This chapter provides an overview of electroencephalography (EEG), event-related potentials (ERP), and both structural and functional neuroimaging, with a focus on MRI. I examine some of the core applications, limitations, landmark studies, and major contributions each of these techniques have made to our understanding of the pathophysiology of mental disorders. Where appropriate, I also discuss clinical applications of these techniques and the effect of various treatments on neurophysiological and neurobiological indices. Last, I offer future directions for neurophysiology and neuroimaging in clinical psychological research.

DESCRIPTION AND DEFINITION

Over the past 3 decades, there has been a growing movement to examine the neurophysiological and neurobiological basis of mental disorders (Insel et al., 2010). This movement has informed our understanding of the pathophysiology of mental disorders, facilitated the identification of biological markers that can aid scientific investigation and differential diagnosis, and helped generate targeted treatments.

Three techniques for investigating brain structure and function that have made important contributions to clinical psychological research are quantitative EEG, ERPs, and both structural and functional neuroimaging. Quantitative EEG uses electrodes placed on the head to measure electrical potentials emitted from the brain and provides an index of how active or inactive brain regions are at a given moment in time. ERPs are extracted from EEG data and are electrical potentials that occur in preparation for or in response to discrete events or stimuli. ERPs provide information on psychological and neurophysiological responses to these events or stimuli. Whereas EEG and ERP are neurophysiological techniques that measure electrical potentials emitted through the skull, structural and functional neuroimaging techniques generate maps of underlying neuronal organization and function.

Each of these techniques has pros and cons, largely involving a trade-off between spatial and temporal resolution (Luck, 2005). Spatial resolution involves the ability to identify the biological source of a particular signal and to distinguish two separate structures close to each other in space. Temporal resolution refers to the ability to determine the order of occurrence of two events close to each other in time.

CORE APPLICATIONS

The first EEG recording in humans was performed in 1924 by a German psychiatrist named Hans Berger (Berger, 1929). Using two electrodes, Berger observed spontaneous rhythmic activity oscillating at approximately 10 hertz during relaxed wakefulness in the absence of sensory input. This rhythmic activity would become known as alpha activity, and Berger was among the first to relate fluctuations in human EEG to different psychological states.

The field of human neurophysiology has come a long way since Berger’s (1929) landmark observation. It is now established that scalp-recorded EEG
oscillations are generated by the summation of both excitatory and inhibitory postsynaptic potentials in tens of thousands of cortical pyramidal neurons (Luck, 2005; Pizzagalli, 2007). Placing electrodes at the scalp allows measurement of these small but reliable potentials, as shown in Figure 23.1.

Over the decades, researchers have developed techniques for reducing raw EEG signals into metrics that reflect the activation or deactivation of brain regions. These techniques, referred to as spectral analyses, typically summarize EEG data into conventionally defined frequency bands (Figure 23.1B). The delta band reflects low-frequency activity (1–4 hertz) typically associated with the deepest stages of sleep in healthy humans, also known as slow-wave sleep. Theta activity involving EEG activity within the 4- to 8-hertz range is also prominent during sleep. Elevated activity in the alpha band (8–13 hertz) is indicative of less cortical neuronal activity. Support for this claim comes from research combining EEG and positron emission tomography (PET) that demonstrates an inverse relationship between glucose metabolism (an index of neuronal activity) and alpha activity in cortical regions underlying the specified EEG electrode (Larson et al., 1998). Both beta (13–30 hertz) and gamma (36–44 hertz) activity reflect increased neuronal activity, arousal, and attention. As discussed below, psychological research involving quantitative EEG typically compares individuals with and without mental disorders on one or more of these frequency bands to index differential profiles of brain activation.

In its raw form, EEG data are coarse measures of brain activity that are difficult to use for the assessment of specific cognitive and affective neural processes that are often the focus of clinical neuroscience. Embedded within EEG data, however, are neural responses associated with specific sensory and cognitive events. It is possible to extract these responses from overall EEG by means of simple averaging techniques. These specific responses are called ERPs to denote the fact that they are electrical potentials that occur in preparation for or in response to discrete events, whether they be internal or external to the participant. Conceptually, ERPs are regarded as neural manifestations of specific psychological functions.

As is EEG, ERPs are generated predominantly from postsynaptic potentials in cortical pyramidal neurons, and the recorded voltage reflects the sum of many underlying ERP components that overlap in time (Fabiani, Gratton, & Federmeier, 2007; Luck, 2005). The advantage of ERP is that it provides arguably the best temporal resolution of any neurophysiological or neuroimaging method used in psychological research. ERPs have a temporal resolution of 1 millisecond or better under optimal conditions, leading to it being referred to as the “reaction time for the 21st century” (Luck, 2005, p. 22).

