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Discovering how the amygdala shapes human behavior: From lesion studies to neuromodulation

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Case studies of patients with amygdala damage or those receiving direct amygdala stimulation have informed our understanding of the amygdala's role in emotion and cognition. These foundational studies illustrate how the human amygdala influences our present behavior and prioritizes memories of our past in service of future experiences. This broad influence makes the amygdala a novel target for clinical neuromodulation.

Introduction

Case studies and case series based on brain lesions have had a large influence on theories of neural correlates of emotion and cognition—from Phineas Gage to the discovery of Broca's area to patient H.M. and the hippocampus. Since the early 1900s, case studies of patients undergoing electrical stimulation have had a similar influence on our understanding of the human brain and behavior. Each experimental model offers unique information about the relationship between brain structure, function, and behavior. Lesion studies reveal specific brain regions that are necessary for particular behaviors. On the other hand, neuromodulation studies can demonstrate either the necessity of a brain region for specific behaviors by blocking that region's normal activity or the sufficiency of a brain region by enhancing its influence on other connected regions and behavior. Recent studies indicate the power of individual cases or series of similar cases to dissect more subtle brain-behavior relationships than previously possible. In particular, the human amygdala has been the subject of many influential case studies and series over the past three decades. We argue that these studies have shown that throughout our daily lives, our amygdala orchestrates the emotional and cognitive behaviors that shape our perceptions of the present, prioritizes which memories last from our past, and informs novel therapies for our future worries and anxieties.

The amygdala's morphology is unique relative to many other brain structures involved in emotion and cognition because it is made up of isolated bundles of neurons (i.e., nuclei) that have vast but distinct structural connections throughout the brain. This nucleated morphology of the amygdala and each nuclei's unique connectivity give rise to its multifaceted function in our emotional life (e.g., basolateral, central, medial, cortical, basomedial, etc). For instance, the amygdala's connections to the fusiform face area affect our interpretation of emotional faces. Its connectivity to the hypothalamus influences the release of stress hormones during emotional experiences, which in turn can influence the prioritization of experiences for later consolidation in memory. This broad connectivity makes the amygdala a central modulator of many daily behaviors. These behaviors can range from the happy memory we make when we get an unexpected "I love you" from our children to the anxiety we feel if we are presenting to an unimpressed audience. Although dissecting these connections has been primarily studied using experimental animals, human case studies have offered uniquely informative perspectives on the nature of emotion and cognition given our capacity to describe our current perceptions and past experiences. In this NeuroView, we review the contributions case studies and series have had on our understanding of amygdala function and the amygdala's central role in a variety of emotional and cognitive behaviors. We conclude by reviewing recent studies that have utilized these discoveries to develop the amygdala as a target for clinical neuromodulation. Finally, given the amygdala's ability to modulate a range of behaviors, we provide recommendations for studies needed to precisely modulate subnetworks of the amygdala's broad connectivity and to generate larger neuromodulation response datasets across clinical sites to discover generalizable insights into the effects of human amygdala stimulation.

How the amygdala shapes our present perceptions

Decades of animal studies throughout the 20th century showed that the amygdala participates in emotion. However, determining the amygdala's function in humans had previously been hampered by the rarity of patients with selective amygdala lesions. Early case studies in individuals with such lesions helped advance our understanding of the amygdala's role in the human brain and the importance of this structure not only in emotional processing but also in social behavior.

Neuroscientists in the early 1990s had the unique opportunity to study patient S.M., a 30-year-old woman with Urbach-Wiethe disease. This condition caused a nearly complete bilateral destruction of the amygdalae early in development while sparing the hippocampus and neocortical structures, thus allowing researchers to study the effects of selective, full amygdala lesions on emotion processing. In a series of experiments, patient S.M. was shown facial expressions of basic emotions and asked to rate each face according to several emotional adjectives (e.g., happy, afraid, angry, etc.). Results indicate that compared to control subjects, S.M. rated expressions of fear as dramatically less intense. Furthermore, S.M. was unable to recognize the blend of multiple emotions that a single face can convey. However, her ability to recognize the identity of the faces presented was preserved, supporting the idea that separate neural systems are responsible for processing the identity of a face.[1] Together, these results suggest the amygdala is a central component of the neural systems subserving social cognition in part because recognition of emotions signaled by faces is vital for successful behavior in social interactions.

