Functional Neuroimaging Studies of the Amygdala in Depression

Paul J. Whalen, Lisa M. Shin,† Leah H. Somerville,* Ashly A. McLean,* and Hackjin Kim**

Here we review human functional neuroimaging studies suggesting that the amygdala may play a key role in depression. We begin by reviewing animal and human data concerning the function of the amygdala. We then compare these results with those of neuroimaging studies of normal human amygdala function. Finally, we discuss functional neuroimaging studies of the amygdala in depression in light of the animal and human data. We conclude that the initial studies of this disorder provide evidence of amygdala involvement. Furthermore, we suggest that the scope of the amygdala's involvement may go beyond its well-known role in fear to its more subtle and generalized role in modulating moment-to-moment vigilance levels.

The youth of neuroimaging as a technique to explore human brain function is at once the most exciting and frustrating aspect of our field. As the number of applications of neuroimaging expands, the quantity of studies within each area of interest remains relatively small. Although it will be difficult to integrate the initial findings collected to date concerning amygdala function in depression, we offer the following review in the hope that it may help in organizing future efforts.

The emergence of functional neuroimaging technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has allowed for the study of the intact, normal amygdala in humans. Functional neuroimaging studies of the normal human amygdala benefit from a relatively large amount of data that has been accumulated in animal models. Studies of the human amygdala in depression also benefit from the animal models literature, as well as from an immense amount of clinical and behavioral data. In the following text we will (1) introduce the proposed role of the amygdala in emotional response, (2) review neuroimaging studies of normal human amygdala function, and (3) review and discuss the initial functional neuroimaging studies of the amygdala in depression.

The Animal Amygdala

One of physiological psychology's most reproducible findings is that the amygdala is a necessary component of a brain system involved in the acquisition and expression of learned fear responses.[1] Pavlovian fear-conditioning procedures in animal subjects implicate the amygdala in responses to aversive events believed to produce fear (ie, unconditioned stimuli), as well as to stimuli that predict these events (ie, conditioned stimuli).[2,3] Importantly, animal studies documenting learning-related changes in response to such events provide evidence of transient[4] as well as lasting changes[5-8] in amygdala-response properties.[9]

The amygdala is composed of distinct subnuclei, including the lateral, basal, accessory basal, central, medial, and cortical nuclei.[10,11] Although some research emphasizes how these subnuclei can operate as a functional unit, other research emphasizes the distinct contributions the subnuclei might make to behavior. For example, a model that has proven useful presents the lateral nucleus of the amygdala as a sensory input nucleus; the basal nuclei of the amygdala as convergent processing areas, and the central nuclei as an output nucleus.[3,11] Because the subnuclei can be shown to be functionally different, many researchers prefer the term *amygdaloid complex*.[10]

Much evidence indicates that the amygdaloid complex represents a system involved in both the

*From the *Departments of Psychiatry and Psychology, W.M. Keck Laboratory for Functional Brain Imaging and Behavior, University of Wisconsin, Madison, WI; and the †Department of Psychology, Tufts University, Medford, MA.*

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Address reprint requests to Paul J. Whalen, PhD, University of Wisconsin, 1500 Highland Ave, Waisman Bldg T227, Madison, WI 53705. E-mail: pwhalen@facstaff.wisc.edu

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expression and acquisition of conditioned fear.[3,9] The lateral and basolateral nuclei of the amygdala receive highly processed sensory information.[12] In turn, these nuclei project to the central nuclei, which then projects to (1) hypothalamic and brain stem target areas that directly mediate autonomic and somatic responsivity,[10,13] and (2) neuromodulatory centers (eg, cholinergic, dopaminergic, serotonergic, and noradrenergic neurons) that can potentiate cortical responsivity (ie, vigilance), and have widespread influences on thalamic transmission.[9] Thus, the afferent and efferent anatomy of the amygdala places it in an ideal position for the ready monitoring of the environment and subsequent behavioral modification.[3,14-16]

The Human Amygdala

Most of what we know about the human amygdala has been derived from the study of the compromised human brain. That is, fruitful avenues of inquiry have been provided by studies using direct electrical stimulation of the amygdala in patients with epilepsy and by assessing perception and recognition abilities in patients with lesions of the amygdala.