Although the first sensory ERP recordings from humans were performed in the 1930s, it was not until the advent of digital computers in the 1960s that ERPs gained traction. The procedures used to derive ERPs begin with the same electrodes and amplifiers used to obtain EEG data. The experimental questions and analytical procedures, however, are different indeed. The ERP is small (a few microvolts) in comparison to EEG (about 50 microvolts).

FIGURE 23.1. A 2-s segment of raw electroencephalography (EEG) data from a single channel (A) and a spectral representation of this epoch (B).
Thus, analysis generally begins with procedures to increase the discrimination of the signal (ERP) from the noise (background EEG). The most common of these procedures involves averaging samples of EEG data that are time locked to repeated occurrences of a particular experimental event. The resulting averaged ERP waveforms consist of a sequence of positive and negative voltage deflections, which are called peaks, waves, or components.

Figure 23.2 displays a typical ERP. In this figure, the peaks are labeled P1, N1, P2, N2, and P3. P and N are traditionally used to indicate positive-going and negative-going peaks, and the number simply indicates a peak’s position within the waveform (ERP waveforms are sometimes plotted with negative voltages upward and positive voltages downward, because this was the convention among early physiologists). The latency of a peak in milliseconds is often approximately 100 times the ordinal position, so that P1 is often referred to as P100, N2 as N200, P3 as P300, and so on. The sequence of ERP peaks reflects the flow of information through the brain. Thus, ERP affords researchers the ability to examine the temporal unfolding of neurocognitive processes to specific stimuli or manipulations.

Early or initial ERP components that occur within approximately 100 milliseconds of the stimulus (e.g., P1, N1) are typically referred to as sensory or exogenous components because they will reliably be generated if the stimulus is perceived. These early sensory evoked potentials index automatic attention to stimuli and are sometimes used in the diagnosis of neurological diseases, such as multiple sclerosis and congenital deafness (e.g., Whelan et al., 2010). Subsequent ERP components (e.g., N2, P3) typically do not depend entirely on the physical properties of the eliciting stimulus but on the task performed by participants and the sustained allocation of attention to emotional stimuli. These components are typically referred to as endogenous components to indicate their dependence on internal rather than external factors.

Whereas neurophysiology assesses EEG oscillations or electrical potentials emitted from the skull, neuroimaging techniques generate maps of underlying neuronal organization and function. Neuroimaging is broadly classified into structural and functional imaging.

The most common structural imaging technique for human research is MRI. MRI uses a series of changing magnetic gradients and oscillating electromagnetic fields. Depending on the frequency of the electromagnetic fields, energy may be absorbed by atomic nuclei. MRI scanners are tuned to the frequency of hydrogen nuclei, which are the most common in the human body because of their prevalence in water molecules. After the electromagnetic energy is absorbed, it is later emitted by the nuclei, and the amount of emitted energy depends on the number and types of nuclei present. Using this emitted energy, researchers are able to generate high-resolution images of underlying biological tissues (Huettel, Song, & McCarthy, 2008).

Despite providing detailed information on neuronal tissue, structural imaging is limited by its static representation of the brain. Functional neuroimaging provides a powerful complement to structural imaging by generating maps of neuronal activation that can be linked to dynamic mental processes (Huettel et al., 2008). Using functional neuroimaging, researchers can measure changes in brain function while participants perform experimental tasks or are at rest. Researchers can then determine which profiles of neuronal activation relate to clinical symptoms or best distinguish individuals with and without a clinical disorder.
Two established functional neuroimaging techniques are PET and fMRI. PET is a nuclear medical imaging technique that involves injection of radioactive isotopes or tracers to image the tissue concentration of molecules. If the chosen tracer is fludeoxyglucose, an analogue of glucose, the concentration of the imaged tracer indexes the level of neuronal activation in a given region. This is because the more active a brain region is, the more glucose that region requires for metabolic purposes (Huettel et al., 2008). An advantage of PET is that the use of different tracers allows researchers to examine the tissue concentration and distribution of receptors of a variety of different molecules and neurotransmitters. For example, using PET neuroscientists have made important contributions to our understanding of the role of dopamine activity in a number of mental and neurological disorders, including depression, bipolar disorder, substance abuse, and Parkinson’s disease (e.g., Strakowski, Delbello, & Adler, 2005; Talvik et al., 2006).

The neuroimaging technique that has arguably garnered the most attention over the past decade is fMRI. fMRI provides reasonable temporal resolution and exquisite spatial resolution, allowing researchers to localize brain activity on a second-by-second basis within millimeters of its origin. In fact, if a researcher’s primary aim is to examine profiles of neural activation or deactivation to experimental manipulations, fMRI is currently the gold standard. The physics of fMRI is based on the assumption that information processing activity of neurons increases their metabolic requirements. The vascular system supplies energy to meet these requirements in the form of two fuel sources, glucose and oxygen, the latter bound to hemoglobin molecules. Once supplied, oxygenated hemoglobin converts to deoxygenated hemoglobin. Given that deoxygenated hemoglobin has magnetic field gradients that alter the properties of nearby hydrogen nuclei, changes in the concentration of deoxygenated hemoglobin provide a measure of the level of neuronal activation. Thus, fMRI does not directly assess neuronal activity; it generates an estimate of neuronal activation by indexing the metabolic correlates of neuronal activation.

