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The amygdala as a target for behavior surgery

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Abstract

The amygdala was a popular target during the era of psychosurgery, specifically for the treatment of intractable aggression. This mesiotemporal structure was thought to primarily mediate fear and anger. However, recent evidence suggests that the amygdala is part of a complex network that mediates the formation of a larger repertoire of positive and negative emotions. Dysfunctions within the network or the amygdala itself can lead to various mental illnesses. In those cases, deep brain stimulation (DBS) applied focally may treat the symptoms. This review presents data supporting the potential therapeutic role of DBS of the amygdala in the treatment of anxiety disorders, addiction, and mood disorders. The success of DBS for psychiatric conditions will likely depend on our ability to precisely determine the optimal target for a specific case.

Key Words: Addiction, amygdala, deep brain stimulation, depression, post-traumatic stress disorder

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INTRODUCTION

The current treatment of psychiatric illnesses depends largely on the pharmacological agents that correct neurotransmiter imbalances, in combination with psychotherapy that uses the mind to heal the disease. Deep brain stimulation (DBS) is currently under investigation to offer another strategy of treatment for otherwise refractory psychiatric illnesses.[18,33,34] The success of DBS for the treatment of various psychiatric disorders will depend primarily on our understanding of the anatomy and the pathophysiology of the underlying condition.[40] This knowledge would help translate psychiatric illnesses in "neurosurgical terms," and thus it would allow us to identify and intervene in the areas of the brain most responsible for the dysfunction. For instance, a patient with neuropathic pain may have a problem originating from a nerve, a root, or the central nervous system. A clinician combines information from the examination, history, and additional studies to determine which part of the network is primarily dysfunctional. This knowledge then guides the treatment. Psychiatric illnesses are more likely to result from dysfunctional circuits accomplishing abstract functions rather than the malfunction of a specific cerebral region. Such a circuit could be dysfunctional because of an aberrant component, a combination of aberrant components, or even miscommunication between components. The symptoms could be very similar despite different underlying pathologies.

In this review, we present the amygdala as a component of a larger network. The role of the amygdala is portrayed through some of the disorders where it plays a pivotal role. The central aim of the article is to show the importance of the interconnections within the network. An aberrant network component will manifest into various disorders depending on the "weight" of its specific connections

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and on the activity of its neighboring components. As such the amygdala can be the source of various mental illnesses when giving more or less weight to certain afferents and efferents.

ANATOMY AND FUNCTION

The amygdala is a nucleus located in the mesiotemporal lobe bilaterally with an approximate volume of 1700 mm^3.[7] It is composed of multiple sub-nuclei including the lateral nucleus, the basal nucleus, and the central nucleus. The basal nucleus can be further subdivided into a basomedial, a basolateral, and a basoventral division.[3] The lateral nucleus is the main sensory input to the amygdala; it possesses dense reciprocal connections to higher-level sensory cortical regions.[21] The central nucleus is the main output from the amygdala for the physiological expression of emotions.[23] Therefore, the central nucleus has multiple connections with the hypothalamus and the brainstem. The basal nucleus receives multiple connections from the lateral nucleus and sends out efferents to the central nucleus,[1] thus acting as a relay nucleus within the amygdala. The basal nucleus forms a connectivity loop with the medial prefrontal cortex (mPFC).[14] This reciprocal connection is thought to be important for the cortical (i.e. top-down) control of the amygdala.

The function of the amygdala is to link sensory inputs with psychological and physiological processes.[39] For instance, the sight of palatable food raises the blood pressure of primates, a response that disappears after destructive lesions to the amygdala.[8] The amygdala also plays a critical role in fear conditioning where it links innocuous stimuli with aversive ones through initial pairing of the stimuli.[31,43] By linking specific autonomic and psychological processes to sensory stimuli, the amygdala establishes the basis of emotional responses to events and situations. In essence, the amygdala helps assigning positive or negative emotions to a given context. In turn, the emotional response improves the subject's readiness to the situation. Because of its basic function, the amygdala influences a vast repertoire of human behaviors and experiences. This influence is carried out through a network of interconnections with critical neural circuits including the memory system, the motivational system, the sympathetic and parasympathetic systems, and higher-order sensory cortices [Figure 1].