Gloor[17] presents stimulation studies of the amygdala in human subjects with epilepsy that provide data consistent with the aversive conditioning literature in animals. For example, stimulation of the amygdala in these awake subjects produces recall of feelings and past events that are usually negatively valenced. These subjects often report that the event they are remembering makes them afraid.

Behavioral data in subjects with lesions of the amygdala are also consistent with the role of this structure in aversive conditioning. Subjects with bilateral lesions of the amygdala show a deficit in processing fearful facial expressions, whereas their processing of other facial expressions is less consistently compromised.[18] Although valence assessments of fearful faces can be intact, the arousal rating of this expression is most consistently compromised.[19] Also, these patients view even the most threatening faces as trustworthy and approachable.[20] Finally, the ability to process the fearful expression can be lost whereas the ability to experience the feeling of fear is relatively intact.[21] Effects such as these appear most consistently when the amygdala insult occurs early in life.[22-25] These studies of the compromised human brain have provided important data that allow for comparison with the vast animal literature. But the ability to document amygdala responses in the intact, human brain is equally important.

Using Functional Neuroimaging to Assess the Role of the Amygdala in Fear and Vigilance in the Normal Human

Both the limited spatial and temporal resolution level of neuroimaging studies, as well as the fact that they are based on an indirect measure of neuronal activation (namely, blood flow/oxygenation), make direct comparison with manipulations in animal subjects challenging. Despite these limitations, neuroimaging studies of the normal human amygdala have already shown promise in informing the animal research that inspired them. For example, neuroimaging studies of Pavlovian conditioning have documented that when previously neutral stimuli are paired with an aversive outcome (eg, shock, loud noise), greater activation is observed in the amygdala.[26,27] Taking a lead from the lesion data presented earlier, initial neuroimaging studies documented that the amygdala signal is indeed greater in response to presented pictures of fearful facial expressions when compared with either happy expressions[28,29] or neutral expressions.[30-32]

It is clear already that, just as in the animal model, the presentation of negatively valenced, biologically relevant, associative stimuli to human subjects is a robust way to activate this system. What remains to be established is the relationship between amygdala responsivity to presented stimuli and the subjective state that the subject reports experiencing. Interestingly, mood state induction alone does not appear to be sufficient to produce amygdala activation.[33,34] The studies that have been most successful in observing amygdala activation during the induction of emotional state have used presentations of external stimuli (eg, facial expressions)[35-40] along with mood state-induction techniques (eg, script-driven imagery). These data emphasize a primary role for the amygdala in the encoding of stimulus contingencies and leave its role in the generation of strong emotional states still an open question.[33,34] That is, although amygdala responsivity to presented stimuli can correlate with one's reported state, this does not necessitate that amygdala activity is the neural substrate for such subjective feelings.

A related but separate point to consider is the relationship between amygdala response to presented stimuli and the subject's overall trait affective style. For example, in normal human subjects, the magnitude of amygdala response to presented stimuli correlates with their dispositional pessimism[41] and neuroticism scores.[42] Again, the activation of the amygdala here is seen in response to external stimulus presentations.

Such data have obvious relevance to the study of psychopathologic disorders in which hyperresponsivity to negative stimuli (or hyporesponsivity to positive stimuli) and mood disturbance are key symptoms. A key question to keep in mind will be, if abnormalities in amygdala function are observed in depression, are they related to the depressed mood state per se, or do they reflect hyperresponsivity to environmental stimuli that then results in a global mood disturbance? This point can be made more clear if we first consider some alternative interpretations of amygdala function that may elucidate both its role in normal emotion and its potential aberration in depression.

