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Looping Circuits: Amygdalar Function and Interaction with Other Brain Regions

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Abstract

The ability to understand the relevance of environmental cues is necessary for animals to adapt and survive. How the brain interprets, understands, and reacts to stimuli is only partially understood. Such higher-order brain processes occur within series of highly interconnected brain circuits that allow the brain to alter its response appropriately to an ever changing environment. The amygdala is one of the brain regions that determine the significance of incoming environmental stimuli. Once the significance of a stimulus or set of stimuli is determined, other circuits utilize this information to initiate physiological and behavioral responses (e.g., alter the attention of the animal to relevant sensory cues, change the emotional state, initiate fight or flight responses, etc.). Because circuits between the amygdala and other brain regions are highly interconnected, dysfunctions in one region of the brain can influence several other brain regions. Such alterations in normal activity can induce psychiatric, psychosocial, or attentional symptomatology. Therefore, identifying the role of individual circuits as well as the interconnected nature of these circuits is essential for understanding how a normal individual survives and adapts to its environment. It also provides the knowledge necessary to devise therapies for both the cause and symptoms of psychosis.

Keywords: stimulus significance, sensory, learning, memory, psychiatric disorders

1. Introduction

To react appropriately within the environment, an individual must first gather information via sensory organs and systems (e.g., sound, sight, smell, touch, taste). Sensory information is then transmitted up to sensory cortex, where the sensation is perceived. Additional circuits route sensory information to the amygdala where it is combined with information from other sensory modalities as well as stored information from memory, association, and executive

cortices. Amygdalar neurons utilize these combinations of inputs to identify the significance of the various environmental stimuli [1–3]. For example, the call of a cat is significant to its prey (e.g., a mouse). Information about the cat vocalization (frequency spectrum, tone, and attenuation) is processed within the auditory system and perceived by the mouse within cortex. This information is sent to the amygdala where it is combined with other sensory information (e.g., cat smell or visualization of the cat's movements), as well as information from the mouse's prior experiences with the set of stimuli to provide an environmental context for a specific experience [4]. These sets of inputs (sensory, memory, and association) are combined within the amygdala to determine whether the given set of stimuli is significant to an individual [4].

Stimulus significance can influence both hormonal and behavioral responses through an intricate system of loops between the amygdala and other brain regions [4]. The amygdala projects directly or indirectly to sensory cortices, as well as modulatory, memory, motor, autonomic, stress, emotional, decision, and executive brain regions [1, 3–5]. Many of these areas of the brain have reciprocal projections back to the amygdala as well as connections between each other; therefore, small modifications in the excitation of one brain region can influence a cascade of adaptations throughout the brain. As each additional brain region is affected, projections from these regions influence both the original nuclei as well as additional looping circuits.

Dysfunctions within one or more of the interconnected circuits can lead to a dissonance within different brain regions or with the timing of inputs within a specific brain region. These alterations in firing patterns can alter processing and dramatically influence an individual's behavioral responses to their environment. Because numerous brain regions are affected, alterations in normal activity can present clinically as a group of seemingly disparate symptoms (e.g., hallucinations, loss of attention, alterations in decision making, working memory, emotional state, etc.) commonly observed in psychiatric disorders [6]. Identifying how brain circuits interact is crucial for understanding normal brain function as well as recognizing how variations can result in dysfunction. Because of the complexity of the circuit interactions, our current understanding is substantially incomplete.

2. Amygdalar circuits: sensory

The amygdala receives and sends projections to multiple regions of the brain (**Figure 1A**). Anterograde, retrograde, or autoradiography studies indicate that the amygdala receives both direct and indirect inputs from each sensory system (**Figure 1A**). Inputs include reciprocal projections from association cortices from each sensory modality (auditory [7, 8]; gustatory [9, 10]; olfactory [11, 12]; somatosensory [4, 13]; vision [14]). These association regions are known for higher-order sensory processing such as visualization of complex movements, facial recognition, and speech processing [15, 16]. Additional polymodal sensory regions have been shown to have reciprocal projections to the amygdala [17]. Such polymodal inputs provide complex sets of sensory information that are necessary components of environmentally relevant stimuli. Because the processing for these combined sensory stimuli are outsourced in

Figure 1. Numerous regions of the brain project to the amygdala (A). Amygdalar neurons may be combination sensitive, having facilitated neuronal responses to multiple inputs (B). EPSP = excitatory post-synaptic potential.

other brain regions, polymodal inputs may facilitate faster responses to these stimuli within the amygdala [18–21].

