CHAPTER 7

Methodological Approaches to Studying the Human Amygdala

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This chapter focuses on the multiple methods that have been used to elucidate the structure and function of the human amygdala. Progress in understanding the amygdala has been hindered by the difficulties in scientifically probing this small subcortical region buried deep within the medial temporal lobe. Since the mid-1990s, there has been a resurgent interest in the neurobiology of emotion, motivation, and social cognition; this interest can be considered an "affective revolution" in psychology and neuroscience. The amygdala has emerged at the crossroads of these endeavors, in part due to improved neuroscientific techniques and experimental paradigms that, for the first time, have permitted cogent assessments of its role in human behavior. However, each of the standard methods is fraught with technical, data-analytic, and interpretational challenges, some of which are exacerbated for the amygdala relative to other brain areas. We first present a brief historical overview of research on the human amygdala, and then critique modern approaches to its study. As will be evident, converging evidence across methodologies is essential for advancing knowledge about this fascinating almond-shaped area of the forebrain.

HISTORY

The Amygdala Concept

There remains considerable debate in the field regarding what the amygdala is, including its structural and functional boundaries. Historically, the term "amygdala" has referred to a group of roughly a dozen nuclei in the ventromedial temporal lobe (see Figure 7.1), originally identified and described by Burdach (1819–1822). The idea that the amygdala was a unified structural entity remained relatively uncontested until recently, when Swanson and Petrovich (1998) argued that the amygdala is better described as four functional units. More specifically, they provide ontological evidence that there are distinct functional subunits of the traditional amygdala: accessory olfactory, main olfactory, autonomic, and frontotemporal cortical. Moreover, they argue against the concept of the amygdala as either a structural or functional unit; their argument is primarily based on evidence from rat studies indicating disparate functions of amygdalar nuclei, such as the role of the central nucleus in controlling motor and autonomic function, and the lateral and basolateral nuclei's modulation of cognitive processes in the temporal and frontal lobes. Whether these functional divisions map onto the human amygdala remains

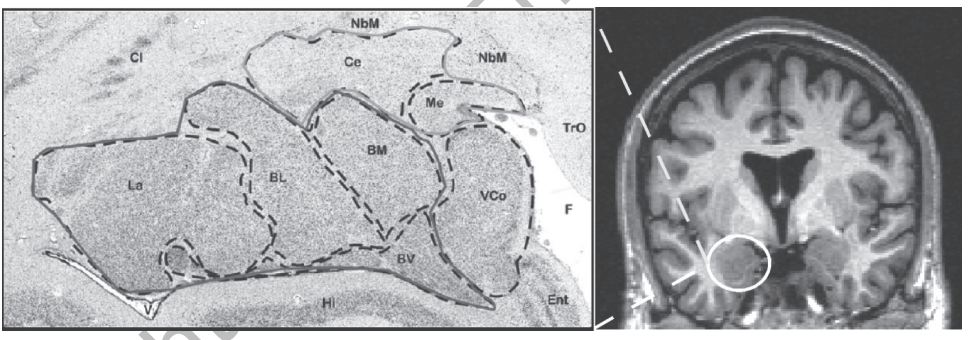

FIGURE 7.1. Anatomy of the human amygdala. *Left:* Cytoarchitecture in a coronal section obtained from postmortem tissue cut through the middle of the amygdala reveals the location of several of its subnuclei, including the basolateral nucleus (BL), basomedial nucleus (BM), basoventral nucleus (BV), central nucleus (Ce), lateral nucleus (La), medial nucleus (Me), and ventral cortical nucleus (VCo). Surrounding structures include the claustrum (Cl), entorhinal cortex (Ent), endorhinal sulcus (F), hippocampus (Hi), nucleus basalis of Meynert (NbM), optic tract (TrO), and lateral ventricle (V). The basolateral group is outlined in dark gray, and the centromedial group is outlined in light gray. From Amunts et al. (2005). Copyright 2005 by Springer Science and Business Media. Reprinted by permission. *Right:* An *in vivo* coronal section obtained from a T1-weighted structural MRI scan at approximately the same level as in the left panel. Note the lack of resolution of subnuclei in the image. From LaBar and Phelps (2005). Copyright 2005 by the American Psychological Association. Reprinted by permission.

unknown. In contrast, Aggleton and Saunders (2000) argue that although there is considerable heterogeneity in the projections of each amygdala nucleus, the disparate nuclei contain multiple intraconnections that do in fact support the notion of a coherent whole. To complicate the amygdala concept further, the term "extended amygdala" was introduced to refer to a scattered set of nuclei in the basal forebrain and ventral striatum that appear to constitute a rostral extension of the central and medial nuclei (De Olmos & Heimer, 1999). Although the structural boundaries of the amygdala remain debatable, it is well accepted that the amygdala (1) receives input from many cortical and subcortical structures; (2) serves an important role in integrating and evaluating interoceptive and exteroceptive sensory stimuli, and thus in permitting an individual to ascribe emotional meaning to events; (3) coordinates adaptive behavioral responses to emotion elicitors; and (4) modulates cognitive processing in other brain regions. The amygdala is the most densely interconnected region of the primate forebrain (Young, Flude, Hellawell, & Ellis, 1994), so its scope of influence must be wide-ranging. Further understanding of its functional and structural subdivisions is critical to guide future experimental questions and targeted hypotheses, particularly as probes of subnuclei become tractable.