The Amygdala and Vigilance

Although a strong state of fear will no doubt produce amygdala activation, strong activation of this system also appears evident during states of lower arousal. Numerous studies suggest that sensory stimuli showing some predictive validity in terms of biologic import (eg, possible threat) appear sufficient to engage the amygdala, even though these stimuli may not be highly arousing (eg, pictures of facial expressions). More than affect itself, amygdala activation in response to subtle emotional stimuli, such as photographs of facial expressions, might represent affective information processing. This hypothesis is supported by the fact that the amygdala is responsive to (1) masked facial expressions of fear that subjects report not having seen, (2) fearful faces even when contrasted with another negatively valenced, equally arousing, facial expression (namely, anger),[43] and (3) in animals, neurons in the central nuclei amygdala that show changes in firing rates to a tone that predicts a shock, also show changes in firing rates that correlate with spontaneous fluctuations in cortical neuronal excitability as measured by cortical electroencephalography in animals.[44,45] This is seen even in experimentally naive animals. These data suggest that the amygdala may be especially involved in increasing vigilance by lowering neuronal thresholds in sensory systems.[9,34]

As we begin to think about a possible role for the amygdala in depression, it will be important to consider this role for the amygdala in vigilance and information processing in parallel with its better known function in emotion, more specifically fear. The usefulness of invoking a process such as vigilance is that it might speak to a greater portion of our daily experience.[46,47] The model presented here emphasizes the amygdala's role as a processor of information and associative contingencies. Even though reported mood and dispositional trait affect might correlate with the responsivity of this system, the activity of the amygdala need not be the neural substrate of these feelings and/or trait styles. In this light, abnormalities of the amygdaloid complex in depression would not necessarily be a record of the subject's negative state or overall trait affective style, but may reflect heightened on-line processing of negatively valenced, predictive stimuli. Depressed mood would then depend on the interaction of the amygdala with other brain systems, and would not be related necessarily to amygdala activity per se.

Preparing for Neuroimaging Studies of Patient Groups

The fact that lesions of the human amygdala were shown to impair the ability to process the facial expression of fear captured the imagination of psychiatric neuroimagers. If one was going to devise neuroimaging probes of the amygdala for later use in patient populations, such as anxiety and depression, then it would be important to select a stimulus of interest that would activate the amygdala, but that also would be tolerable by patient groups. Standardized pictures of facial expressions are an example of a stimulus set that is proving to serve these purposes nicely. As noted earlier, in normal adult subjects, fearful facial expressions have been shown to activate the amygdala to a greater degree than neutral[30-32] and happy facial expressions.[28,29]

The Depressed Amygdala

In this section, we review functional imaging studies that have sought a priori to assess amygdala abnormalities in depression. We do not attempt to integrate this information with the larger structural and neurochemical literature here because

such integrated reviews exist in other articles in this issue and elsewhere.[48-50]

Two study strategies that investigators have used to elucidate a possible role for the amygdala in depressed subjects compared with a control group are (1) studies of resting baseline blood flow or metabolism in the amygdala and (2) cognitive activation studies of amygdala response to stimulus presentations superimposed on a normalized baseline. The former involve PET studies whereas the latter consist of both PET and fMRI studies. Subject information for the studies reviewed here can be found in Table 1.