There is evidence that the amygdala receives some primary or simple sensory information from both cortical and thalamic nuclei. Auditory, somatosensory, and visual thalamic nuclei have direct projections to the amygdala [4, 22–25]. Because the regions of thalamus that project to the amygdala are known to receive both simple as well as polymodal sensory input, the type of sensory input (complex or simple) coming from these regions is not well understood.

Another source of simple sensory information is primary sensory cortices. The olfactory cortex has direct projections to the amygdala [26–28]. It is still debated whether the primary regions of other sensory cortices have direct projections or not. Several studies indicate that the amygdala receives no or few inputs from primary auditory, visual, or somatosensory cortices [17]. However, most of these studies utilized nonspecific techniques. Studies using fluorescent tracing techniques observe a small or moderate reciprocal connection with auditory cortex (preliminary data from my laboratory [8, 27]). Similar experiments in other primary sensory cortices are needed to confirm the existence of similar pathways for the other sensory modalities.

3. Amygdalar circuits: conditioned response

Classical conditioning is the pairing of an unconditioned stimulus (e.g., foot-shock) with a conditioned stimulus (e.g., sound of a bell). When the two are repeatedly paired together, the conditioned individual associates the two stimuli with each other (i.e., the foot-shock with hearing the bell). Once the pairing is learned, individuals exhibit a similar behavioral response any time they hear the bell whether the shock follows or not [2]. The memory of the rule allows individuals to respond faster to subsequent stimuli, and thus facilitates more timely, accurate, and environmentally advantageous behaviors.

Because the environment is constantly changing, conditioning can induce either long- or short-term associations. Short-term associations are important for allowing individuals to react to the fast-paced shifts in the context of environmental signals. Short-term plasticity can be mediated by altering the firing rate of cortical neurons through local circuit facilitation, inhibition, or disinhibition. Long-term associations are important for creating behaviorally relevant rules that will be important for the individual over extended periods of time. These longer associations can be created by altering receptors and dendritic spines to strengthen connections between regions of the brain [29].

Conditioning begins within the amygdala. Amygdalar neurons typically respond to significant or behaviorally relevant pairings of stimuli [18, 30–32]. Physiological recordings in the amygdala, for example, show an increase in neuronal firing to stimuli with positive or negative affect but no increased response to stimuli with neutral affect [18, 26]. During experimental conditioning, behavioral relevance can be created, and thus amygdalar responses provoked. During fear conditioning, a negative affect can be created by pairing a sensory stimulus (sound) with a noxious stimulus (foot-shock). Single-unit recordings in the amygdala indicate that amygdalar neurons have a higher rate of firing to the combined sound and foot-shock stimuli than to a sound alone [33]. They also respond with higher firing rates to novel combinations of inputs than to previously learned combinations [32]. Such deference to novelty information indicates that circuits from memory or association cortex are likely to provide additional inputs that influence the firing rate. Therefore, combinations of inputs from auditory and sensory cortex, as well as specific inputs from memory or association cortex, can increase the firing properties of AM neurons. These neuronal responses are created by combining inputs from multiple sensory stimuli with inputs that provide information about previous memories (context; e.g., hippocampus), prior motivation (rewards/punishments; prefrontal cortex), as well as other prior associations about similar sets of stimuli (association cortices; **Figure 1**).

The mechanism by which amygdalar neurons have higher rates of activity when presented with two distinct inputs (i.e., neuronal facilitation) is not known. It has been hypothesized that combinations of inputs alter amygdalar neuronal excitability and that these changes encode information about stimulus significance [2, 4]. This could mean that neurons within the amygdala are combination sensitive, a process by which combinations of inputs can facilitate or inhibit neuronal responses when presented within specific temporal delays. Combination sensitivity has been observed in several different brain regions (e.g., lateral lemniscus, inferior

colliculus [34–37]). Within the auditory system, combination-sensitive neurons are thought to encode specific spectral-temporal features of sound combinations to facilitate functions such as deciphering speech patterns or echolocation information. These types of responses have been observed within the amygdala (preliminary data from my laboratory); however, only a few of these types of responses were observed. The lack of abundant responses may have been due to the selection of stimulus combinations we presented to our animals, or it may indicate that simple electrical summation (i.e., each input has a hyperpolarization influence on the targeted amygdalar neuron that when added together can surpass threshold) is more prevalent within the amygdala. In either scenario, it is likely that multiple inputs are required to hyperpolarize the amygdalar neuron (**Figure 1B**).