Further testing with S.M. emphasized the nuances of amygdala lesions and their influence on emotional perception. In comparing S.M.'s bilateral amygdala destruction to subjects with unilateral amygdala damage, researchers discovered that unilateral lesion alone is not sufficient to produce deficits in sensitivity to the emotion of fear in facial expressions.[2] Furthermore, to observe deficits in processing facial expressions, bilateral amygdala damage must occur early in development. In a separate case series, individuals who sustained bilateral amygdala damage later in adulthood were unimpaired in their ability to recognize emotion in facial expressions.[3] This suggests that in the absence of early-life damage, recognition of facial emotion in adults does not have an absolute dependence on the amygdala.

Later studies demonstrated the effects of direct amygdala modulation on a person's facial emotion perception. For example, direct electrical stimulation of the human amygdala induces transient changes in affective bias (AB) toward emotional facial expressions in epilepsy patients undergoing intracranial monitoring for drug-resistant seizures. As described by Bijanki and colleagues,[4] AB refers to the notion that depressed patients tend to interpret ambiguous or positive events as relatively negative. A case study was conducted by the same group with a 48-year-old male patient with depth electrodes implanted bilaterally in the basolateral nuclei of the amygdala. Additionally, this patient had a history of major depressive disorder. Amygdala stimulation caused the patient to rate emotional facial expressions as significantly more positive compared to facial expressions paired with no stimulation. This case study suggests a causal role of the amygdala in emotional facial processing in a patient with intact amygdala connectivity to facial processing regions.

The human face conveys information about a person's identity and their present emotional state, and it often signals a blend of several emotions at the same time, all of which are elements critical to social behavior. The aforementioned experiments highlight the utility of case studies and suggest the amygdala is important in the experience and expression of emotion, which is crucial for our capacity to respond appropriately in complex social environments in the present.

In addition to its key role in emotional perception, the amygdala also significantly influences the autonomic nervous system. In a study of the effects of direct electrical stimulation to the human amygdala on autonomic arousal, eight patients undergoing intracranial EEG monitoring were tasked with sitting quietly with minimized movement, while receiving 30 s of direct electrical stimulation to the amygdala.[5] Unilateral amygdala stimulation was delivered in a stepwise fashion from 1 to 12V with a sham stimulation condition randomly interspersed between trials. Immediately after the stimulation period, patients were asked to report any subjective emotional or physiological sensations after each stimulation. This study found that basolateral amygdala stimulation increased sympathetic arousal, as indexed by time-locked increases in skin conductance and decreases in heart rate, in an amplitude- or dose-dependent fashion without any subjective emotional responses from the participants (7 of 8 patients). These effects were specific to the amygdala and did not occur with unilateral lateral temporal lobe stimulation. These results demonstrate the human amygdala's role in modulating sympathetic nervous system activity.

Interestingly, 1 of the 8 participants showed a robust subjective fear response to direct amygdala stimulation in tandem with distinct changes in sympathetic nervous system responses. In particular, at higher doses of direct amygdala stimulation (>5 V), this patient reported "feeling scared on the left side of (his) body" and "the worst fear I've ever felt." He also spontaneously reported that the emotion he was feeling "… was not pain, as much as fear." This immediate increase in subjective fear coincided with time-locked and dose-dependent increases in skin conductance and heart rate, suggesting a more immediate fight-or-flight response than the more defensive, preparatory sympathetic nervous system response shown in the other seven patients. Notably, electrode placement in the one patient with a subjective experience of fear was closer to the amygdala's central nucleus, which has more direct projections to the hypothalamus, as opposed to the basolateral amygdala, which projects more directly to the hippocampus.[5] Taken together, findings from both lesion and neuromodulation case studies and series complement one another to show strong evidence that the human amygdala is causally involved in the modulation of autonomic arousal and perception of fear on a moment-to-moment basis as we perceive the world around us.