ROLE OF THE AMYGDALA IN ANXIETY DISORDERS

The critical role of the amygdala in fear conditioning is well established.[31,43] In this paradigm, a noxious stimulus (unconditioned stimulus) is paired with an innocuous stimulus (conditioned stimulus). Once fear conditioning has been established, the conditioned stimulus presented

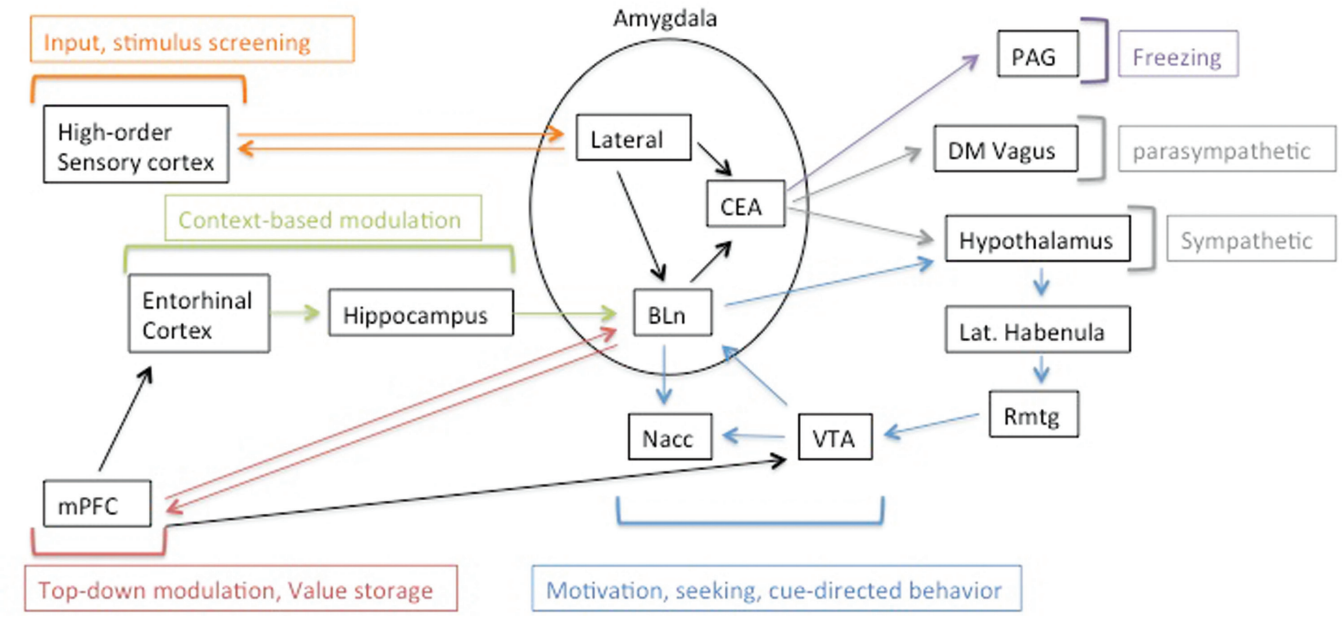

Figure 1: The amygdala and its network. This figure shows selected afferents and efferents of the amygdala. Functional groups are color coded. The amygdala screens stimuli received from high-order sensory cortices (orange pathway). The response of the amygdala to the incoming stimulus is determined by the activity of several modulation pathways. These pathways include a context- and memory-based modulation (green pathway), a top-down modulation (red pathway), and a reward-based modulation (blue pathway). BLn: Basolateral nucleus, CEA: Central nucleus of the amygdala, DM Vagus: Dorsal motor nucleus of the Vagus, Lat. Habenual: Lateral habenula, mPFC: medial prefrontal cortex, Nacc: Nucleus accumbens, PAG: Periacqueductal gray area, Rmtg: Rostromedial tegmental nucleus, VTA: Ventral tegmental area