Intracranial Stimulation

In the 1940s and 1950s, studies of patients with intractable epilepsy and severe behavioral disturbances provided the first *in vivo* look at the human amygdala. The earliest electrical stimulation studies were conducted by Walter Penfield and his colleagues, to assess electrocortical responses and seizure activity in patients with medial temporal lobe epilepsy. Stimulation studies and observations of patients during endogenous seizures indicated a role for the amygdala in visual hallucinations, emotional experiences, feelings of *déjà vu*, and memory recall (e.g., Feindel & Penfield, 1952; Penfield, 1958). Penfield noted that when medial temporal regions were stimulated, patients experienced vivid memories that often had strong emotional content or personal relevance. Moreover, in his discussion of phenomena preceding temporal lobe seizures, many patients reported auras or were observed to engage in automatisms that preceded their typical attacks. Chapman and colleagues (1954) noticed that during presurgical evaluation of medial temporal lobe epilepsy, four out of five patients reported sudden-onset fear and anxiety related to stimulation. Changes in heart rate and blood pressure were also observed, providing early human evidence regarding the amygdala's role in engaging autonomic effectors during emotional states.

In the 1970s and 1980s, investigations by Eric Halgren, Pierre Gloor, and colleagues extended and improved upon the initial studies of Penfield and others by employing more precise methodology and by providing details of the experiential phenomena elicited during stimulation and seizure activity (for reviews, see Gloor, 1992; Halgren, 1992). These researchers were more care-

ful to distinguish effects arising from the amygdala relative to other medial temporal lobe structures, and noted when widespread afterdischarges accompanied the electrical activity. They found that sensations elicited by electrical activity in the amygdala almost always had emotional content, with fear being the most common emotion reported. A particularly striking example of fear elicitation is provided in the following anecdote:

> A 19-year-old woman had seizures that started with a feeling of intense fear followed by loss of consciousness and automatism in which she acted as if she were in the grips of the most intense terror. She let out a terrifying scream and her facial expression and bodily gestures were those of someone having a horrifying experience. She was able to recall her fear, but had no recollection of acting it out in the later part of her seizures. (Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982, p. 132)

Although the memories elicited were vivid, they almost always had a dreamlike quality, and it was sometimes difficult to determine whether the events were real or reconstructed interpretations of experiences arising from the electrical activity. For example, one patient reported the following:

> It was one of those feelings, a feeling of being someplace very far away. . . . It recalls to mind the day in the country with Tracy and brother Jamie. It was very spooky, but it was so far away. It was out by the sea and high up on a cliff, a feeling as if I were going to fall. It was a scary feeling. We are there, a world within that world, all of us were there. It is so real, yet so artificial. (quoted in Gloor et al., 1982, p. 135)

However, the researchers also found that repeated stimulation of the same site did not elicit identical emotions, memories, or hallucinations within or across patients. Thus, although such observations provided a fascinating and unique opportunity to characterize the phenomenology associated with amygdala stimulation in individual epileptic patients, the functional organization of this structure was nonetheless difficult to discern from these explorations.

Amygdalotomy as Psychosurgery

Rat and macaque studies have shown that the anterior cortical nucleus and periamygloid cortex receive direct projections from the main and accessory olfactory bulbs (Aggleton, 2000). An early set of studies (Chitanondh, 1966) provided evidence of the role of the human amygdala in olfactory processing. Stereotaxic amygdalotomy was performed on seven patients, all with olfactory hallucinations or other behavioral dysfunction. In this surgical series, the amygdala was located via ventriculography of the temporal horn of the lateral ventricle. All patients showed short-term improvement in olfactory symptoms. Despite its early promise as a treatment for intractable seizures, olfactory hal-

lucinations, and hyperaggression, additional studies lacked appropriate control and adequate sample sizes to permit interpretation (e.g., Narabayashi & Uno, 1966). Similarly, although the use of stereotaxic amygdalotomy for medically intractable psychiatric problems such as hyperaggression has had promising results (Kim, Lee, & Choi, 2002), these studies are hampered by inadequate controls, and long-term follow-up studies are sparse and report inconsistent results. Moreover, although the advent of magnetic resonance imaging (MRI) has enhanced the spatial accuracy of amygdalotomy, the need for surgical intervention has decreased as additional medications and alternative treatments have been developed.