LIMITATIONS OF THE APPROACHES

Quantitative EEG has a number of advantages for clinical psychological research. First and foremost, it is feasible and cost effective. Unlike MRI, once an investigator has purchased an EEG system the costs associated with maintenance and data collection are minimal. Accordingly, EEG technology is very amenable for use in more clinical or treatment-oriented settings. Second, EEG technology is noninvasive and relatively resistant to movement and muscle-related artifact. This advantage is particularly relevant when studying children or clinical conditions such as mania or attention deficit hyperactivity disorder when it can be challenging for participants to sit still for extended periods of time. Last, given that EEG involves recording electrical activity of neuronal assemblies, it has the potential to provide temporal resolution on the order of milliseconds as opposed to the seconds afforded by fMRI.

The primary limitation of EEG is that it provides poor spatial resolution. Considering that the diameter of EEG electrodes is orders of magnitude larger than single neurons and the area of an electrode covers approximately 250,000 neurons, it is clear that many neurons must be activated to detect an EEG signal at the scalp. The distorting effects of the head volume, low signal-to-noise ratios, and the limited spatial sampling as a result of practical limits on the number of electrodes that can be used also contribute to poor spatial resolution in EEG. Perhaps most troubling, however, is what is typically referred to as the inverse problem (Luck, 2005), which refers to the fact that there are an infinite number of neuronal source configurations that can explain a given set of scalp-recorded signals. Thus, we cannot know with certainty the correct configuration, and there is no way to generate a reliable margin of error for any attempt to localize the source configuration. Given that one objective of clinical neuroscience is to link clinical symptoms to specific neural processes, EEG is limited in this capacity.

Despite these challenges, researchers have developed mathematical techniques that attempt to model the neuronal generators of scalp-recorded signals (Pizzagalli, 2007). These source localization techniques are relatively robust to noise and...
informed by anatomy, neurophysiology, MRI, and volume conduction physics. Common source localization techniques include low-resolution brain electromagnetic tomography and brain electrical source analysis. Although promising, these techniques are typically restricted to cortical gray matter, given that scalp-recorded EEG oscillations reflect postsynaptic potentials in cortical neurons. Thus, many of the subcortical neural regions implicated in clinical disorders (e.g., amygdala) are not particularly accessible by source localization or EEG, more generally. Researchers have also raised conceptual and technical concerns about source localization and the assumptions underlying these techniques (Luck, 2005). However, with these considerations in mind, there have been many successful implementations of source localization techniques (Pizzagalli et al., 2005).

As noted, ERPs can provide temporal resolution of 1 millisecond or better under optimal conditions. This is a thousand-fold advantage over the temporal resolution afforded by hemodynamic measures such as fMRI. Furthermore, ERPs provide a continuous measure of the neural processing of stimuli that allows researchers to examine specific neurocognitive deficits (e.g., attention, error detection, response inhibition) associated with clinical disorders. Unlike behavioral measures, ERPs provide an online measure of stimuli processing in the absence of a behavioral response. This allows researchers to covertly monitor neurocognitive processes that are outside the scope of conscious awareness. Many ERP components, such as the P3, have a test–retest reliability on the order of .8 or greater, which is comparable to many leading psychological tests (Luck, 2005). Last, as with EEG, ERP is highly cost effective, noninvasive, and resistant to movement and muscle-related artifact.

As with EEG, the primary limitation of ERP is that it provides poor spatial resolution and because of the inverse problem (Luck, 2005) we are unable to know with certainty the neuronal source configuration for a set of scalp-recorded signals. Furthermore, ERPs, like EEG, are generated by postsynaptic potentials in cortical pyramidal neurons that have a very specific spatial organization (i.e., open-field organization). Thus, ERPs represent just a portion of the brain’s electrical activity in response to a particular event or stimulus. This limitation is relevant to clinical psychological research because many of the neural regions implicated in clinical disorders (e.g., amygdala, ventral striatum) are located in subcortical portions of the brain that cannot be indexed by ERP techniques. For this reason, some caution should be used in the interpretation of ERP data and EEG data, for that matter. For instance, if an experimental manipulation has no effect on ERP profiles, we cannot be certain that it has no effect on the brain. Likewise, if two experimental conditions have the same effect on ERP, we cannot conclude that they influence identical neuronal processes. Thus, ERP is suited to answer a subset of questions, and it is important for researchers to be clear about what those questions are before conducting an ERP study.