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by itself produces the same behavioral response as the unconditioned stimulus. The neural mechanisms involved in fear conditioning are thought to be the basis of certain anxiety disorders such as post-traumatic stress disorder (PTSD). PTSD is a syndrome characterized by flashbacks, hyperarousal, and avoidance that occur as a result of the exposure to a life-threatening event.

A number of recent discoveries have highlighted the role of the amygdala in the pathophysiology of PTSD. In several studies, PTSD patients were exposed to cues (images or sounds) reminiscent of their trauma and then scanned with functional magnetic resonance imaging (fMRI), positron emission tomography computerized tomography (PET CT), or single-photon emission computerized tomography (SPECT). Using this paradigm, the amygdala of PTSD patients was shown to be "overactive" compared to normal controls.[13,47] A meta-analysis of these functional neuroimaging studies confirmed the finding and further located the focus of hyperactivity in the basal portion of the amygdala.[10] The intensity of BOLD signals on fMRI and regional blood flow on CT PET in the amygdala correlated with the severity of PTSD symptoms.[4,51] In addition, patients who responded to cognitive-behavioral therapy by an improvement of their PTSD symptoms displayed a reduction in pre- to post-treatment amygdala hyperactivity.[11,45]

Functional neuroimaging studies can rarely establish a causal effect between areas of activity and the underlying condition. However, lesioning studies are more successful in this regard. Koenigs *et al.*[28] studied veterans in the Vietnam Head Injury Study (VHIS) to see if there was a correlation between the location of the brain damage and the incidence of PTSD. In the control group (i.e. combat veterans without brain injury), the prevalence of PTSD was 48%. However, the prevalence dropped to 0% in the group where the damage was to the amygdala.[28]

Taken together, these results reveal the importance of the amygdala in mediating the symptoms of PTSD. Functional inhibition of the amygdala using DBS may therefore prove successful at treating PTSD. We tested this hypothesis[30] in a rat model using inescapable shocks which produce long-lasting behavior changes that mimic PTSD faithfully.[36] Recently, Mikics *et al.*[37] demonstrated that rats traumatized by inescapable shocks, in the presence of a conspicuous object, had the tendency to bury the object when re-exposed to it 28 days later. Burying behavior does not occur normally in rats. In this experiment, 10 rats underwent the implantation of an electrode in the right basolateral nucleus of the amygdala (BLn) and then were subjected to inescapable shocks in the presence of a miniature ball. Half of the animals received DBS therapy for 4 hours/day for 7 days, whereas the other half was connected to the pulse generator but received no stimulation (i.e. sham). Seven days later, all the rats were re-exposed to the ball and the burying behavior was timed. The difference in behavior was striking. The sham control rats spent, on average, 13 times more time burying the ball then the DBS-treated rats ($P < 0.005$).[30] More recently, we used the same animal model to compare the effects of DBS to paroxetine. Paroxetine is a selective serotonin-reuptake inhibitor approved for the treatment of PTSD. Our results confirmed the superiority of DBS over paroxetine.[55]

The decision to choose the BLn as a target was motivated by the fact that it is thought to be critical in both the acquisition and expression of fear conditioning. In addition, it plays a critical role in the modulation of amygdalary activity. The BLn receives important afferents from the mPFC and the hippocampus [Figure 1, red and green pathways]. The input from the mPFC is thought to mediate extinction of fear. Unfortunately, this region shows reduced activity in PTSD patients,[13,52] presumably leading to the failure of fear extinction seen in this population. The hippocampus input likely relates contextual information regarding the event. This allows the encapsulation of the emotional response within a specific context. However, in periods of stress, this neutral contextual information is not memorized reliably.[44] This lack of control may allow the amygdala to generalize the emotional response (e.g. fear) across multiple contexts where it is not appropriate (e.g. peaceful situation).

