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Review Article

Molecular signatures of Social Fear Learning with regenerative medicine

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Abstract

Social Fear Learning (SFL), the mechanism through which people develop fear by watching others, is an important focus in life sciences, particularly for comprehending the origins of anxiety disorders and the passing of trauma across generations. This study explores the molecular foundations of SFL, emphasizing the identification of crucial brain areas and genes that play a role in this mechanism.

An extensive examination of current literature indicated the participation of the amygdala, prefrontal cortex, hippocampus, anterior cingulate cortex, and insular cortex in SFL. In these areas, particular genes such as Lsamp, Hpcal4, Kif2a, Nsf, Ppid (found in the amygdala), and ADAR3 and CREBRF (located in the hippocampus) were identified, and their roles in forming fear memory, synaptic function, and processing emotions were studied. Protein-protein interaction (PPI) networks were developed to clarify the molecular framework of these genes.

The results emphasize the interrelated functions of particular brain areas and gene networks in influencing how beings perceive threats via social signals, providing a basis for upcoming molecular and behavioral studies in disorders linked to fear and anxiety. This research fills the gap in comprehending the molecular processes of SFL, opening possibilities for therapeutic strategies as Regenerative Medicine aimed at addressing dysfunctional social learning.

Keywords: Social fear learning, Regenerative medicine, Fear conditioning, Vicarious fear learning, Social cognition.

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1. Introduction

To understand how fear is passed between individuals and across generations, we need to get familiar with a concept known as Social Fear Learning. This idea isn't just another scientific term—it's actually a key to understanding how people (and animals) learn to fear things not through direct experience, but by watching someone else react with fear. Also known as Vicarious Fear Learning, this process has been the focus of a lot of research, especially in understanding conditions like PTSD and phobias, where certain cues or signals often trigger fear responses. In basic terms, Social Fear Learning happens when an individual picks up on a fear response from someone else and then starts to fear the same thing, even if they've never had a bad experience with it themselves. Think of it this way: instead of learning that fire burns because of touching a flame, you learn to fear it because you saw someone else recoil in pain. That's the core of Social Fear Learning—it's a form of associative learning, but the fear isn't acquired through a physical shock or threat. Instead, it's transmitted through behavior and emotion.[1]

From a survival standpoint, this type of learning makes a lot of sense. Recognizing danger quickly, even without firsthand experience, gives us a clear evolutionary edge. We learn about threats either through direct exposure or by watching others—Social Fear Learning falls into the latter category. Researchers use this framework to explore how fear spreads within groups or families, and they've looked at both human and animal behavior to figure out what's happening beneath the surface. What's becoming clear is that both behavioral patterns and brain activity are involved, and even

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deeper than that, molecular and genetic processes seem to play a role too.[1]

In humans, Social Fear Learning depends on a mix of social awareness and the brain's built-in fear-learning systems. We often learn through watching or being told, and a number of brain regions are central to this process. The amygdala, which is heavily involved in processing emotions like fear, plays a major role. So does the anterior cingulate cortex, which helps us recognize emotions in others and feel empathy. The hippocampus, known for memory and context processing, is also active. Research shows that even infants can pick up on their caregivers' fear reactions, learning to be wary of certain things before they're even physically capable of exploring on their own. This kind of early emotional learning can shape how we react to the world—and it may even lay the foundation for cultural behaviors and traditions based on fear and avoidance.[1]

1.1. Social fear and anxiety

Interestingly, these socially learned fears don't just help with survival—they also seem to contribute to anxiety, especially when fear is learned from trusted figures like parents. Experiments in both human and animal models show that social fear can be transmitted in daily life in subtle ways, and these early experiences can have long-term effects. One example comes from studies in mice. When mice are raised in social isolation, they struggle to learn fear by observation. Even though they still respond normally to direct fear conditioning (like a shock), they don't pick up on social fear cues the way mice raised with others do. This suggests that social development is essential for learning fear from others.[2]

Zooming in further, there's growing interest in what's happening at the molecular level during Social Fear Learning. Many of the brain areas involved overlap with those seen in classical fear conditioning, and similar chemical pathways are activated. This molecular insight could help us better understand disorders where fear responses are heightened or poorly regulated. By identifying specific brain circuits and molecules involved, we might one day develop more effective treatments—whether through drugs, behavioral therapy, or even regenerative medicine approaches that repair damaged fear circuits or regulate emotional memory.[3]