Resting Baseline Blood Flow or Metabolism in the Depressed Amygdala

Drevets et al[51] published an early report on differences in baseline blood flow levels in the amygdala in a specific group of subjects with unipolar depression, namely familial pure depressive disorder. Although studying this select group of depressed subjects might limit generalization of the findings to other depression subtype groups, it has the more compelling strength that the data collected will be homogeneous and, thus, relatively interpretable. This seminal study[51] documented abnormally elevated, resting cerebral blood flow in the amygdala that persisted through remission. This finding has been replicated,[52,53] is probably not caused by the stress of the scanning environment because it has been documented in sleeping subjects,[54] and can even be shown to predict symptom relapse.[55] Recently, this same finding has been extended to a group of subjects with bipolar disorder who were currently in a major depressive episode.[52] As pointed out by Drevets,[53] this abnormal activity may be related to both the severity of major depressive episodes and susceptibility to their recurrence. Drevets et al[51] and Abercrombie et al[56] also reported that elevated activity in the amygdala correlated positively with scores of depression severity. Although these 2 studies differed in the laterality of their findings, a recent replication by Drevets et al[52] is consistent with the earlier study by Abercrombie et al[56] (see Table 1).

These points resonate with our earlier discussion of amygdala function. Studies that have sought to provoke a negative mood state in healthy subjects provide the strongest evidence of amygdala involvement if these mood inductions are combined with the presence of negatively valenced stimuli in the external environment. The amygdala's primary role is that of a processor of biologically relevant predictive information. Perhaps in depression, external stimuli and circumstances that do not elevate activity in the normal amygdala have such an effect on the depressed amygdala. Hyperactivity or responsivity in the amygdala will put more global brain systems on alert, leading to a host of symptoms seen in depression and comorbid anxiety. Dougherty and Rauch[48] have referred to this possibility as *limbic shift*.

Cognitive Activation Studies of Response to Stimulus Presentations in the Depressed Amygdala

Imaging studies of depressed subjects have used the presentation of fearful facial expressions to specifically target the amygdala. Yurgelun-Todd et al[57] showed amygdala hyperresponsivity in adults with bipolar disorder to the presentation of fearful facial expressions. This finding is interesting because subjects showed this effect though many were not necessarily in the midst of a depressive episode (see Table 1).

Thomas et al[58] showed that though anxious children showed exaggerated amygdala response to fearful facial expressions, depressed children showed a blunted response. In addition to this difference across diagnosis, this study also documented an interesting laterality effect. The exaggerated response in anxious children was a right amygdala response whereas the blunting effect in the depressed children was a left amygdala response. Though preliminary, these findings are of interest because they parallel findings in adults showing greater right-hemisphere responsivity in anxiety and blunted left-hemisphere responsivity in depression.[59-61]

Thus far, the studies we have mentioned involved subjects with depression who were fully aware of what they had been presented with or how they happened to feel at a particular moment. But surely our brains are inundated with countless stimuli that we do not consciously perceive.[62] Sheline et al[63] used backward masking of facial expression as a technique to examine amygdala function in depressed subjects who reported being unaware of these expressions. Both behav-

Table 1. Functional Neuroimaging Studies of Depression With an A Priori Focus on the Amygdala