ROLE OF THE AMYGDALA IN ADDICTION

The rewarding and pleasurable effects of drugs of addiction are thought to arise from the activity of the mesolimbic system whereby the dopaminergic neurons of the ventral tegmental area (VTA) activate the nucleus accumbens (Nacc) through changes in their tonic and phasic activity.[48] In addition, recurring use leads to synaptic changes at the VTA–Nacc junction that render the drug less effective, a mechanism thought to be responsible for physical dependence. Although this model may explain the initial effects of the drugs and subsequent withdrawal symptoms, the daunting challenge of addiction treatment revolves largely around the prevention of long-term relapse.[50]

Relapse is the return to drug consumption after a long period of successful abstinence. Relapse in animal models of addiction occurs as a result of re-exposure to a small dose of the drug, exposure to stress, or exposure to environmental cues of the drug administration. The latter form of relapse can be described as a form of conditioning where an environmental cue is associated with the pleasurable effect of the drug, and later, when presented by itself triggers the seeking behavior associated with the drug. This phenomenon appears to play a significant role in human addiction where reminders

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of drug consumption (e.g. drug paraphernalia, specific building or room) can trigger relapse. Presentation of the cue, even long after withdrawal has resolved, can activate the circuits involved in the drug effect.[15,29,42] In turn, this activation triggers craving and seeking behavior. The action of pairing a stimulus (e.g. drug) to a behavior and an emotional state is reminiscent of the function of the amygdala.

The BLn is closely linked to the mesolimbic system, making it a potential mediator of the cue-conditioning phenomenon at the basis of relapse [Figure 1, blue pathway]. The BLn receives dopaminergic afferents from the VTA[12] that increases its activity.[17] In addition, the BLn has reciprocal connections with the Nacc involved with the formation of seeking behavior.[2] Rats presented with an environmental cue (e.g. light or tone) at the time of drug self-administration will relapse into drug administration when re-exposed to the same cue several days following abstinence. See *et al*.[49] demonstrated that tetradoxine inactivation of the BLn at the time of the initial period of cocaine self-administration or at the time of the cue re-exposure prevented relapse. These results show that the BLn mediates both the initial acquisition of the cue conditioning and the subsequent expression of the relapse.

Frenois *et al*.[15] also demonstrated that the BLn mediates the acquisition of aversive conditioning related to withdrawal in a morphine addiction model. As previously mentioned, the amygdala links cues related to drug intake to positive rewarding emotions. However, it also links cues related to the absence of drug or withdrawal to negative emotions. Therefore, rats re-exposed to environmental reminders of a previous period of withdrawal also have a tendency to relapse in drug self-administration in order to avoid reliving withdrawal. Frenois *et al*.[15] illustrated the role of the BLn in mediating this response through elevated levels of c-fos protein.

Substance abuse leads to diffuse changes in the cortical surface and the mesolimbic system. These changes are likely to contribute to persistent drug self-administration behavior in patients suffering from addiction. Nevertheless, the amygdala and, in particular, the BLn appear to play a critical role in certain forms of relapse related to exposure of reminders of drug intake or drug withdrawal. In individuals with intractable and life-threatening substance abuse disorder, BLn DBS could improve the chance of remission by reducing the incidence of relapse.