The amygdala's role in memory prioritization

Due to its direct connectivity to the hippocampus, entorhinal, and perirhinal cortices, as well as its dense connections to other downstream memory processing regions, the amygdala is also known for its role in a variety of memory functions. S.M.'s case study provided the unique opportunity to study the amygdala's role in some of these memory functions by engaging her in more qualitative experiments to assess whether amygdala lesions impair the recognition and recall memory of facial expressions. S.M. was asked to draw upon her experience as

an artist and illustrate pictures of facial expressions from memory. Interestingly, she was able to produce without difficulty detailed renditions of all facial expressions except fear.[2] This suggests the amygdala's role in the human brain extends to both recognition and recall of fearful facial expressions, and that the amygdala is essential to retrieve comprehensive knowledge related to the concept of fear when it is damaged early in life.

Further, a case study with patients S.M. and B.P.,[6] two patients with bilateral amygdala lesions, suggests that declarative memories for emotional stimuli are impaired without the amygdalae. These subjects struggled to remember details of emotional stimuli compared to matched controls, suggesting that amygdalae are necessary for memory prioritization for emotional stimuli. These results indicate the amygdala may have a dual function for the experience of emotional arousal and the prioritized encoding of the details of our experiences into long-term memory.

The amygdala plays a crucial role in memory prioritization when activated by an emotional stimulus, a process by which certain memories are prioritized for later recollection. This process occurs during memory consolidation, where the amygdala signals nearby medial temporal lobe (MTL) regions like the hippocampus to tag specific events to be consolidated for later recollection, creating lasting memories. This effect has been demonstrated through decades of pharmacological and electrical modulation of the amygdala in animal models. Recently, a case series of 14 drug-resistant epilepsy patients with intracranial EEG recordings showed that stimulating the basolateral amygdala while participants viewed images of neutral objects enhanced memory for those objects after 1 day, but not immediately, compared with objects not paired with stimulation.[7] Furthermore, during retrieval, when presented with an image that had been previously paired with amygdala stimulation during encoding, the participants' medial temporal lobe structures exhibited electrophysiological patterns that were similar to the theta-burst stimulation (i.e., theta-modulated gamma) introduced during encoding. This finding suggests that stimulation of the basolateral amygdala encodes a marker of prior stimulation in the MTL memory network that might replay during reexposure to the tagged stimulus. Moreover, patients had no subjective awareness of the amygdala stimulation, suggesting the amygdala's role in emotional arousal may be distinct from its memory-modulating capacity. These findings suggest that direct amygdala stimulation causes prioritization of temporally specific declarative memories for later recognition without eliciting an emotional response. This approach to studying amygdala-mediated memory enhancement opens the door to modulating hippocampal consolidation processes in humans in an experimentally controlled fashion and further dissection of the medial temporal lobe interactions that support the prioritization of experiences into lasting memories.

In an unpublished case study, the same researchers took a rare opportunity to test the hippocampal dependence of this amygdala-mediated memory-enhancement effect in humans. The hippocampal dependence of the effect was tested by having the same patient perform the amygdala stimulation for memory enhancement experiment described above two separate times: once with stimulation to the patient's intact amygdala-hippocampal circuit in the right hemisphere and once with stimulation to their left amygdala with no intact ipsilateral hippocampus due to previous ablation for epilepsy. Functional physiology of the patient's residual left amygdala was established by performing 15 s of high-amplitude (>3 mA) amygdala stimulation during simultaneous recordings of electrodermal activity and electrocardiography. Similar to prior studies,[5] high-dose amygdala stimulation of this residual amygdala tissue (>90% residual) evoked an immediate increase in electrodermal activity and change in heart rate, suggesting it still maintained the functional ability to modulate autonomic arousal. Critically, this patient showed a clear memory-enhancement effect for stimulation to their right amygdala with an intact ipsilateral hippocampus but showed no memory-enhancement effect with stimulation to their left amygdala with no intact ipsilateral hippocampus. This novel case study suggests hippocampal dependence of the amygdala-mediated memory-enhancement effect. Overall, these complementary studies show that, through its interactions with the hippocampus, the human amygdala is involved in memory prioritization for long-term consolidation, even without provoking an emotional response.

