be combined with EEG, transcranial sonography, and other functional neuroimaging sensors. Unlike fMRI, where the subject is confined to the bore of the magnet, NIRS movement artifacts can be limited by proper affixation of sensors to the scalp. The major limitation is that NIRS best measures the first 2 or 3 centimeters of cortex so that deep brain imaging, at least through an intact skull, is challenging. Ongoing work, however, suggests that soon they will be able to image up to 5 cm deep.

### Monitoring Advanced Cognitive Processes via Neuroimaging

There is a large body of published research on the use of various neuroimaging modalities to investigate the neural circuitry associated with deception. Recent PET and fMRI studies have provided insights, with specific areas in the prefrontal cortices and amygdala being the most commonly implicated regions (Abe et al., 2007; Abe et al., 2006; Mohamed et al., 2006; Davatzikos et al., 2005; Kozel et al., 2005; Langleben et al., 2005; Lee et al., 2002; Lee et al., 2005; Nuñez et al., 2005; Phan et al., 2005a; Kozel, Padgett, and George, 2004; Kozel et al., 2004; Ganis et al. 2003; Langleben et al., 2002; Spence et al., 2001). Recent NIRs studies of deception have also implicated prefrontal brain regions in the neural circuitry associated with deception (Bunce et al., 2005). Another recently published study that correlated fMRI measurements with standard skin conductance measurements during a concealed information paradigm had interesting results (Gerard et al., 2007). There are other possible uses for fMRI and other neuroimaging technologies that would indirectly provide information about deception and that are far more likely to be successful in the near future. These indirect measures would not require any response from the subject but would provide passive information about the subject's experience. fMRI can already be used to judge recognition of items on a trial-by-trial basis. For example, one can imagine showing a subject a series of pictures of other people or crime scenes, and using fMRI to detect those that are familiar to the subject. The fMRI data could then be compared to the subject's own statements about familiarity; this would be an indirect measure of lying. Such trial-by-trial measures are already under active investigation in the fMRI field, and it is entirely possible that they could be enhanced to aid in detection of deception using targeted research funding.

**Finding 2-5.** Functional neuroimaging is progressing rapidly and is likely to produce important findings over the next two decades. For the intelligence community and the Department of Defense, two areas where such progress could be of great interest are enhancing cognition and facilitating training. Additional research is still needed on states of emotion; motivation; psychopathology; language; imaging processing for measuring workload performance; and the differences between Western and non-Western cultures.

[13]Currently, NIRs can localize hemodynamic changes within about 1 cm while the best fMRI scanner can localize changes within a few millimeters.

## CONCLUDING REMARKS

The purpose of this chapter was to explain, in detail, three selected areas of current cognitive neuroscience research. The chapter also serves as the scientific foundation for Chapter 3, the main purpose of which is to explore how cognitive neuroscience is starting to be applied in useful ways. Some of these applications are already beginning to appear and may one day impact the intelligence and military communities.

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