ROLE OF THE AMYGDALA IN MOOD DISORDER

The importance of the frontal-limbic circuitry in depression has been shown in several studies. Notably, Mayberg *et al*.[35] demonstrated, through a series of experiments using functional neuroimaging, that depressive states were associated with overactivity of a ventral frontal-limbic component and hypoactivity of a dorsal frontal-limbic component. The rostral anterior cingulate (cg24a) is located in between these two regions and may mediate the poorly understood shift between ventral and dorsal activity. Successful treatment is associated with a correlational normalization of the activity of the ventral and dorsal components. Presumably, the correction of one component leads to the correction of the other through interconnections. Therefore, in an effort to treat chronic refractory depression, DBS was applied to the overactive ventral frontal-limbic circuit. The subgenual cingulate gyrus, a component of this ventral circuit, was chosen as the specific target. This therapy has led to a long-term response rate of 64.3% for patients who were otherwise refractory to conventional treatments.[24]

An analysis of the position of DBS electrodes in those patients confirmed that the optimal location is the subgenual cingulate gyrus (cg25), which has dense connections with the amygdala, Nacc, hypothalamus, and the orbitofrontal cortex.[22] Several other studies have demonstrated sustained increased activity in the amygdala of depressed patients on SPECT, PET, or fMRI. The current model presented by Mayberg *et al*.[35] suggests that depression occurs primarily as a result of imbalance in the cortical activity which then translates into abnormal activity within subcortical structures such as the amygdala in a top-down mechanism. Although this view appears correct for a majority of patients based on the striking results obtained with Cg25 DBS, it is conceivable that in a number of patients depression occurs primarily as a result of a bottom-up mechanism. In this view, abnormal activity in subcortical structures such as the amygdala would then lead to the imbalance in cortical activity. As previously mentioned, the BLn forms a loop with the mPFC [Figure 1, red pathway]. Despite interconnections in the frontal-limbic circuit, a treatment focused at an area adjacent to the true epicenter would work through indirect modulation and may only offer a partial response.

Some evidence suggests that the amygdala could act as a primary focus in depression. For instance, several patients suffering from PTSD with symptoms associated with overactivity of the amygdala area often suffer from co-morbid depression. In addition, direct stimulation of the amygdaloid area in humans may lead to dysphoria, anger, fear, and tension.[19,56] However, the expression of those negative emotions with electrical stimulation may also depend of the underlying mental state of the patient at the time of the experiment.[56] More recently, Piacentini *et al*.[46] reported a case where inadvertent unilateral DBS of the left stria terminalis, the main

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output from the amygdala, led a man to suffer from depression with psychotic features. The symptoms reversed after re-positioning the electrode. The precise mechanism through which the amygdala could generate depression is still unclear. Siegle *et al.*[53] showed that depressed subjects have persistent amygdala activation, on fMRI, following the presentation of an emotionally negative word compared to normal subjects. This sustained activation could represent a neural correlate for the rumination of negative emotions seen in depressed patients. Murray *et al.*[40] studied the effects of lesions of the amygdala or the orbital PFC on devaluation tasks in monkeys. These tasks are based on the premise that objects have different values depending on the context. For instance, the value of a certain food will be lowered if the animal just ate this specific product to satiety. Further, the value of a given object may be increased or lowered depending on the likelihood of being rewarded for selecting it. These experiments demonstrated that the amygdala is necessary for screening objects and constantly updating their value. On the other hand, the orbital PFC stores and retrieves the assigned value, therefore allowing decision making based on it. Assigning value to objects and activities is an important aspect of mood regulation. An inability to recognize positive value to specific objects or events could lead to anhedonia and apathy. Ultimately, the inability to assign value to oneself would lead to low self-esteem as seen in depressed patients. This problem could occur as a result of a dysfunction within the PFC or the amygdala. Potentially, DBS of the amygdala could normalize the value-assignment function and reduce the vegetative symptoms associated with depression.