Longer-term associations within the amygdala are thought to occur through anatomical changes in receptors, transmission, activity, and dendritic spines of amygdalar neurons (long-term potentiation). This type of long-term change has been observed after electrical stimulation of the thalamus, external capsule, hippocampus, and entorhinal-amygdalar circuits [37–40]. Although the direct circuits that influence this type of amygdalar change are known, these types of experiments create extended excitatory influences from the stimulated brain region that could excite a plethora of secondary or tertiary looping circuits. For example, excitation of the medial geniculate nucleus (auditory thalamus) could influence amygdalar processing through direct excitation as well as indirect excitation through auditory cortex, auditory association cortices, polymodal cortices, as well as memory network circuits (i.e., thalamus-association cortex-hippocampus-amygdala), prefrontal cortex circuits (i.e., thalamus-association cortex-prefrontal cortex-amygdala), or modulatory centers (e.g., thalamus-auditory cortex-nucleus basalis-amygdala). Each of these circuits is likely to have heightened excitatory influences, and when combined results in long-term alterations in amygdalar activity.

Once significance is determined within the amygdala, this information is sent to a variety of brain regions to allow the brain to consolidate that new information within memory, decide how to respond, create or modulate rules about behavior, and provide appropriate physiological and behavioral responses. Projections from the amygdala to the nucleus basalis of Meynert, for example, initiates cholinergic modulation of cortical neuronal responses that are thought to shift the attention of an individual toward relevant sensory cues. Nucleus basalis projections are also sent to memory, association, and frontal network circuits to facilitate alterations in activity based on conditioning [1, 3, 41, 42].

Numerous experiments have shown that cholinergic projections from the nucleus basalis are involved with cortical conditioning. Lesions of the nucleus basalis have been shown to inhibit learning acquisition [43], while electrical stimulation studies induced significant changes in cortical activity as well as increases in the retrieval of behavioral learning tasks [44–49]. Electrical stimulation, in these experiments, was thought to facilitate acetylcholine release from the nucleus basalis, which in turn increased the animal's ability to consolidate learned information. This hypothesis was substantiated by experiments that applied atropine (acetylcholine antagonist) to auditory cortex to eliminate the influence of the nucleus basalis pathway. These experiments showed a complete inhibition of the conditioned responses, thus indicating that acetylcholine circuits are necessary for conditioned-based plasticity in

cortex [50]. Together, these results provide a substantial argument that amygdalo-nucleus basalis projections excite cholinergic neurons that project to auditory cortex, and that these neurons facilitate long-term plasticity in cortex that is based on conditioning.

Acetylcholine has modulatory effects; therefore, cholinergic inputs by themselves are not sufficient to induce long-term plasticity in cortex. Experiments that emphasize this point have examined the timing of cholinergic-cortical inputs at various temporal intervals surrounding conditioning. The results indicate that nucleus basalis stimulation before or within the first few minutes of conditioning augmented conditioned responses [48]. Similarly, atropine applied directly to the surface of cortex eliminated these changes [51]. In other experiments, similar atropine applications given 35 and 55 min postconditioning decreased observed plasticity by 56 and 66%, respectively [51]. These results indicate that acetylcholine is an essential component for conditioned response facilitation and that the timing of its inputs in cortex can alter plastic effects within cortex. It is unclear what additional inputs when combined with the cholinergic inputs are necessary to elicit the conditioning induced changes in cortex.