There's a strong connection between social cognition—our ability to read and understand others—and the way we learn fear socially. Compared to classical fear learning, which is based on direct harm, Social Fear Learning is all about interpreting and processing social information. And it's not just about watching—it's about understanding and internalizing what we see. Social fear isn't learned in a vacuum, it depends on interaction, connection, and development. Without that social exposure, the system doesn't work the same way. That's why understanding these mechanisms is not just important for neuroscience, but also for psychology, child development, and even public health. Social Fear Learning is more than a scientific concept—it's a powerful insight into how we share emotional experiences, how fear spreads in a community, and how deeply these patterns are embedded in our biology. By studying it from a molecular, behavioral, and social perspective, we open the door to better mental health interventions, deeper understanding of trauma, and maybe even ways to break harmful fear cycles that get passed down through generations.[4,5]

Regenerative medicine is a field that focuses on restoring or replacing tissues and organs damaged by injury, disease, or aging. This is achieved through a variety of advanced biomedical approaches, including the use of stem cells, gene therapy, biocompatible materials, and targeted neuroregenerative techniques.

In the context of the brain, regenerative strategies are being actively investigated for their potential to:

1. Repair neural damage caused by conditions such as stroke, traumatic brain injury, or neurodegenerative diseases like Parkinson's disease.
2. Enhance neural plasticity, allowing for the reorganization and strengthening of brain circuits that support learning, memory, and emotional regulation.
3. Support recovery from psychiatric and neurodevelopmental disorders, where disruptions in brain connectivity and function contribute to cognitive and emotional impairments.

These approaches hold promise for not only healing damaged neural tissues but also for restoring critical functions involved in mood, behavior, and cognition.[6]

2. Methodology

The primary objective of this review is to investigate Social Fear Learning (SFL) from a molecular perspective and discussing the Regenerative Medicine as a therapeutic tools to effectively tackling dysfunctional Social Fear Learning. The study aims to identify and analyze the specific brain regions, genes, molecules, and hormones involved in regulating SFL, with a particular focus on how these elements interact within the brain to mediate fear learning via social exposure. To build a foundational understanding, it began with a comprehensive review of scientific literature, particularly studies that examine SFL from neurobiological and molecular viewpoints. This was achieved through an extensive literature review using platforms such as PubMed and NCBI, where peer-reviewed articles on molecular neuroscience and fear conditioning were consulted. The genes identified are functionally linked to fear regulation, synaptic plasticity, and stress responses, specifically within the amygdala and hippocampus—two regions central to SFL.

Upon identifying the core genes involved in SFL, a Protein-Protein Interaction (PPI) Network has been

constructed for all the identified genes, helps elucidate the broader network of protein interactions involved in the cellular processes underlying social fear responses. Using the STRING Database, the PPI network for all the identified genes has been constructed.

Future work will expand the PPI network to include other identified genes and explore potential therapeutic targets for conditions where social fear becomes maladaptive, such as PTSD, phobias, or autism spectrum disorders. Further experimental validation of these gene functions using transgenic models and brain imaging will be essential to map the molecular architecture of Social Fear Learning.

3. Results

Several key findings were obtained, supporting the central aim of investigating Social Fear Learning (SFL) from a molecular perspective. The results are organized into four main categories, reflecting the progression from identifying brain structures, to gene discovery, functional characterization, and finally, protein-protein interaction (PPI) mapping.

3.1. Result I: Brain regions involved in social fear learning

Through an extensive literature review and analysis of current neuroscience research, several brain regions were identified as being involved in the regulation of Social Fear Learning. These regions are associated with emotional processing, cognitive appraisal, memory formation, and the social evaluation of threat cues. The primary brain areas implicated in SFL include:

1. Amygdala (Lateral and Basal nuclei)
2. Prefrontal Cortex
3. Hippocampus
4. Anterior Cingulate Cortex (ACC)
5. Anterior Insular Cortex (AIC)
6. Inferior Parietal Lobule
7. Temporoparietal Junction (TPJ)

These areas interact dynamically during socially transmitted fear responses and are thought to integrate emotional signals with contextual and social information.

3.2. Result II: Genes identified in key brain regions related to SFL

Following the identification of brain regions involved in SFL, a detailed examination of scientific databases (including PubMed and NCBI) enabled the identification of specific genes expressed within these regions. These genes are known to influence synaptic plasticity, neurotransmission, stress response, and memory—all critical functions during Social Fear Learning.