There is a growing consensus on the amygdala's dual role in emotional arousal and memory modulation, as it is involved in both processes separately and combined. The amygdala's multifaceted role might be tied to the broad structural connectivity from its nuclei to areas throughout the brain. These features of the amygdala's influence throughout the brain and behavior make it an excellent candidate for developing novel neuromodulation therapies to treat disorders of both emotional dysregulation and memory, including post-traumatic stress disorder (PTSD) and traumatic brain injury.

The amygdala as a novel target for clinical neuromodulation

As described above, lesion and neuromodulation studies over the last three decades have provided rich insights into the causal role of the amygdala in memory, emotion, and autonomic arousal. Recent reports, however, have turned the focus toward the future, highlighting ways in which these discoveries might have direct translational relevance. One case series of two patients with comorbid post-traumatic stress disorder (PTSD) and refractory epilepsy observed a profound reduction in PTSD symptoms with unilateral (right-sided) laser ablation of the amygdala and hippocampus.[8] Moreover, clinical outcomes were corroborated by a robust normalization in neurophysiological markers of hyperarousal and global improvements in emotional memory recall. The results from this prospective investigation of amygdala ablation are particularly noteworthy when considering that many afflicted with PTSD are treatment resistant and do not respond to standard courses of psychotherapy, pharmacotherapy, or combinations thereof.

This research has since motivated an open-label clinical trial involving electrical stimulation of the amygdala in individuals with treatment-resistant PTSD (NCT04152993). Researchers involved

in this study characterized selective increases in the power of amygdala theta oscillations (5–9 Hz) associated with PTSD symptoms and designed a closed-loop approach that delivered stimulation to the amygdala when the biomarker was detected.[9] The two individuals with PTSD who received closed-loop stimulation over an 11-month period exhibited clinically meaningful reductions in PTSD symptoms, which paralleled reductions in the oscillatory biomarker of interest. This preliminary evidence supports a growing consensus that precision neuromodulation may be an effective therapy across a range of treatment-resistant conditions, particularly when informed by online recordings of the neural signatures of disease-related biomarkers.

In addition to PTSD, neural recordings from the amygdala have proven instrumental for interventions targeting other neuropsychiatric applications. A recent case study used intracranial recordings from the amygdala as a candidate biomarker in a closed-loop system for an individual with treatment-resistant major depressive disorder.[10] In this study, low- and high-frequency amygdala gamma oscillations (31–70 Hz and 71–150 Hz, respectively), were most predictive of anxiety and depression severity. Upon characterizing patient-specific neural signatures of mood state and tailoring the parameters of the therapy in response to these neural signals, the authors observed a rapid and sustained improvement in depression symptoms from closed-loop stimulation of the ventral capsule/ventral striatum triggered by changes in the patient's ongoing amygdala activity.

Taken together, these recent case reports of neurosurgical patients illustrate the therapeutic potential of precision therapies that target, or are informed by, activity in the human amygdala. Although it is difficult to draw robust, generalizable conclusions from limited investigations of the rare patients who undergo intracranial recording or stimulation, these results nonetheless motivate a sense of optimism about the future role of the amygdala in science and medicine.