Potential circuits that could facilitate cortical plasticity based on conditioning include inputs from the ascending sensory system, other sensory cortices, association cortices, memory or decision cortices, direct inputs from the amygdala, or looping circuits between these regions [4, 49]. Cholinergic circuits from the nucleus basalis target many of the cortical input circuits mentioned above [42]. These cholinergic circuits could have a variety of influences that individually or combined may help facilitate cortical plasticity. They may enhance amygdalar stimulation (to strengthen learned stimuli significance), strengthen synapses between the thalamus and cortex, or improve memory consolidation within the hippocampus [52]. In addition, the hippocampus projects back to the amygdala, nucleus basalis, prefrontal cortex, and frontal cortex [53, 54]. These circuit loops can strengthen or diminish activity within each of these other regions [53, 54]. Because all of the regions above have either direct or indirect projections to auditory cortex, there are several cortical inputs that are likely candidates to generate long-term plasticity within cortex.

Although conditioning research has primarily focused on cholinergic projections, the nucleus basalis has additional GABAergic projections to auditory cortex [4, 55, 56]. The GABAergic projections from the nucleus basalis, as well as the direct amygdalo-cortical projection, have been shown to alter the spiking characteristic of cortical neurons. However, these changes are transient and do not seem to alter the frequency specificity of neurons [57, 58]. Because frequency shifts may indicate a long-term plastic change, it is hypothesized that the direct amygdalo-cortical and indirect GABAergic pathways from the nucleus basalis may function to alter the short-term attention of the animal, while the cholinergic projection from the nucleus basalis may have a longer-term plastic effect based on conditioned responses [1, 2].

4. Amygdalar circuits: memory

Several regions of the brain have been shown to interact during consolidation of long-term declarative memory (perirhinal cortex, entorhinal cortex, parahippocampus, and hippocampus [59]).

The amygdala has extensive reciprocal connections with these nuclei [17, 59]. Because disruption of the circuits between the amygdala and this memory network can lead to deficits in contextual conditioning [60], it has been hypothesized that contextual information is determined within the memory network and then transmitted to the amygdala. However, environmental stimuli are not static. Therefore, another interpretation could be that the memory system provides information about an individual's prior experience with a set of stimuli (prior context). This prior information, when combined with current sensory inputs, could then help to shape the evolving (present context) of environmental cues within the amygdala.

Because the circuits between the amygdala and memory networks are reciprocal [17], these circuits have also been hypothesized to enable declarative memory information from the hippocampus to be integrated with emotional memories within the amygdala [61]. This hypothesis, while fundamentally sound, seems fairly limited in scope. It is reasonable to imply that emotional memories must include amygdalar processing, because emotion is not viable without salience information; however, the amygdala is not the only brain region involved with this process. Neurons within several brain regions have exhibited characteristics such as prolonged neuronal activity, formulate long-term potentiation responses, or exhibit altered dendritic morphology that are commonly believed to be neuronal forms of short or long-term memory (amygdala [31, 62]; ventral tegmental region [63]; prefrontal cortex [63, 64]; bed nucleus of the stria terminalis [65]; paraventricular nucleus [66]). Because each of these regions is highly interconnected, it is more likely that a larger network of circuits involving multiple looping circuits between executive, decision, emotion, and modulatory brain regions work with amygdalar and memory networks to perform these functions.

Like the amygdala, the memory network circuits have extensive set of inputs from multiple brain regions, and many of these regions are also interconnected. Memory regions receive either direct or indirect reciprocal inputs from sensory cortices, sensory association cortices, and polymodal sensory cortices that provide information about the environment. The reciprocal nature of these inputs is thought to be critical for long-term storage of memories in association cortices [8, 43, 53]. Additional inputs from frontal and prefrontal cortex provide higher-order information about the incoming sensory stimuli. Other inputs from the nucleus basalis, raphe, and hypothalamus provide modulatory influences over memory acquisition which in turn form reciprocal feedback loops to help maintain homeostasis within the system [43, 53].