1. Genes expressed in the amygdala
   a. Lsamp – *Limbic system-associated membrane protein*: Involved in neuronal connectivity and emotional behavior.
   b. Hpcal4 – *Hippocalcin-Like 4*: Plays a role in calcium signaling and synaptic transmission during fear learning.
   c. Kif2a – *Kinesin Family Member 2A*: Participates in axonal transport and neural network formation.
   d. Nsf – *N-Ethylmaleimide Sensitive Factor*: Crucial for vesicle fusion and neurotransmitter release.
   e. Ppid – *Peptidylprolyl Isomerase D*: Implicated in protein folding and synaptic regulation under stress conditions.
2. Genes expressed in the hippocampus
   a. ADAR3 – *Adenosine Deaminase Acting on RNA 3*: Regulates RNA editing processes involved in memory and learning.
   b. CREBRF – *CREB3 Regulatory Factor*: Linked to cellular stress responses and modulation of energy balance; contributes to memory formation.

These genes were selected for further functional analysis due to their relevance in both classical fear conditioning and socially mediated fear learning, particularly in rodent models.

3.3. Result III: Functional roles of identified genes in social fear learning

Having identified these genes, the next phase of research involved examining their functional significance during Social Fear Learning, specifically within the framework of fear conditioning paradigms.

1. Genes such as Lsamp, Hpcal4, and Kif2a, found in the lateral nucleus of the amygdala, were shown to be activated following fear conditioning, indicating their role in synaptic remodeling and signal integration in response to social threat cues.
2. ADAR3, expressed in both the hippocampus and amygdala, was linked to contextual fear learning, with knockout models demonstrating deficits in memory and increased anxiety-like behavior.
3. CREBRF was shown to be upregulated during learning events that involve emotional or social content, suggesting a role in encoding emotionally salient experiences.

Together, these findings provide molecular evidence that these genes contribute to the neuromolecular circuitry supporting Social Fear Learning.

3.4. Result IV: Protein-protein interaction (PPI) networks for genes involved in SFL

To understand how these genes operate within broader molecular networks, Protein-Protein Interaction (PPI) Networks were constructed using the STRING database. These networks help illustrate the molecular context in which each gene operates, shedding light on potential co-regulatory proteins and signaling pathways.

PPI networks were generated for the following genes:

1. Amygdala-associated genes: *Lsamp*, *Hpcal4*, *Kif2a*, *Nsf*, *Ppid*
2. Hippocampus-associated genes: *ADAR3*, *CREBRF*

3.4.1. Example: Lsamp PPI network

The Lsamp protein interacts with several functionally relevant proteins involved in neural development, cell adhesion, and synaptic modulation, including:

1. NCAM1 – Neural Cell Adhesion Molecule 1
2. CNTN2 – Contactin-2
3. GAP43 – Growth-Associated Protein 43
4. NEGR1 – Neuronal Growth Regulator 1
5. NRCAM – Neuronal Cell Adhesion Molecule

These interactions suggest that Lsamp plays a critical role in neuronal wiring, fear-related behavior, and adaptive emotional learning, particularly in social contexts.

These results collectively support the central hypothesis that specific genes expressed in distinct brain regions orchestrate the molecular underpinnings of Social Fear Learning, particularly through their involvement in fear memory formation, synaptic function, and emotion processing. The combination of neuroanatomical and molecular insights provides a comprehensive foundation for future experimental work exploring therapeutic targets for disorders involving abnormal social fear processing, such as PTSD, phobias, and ASD.

In the below-mentioned Protein-Protein Interaction network of the “Lsamp” protein, (**Figure 2**a) associated protein partners that are accompanied by the “Lsamp” protein identified. Cntn3, Sprn, Opcml, Mdga2, Cntn5, Thy1, Ntng1, etc., are the associated protein partners of the Lsamp gene.

The figure provided illustrates the protein-protein interaction network for the specific gene “Hpcal4,” (**Figure 2**b) which plays a role in the regulation of Social Fear Learning. This Protein-Protein interaction network of the “Hpcal4” gene reveals additional protein partners linked to “Hpcal4,” including Rnpep, Dgkg, Rasgrf1, Caly, Slc35f4, Inpp5b, Wdr96, Nxt2, Pole4, and Rsbn1, which assist the “Hpcal4” gene in carrying out its functions.