Critique of Early Findings

Although these early studies provided important clues about the role of the amygdala in various perceptual, cognitive, and emotional processes, some limitations are noteworthy. First, most descriptions of experiential phenomena were vague and lacked standardized probes or tests of emotional function. Second, the role of adjacent cortical structures should be considered, as surgical approaches often included the periamygdaloid cortex and hippocampus, and intracranial stimulation and seizure activity were often accompanied by afterdischarges that spread widely in the temporal lobe (Gloor, Halgren, and their colleagues attempted to clarify this issue in their analyses). Third, because these reports were limited primarily to patients with preexisting clinical conditions such as epilepsy or psychosis, the generalizability of the findings to the healthy brain is uncertain.

This literature is also notable for heterogeneity in patient selection, lesion or seizure focus locations, and techniques used. For instance, the duration and intensity of intracranial electrical stimulation or surgical approach varied across treatment sites (see also Parrent & Lozano, 2000). Stereotaxic surgery was also somewhat limited by the localization in individual patients, given the inherent variation in brain anatomy, particularly for a structure as small as the amygdala. Before the application of MRI to lesion assessment in the 1980s, there was only crude verification of the location and extent of the lesions/recording sites, and there was little standardization in terms of clinical evaluation and long-term follow-up. Furthermore, the fiber tracts that connect frontal and temporal cortices lie just lateral to the amygdala proper, and their section probably contributed to some of the behavioral effects (for a discussion of this issue in monkeys, see Meunier, Bachevalier, Murray, Malkova, & Mishkin, 1999). Finally, one must always interpret the results within the emotional context of the experimental setting. For example, Halgren, Walter, Cherlow, and Crandall (1978) noted that personality could influence the kinds of emotions elicited by brain stimulation, with individuals who were most fearful of the intracranial recording procedure being the most likely to experience fear in response to stimulation. In other words, fear may have been

more readily elicited in some individuals in the experimental setting. These methodological issues are important to consider in interpreting these early results, particularly with respect to the coupling of function and brain structure in clinical–pathological correlations. Despite these concerns, there are good reasons why MRI-guided stereotaxic surgery and invasive procedures can contribute to research progress concerning the amygdala, and depth electrode monitoring in epileptic patients remains the primary way to probe its electrical activity directly.

MODERN TECHNIQUES

Electrophysiology

Intracranial Recording in Presurgical Epileptic Patients

Today, clinical assessment of seizure focus activity in patients with medically refractory temporal lobe epilepsy often includes depth electrode recording from the amygdala, although anterior temporal lobe resections are now less frequent because of the improved efficacy of anticonvulsant medications. Recordings are usually done bilaterally, with valuable information obtained from the hemisphere that is contralateral to the seizure focus (although in the case of some seizures, the activity spreads to the other hemisphere, which can exhibit additional sclerosis). A recent study (Naccache et al., 2005) obtained local field potential recordings in the amygdala during presurgical evaluation for neurosurgery in patients with seizure epileptogenesis located away from the amygdala. Data from single-photon emission computed tomography (SPECT) and electroencephalography (EEG) confirmed the structural integrity of the amygdalae in these patients. Results indicated that subliminally presented emotional words activated the amygdala prior to supraliminal processing. Another study has provided precise information regarding the temporal processing of emotional information, indicating that fear is initially processed in the amygdala prior to disgust and then spreads to cortical regions (Krolak-Salmon, Henaff, Vighetto, Bertrand, & Mauguière, 2004). Thus intracranial recording remains a useful methodology that provides information regarding the temporal engagement of the amygdala during emotional processing. Imaging studies have also generated hypotheses that require more specific spatiotemporal resolution, and depth electrode studies can answer some of these questions, albeit in small, select patient populations.

Scalp EEG

In healthy participants, scalp recordings of the ongoing EEG and its demarcation into event-locked time averages (event-related potentials, or ERPs) are promising for identifying how emotion influences different oscillatory

frequency bands in the EEG signal and for detailing the temporal profile of emotional effects on a time scale of tens of milliseconds. However, electrical signals emanating from the amygdala do not propagate readily, if at all, to the scalp. The small size and deep location of the amygdala, combined with the lack of an orderly laminar arrangement of its pyramidal neurons (which results in a relatively closed-field electrical configuration), does not permit the spatial integration and volume conduction necessary to observe electrical signals at the scalp. Moreover, emotional effects on ERPs tend to be quite broad both spatially and temporally, making spatial localization and source modeling difficult. For instance, encoding emotional relative to neutral words induces a broadly distributed positive shift in ERP activity over a long latency window, from about 450 to 1000 msec (Dillon, Cooper, Grent-'t-Jong, Woldorff, & LaBar, 2006). However, experimental manipulations that emphasize processing of a given ERP component can yield more specific findings, and downstream effects of emotion (and presumably amygdala activity) on cognition can be observed from ERPs elicited from the cortex. As an example, studies of covert attention have shown how facial expressions alter spatial orienting to subsequent targets, including enhancements of early ERP components linked to visual cortex processing (e.g., Fichtenholtz, Hopfinger, Graham, Detwiler, & LaBar, 2007; Pourtois, Grandjean, Sander, & Vuilleumier, 2004). Nonetheless, such indirect effects restrict interpretation in any attempt to combine scalp EEG and functional neuroimaging measures of emotion, given their differential sensitivity in detecting amygdala function.