5. Amygdalar circuits: decision and executive function

The amygdala has both direct and indirect connections with many regions of the brain involved with executive functions. These include functions such as selecting relevant information, planning how to act, deciding what type of action to take, initiating or inhibiting specific actions, evaluating the consequences of actions, and forming rules to guide future behavior [29]. Two brain regions important for these functions are the prefrontal and frontal cortices. Frontal cortex is a brain region that has been shown to encode task-specific meaning of stimuli during behavioral tasks [67]. It receives sensory input, thalamic input, as well as modulatory

inputs. Its primary projection is to the frontostriatal loops [68, 69]; however, it also interacts indirectly with association cortices, hippocampus, and the amygdala [68]. Because of the ability of neurons in this region to quickly adapt to various behavioral paradigms, it is thought that this region may contribute to decision processes that shift behavior based on changing environmental and reward salience [67].

Although the extrinsic circuitry of the frontal cortex is not as complex as prefrontal cortex circuits, manipulation of these circuits can significantly influence numerous regions of the brain through secondary looping circuits. Local field potential shifts within the frontal cortex, for example, resulted in alterations of neuronal responses within auditory cortex that correspond to the behavioral task [67]. Thus, descending circuit from the frontal cortex is likely to facilitate shifts in cortical activity (i.e., attention) toward behaviorally relevant stimuli.

Prefrontal cortex is a more highly connected executive brain area than frontal cortex. It has reciprocal projections to the amygdala, neuromodulatory centers (e.g., raphe, locus coeruleus, nucleus basalis, and ventral tegmental area), basal ganglia, cingulate cortex, hypothalamus, association cortices, striatum, thalamus, insula, nucleus accumbens [4, 17, 23, 70–76]. It also receives unidirectional inputs from the hippocampus [72].

The primary function of the prefrontal cortex is formulation of decisions; but it has also been implicated in assisting with emotional regulation [77]. These functions are highly dynamic due to rapid changes in environmental signals and contexts that require analysis for optimal behavioral responses. Therefore, it is not surprising that prefrontal cortex activity can be substantially impacted by various regions of the brain. Hippocampal inputs, for example, synchronize the activity of the hippocampus and prefrontal cortex during working memory tasks [78]. The synchrony is maximized during acquisition of new roles or during moments of decision [79]. During these synchronous moments, the prefrontal cortex exhibits increases in neuronal firing that through indirect circuits influence the hippocampus and further synchronize the regions [79]. Lesions or desynchrony of the pathways can dramatically impact the accuracy of decision and emotional processing [80].

The synchrony of the hippocampus and prefrontal cortex may also be instrumental for convergence of inputs from these regions within the nucleus accumbens. Experiments have shown that precisely timed inputs facilitate neuronal responses [81, 82]. Because this region has reciprocal projections with the prefrontal cortex, nucleus accumbens facilitation is thought to gate goal-directed behaviors. Increased synchrony between the hippocampus and prefrontal cortex induces augmented facilitation within the nucleus accumbens. This augmented response can then be sent back to the prefrontal cortex to increase the accuracy of behavioral responses [80, 83].

Neuromodulators (e.g., acetylcholine, dopamine, serotonin, noradrenaline, and histamines) can also alter prefrontal cortex activity. Infusion of these modulators into the prefrontal cortex has been shown to dramatically alter behavioral performance [76]. Because the influence of these modulatory circuits is fairly critical to prefrontal cortex function, it is reasonable to assume that the reciprocal nature of the circuit helps to tightly regulate modulatory output for optimal performance [76]. Such regulation can become fairly complex because the modulatory

circuits have numerous input and output circuits that both influence and interact with each other [76].

Outputs of the prefrontal cortex to the amygdala alter amygdalar activity based on dynamic changes in perceived significance to the individual [77]. In animal models, lesions of the prefrontal cortex cause losses in an animal's ability to alter its perception of a stimulus as well as change its behavioral responses to the stimulus [84, 85]. In humans, similar lesions lead to additional symptoms that include the inability to reason and suppress impulses [86].

6. Amygdalar outputs: emotion

Stimulation of the amygdala in humans has been shown to produce emotional responses including hallucinations, fear, rage, and pleasure [17]. Emotion can be defined as physiological changes (e.g., hormonal changes, changes in heart rate, etc.) that occur as a result of conditioned responses. Another way of thinking about this concept is that emotions are alterations in physiology produced by positive or negative reinforcement. Positive reinforcement is the addition of stimuli that increase or maintain a behavior, while negative reinforcement is the removal of noxious or aversive stimuli [87].