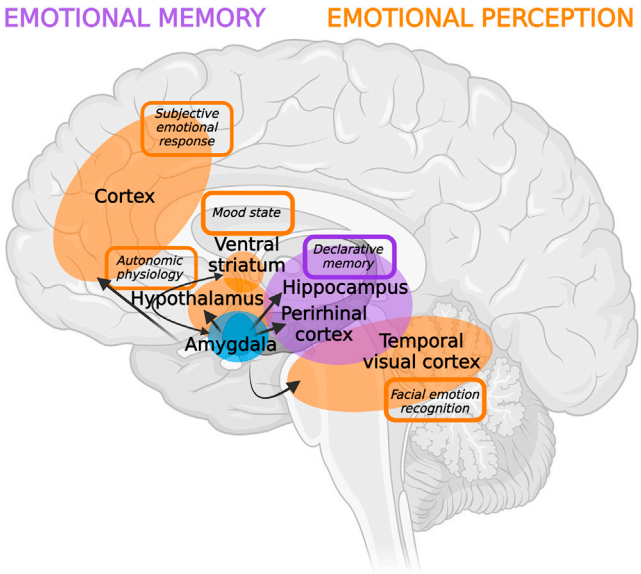

Figure 1. Illustration of the multifaceted influence the human amygdala has on behavior and the network of potential therapeutic targets for clinical neuromodulation

Orange represents the regions important for amygdala regulation of our present emotional perception and mood. Purple represents the regions critical for amygdala influence on our memories of past experiences. The broad influence the amygdala has on a variety of behaviors including autonomic physiology, subjective emotional response, emotion recognition, declarative memory, and mood state makes it a well-situated candidate for future clinical neuromodulation applications. However, given the wide-ranging influence of the amygdala, future studies must appreciate the difficulty in determining the best approach to target this region and the surrounding network with a precision that minimizes unwanted side effects. Created with BioRender.com.

Conclusion

In line with decades of incredibly detailed findings from animal studies, the human amygdala plays a central role in our experience of life (Figure 1). Experiments with small cohorts of patients have offered new insights only possible in humans relative to our deep knowledge of amygdala function in experimental animals. In particular, these rare case studies of different forms of neuromodulation (i.e., lesions or direct brain stimulation) offer the unique opportunity for patients to subjectively report their experience while gathering measures that can bridge the animal and human literatures and for researchers to look for commonalities across their reports and measures (local field potentials, single-unit recordings, autonomic reactivity, eye tracking, etc). Thus far, these findings have provided complementary evidence that the human amygdala plays a multifaceted role in our emotional experience in the present and memory for the past.

Amygdala lesion studies have demonstrated that our experience, perceptions, or recognition of fear are impaired when this broadly connected and widely influential structure is missing. Interestingly, these studies show that this disruption of negative emotions like fear or threat does not severely affect the daily life or longevity of those that grew up with no amygdala from a young age.[1–3,6] On the other hand, the removal of a dysfunctional right amygdala later in life can help patients who have suffered from PTSD for decades after a traumatic experience.[8] Amygdala neuromodulation studies have pushed these insights further by demonstrating that targeted stimulation of the brain based on the amygdala's ongoing activity can help clinicians gain control over emotional dysregulation in both patients with depression and PTSD.[9,10] These therapeutic possibilities are bolstered by the wealth of data from basic research showing that direct electrical stimulation of the human amygdala modulates autonomic arousal in a dose-dependent fashion independent of changes in subjective experience,[5] modulates subtle subjective ratings of facial emotion,[4] and enhances long-term memory through basolateral interactions with the hippocampus.[7] This broad influence makes the amygdala a well-situated candidate for future clinical neuromodulation applications. However, given this same wide-ranging influence provided by the diverse connectivity of the amygdala's subnuclei (i.e., basolateral, central, etc.), future studies must appreciate the difficulty in determining the best approach to target this region and the surrounding network with a precision that minimizes unwanted side effects.