Lesion Studies

Although amygdalotomy as psychosurgery is rarely performed today to treat psychiatric disorders, observations of patients with organic lesions to the amygdala provide key insights into the necessity of this brain region for socioemotional and motivational functions. The major disadvantage of this method in humans is that it is not possible to control the size, location, or extent of a lesion. An exception is the use of *en bloc* resection to treat medically refractory epilepsy, in which the surgeon uses a similar approach to excise the amygdala, hippocampus, and surrounding structures unilaterally (Spencer, Spencer, Mattson, Williamson, & Novelly, 1984). However, adjacent structures are always included in the resection to prevent recurrence of epilepsy, and there remains individual variability in the extent of cortex removed. Because of the distribution of blood supply to this region, and the nature of the syndromes that target the medial temporal lobe, it is extremely rare to observe amygdala damage in isolation (see Figure 7.2).

We remark here on a few additional limitations of neuropsychological studies of emotion and amygdala dysfunction. First, premorbid emotional/motivational status and personality characteristics are rarely quantified other than by retrospective reports from a patient or caregiver. Thus it is difficult

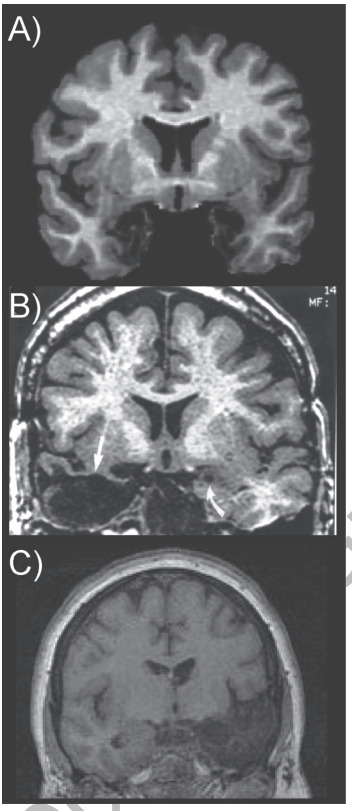

FIGURE 7.2. Human amygdala pathology associated with various disease processes in individual patients. (A) A case of Urbach–Wiethe syndrome, in which the bilateral amygdala was targeted relatively selectively, with some damage to the entorhinal cortex. From Adolphs, Tranel, and Buchanan (2005). Copyright 2005 by the Nature Publishing Group. Reprinted by permission. (B) A case of right anteromedial temporal lobe resection performed to treat medically refractory epilepsy, with selective gliosis in the left amygdala. From Phelps et al. (1998). Copyright 1998 by the Taylor & Francis Group. Reprinted by permission. (C) A case of herpes simplex encephalitis that produced widespread damage to the left temporal lobe. From Graham, Devinsky, and LaBar (2006). Copyright 2006 by Elsevier. Reprinted by permission.

to know the extent to which the onset of acquired brain damage promoted behavioral changes relative to the patient's existing baseline. Second, changes in socioemotional behavior and motivation may be secondary to lifestyle changes necessitated by the insult or disease process, rather than a direct consequence of brain damage. For instance, patients may become depressed after strokes because of their functional limitations; in this case, the depression is not directly associated with stroke-related damage to specific brain regions per se. Third, due to the extensive reciprocal interconnections of limbic fore-

brain structures, damage to one area, such as the amygdala, may affect the functioning of other network components, such as the anterior cingulate or orbitofrontal cortex (this phenomenon is called "diaschisis"; see Markowitsch et al., 1994). Fourth, because disease processes may be congenital or progressive, there may be long-term reorganization of brain function, and patients may compensate by using alternate strategies to solve experimental tasks. For example, amygdala-lesioned patients may use featural displacements as a perceptual heuristic to make judgments of facial affect, rather than processing the face in a holistic manner (Graham, Devinsky, & LaBar, 2006, 2007). Finally, it is difficult to determine emotional influences on select stages of information processing in patients with preexisting damage (e.g., to distinguish the effects of amygdala damage on the encoding vs. retrieval stages of emotional memory processing). These caveats notwithstanding, patients who have sustained amygdala damage have provided researchers with a wealth of valuable information. We limit our discussion here to a few neurological syndromes, although we recognize that the amygdala is implicated broadly in many neuropsychiatric disorders.