EXPERIENCE FROM STEREOTACTIC AMYGDALOTOMY FOR INTRACTABLE AGGRESSION

The main experience using the amygdala as a target in behavior surgery comes from stereotactic amygdalotomy for intractable aggression. The role of the amygdala in mediating aggression or violent behavior has long been recognized. For instance, Kluver and Bucy[27] demonstrated that the bilateral destruction of the mesiotemporal structures, including the amygdala, led to hypersexuality, hyperorality, and loss of anger or fear responses. Based in part on this work, Narabayashi[41] introduced the stereotactic amygdalotomy. Initially, the procedure was offered to patients suffering from epilepsy or EEG abnormality in addition to aggressive behavior, but eventually it was offered more broadly to patients suffering from "intractable aggression." Following this initial report, several other authors reported their outcomes for the treatment of aggression and over a thousand cases have been studied.[6,9,20] The overall improvement in symptoms was reported to range between 33 and 100%, with most authors reporting 70–85% improvement.[38] The complication rate across different studies ranged from 0 to 42%. The large variation across these reports may be related to the heterogeneity among the treated patients. "Intractable aggression" is not a pathological entity defined as a diagnosis in the DSM-IV TR. Aggression is a behavior found in a variety of psychological disorders including cognitive disorders, substance abuse, psychosis, and personality disorders.[54] These entities vary widely in their underlying neural substrates, and it follows that the response to the amygdalotomy may differ. Depending on the specific condition leading to aggression, the optimal target of treatment may be different. After an initial period of increasing popularity, the stereotactic amygdalotomy has become nearly obsolete. It is now performed only rarely in the US.[32] Nevertheless, important knowledge can be gained from the complications listed from this early experience. Few complications were reported from the transfrontal approach, but several side effects were noted after lesioning the amygdala. Kiloh *et al.*[25] reported seven complications following 18 operations. There were four cases of new-onset epilepsy and three cases of hypersexuality behavior. Fortunately, the epilepsy resolved over a period of several months.

The surgical technique has improved since these reports. Nevertheless, the risks of amygdala DBS include anger, mood disturbances, neuropsychological deterioration, and seizures. Interestingly, very few patients who underwent electrical stimulation at low frequency and high amplitude reported anger.[19] Some authors have suggested that the specific symptoms experienced with stimulation depend on the underlying mental state of the patient. For instance, only aggressive patients tend to report anger with amygdala stimulation;[26] fear was experienced primarily by patients who were apprehensive of the session.[56] Seizures have been reported in humans following electrical simulation of the mesiotemporal structures.[19] However, the number of seizures elicited was relatively low given that the patients were suffering from mesiotemporal epilepsy and were stimulated at high amplitude.[19] Bawden and Racine[5] reported that electrical stimulation of the amygdala with a charge density below the threshold to produce afterdischarges does not significantly lower the afterdischarge threshold in rats over time. Other authors[16,58] have reported that electrical stimulation of the amygdala and the hippocampus, respectively, raise the threshold for electroconvulsion, therefore leading to protection against seizure. In humans, chronic high-frequency stimulation of the mesiotemporal structures has been shown to raise the seizure threshold. For instance, Velasco *et al.*[57] reported that the chronic high-frequency stimulation of the normal or the sclerotic hippocampus reduces the incidence of seizures in refractory epileptic patients without causing side effects.

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CONCLUSION

The fundamental role of the amygdala is to link stimuli or events to a series of physiological and psychological processes. The constellation of these processes translates into a specific emotion within the mind. Whether the emotion is negative or positive depends on the nature of the processes activated by the amygdala. In turn, the decision making of the amygdala is determined by several modulatory inputs including the hippocampus (context modulation), the VTA (motivation, reward motivation), and the PFC (higher-order modulation).

This basic function of the amygdala is recruited to participate in several complex behaviors and human experiences. A dysfunction of the amygdala can therefore manifest in different mental illnesses depending on the relative "weight" of individual connections within the circuit and on the activity of other components of the circuit. DBS of the amygdala and, in particular, of the BLn can likely be utilized for the treatment of some mental illnesses. However, the success of this strategy will depend on our ability to determine pre-operatively the likelihood that the symptoms are caused by amygdalary dysfunction.

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