In the previously described Protein-Protein Interaction Network of the “Kif2a” Gene (**Figure 2**c) , we can observe its interacting protein partners like Plk1, Incenp, Bub1, Cdk1, Clasp1, Auekb, Ckap5, Ndc80, and others, which are involved with the “Kif2a” Gene to effectively carry out the specified process.

The figure discussed below illustrates the Protein-Protein Interaction Network for the 'Nsf' Gene (**Figure 2**d) located in the amygdala, which plays a role in regulating Social Fear Learning. In addition, it distinctly illustrates the related protein partners like Snap25, Stx5a, Ykt6, Scfd1, Napa, Stx16, Stx17, etc., which are discovered to be engaged with the "Nsf" gene in carrying out the specified process.

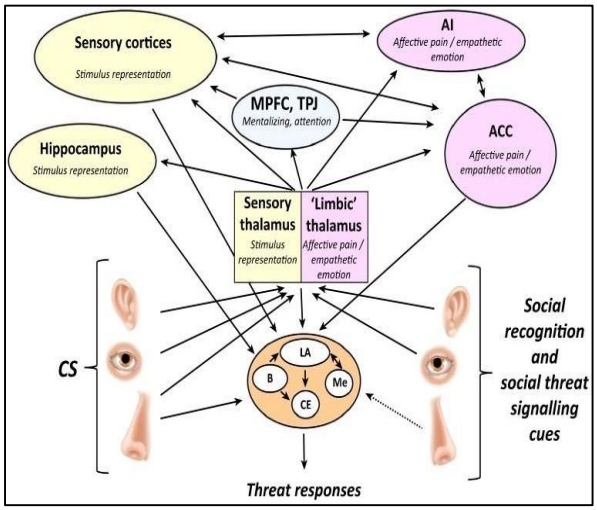

Figure 1: Neural systems of social fear learning[1]

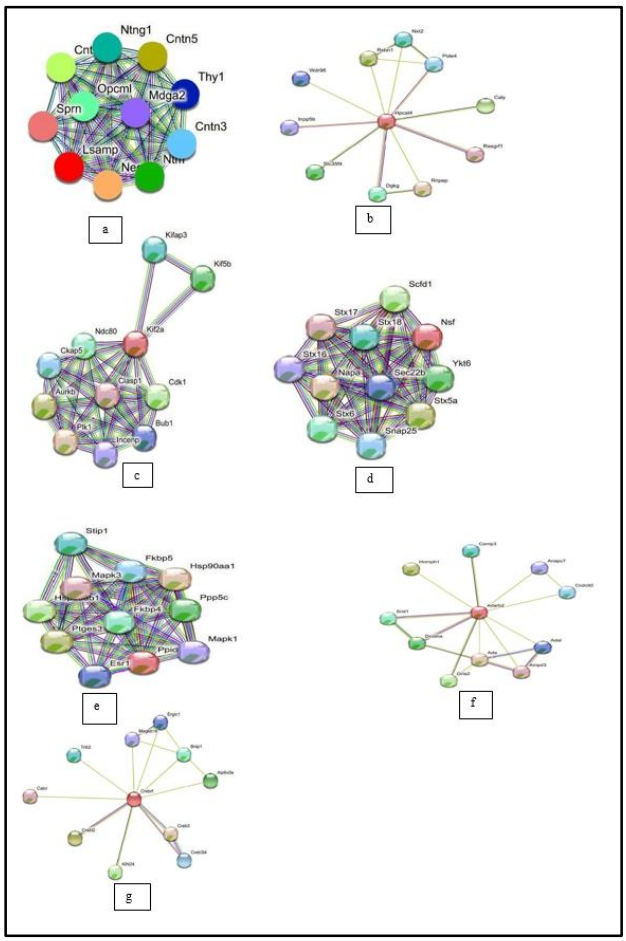

Figure 2: a: STRING Network of “Lsamp” protein; **b:** STRING Network of “Hpcal4” Gene; **c:** STRING Network of “Kif2a” Gene; **d:** STRING Network of “Nsf” Gene; **e:** STRING Network of “Ppid” Gene; **f:** STRING Network of “ADAR3” Gene; **g:** STRING Network of “CREBRF” Gene.

The Protein-Protein Interaction Network for another specific gene located in the amygdala, namely the "Ppid" gene (**Figure 2**e), which plays a role in the regulation of Social Fear Learningis detailed here. This gene interacts with other related protein partners, including Ptges3, Mapk1, Esr1, Stip1, Fkbp5, Hsp90aa1, Ppp5c, and others, which, along with the 'Ppid' gene, contribute to the overall process.