Klüver–Bucy Syndrome

The Klüver–Bucy syndrome was popularized following the publications by Klüver and Bucy (1937, 1939) that demonstrated a taming effect and inappropriate emotional reactions to stimuli in monkeys with bilateral temporal lobe lesions. The monkeys engaged in socially and motivationally inappropriate behaviors, such as hyperorality and hypersexuality, and they appeared to lack the ability to evaluate the significance of stimuli by sight alone (this lack was called "psychic blindness" by Klüver and Bucy, but today it may be considered a type of "motivational visual agnosia"). The Klüver–Bucy syndrome is rarely seen in humans, particularly in its full profile, but when it is, it generally follows amygdala damage combined with additional damage to the frontal lobes or hypothalamus. Although rare, features of Klüver–Bucy syndrome can be observed consequent to multiple etiologies, including subdural hematoma (Yoneoka et al., 2004), herpes simplex encephalitis (Bakchine, Chain, & Lhermitte, 1989; Marlowe, Mancall, & Thomas, 1975), left anterior temporal resection (Ghika-Schmid, Assal, De Tribolet, & Regli, 1995), right temporal resection (Bates & Sturman, 1995), and early Pick's disease (Cummings & Duchen, 1981). Klüver–Bucy syndrome demonstrates a difficulty with drawing strong conclusions from studies of brain-damaged patients: There is considerable variability in patient characteristics, etiology, and premorbid genetic and environmental influences that cannot be controlled. That being said, any similarities that result among patients despite these characterological differences may indicate robust findings. In these patients, the brain area that was consistently implicated was the amygdala, although the additional brain damage necessary to observe such effects implicates a broader disconnection syndrome.

Urbach–Wiethe Syndrome (Lipoid Proteinosis)

Urbach–Wiethe syndrome is a rare, autosomal recessive, multisystemic disease linked to chromosome 1q21. It is caused by mutations in the extracellular matrix protein 1 gene, and is characterized by hardening of the skin, mucosa, and viscera; hyaline deposition; and occasionally calcifications of medial temporal lobe structures (Hamada et al., 2002). In very few cases, calcifications are limited to the amygdala proper or to the amygdala plus periamygdaloid cortex. Despite an early paper detailing rage attacks and neurologic involvement in the disorder (Newton, Rosenberg, Lampert, & O'Brien, 1971), Urbach–Wiethe syndrome and its potential contribution to the study of the amygdala had remained overlooked until Tranel and Hyman's (1990) original report of patient S. M., who sustained calcifications largely restricted to the amygdala bilaterally. Subsequent studies of S. M. and similar patients have sparked interest in studying emotional functions, in much the same way that descriptions of amnesic patient H. M. bolstered memory research in the mid-20th century. For instance, Adolphs, Tranel, Damasio, and Damasio (1994) reported that patient S. M. was unable to identify facial expressions of fear, despite being able to name and identify other facial expressions. This seminal study, in conjunction with a contemporaneous report of two other patients (Markowitsch et al., 1994), provided evidence that the amygdala is essential for the evaluation of threat signals and emotional memory—themes in affective neuroscience research that have been extensively elaborated ever since.

Epilepsy

Patients who have undergone selective unilateral amygdalohippocampectomy or resection of the anteromedial temporal lobe for intractable epilepsy constitute the vast majority of patients in modern lesion studies. Although such patients provide a relatively homogeneous sample (compared to, say, those with Klüver–Bucy syndrome), the epilepsy and subsequent surgical procedure have a unilateral focus, which often yields only subtle behavioral deficits. Phelps and colleagues (1998) described an epileptic patient (S. P.) who received a unilateral right anteromedial temporal lobe resection, and who had additional gliosis that was circumscribed to the left amygdala. This patient, like patient S. M., has provided important insights into the effects of bilateral amygdala damage on emotional functions without significant comorbid impairments in other cognitive domains. S. P. exhibits deficits on tests of facial expression processing (Adolphs & Tranel, 1999; Graham et al., 2007), fear conditioning (Phelps et al., 1998), arousal-mediated memory consolidation (Phelps et al., 1998), and emotional modulation of the attentional blink paradigm (Anderson & Phelps, 2001), although her other socioemotional functions are relatively well preserved (see Anderson & Phelps, 1998, 2000; Graham et al., 2006; Phelps, Cannistraci, & Cunningham, 2003; Phelps, LaBar, & Spencer, 1997; Phelps et al., 1998).