Finally, future studies that take advantage of cloud computing might hold enormous potential for accumulating case-study evidence across the thousands of neurosurgical centers across the world. Every day clinicians encounter patients with damage to specific and broad areas of the brain that include the amygdala or patients undergoing clinical stimulation mapping to verify the seizure-onset zone for epilepsy treatment. In both cases, a wealth of imaging, subjective reports, and neural response data are collected about the patient that could be informative to our understanding of neural function. Accumulating these data in a centralized case-report database via privacy-sensitive cloud computing would allow basic scientists to discover the commonalities across much larger samples of patients with brain damage and undergoing neuromodulation. Of course, the challenge is how to coordinate and collect this wealth of data. Further developments in automatic de-identification of protected health data and coordination of neurology centers toward large, moonshot research efforts to share and combine these important data will open new avenues for understanding the consistency and variability of human brain-behavior relationships. Altogether, our current knowledge of amygdala function has been shaped by case series using both lesion and neuromodulation approaches, but there is still substantial untapped potential to discover novel aspects of how the amygdala shapes our experience of the present and memories of the past in service of our future experiences.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature *372*, 669–672. https://doi.org/10.1038/372669a0.

2. Adolphs, R., Tranel, D., Damasio, H., and Damasio, A.R. (1995). Fear and the human amygdala. J. Neurosci. *15*, 5879–5891.

3. Hamann, S.B., Stefanacci, L., Squire, L.R., Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. (1996). Recognizing facial emotion. Nature *379*, 497. https://doi.org/10.1038/379497a0.

4. Bijanki, K.R., Kovach, C.K., McCormick, L.M., Kawasaki, H., Dlouhy, B.J., Feinstein, J., Jones, R.D., and Howard, M.A., III (2014). Case Report: Stimulation of the Right Amygdala Induces Transient Changes in Affective Bias. Brain Stimul. *7*, 690–693. https://doi.org/10.1016/j.brs.2014.05.005.

5. Inman, C.S., Bijanki, K.R., Bass, D.I., Gross, R.E., Hamann, S., and Willie, J.T. (2020). Human amygdala stimulation effects on emotion physiology and emotional experience. Neuropsychologia *145*, 106722. https://doi.org/10.1016/j.neuropsychologia.2018.03.019.

6. Adolphs, R., Cahill, L., Schul, R., and Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. Learn. Mem. *4*, 291–300. https://doi.org/10.1101/lm.4.3.291.

7. Inman, C.S., Manns, J.R., Bijanki, K.R., Bass, D.I., Hamann, S., Drane, D.L., Fasano, R.E., Kovach, C.K., Gross, R.E., and Willie, J.T. (2018). Direct electrical stimulation of the amygdala enhances declarative memory in humans. Proc. Natl. Acad. Sci. USA *115*, 98–103. https://doi.org/10.1073/pnas.1714058114.

8. Bijanki, K.R., van Rooij, S.J.H., Ely, T.D., Stevens, J.S., Inman, C.S., Fasano, R.E., Carter, S.E., Winters, S.J., Baman, J.R., Drane, D.L., et al. (2020). Case Series: Unilateral Amygdala Ablation Ameliorates Post-Traumatic Stress Disorder Symptoms and Biomarkers. Neurosurgery *87*, 796–802. https://doi.org/10.1093/neuros/nyaa051.

9. Gill, J.L., Schneiders, J.A., Stangl, M., Aghajan, Z.M., Vallejo, M., Hiller, S., Topalovic, U., Inman, C.S., Villaroman, D., Bari, A., et al. (2023). A pilot study of closed-loop neuromodulation for treatment-resistant post-traumatic stress disorder. Nat. Commun. *14*, 2997. https://doi.org/10.1038/s41467-023-38712-1.

10. Scangos, K.W., Khambhati, A.N., Daly, P.M., Makhoul, G.S., Sugrue, L.P., Zamanian, H., Liu, T.X., Rao, V.R., Sellers, K.K., Dawes, H.E., et al. (2021). Closed-loop neuromodulation in an individual with treatment-resistant depression. Nat. Med. *27*, 1696–1700. https://doi.org/10.1038/s41591-021-01480-w.