Structural and functional neuroimaging provide researchers with powerful techniques to examine abnormalities in both brain tissue and function in mental disorders. Functional neuroimaging is able to circumvent the inverse problem encountered in neurophysiology and generate precise maps of underlying brain function. Furthermore, functional neuroimaging is able to index neuronal activation in subcortical regions such as the amygdala and ventral striatum that are typically inaccessible to neurophysiology. fMRI provides very strong spatial resolution and is most suited for examining a spatial range from millimeters to centimeters.

There are, however, some logistical challenges associated with neuroimaging. First, relative to neurophysiological techniques, neuroimaging is quite expensive and requires a significant infrastructure. Second, both PET and MRI require participants to lie in a fairly small tubelike structure, referred to as the bore. The confined nature of the bore can be restrictive for participants with claustrophobia or weight-related issues. Third, neuroimaging data are sensitive to movement-related artifact, which can make it challenging to scan individuals prone to engage in significant motor or muscle-related movement (e.g., individuals in a manic episode, individuals with Parkinson’s disease, individuals with elevated anxiety or panic, children). Fourth, compared with ERP, functional neuroimaging
techniques that index hemodynamic activity such as fMRI provide relatively slow temporal resolution. The temporal resolution of fMRI is largely limited by the fact that the hemodynamic response that it indexes does not occur until 1 to 2 seconds after neuronal firing. Thus, the constraint on the temporal resolution of fMRI is as much biological as it is related to the capabilities of MRI technology. Last, a limitation specific to PET is the invasiveness of injecting radioactive isotopes.

**LANDMARK STUDIES**

EEG is used in clinical research to examine differential profiles of neurophysiological activation across various mental disorders. A topic in mood and anxiety disorder research that has received considerable attention over the past 3 decades involves asymmetrical activity in the alpha frequency band over the frontal cortex. Investigators conducting this research often use a difference score (ln[Right] − ln[Left] alpha power) to conveniently summarize the relative activity at homologous right hemisphere and left hemisphere electrodes (Allen, Coan, & Nazarian, 2004). Given that alpha power is inversely related to cortical activity (Larson et al., 1998), this asymmetry index provides a unidimensional scale in which greater values indicate greater relative left hemispheric cortical activity and lower values indicate greater relative right hemispheric cortical activity.

The approach–withdrawal model of frontal alpha asymmetry argues that increased relative left frontal cortical activity reflects an elevated sensitivity to reward-relevant cues and a propensity to approach or engage a stimulus (Coan & Allen, 2004; Davidson, 1998). By contrast, increased relative right frontal cortical activity reflects decreased reward sensitivity and a propensity toward reduced approach-related motivation.

In line with this view, more than two dozen studies have reported that individuals with unipolar depression display increased relative right frontal cortical activity (see Thibodeau, Jorgensen, & Kim, 2006, for meta-analytic review). These data are in line with clinical and epidemiological research indicating that depression is associated with decreased sensitivity to reward-relevant cues and decreased approach motivation and goal-directed behavior (Kasch et al., 2002). Furthermore, these data have been interpreted in the context of a vulnerability–stress framework in which elevated right frontal cortical activity reflects a preexisting risk factor for depression onset (Coan & Allen, 2004). Consistent with this view, elevated right frontal cortical activity has been observed in offspring of depressed individuals who have yet to experience a depressive episode themselves (Bruder et al., 2005) and prospectively predicts onset of first depressive episode (Nusslock et al., 2011). Collectively, these data suggest that increased relative right frontal cortical activity may be a neurophysiological marker of depression risk status.

Contrary to unipolar depression, bipolar disorder has been characterized by abnormally elevated relative left frontal cortical activity (Nusslock, Young, & Damme, 2014). These data are in line with evidence that bipolar disorder is characterized by elevated approach-related affect and increased approach-related physiological activity and have been conceptualized in the context of the behavioral approach system–reward hypersensitivity model of bipolar disorder. This model proposes that risk for bipolar disorder symptoms, in particular hypomanic or manic symptoms, is characterized by a hypersensitivity to goal- and reward-relevant cues (Alloy & Abramson, 2010). This hypersensitivity can lead to an excessive increase in approach-related affect and motivation during life events involving rewards or goal striving and attainment. In the extreme, this excessive increase in approach-related affect is reflected in hypomanic and manic symptoms.

In line with the behavioral approach system hypersensitivity model, individuals both with (Harmon-Jones et al., 2008) and at risk (Harmon-Jones et al., 2002) for bipolar disorder display elevated relative left frontal cortical activity during laboratory tasks designed to elicit approach-related affect. Furthermore, among individuals with a bipolar spectrum diagnosis, elevated relative left frontal activity is a risk factor for a more severe course. Elevated left frontal activity has been associated with a greater likelihood of converting from cyclothymia or bipolar II disorder to bipolar I disorder.
Collectively, these findings suggest that risk for unipolar depression and bipolar disorder is characterized by distinct profiles of relative left frontal cortical activity. They further suggest that profiles of frontal EEG asymmetry may be used as a potential neurophysiological marker of differential risk for unipolar depression versus bipolar disorder that could be used in clinical or research settings. An advantage of EEG data is that they are cost effective and relatively noninvasive to obtain. This, coupled with research indicating that close to 60% of individuals with bipolar disorder are misdiagnosed as having unipolar depression (Hirschfeld, Lewis, & Vornik, 2003) suggests that neurophysiological indices, such as frontal EEG asymmetry, may serve as a biological marker to facilitate diagnosis and prevention strategies.