Study	*Scan*	*n*	*Diagnosis*	*Gender*	*Mean Age*	*Medication*	*Other Measures*	*Finding*
Drevets, et al. (1992)	PET–$H_2{}^{15}O$	13	FDPP (DSM-IIIR)	6 male 7 female	36	None for at least 3 weeks	HAM-D Mean = 27	Elevated resting blood flow in left amygdala in depression, remained elevated in remission; Positively correlated with HAM-D score
		10	In remission from FPDD	3 male 7 female	33			
		33	Control	13 male 20 female	30			
Abercrombie, et al. (1998)	PET–^{18}FDG	Sample 1:				None	BDI Mean = 33 (sample 1) Mean = 29 (sample 2)	Resting metabolism in right amygdala positively correlated with PANAS-neg score
		10	MDD (DSM-IV)	4 male 6 female	31			
		11	Control	5 male 6 female	38		PANAS-neg Mean = 28 (sample 1) Mean = 23 (sample 2)	
		Sample 2:						
		17	MDD (DSM-IV)	8 male 9 female	34			
		13	Control	6 male 7 female	34			
Yurgelun-Todd, et al. (2000)	fMRI–1.5T	14	BD (DSM-IV)	7 male 7 female	31	86% taking mood stabilizers,92% taking antipsychotics	HAM-D 24 (n = 1); 10-15 (n = 6); 4-8 (n = 7); YMRS 20-29 (n = 3); 10-17 (n = 5); 2-8 (n = 6)	Left amygdala activity greater than controls to fearful facial expressions
		10	Control	5 male 5 female	Unknown			
Sheline, et al. (2001)	fMRI–1.5T	11	MDD (DSM-IV)	5 male 6 female	40	None for at least 4 weeks	HAM-D > 17	Greater left amygdala activity to masked fearful facial expressions remits w/treatment
		11	Control	5 male 6 female	39			
Thomas, et al. (2001)	fMRI–1.5T	12	GAD (n = 11) and/or panic (n = 2) (DSM-IV)	7 male 5 female	12	None for at least 2 weeks	SCARED	Right amygdala hyperresponsive in anxiety; Left amygdala hyporesponsive in depression in response to fearful facial expressions
		12	Control	7 male 5 female	12			
Drevets, et al. (2002)	PET–^{18}FDG	5	MDD (DSM-IV)	5 female	12			
		12	FPDD (DSM-IV)	3 male 9 female	36	None for at least 2 weeks Exception: n = 4 in remitted BD-R group taking mood stabilizers	Plasma Cortisol HAM-D FPDD = 31 (mean) BD-D = 23 (mean) BD-R = 3 (mean) DSD = 24 (mean) STAI-S ATQ	Elevated resting left amygdala metabolism in FPDD and BD-D, remained elevated in remission, normalized with drug therapy. In FPDD and DSD, HAM-D score positively correlated with right amygdala metabolism. In FPDD, DSD & BD-D, higher cortisol concentration positively correlated with left amygdala metabolism.
		7	BD-D (DSM-IV)	3 male 4 female	37			
		8	BD-R (DSM-IV)	1 male 7 female	33			
		9	DSD (DSM-IV)	2 male 7 female	40			
		12	Control	4 male 8 female	35			

Abbreviations: ATQ, Automatic Thought Questionnaire; BD, Bipolar Disorder; BD-D, Bipolar Disorder in a depressive episode; BD-R, Bipolar Disorder remitted; BDI, Beck Depression Inventory; DSD, Depression Spectrum Disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; FPDD, Familial Pure Depressive Disorder; GAD, Generalized Anxiety Disorder; HAM-D, Hamilton Rating Scale for Depression; MDD, Major Depressive Disorder; PANAS-neg, Positive and Negative Affect Scale, negative affect schedule (trait); PET, positron emission tomography; SCARED, Screen for Child Anxiety Related Emotional Disorders; STAI-S, Spielberger State-Trait Anxiety Inventory (state scale).

ioral and neuroimaging studies in normal and anxious subjects[29,64-66] offer evidence that increases in amygdala activity can be observed to negatively valenced facial expressions, even when subjects report not having seen these expressions. These data speak to the automaticity of the amygdala and the importance of these social signals for predicting biologically relevant outcomes. Indeed, Sheline et al[63] showed that similar to subjects with an anxiety disorder,[66] depressed subjects show an exaggerated response to masked fearful stimuli that they report not having seen. Convincingly, this effect normalizes with antidepressant treatment.

This finding suggests that depressed subjects can show changes in neural systems consistent with an aberration of preattentive processing. Alternatively, the increased amygdala response seen in depression may reflect comorbid anxiety present in these subjects. But this is far from clear, and it is just as likely that exaggerated amygdala response in anxiety is related to the presence of depression. Indeed, in a study showing exaggerated amygdala response to masked faces in anxiety (posttraumatic stress disorder),[66] some subjects had comorbid depression. Arguing against the possibility that it was their depression that accounted for the observed effect, the exaggerated amygdala response in these subjects was correlated with posttraumatic stress disorder symptom severity scores, but not with depression scores. Finally, in the first neuroimaging study of children with anxiety and depression, amygdala hyperresponsivity to fearful facialexpressions was shown to be related to both anxiety and depression scores.[58] Clearly, the complicated relationship between these highly comorbid conditions and amygdala reactivity will be a challenge to disentangle. Future studies of depression might aim to study groups of depressed patients with and without anxiety to tease apart these most interesting possibilities.