Inducing Temporary Brain Inactivation by Transcranial Magnetic Stimulation

Given the inherent limitations in studying patients with organic brain damage, researchers have moved to inducing temporary inactivation of structures in the healthy human brain via transcranial magnetic stimulation (TMS). A major advantage of this approach is that it can be used to validate findings from patient populations about the role of specific brain regions in cognitive and emotional functioning. TMS can be applied at specific time points relative to an ongoing task to isolate a given information-processing stage, and the research subjects can serve as their own unstimulated controls. TMS has also been applied to prefrontal regions as a potential treatment for depression (e.g., George, Wassermann, & Post, 1996). Notable in these treatment studies of depressed patients is evidence that amygdalar functioning is affected, albeit indirectly. Specifically, some studies that have assessed changes in regional cerebral blood flow after repetitive TMS in the left prefrontal cortex describe changes in the left amygdala (Speer et al., 2000). However, a primary limitation of TMS is that the surface coils used to generate the magnetization pulses do not have sufficient penetration to reach the subcortical location of the amygdala. As surface coil technology improves to target deeper structures, it may be possible to temporarily inactivate the healthy amygdala with TMS, but due to the small size of this structure, it is unlikely to be selectively implicated. Because this methodology is still in its infancy, safety and practical concerns, such as optimal frequency and duration of stimulation, remain open issues (e.g., Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006).

Neuroimaging Techniques

Structural Imaging: Volumetry

Volume estimates of the amygdala by means of structural MRI have been used for over two decades to correlate changes in structure with altered emotional processing in neuropsychiatric disorders. High-resolution, T1-weighted, 3-D spoiled gradient recalled acquisition images with a resolution of 1.0–1.5 mm^3 are typically needed, with excellent contrast between gray and white matter in order to obtain accurate volumetric estimates. Quantifying interrater reliability is critical to validate the methodology used, given the difficulties in identifying amygdalar boundaries. Because volume changes provide only crude insight into function and are sensitive to both glial cell and neuronal atrophy, this method is often used in conjunction with other behavioral tests to determine correlations between volume changes and functional impairment.

Using computer-mouse-driven software programs to draw borders manually on individual brain slices is preferred over using automated segmentation protocols based on normalized brain atlases, although quantitative comparisons between these procedures are warranted. Borders that are most difficult to identify include the amygdalohippocampal transition area ventrocaudally,

the amygdalostriatal transition area dorsorostrally, the terminus of the anterior amygdaloid area, and the anteromedial transition to entorhinal cortex, where the angular bundle becomes indistinct (Doty et al., 2008). Whereas differentiation of medial–lateral boundaries is facilitated in the coronal plane, assessment of the amygdalohippocampal transition area is facilitated in the axial plane with simultaneous co-planar visualization and verification (Convit et al., 1999). Landmarks such as the optic chiasm can facilitate definition of anterior borders, but should be used with caution and only after standard realignment prior to tracing. Inclusion of adjacent structures generally overestimates the volume of the amygdala in studies of lesser quality. A meta-analytic review by Brierley, Shaw, and David (2002) provides mean amygdala volume estimates (±95% confidence interval) of 1726.7 ± 35.1 mm^3 in the left hemisphere and 1691.7 ± 37.2 mm^3 in the right hemisphere of the adult brain.

Functional Imaging: Positron Emission Tomography

Initial activation studies using positron emission tomography (PET) have provided important insights into emotional functions of the amygdala, such as its role in facial expression processing (Morris et al., 1996) and emotional memory (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999). Recording concurrent physiological and verbal responses is more straightforward with this technique than with functional MRI (fMRI). However, analysis of typical PET data requires a degree of spatial smoothing that is larger than the extent of the amygdala itself, thereby recruiting brain signals from adjacent regions such as the hippocampus and entorhinal cortex. In addition, the temporal parameters of PET studies are limited by the half-life of the radioisotope injected into the participant (e.g., data are typically accumulated across 45- to 60-sec time periods with ^{15}O), as well as the limited repeatability of the experiment within subjects, due to ethical considerations concerning cumulative exposure to radioactive substances (George et al., 2000). For studies of sustained mood effects, the temporal scale of PET activity may be particularly useful (e.g., Schneider et al., 1995), but for investigations of emotional influences with shorter durations, trial blocking is required. In addition to untoward effects on cognitive functions (e.g., changing cognitive "set"), blocking trials by emotional category confounds emotional processing with anticipatory emotions and mood induction, and PET may miss transient amygdala activation that habituates over repeated trials (e.g., Breiter et al., 1996; Wright et al., 2001). Recent advances in PET technology have improved upon some of these issues, but this technique has been largely supplanted in cognitive activation studies by fMRI because of fMRI's superior spatial and temporal resolution, as well as other advantages (cost, noninvasiveness, etc.). PET nonetheless remains a powerful tool for examining emotional influences on resting-state cerebral blood flow and for pharmacological investigations, as radioisotopes can be designed that bind to specific receptor molecules to provide a unique

view into the anatomical distribution of neurotransmitter systems in healthy and psychiatric populations.