With respect to treatment-based research on frontal EEG asymmetry, an 8-week mindfulness-based stress reduction program increased relative left frontal cortical activity, and this increase mediated an increase in physical health (Davidson et al., 2003), suggesting a certain degree of plasticity or malleability in frontal EEG asymmetry. Furthermore, preliminary evidence has suggested that frontal EEG asymmetry predicts treatment responses such that individuals with elevated relative left frontal cortical activity have a more favorable response to a selective serotonin reuptake inhibitor (Bruder et al., 2001).

Research using EEG has also made important contributions to understanding sleep disturbances in clinical disorders. Given the noninvasiveness of EEG systems, neurophysiological data can be recorded while participants sleep either in their own home or in a sleep laboratory. Relevant to this research, sleep architecture refers to a specific type of EEG patterning and is typically divided into rapid eye movement (REM) and non-REM sleep (Fuller, Gooley, & Saper, 2006). Non-REM sleep is further categorized into four stages, with Stages 1 and 2 considered lighter sleep stages and Stages 3 and 4 referred to as slow-wave, delta, or deep sleep. REM sleep is characterized by rapid and random eye movements and vivid dream recall. REM latency refers to the interval of time from sleep onset to REM onset, and REM density is the ratio of REM activity to the total duration of REM sleep recorded during a night. Clinical disorders such as major depressive disorder are associated with an increase in both REM activity and REM density as well as with a decrease in both REM latency and delta-wave sleep (Kupfer, 1995). Considerable evidence exists, however, that psychotropic medications are effective in normalizing profiles of sleep architecture and that sleep architecture predicts treatment response (e.g., Held et al., 2004). Thus, EEG profiles of sleep architecture may serve as a useful neurophysiological indicator of treatment efficacy and a possible marker of treatment response.

**Event-Related Potential**

ERP research has also made important contributions to our understanding of the neurophysiology of clinical disorders such as depression, anxiety, and schizophrenia. With respect to depression, evidence is increasing that individual differences in reward sensitivity can be measured using the feedback negativity, an ERP component elicited by stimuli that indicate monetary gain versus loss (Gehring & Willoughby, 2002). In gambling tasks, the feedback negativity appears as a relative negative deflection in the waveform approximately 300 milliseconds after feedback indicating monetary gain versus loss, and it is thought to reflect early, binary evaluation of outcomes as either better or worse than expected. In line with the approach–withdrawal model’s hypothesis that depression is characterized by a reduced sensitivity to reward-relevant cues (Coan & Allen, 2004), individuals with depression display decreased amplitude of reward-related feedback negativity (Foti & Hajcak, 2009). Furthermore, lower feedback negativity amplitude prospectively predicts depression onset (Bress et al., 2013). Thus, both quantitative EEG and ERP research have suggested that reduced reward-related brain activity may represent a neurophysiological marker of depression risk status.

ERP research has also contributed to our understanding of cognitive and attentional deficits in depression and anxiety. Both depression and anxiety are associated with an elevated sensitivity to
negative stimuli, as reflected in an enhanced early ERP component (P1) to negative or threatening stimuli (Weinberg & Hajcak, 2011). Considerable behavioral and neuroimaging evidence has shown that both depression and anxiety are associated with impairment in an executive control system that might account for patients’ difficulties on cognitive tasks (e.g., Rogers et al., 2004). In line with these data, ERP research has identified neural deficits in depressed and anxious individuals during executive control tasks involving both error processing (error-related negativity) and response inhibition (N2 during response inhibition; Holmes & Pizzagalli, 2010; Weinberg, Olvet, & Hajcak, 2010).

Last, there has been considerable interest in using ERP to examine deficits in sensory gating in psychotic disorders such as schizophrenia. Sensory gating is a neurological process of filtering out redundant or unnecessary information (Lijffijt et al., 2009). Individuals with schizophrenia have a deficit in attending to stimuli and are often overloaded by attended stimuli (Gjini, Burroughs, & Boutros, 2011). The P50 ERP test of sensory gating involves measuring the amplitude of the P50 component in response to two auditory clicks separated by 500 milliseconds (Lijffijt et al., 2009; Patterson et al., 2008). In normal participants, the second P50 wave is suppressed, or “gated,” because of the inhibitory effects of the first click. Impaired suppression of the P50 wave has been identified as a vulnerability marker for sensory gating deficits in schizophrenia and is one of the most established biological traits of schizophrenia (Patterson et al., 2008).