An example of a positive reinforcement may be a food reward to an animal, such as Pavlov's dog [88]. In these experiments, dogs learned to associate a food reward with the presentation of a bell [88]. The positive influence of the food was caused by amygdalar activation of dopaminergic mesolimbic pathways (i.e., pleasure centers within the brain). These centers include the nucleus accumbens and ventral tegmental area reward systems [89]. Release of dopamine from pleasure centers leads to behavioral and physiological changes in an animal or individual (e.g., smiling, dancing, foot tapping, physiological arousal) [89]. In the case of Pavlov's dog, the drooling response occurs via activation of the reward circuits that release dopamine. Because dopamine has been shown to directly influence salivary glands [90], activation of pleasure centers induced the behavioral effect of drooling in the dog. In this way, stimulation of the amygdala can activate a wide array of circuits that in turn have measurable physiological and behavioral effects [17].

Another brain system that helps to control emotional physiology is the hypothalamus. The hypothalamus synthesizes neuropeptides that are able to modulate both brain and body physiology [91] as well as numerous reciprocal circuits (e.g., prefrontal cortex, nucleus accumbens, hippocampus, amygdala, nucleus basalis, raphe). The hypothalamus also receives input from the midbrain and brainstem, and helps to modulate autonomic function within the parabrachial nucleus and periaqueductal grey [91]. The connections with autonomic circuitry regulate breathing, blood pressure, heart beat, dilation and constriction of blood vessels, as well as fight or flight, and rest or digest responses.

Many researchers utilize auditory stimuli when studying emotional processing. In several studies, amygdalar circuits have been shown to respond to sounds with either positive or negative affect, but are not responsive to sounds with neutral affects [31, 92]. Other functional

magnetic resonance imaging (fMRI) human studies used visual stimuli (i.e., kissing scenes from romantic comedies) paired with an auditory stimulus (i.e., happy, sad, or no music). Results from these studies showed decreases in cortical activation to sad music and increases to happy music. The changes in cortical activation correlated to increases or decreases in transmission between the fusiform gyrus and the amygdala, respectively. Therefore, it was proposed that amygdalo-fusiform gyrus connections modulate the emotional experience of the viewer to the movie and thereby help to alter the attention of the individual to relevant auditory cues. In this way, the auditory stimuli may help to initiate an emotional response to the stimuli, while the emotional response strengthened the attention of the individual to the auditory stimuli [93].

The physiological changes that we classify as emotion can also occur via alterations in hormones. For example, mothers have a hormonal response to the cry of their own child, but not to the cry of other children [5]. We hypothesize that the maternal attention is facilitated by interconnected feedback loops from the amygdala, prefrontal cortex, and memory network. This response is likely augmented by hormonal release that interacts with each of these brain regions [5]. Depressed mothers, on the other hand, do not have the same hormonal response to the sound of the infant's cry [94]. They attend less to the sound, and are less likely to actively care for the needs of the infant [95]. It is possible that disruption of one or more of cortical, limbic, and executive loops may dampen the significance of the infant cry within the amygdala and thus either actively inhibit or dampen the influence within the hypothalamus (increasing hormonal release) and decreasing hormonal activity within other regions of the brain (e.g., frontal cortex, bed nucleus of the stria terminalis, and amygdala) [96]. Reduced circuit activation could also decrease facilitation within modulatory, memory networks, and executive centers. This overall dampening of excitation would lessen the inclination of the individual to respond appropriately to the infant cry.

7. Dysfunction and pathology

There are varying forms of psychosis (schizophrenia, affective disorders: bipolar disorder, depression, anxiety disorder) as well as behavioral disorders (e.g., autism, attention deficit disorder) in which the brain does not accurately decipher or convey appropriate behavioral responses to environmental stimuli [97–99]. These issues are caused by problems with one or more of the interconnected circuits between the limbic, memory, sensory, and executive centers of the brain [99]. Because of the multiple interactions of each circuit, a wide array of disparate symptomologies can occur: problems with attention, memory, incongruous decisions, hallucinations, problems identifying accurate significance to stimuli, and exaggerated or inappropriate reactions to stimuli [97–99].