Event-Related fMRI

Event-related fMRI has emerged in the last decade as a primary tool for neuroimaging of amygdala function, although it is not without its challenges. A first challenge relates to the sensitivity of this technique to movement artifacts, which hinders the ability to study the generation of emotional expression/prosody, startle reflexes, and individuals who can't lie still for extended periods of time (which may be more problematic in some psychiatric disorders). There are also technical difficulties with setting up concurrent physiological recording in the MRI environment (e.g., heating of electrodes by the magnet, radiofrequency interference from the scanner pulses, blowout of frontal lobe signal with concurrent eye tracking and facial electromyography, attenuation of physiological signals prior to amplification in an external control room), but these issues have been largely resolved in recent years. Although the spatial resolution of fMRI is better than that of PET, it can be difficult to distinguish amygdala responses from those of adjacent structures when standard 8-mm smoothing kernels are used, particularly for tasks where nearby structures (such as the hippocampus and entorhinal cortex) make complementary and/or interactive contributions (e.g., Dolcos, LaBar, & Cabeza, 2004, 2005). The signal-averaging requirements of event-related fMRI can be problematic in terms of sustaining emotional processes over repeated exposures to the same stimulus, which can mask a transient amygdala response to novel stimuli and changes in emotional salience. Furthermore, the profile of the hemodynamic response function in the amygdala sometimes does not conform to a standard gamma function often used to model cortical responses, especially when depressed individuals are studied (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002) or when healthy participants are asked to elaborate the emotional meaning of the stimulus (Schaefer et al., 2002). Therefore, extracting the raw percentage of signal change over points in time after stimulus onset without reference to a standard hemodynamic template often leads to improved measurements.

Perhaps the most troubling issue relates to the problem of overcoming susceptibility artifact to obtain reliable hemodynamic signals from the amygdala. Because the amygdala is bounded medially by sinuses and ventrocaudolaterally by the lateral ventricle, it is situated in a region characterized by magnetic-susceptibility-induced signal loss. As illustrated in Figure 7.3, quantitative analysis of signal-to-noise ratios (SNRs) in the vicinity of the amygdala shows that the signal losses contribute to intersubject and interhemispheric variability in amygdala activation during emotional processing (LaBar, Gitelman, Mesulam, & Parrish, 2001). These issues are more difficult to resolve at high field strengths, and are particularly critical for voxel-wise statistical analyses that require precise spatial registration of signal changes across subjects.

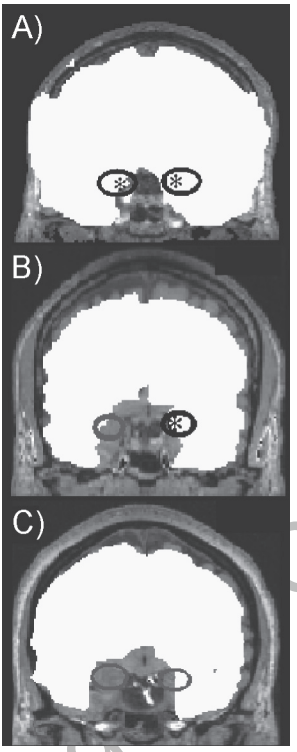

FIGURE 7.3. Quantification of fMRI signal loss in the vicinity of the amygdala for three normal adults. Computer simulations determined the minimum signal-to-noise ratios (SNRs) needed to observe reliable activation for an fMRI study that compared the processing of emotional versus neutral pictures. Location of peak amygdala activity for the *t*-test contrast (emotional > neutral) is indicated by asterisks and is overlaid onto SNR masks indicating brain regions that have sufficient sensitivity to detect a 1% signal change with $\alpha = .05$ for the study. Amygdalae with sufficient SNRs are outlined in black; amygdalae located in signal voids are outlined in gray. Bilateral activity was found in an individual with no signal voids (A); unilateral activity was found in an individual with an asymmetric signal void pattern (B); and no activity was found in an individual with large signal voids (C). Results highlight the importance of considering individual differences in fMRI-related susceptibility artifacts when investigators are interpreting neuroimaging results from the human amygdala. From LaBar, Gitelman, Mesulam, and Parrish (2001). Copyright 2001 by Lippincott Williams & Wilkins. Reprinted by permission.

Specializing shimming and pulse sequences, including double-shot echoplanar and inward spiral protocols, can improve SNRs in the amygdala even at high field strengths (Posse et al., 2003; Wang, McCarthy, Song, & LaBar, 2005). Although current methods do not allow resolution of individual amygdaloid subnuclei, it is possible to segregate signals grossly into anterior–posterior, medial–lateral, and dorsal–ventral subdivisions (e.g., Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Dolcos et al., 2004; Whalen et al., 1998). More detailed parsing of functional subdivisions will require high-resolution imaging techniques that also recover susceptibility artifact and are combined with analysis tools that do not rely on spatial smoothing.