Neuroimaging

With respect to structural MRI, more than 300 peer-reviewed articles have delineated subtle neuroanatomic abnormalities in schizophrenia (Glahn et al., 2008). These abnormalities include increased lateral ventricular size and reduced gray-matter density in a distributed network of neural regions relative to healthy controls. Meta-analytic research has indicated that these structural abnormalities may be present before the onset of the first psychotic episode and may be predictive of the development of psychosis in high-risk participants (Pantelis et al., 2003). Indeed, certain researchers are using structural MRI and associated behavioral abnormalities to identify individuals at risk for schizophrenia and implement preventive treatment strategies to manage, and ideally prevent, symptom onset (Mittal et al., 2010).

Other structural MRI research has identified volumetric reductions in prefrontal regions involved in emotion regulation and volumetric enlargement in subcortical regions involved in emotion generation (e.g., amygdala) in multiple psychiatric disorders, including depression (e.g., Frodl et al., 2002), bipolar disorder (e.g., Strakowski, Adler, & DelBello, 2002), and attention deficit hyperactivity disorder (e.g., Mostofsky et al., 2002). This work is in line with the perspective that many mental disorders involve an excess of bottom-up emotion generation and deficits in top-down prefrontal regulation of emotion (Phillips & Vieta, 2007). Last, considerable evidence has shown that multiple forms of psychological treatment can alter structural abnormalities in mental disorders and that these alterations are associated with symptom improvement (see Navari & Dazzan, 2009, for meta-analytic review). This work has implications for understanding the mechanics of treatment and the neuroplasticity or malleability of the brain.

Structural MRI may also help delineate the neurodevelopmental processes associated with clinical disorders. For example, although adults with bipolar disorder typically display enlarged amygdala volume relative to healthy controls, children with bipolar disorder often display reduced amygdala volume relative to healthy controls (Blumberg et al., 2003). This discrepancy suggests either that child bipolar disorder and adult bipolar disorder are distinct disease processes or that there are important neurodevelopmental processes associated with the course of bipolar disorder.

Structural MRI research in clinical neuroscience has focused predominantly on gray matter, which contains neural cell bodies. More recently, however, clinical neuroscientists have begun to use diffusion MRI techniques such as diffusion tensor imaging and diffusion spectrum imaging to examine white-matter pathways in clinical disorders (Vestynen et al., 2012). White matter consists mostly of glial cells and myelinated axons that serve as the
anatomical pathways through which information is transmitted between different parts of the brain. Diffusion MRI techniques use radio frequency and magnetic field gradient to measure the strength and direction of water diffusivity in brain tissue. The diffusivity of water molecules in white matter is modulated by axonal membrane thickness and diameter, the degree of myelination, and the amount of parallel organization of axons. Summary statistics of water diffusivity serve as an indicator of white-matter pathway strength and integrity. Evidence is growing that multiple clinical disorders including depression, anxiety, and bipolar disorder involve altered white-matter microstructures in neural pathways connecting the prefrontal cortex to subcortical regions involved in emotion generation such as the amygdala, which potentially underlies mood and emotional dysregulation (Carballedo et al., 2012; Versace et al., 2008).

Many significant contributions in clinical neuroscience have emerged from fMRI research. This research typically involves examining abnormalities in core brain–behavior dimensions in individuals with clinical disorders or the relationship between these dimensions and specific symptom profiles. A dimension that has received considerable attention in clinical neuroscience is threat processing or threat-related brain function. The amygdala is a neural region that is integral to threat processing and fear acquisition (Delgado et al., 2008). fMRI research has identified amygdala hyperactivity to emotional stimuli in numerous clinical disorders, including depression, bipolar disorder, anxiety disorders, and personality disorders such as borderline personality disorder (e.g., Milad et al., 2009; Schweckendiek et al., 2011). This hyperactivity is in line with research suggesting that risk for bipolar disorder, particularly hypomanic or manic symptoms, is characterized by a hypersensitivity to reward-relevant cues (e.g., Alloy & Abramson, 2010). Collectively, these findings suggest that risk for unipolar depression versus bipolar disorder may be characterized by distinct and opposite profiles of ventral striatal activity.

As with EEG, these profiles of brain activation in the striatum could be considered biological markers of differential risk for unipolar depression versus bipolar disorder that could be used to help facilitate assessment and diagnosis. Specifically, an individual with depression symptoms who displays elevated reward-related brain function, whether assessed by EEG, ERP, or fMRI, may be someone at elevated risk for conversion to bipolar disorder (mania onset). Biological indices that could aid differential diagnosis could facilitate early intervention and prevention strategies to manage symptoms.