Human populations with these disorders have shown various anatomical, electrical, and functional pathologies. The activity and overall brain size of the prefrontal cortex, hippocampus, and amygdala have shown to be altered in patients with schizophrenia, bipolar disorder, and depression [97, 99, 100]. Although these types of variations are common in psychiatric patients, the number of days that a depressed individual goes untreated has been shown to

dynamically affect the size of their hippocampus [101]. Therefore, these forms of psychosis are dynamic.

The adaptable nature of brain systems associated with psychosis also allows for the development of successful therapeutic alternatives to help reset the synchrony of the system. However, finding effective therapies has been a challenge. Because of the progressive nature of several disorders, the original impetus is difficult to discern. Altered activity within the amygdala, hippocampus, and prefrontal cortex may either be resultant from, or the cause of, additional variations in the activity of the thalamus, [102]; disrupted gamma oscillations in cortex [103], inappropriate excitation within the anterior cingulate cortex [100], and more reactive dopamine circuits [99]. Understanding the interconnections and intricacies of the loops will help build a framework of potential pathology whereby more effective therapeutic strategies can be formulated in the future.

Because many psychiatric illnesses are progressive, the prognosis of affected individuals would be improved if they could be identified and treated earlier. Beyond genetic risk factors, there are several groups of individuals in the general population that are at-risk for mental dysfunction (i.e., individuals exposed to external stressors or various forms of mind-altering drugs).

Although stress and alcohol consumption, in moderation, do not directly lead to psychosis, they could increase desynchrony of brain circuits. In a normal system, the highly interconnected nature of limbic, sensory, associative, memory, and executive brain regions allows an individual to maximize appropriate behavioral responses to their environment. Feedback mechanisms between these regions help to keep the system functioning within normal rhythms when presented with external stressors or manipulations. These rhythms can be compromised by sudden changes in electrical activity.

Alcohol consumption, for example, has depressive influences on brain activity by temporarily potentiating GABAergic and glycine receptors while depressing N-methyl-D-aspartate receptors [104]. In normal individuals, the influence of moderate alcohol consumption can be overcome as the system rapidly adapts to the temporary insult. However, when the external stressor becomes more pronounced, it can destabilize the rhythms of these circuits to a degree that leaves them more vulnerable to the dysrhythmia of psychosis. This idea is supported by the fact that individuals that utilize alcohol chronically have been shown to be much more prone to the development of a psychosis (e.g., depression, schizophrenia) [105].

Other stressor can have similar effects. Stress can inhibit plasticity in the hippocampus, increase excitability in the anterior cingulate cortex, elevated cortisol release through the hypothalamic-pituitary-adrenal circuits, and modulate hormonally modulate executive and memory circuits [106–109]. Excessive exposure to stress over extended periods of time can lead to long-term alterations in brain patterns, de-optimize circuit function, and leave the brain more prone to additional desynchrony and psychosis [109]. Therefore, education of the general populous (including children) as well as military personnel about the importance of moderation and stress-relieving techniques may help to decrease the number of individuals that develop psychosis or behavioral disorders into the future.

8. Conclusions

Current research supports the idea that multiple looping circuits from sensory, memory, association, and executive brain regions are combined within the amygdala to determine the significance of environmental stimuli. This information is utilized to alter the firing characteristics of other brain circuits and support higher-order functions such as focusing attention on relevant sensory cues as well as learning and decision making. Because the targets of amygdalar circuits are highly interconnected with each other, changes in one region of the brain have widespread influences throughout the system. We hypothesize that the interconnected nature of the circuits facilitates flexibility within the system, which in turn enables the brain to respond and react quickly to environmental changes.

Although the complexity of the circuitry may allow rapid adaptations, dysfunctions in the firing rhythms, neurotransmitter release, or abnormalities in connections can influence numerous brain regions. This results in cortical processing and behavioral actions that are dissonant with the environment. Psychiatric, mood, and attention disorders are ideal examples of limbic circuit dysfunction. Symptoms from these disorders range from visual or auditory hallucinations, paranoia, delusions, inappropriate social or emotional responses, as well as learning and memory deficits [110–114]. The interconnected nature of the circuits involved make treatment of these patients more complex. Better understanding of the interconnections and functions of each circuit can help us identify the mechanisms and progression of these disorders and devise effective therapies for both the symptoms and psychosis.

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