Further complicating the interpretation of fMRI amygdala responses to emotional stimuli is the role of individual differences. Amygdala activity has been shown to vary across individuals according to many personality, social, and genetic factors. These include gender (Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Canli, Desmond, Zhao, & Gabrieli, 2002a), age (Mather et al., 2004), extraversion (Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002b), implicit measures of racial bias (Phelps et al., 2000), trait anxiety (Etkin et al., 2004), motivational regulatory focus (Cunningham, Raye, & Johnson, 2005), and genetic variation in serotonin receptor function (Hariri et al., 2002). Standard group-averaged analytic approaches typically neglect to account for such variables, which may reduce amygdala activity overall and contribute to the lack of replication across population samples. Other state effects also have an impact on amygdala activation, including effects of hunger (LaBar, Gitelman, Parrish, et al., 2001), state anxiety (Bishop, Duncan, & Lawrence, 2004), and mood (Wang, LaBar, & McCarthy, 2006) on the processing of visual stimuli that have emotional or motivational salience. Comprehensive characterization of personality, genomic, and demographic characteristics, as well as mood and other state variables of the participants, is becoming critical; statistical approaches that explicitly include assessment of individual differences are also urgently needed.

THE IMPORTANCE OF BEHAVIORAL ASSESSMENT AND CONCURRENT PSYCHOPHYSIOLOGY

Even with the most powerful magnets, the most selective lesions, and direct electrophysiological recordings from epileptic patients, our understanding of human amygdala function will not advance without adequate behavioral probes and psychophysiological measures. Emotion is a complex construct that consists of several underlying dimensions or categories (which vary according to different theories) and engages several stages of information processing, including evaluation, experience, and expression. Systematic characterization and experimental manipulation of these components of emotional processing are critical to infer mechanisms. Moreover, the amygdala not only is engaged during emotional processing, but also contributes to a variety of other social

and motivational functions, as described throughout this book. Therefore, mere observation of amygdala signal changes during an fMRI experiment is insufficient to prove that emotion has been elicited or is contributing to task performance. Such "reverse inference" problems have been discussed with respect to other brain areas (see Poldrack & Wagner, 2004), and are especially germane when the emotional manipulation is not independently validated by concurrent psychophysiology, self-report measures, or behavioral assessments.

Although emotion research has benefited by development of standardized stimulus databases, MRI-compatible psychophysiological recording systems, and self-report batteries, efforts to link fMRI- or intracranial ERP-related amygdala activation with such data are inherently correlational in nature. As such, causality cannot be inferred, and the necessity of the structure's involvement is unknown. For this reason, obtaining converging evidence across multiple methods, including studies of patients with selective brain lesions, is of the utmost importance. A similar difficulty is that researchers must develop and rely on particular paradigms, which have been designed to be sensitive but may or may not be specific to the brain structure in question. Multiple paradigms—including fear conditioning; processing and memory for emotional auditory, olfactory, and visual stimuli; and viewing faces and other socially relevant stimuli—have been implemented to tap amygdala functioning, but also activate other brain regions due to the distributed nature of neural processing. Characterizing the amygdala's interactions with these areas and using neuroimaging observations to guide future behavioral task development would facilitate more sensitive *and* specific means to probe this enigmatic brain region.

WHAT WE THINK

Initial studies of the human amygdala pointed to its specific role in fear processing. Although some have taken the view that the amygdala is a dedicated fear module in the brain (Öhman & Mineka, 2001), the past decade has revealed an impressive diversity of emotional, motivational, and social-cognitive functions subserved by this constellation of nuclei. Moreover, its responses to specific emotional elicitors and emotion categories have been shown to change according to different experimental manipulations (e.g., Adams, Gordon, Baird, Ambady, & Kleck, 2003; Anderson et al., 2003; Schaefer et al., 2002), and patients with amygdala damage can compensate under some circumstances for their loss of fear recognition (Adolphs, Tranel, & Buchanan, 2005; Graham et al., 2006, 2007). Factors that may contribute to observing potentiated amygdala responses to fear stimuli in neuroimaging studies include (1) the scary context of the experimental setting (loud noises, dark confining chamber, etc.), which may yield a match between the stimulus presented and the context and/or a relative ease of eliciting fear in this context (see the chapter text for a similar discussion with regard to intracranial monitoring); (2) the use of blocked designs in which repeated presentations of threat signals induce potentially

confounding influences of prolonged fearful states and anticipatory anxiety; and (3) the difficulty of reliably inducing highly arousing positive affect. Although there is no question that the amygdala is important for fear learning and for detecting threats in the environment, its role can also be characterized as a salience detector, whereby it monitors and signals events of most importance to the organism's state at any particular point in time (see also Sander, Grafman, & Zalla, 2003). For instance, we have observed increased amygdala activity to food stimuli when participants are in a hungry relative to a satiated state (LaBar, Gitelman, Parrish, et al., 2001); to sad images when participants are in a sad relative to a happy mood state (Wang et al., 2006); to both positively and negatively arousing pictures that are subsequently remembered, relative to those that are forgotten (Dolcos et al., 2004); and to changes in emotional salience during different phases of fear conditioning training (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). How the amygdala combines and weights goal-directed and stimulus-driven information to determine what is important to signal from one moment to the next remains an interesting and unresolved question.

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