As with structural MRI, evidence is growing that both psychosocial and pharmacological treatments alter functional brain activation as indexed by fMRI (e.g., Goldapple et al., 2004; Kennedy et al., 2001). This evidence highlights both the structural and the functional plasticity of the brain. Furthermore, preliminary fMRI evidence has indicated that pharmacological and psychosocial treatments modulate symptoms through different neurobiological pathways (Goldapple et al., 2004). This evidence has important implications for understanding the mechanism by which treatments work and may facilitate targeted treatment development.
Last, research has indicated that functional indices of brain activation before treatment can prospectively predict treatment response. Studies have suggested that elevated activation in the anterior cingulate before treatment is associated with increased treatment response (Pizzagalli, 2011). The cingulate is involved in conflict monitoring and conflict detection and, in this context, may reflect increased recognition of the need for treatment and enhanced engagement in the therapeutic process.

MAJOR ACCOMPLISHMENTS

Advancements in neurophysiology and neuroimaging over the past 3 decades have made important contributions to our understanding of the pathophysiology of mental disorders. Indeed, there is a new initiative put forth by the National Institute of Mental Health, called the Research Domain Criteria (RDoC) initiative, to develop new ways of classifying mental disorders on the basis of core brain–behavior dimensions identified through neurophysiology and neuroimaging (Insel et al., 2010). Rather than start with a definition based on clinical observations and seek its neurophysiological or neurobiological underpinnings, RDoC begins with our current understanding of physiological mechanisms and aims to link these mechanisms to clinical phenomena. RDoC may eventually generate a classification system grounded in contemporary neuroscience.

Given that many of the advancements in neurophysiology predated the development of neuroimaging, neurophysiology research set the foundation for biological models of mental illness. EEG technologies have made important contributions to understanding differential profiles of cortical activation across different mental disorders as well as abnormalities in sleep architecture. ERP has been highly effective in examining abnormalities in psychological processes associated with mental disorders with strong temporal resolution.

It was with the breakthrough in neuroimaging technologies, however, that researchers were truly able to start peering into the brain to identify the neuronal generators or neural sources of abnormal psychological processes in mental disorder. MRI identified enlarged ventricles in schizophrenia (Pantelis et al., 2003) and attenuated prefrontal volume and enlarged amygdala volume across multiple forms of mental disorders (Frodl et al., 2002; Mostofsky et al., 2002; Phillips & Vieta, 2007; Strakowski et al., 2002). Furthermore, new developments in both structural and functional connectivity have allowed clinical researchers to move beyond a static model of the human brain to examine abnormalities in how neural regions communicate with each other, as opposed to examining neural regions in isolation.

Three important implications for mental health research and practice have emerged from this work. First, when integrated with sophisticated psychological models of mental disorder, biological models have the potential to generate a powerful understanding of the mechanics of mental disorder. By taking a multimodal perspective (combining multiple neurophysiological and neuroimaging techniques), researchers can examine these mechanics at multiple levels of analysis, incorporating information about neurophysiology, brain structure, brain function, and neurotransmission.

Second, biological models of mental disorder can generate biological markers that can facilitate clinical assessment and differential diagnosis. Take, for example, bipolar disorder, which has been ranked as one of the six most debilitating of all noncommunicable disorders in the world (Ayuso-Mateos, 2006). Despite the severity of this illness, bipolar disorder is frequently misdiagnosed or there is a lengthy time period from the point of illness onset to correct diagnosis. Delays ranging from 6 to 10 years or longer have been reported before individuals with bipolar disorder receive an accurate diagnosis and appropriate treatment (Ghaemi, Boiman, & Goodwin, 2000). Data from the National Depressive and Manic Depressive Association survey indicated that close to 70% of respondents with bipolar disorder were initially misdiagnosed (Hirschfeld et al., 2003), with the most frequent misdiagnosis being unipolar depression (60%). Those who were misdiagnosed consulted a mean of four physicians before receiving the correct diagnosis, and more than one third waited 10 years or more before receiving an accurate diagnosis. The misdiagnosis of bipolar disorder not
only delays administration of appropriate treatment but may have a deleterious effect on the course of bipolar disorder, given research suggesting that antidepressant medications typically used for treating unipolar depression may be a risk factor for switching into hypomanic or manic episodes among individuals at risk for bipolar disorder (Ghaemi et al., 2003).

Finally, biological models of mental disorder have important implications for the development and refinement of both pharmacological and psychosocial treatments. At the pharmacological level, biological models can help identify neurotransmitters and receptors that may be useful targets for medications. At the psychosocial level, researchers and clinicians can draw on biological models to develop strategies to help manage the psychobiological instability underlying mental symptoms. Take, for example, interpersonal and social rhythm therapy, a psychosocial intervention for bipolar disorder (Frank, 1999). The social rhythm component of this therapy emerged directly from animal and human research on the brain’s circadian clock system (including the suprachiasmatic nucleus), as well as clinical research indicating that this system is highly dysregulated in bipolar individuals (Levenson, Nusslock, & Frank, 2013). Interpersonal and social rhythm therapy integrates interpersonal psychotherapy for unipolar depression with behavioral and environmental strategies to help stabilize these irregularities in the circadian clock and sleep–wake cycle among bipolar individuals to manage bipolar symptoms.