Considering the Depressed Amygdala's Future

Just as in studies of baseline brain activity,[51-53] future cognitive activation studies in depression might aim to dissect the effect of the depressed state versus its remission. A behavioral study has shown that the more negative ratings that depressed subjects give to ambiguous schematic faces resolve with remission.[67] This finding may be consistent with the fact that exaggerated amygdala response to masked fearful faces returns to normal levels with drug treatment.[63] Drevets et al[52] have begun to compare depressed subjects in remission with and without medication. They have shown that elevated resting amygdala activity persists in remission but normalizes with drug therapy. Our field awaits similar studies using cognitive activation paradigms.

With such a small number of functional imaging studies available to us across different disorders, the role of the amygdala remains less than clear. Most of the bipolar subjects in the Yurgelun-Todd et al[57] study showing exaggerated amygdala response to fearful facial expressions were not depressed at the time of study (see Table 1), suggesting a trait-like effect in bipolar disorder. Indeed, Drevets et al[52] have documented that bipolar patients in remission continue to show elevated resting amygdala metabolism. An interesting question for future research will be to assess the relationship of elevated resting measures in the amygdala and hyperresponsivity of this brain region to external stimulus presentations.

Another area to keep a close eye on will be differences between studies of children and adults. Adult depressed patients show exaggerated amygdala response to fearful faces,[57] whereas depressed children exhibit a blunted amygdala response to these same stimuli.[58] Amygdala response to stimulus presentations does not correlate with depression scores in adults[66] but correlates with measures of both depression and anxiety in children.[58] Although these discrepancies may be related to interesting developmental differences, they also could be the result of the differing disorders involved or to the medication status of the subjects of study.

Finally, laterality will no doubt play an important part in understanding the role of the amygdala in mood disorders and anxiety. Thomas et al[58] showed in a single study that depression may involve a left amygdala abnormality while anxiety may compromise the right amygdala. Indeed, this pattern of laterality can be observed across a small number of neuroimaging studies of depression and anxiety done to date.[51,57,58,63,66]

Thus, as exciting as these preliminary data are, they make it clear that understanding the role of the amygdala in depression will require studies that are explicitly designed to answer the follow-

ing outstanding questions: (1) What is the relationship between abnormally elevated amygdala blood flow in the resting state and exaggerated amygdala responsivity to stimulus presentations? (2) What is the relationship between abnormally elevated amygdala blood flow in the resting state and a current versus remitted major depressive episode? (3) Are functional abnormalities in the amygdala different across different mood disorders? (4) How can we tease apart the role of the amygdala in anxiety and depression given the high comorbidity of these disorders? (5) How is depression in children related to depression in adults with respect to amygdala abnormalities?

Our hope is that the model of amygdala function presented here might instruct the design and interpretation of future studies. If the subnuclei of the amygdaloid complex have different roles in the process of vigilance, the detection of biologically relevant contingencies, and the eventual outcome of fear, then surely this will impact our interpretation of neuroimaging results in depression. Although it is possible that amygdala hyperresponsivity is the neural substrate of negative mood in depression, it may also represent hypervigilance to the presence of potentially negative contingencies in the environment. This would then lead to hyperactivation of distributed neural systems that are the neural substrate of negative mood itself. These ideas call for future neuroimaging studies that provide the necessary spatial resolution to assess differential function across the amygdaloid complex. Ultimately, we hope such designs elucidate the questions presented earlier concerning the neural substrates of trait and state effects and the disentangling of comorbid depression and anxiety.

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