**FUTURE DIRECTIONS**

An important future direction for EEG research relates to how researchers most commonly process and analyze EEG-related data. The spectral analyses typically used in quantitative EEG research to compute power estimates for resting data average across a series of 1-minute epochs or time windows (Allen et al., 2004). Task-related spectral analyses frequently involve 6- to 7-second epochs. Thus, despite measuring electrical activity of neuronal assemblies on the order of milliseconds, the spectral analyses typically used in clinical research provide surprisingly poor temporal resolution. In fact, the temporal resolution afforded by these analytic strategies is equivalent to the limited temporal resolution of fMRI.

Furthermore, the EEG data from which ERPs are derived in ERP studies have received relatively little attention and typically go unused. To address these issues, researchers have begun using time–frequency analyses that take full advantage of the millisecond temporal resolution that EEG data are able to provide. These analyses stem from developments in basic and systems neuroscience that have suggested that neural oscillations and their synchronization represent important mechanisms for interneuronal communication and binding information that is processed in distributed brain regions. Examining neural synchrony has important implications for understanding perceptual, cognitive, and affective processes.

Likewise, examining abnormalities in neural synchrony may have implications for understanding problems in organizing and coordinating neuronal information in clinical disorders. For example, Roach and Mathalon (2008) reported that prominent gamma-phase locking at frontal electrodes between 20 and 60 milliseconds after the onset of a tone was significantly reduced in individuals with schizophrenia. This finding suggests that early evoked gamma band response to auditory stimuli is deficiently synchronized in schizophrenia. These types of analyses not only have implications for understanding deficits in the synchronization of information in clinical disorders, but also take full advantage of the temporal resolution afforded by EEG-related data. Time–frequency analyses of EEG data are an important topic for future research.

With respect to neuroimaging, fMRI research has historically examined activation in one brain region in isolation from its relationship to other brain regions. This localization of function approach, however, is limited by the fact that no brain region exists in isolation. An active area of neuroimaging research involves examination of the functional connectivity between spatially remote areas in the brain. Connectivity analyses allow researchers to characterize the relationships between distinct neural regions during cognitive, affective, or motoric
tasks or from spontaneous activity during rest. Connectivity analyses have important implications for understanding the etiology of clinical disorders because clinical disorders may be characterized as much by abnormalities in the communication between brain regions as they are by abnormalities in any one specific area of the brain. Future research is needed to test this hypothesis, and connectivity analyses will likely play an important role in clinical neuroscience for the foreseeable future. Likewise, advancements in diffusion tensor imaging analyses will allow researchers to complement analyses of functional connectivity with analyses of structural connectivity.

It is clear that the strengths and limitations of neurophysiology and neuroimaging techniques are often complementary. That is, the strength of one technique is frequently the limitation of another, and vice versa. Accordingly, in the future, researchers should move toward a multimodal approach in which multiple assessment tools (e.g., EEG, ERP, fMRI) are used in the same study, which would allow them to assess psychopathology at multiple levels of analysis along the continuum of spatial and temporal resolution.

Complementing methodological and technical advancements are also important questions regarding the extent to which these techniques can be used in a clinical setting to facilitate clinical assessment and diagnosis. I am optimistic that this will occur in the future and that the use of these markers can result in more accurate and timely diagnoses. With that said, however, significant challenges to using biological markers in a clinical setting will need to be addressed. The first is pragmatic. Neurophysiology and neuroimaging are expensive and technically demanding. Thus, there are a limited number of settings in which it would be feasible to use these techniques in psychiatric assessment, and most of these settings are larger metropolitan cities. Another challenge relates to the precision with which neurophysiology and neuroimaging data can classify individual patients and predict individual behavior. The majority of studies reviewed in this chapter involved mean-level differences between groups in reward-related neural activation and do not characterize individual patients. Furthermore, if we were to plot the individual data points from these studies there would likely be considerable overlap in the distribution of neural activation across individuals with and without mental disorder.

A final important future direction is incorporating neuroscience and biological models of mental disorder into diagnostic classification systems. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) is agnostic on the etiology of mental disorder in defining its diagnostic criteria and instead focuses on the reliable measurement of self-reported symptoms. There is a growing chorus that recognizes that its diagnoses likely do not map onto brain structure or function in a meaningful or precise manner (Insel et al., 2010). The National Institute of Mental Health RDoC initiative is designed to help remedy this issue by developing a taxonomy of mental disorders that is grounded in neuroscience. The vision is that this will help develop treatments that directly target the mechanism underlying symptoms. It will be years before such a brain-based diagnostic system is validated, if ever. Yet, regardless of the time needed to create such a system, it is clear that neurophysiological and neuroimaging techniques will play a large role in the future of clinical psychology.

**References**


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