The Protein-Protein Interaction Network of the "ADAR3" Gene (**Figure 2**f) is described clearly, allowing us to comprehend its operation and other related protein partners like Snd1, Anapc7, Ccdc92, Adal, Ampd3, Gria2, Ada, etc., which assist the "ADAR3" Gene in completing its tasks effectively.

The Protein-Protein Interaction Network for the "CREBRF" Gene (**Figure 2**g) can be comprehended from this, as well as the other related protein partners of the "CREBRF" Gene , like Mageb16, Bnip1, Ergic1, Trib2, Calcr, Atp6v0e, Creb3, etc., each of which plays a distinct role alongside the "CREBRF" Gene in appropriately regulating the specified process.

4. Discussion

Attributes of different brain regions involved in social fear learning

Social Fear Learning (SFL) engages a network of brain regions, many of which are also implicated in Classical Fear Conditioning. Notably, areas such as the amygdala, hippocampus, insular cortex, and anterior cingulate cortex each contribute uniquely to the processes underlying socially acquired fear.[1]

4.1. The role of the amygdala

The amygdala, particularly the lateral nucleus (LA), plays a central role in Social Fear Learning. This region is where sensory inputs related to both the conditioned stimulus (CS) and the unconditioned stimulus (US) converge, facilitating synaptic plasticity—a core mechanism behind learning and memory in fear conditioning. Studies involving both humans and rodents have consistently demonstrated heightened amygdala activity during SFL. In rodent models, pharmacological inactivation of the LA disrupts the acquisition of Social Fear Learning, indicating that a functioning amygdala is essential for encoding socially transmitted threat responses. These findings parallel its established role in Classical Fear Conditioning, confirming the amygdala's broader importance in both direct and indirect forms of fear learning.[7,8] The amygdala is widely recognized as the core structure involved in both classical and socially mediated fear learning. Within the amygdala, several nuclei—including the lateral amygdala (LA) and medial amygdala (MeA)—are critically involved in encoding, integrating, and responding to emotionally salient stimuli. Research has identified a specialized intra-amygdala circuit connecting the LA to the MeA, which enables organisms to interpret and act on socially derived environmental cues indicating threat. Disruption to this intra-amygdala pathway diminishes the ability to recognize and respond appropriately to such cues, thereby impairing Social Fear Learning. Notably, gene knockout studies in rodents have shed light on the molecular basis of these circuits. For example, deletion of the NRXN1 gene—linked to autism spectrum disorders—has been shown to impair behavioral responses associated with the LA-MeA pathway, indicating that proper gene expression in the amygdala is essential for processing socially transmitted fear.[8]

In animal models using the Social Fear Conditioning (SFC) paradigm, a demonstrator rat undergoes classical conditioning, while an observer rat is exposed to the demonstrator's fear responses. The observer's acquisition of fear depends on the functional integrity of the LA-MeA connection. Chemogenetic inactivation of either the LA or MeA during this paradigm disrupts fear learning, demonstrating that this connection is both necessary and sufficient for SFL. Interestingly, these pathways appear to be specific to social learning, as the same disruptions do not impair direct (non-social) associative learning.[8]

4.2. Anterior cingulate cortex (ACC)

The anterior cingulate cortex (ACC) is another key region implicated in the regulation of threat responses. In both animal and human studies, ACC activity increases during Social Fear Learning, reflecting its involvement in emotional and cognitive processing of socially derived threats. Interestingly, rodent studies have shown that inactivating the ACC impairs Social (or Observational) Fear Learning while leaving classical fear conditioning intact. This suggests that while the ACC plays a critical role in the social transmission of fear, its function in traditional fear conditioning may be more limited. **[1,9]** The ACC is part of the brain's affective processing system, receiving projections from several key regions, including the midline and intralaminar thalamic nuclei (MITN)—components of the medial pain system. In rodent models, Social Fear Learning has been shown to correlate with MITN activity, and pharmacological suppression of MITN can inhibit the social transmission of fear. This indicates that the ACC, in coordination with MITN, may act as a crucial interface between emotional pain processing and socially derived threat learning.[9]

4.3. Ontogeny of social fear learning

Understanding the developmental trajectory of Social Fear Learning provides insight into how socially transmitted fear responses emerge and evolve, particularly during infancy and early childhood. (**Figure 1**)

4.4. Early life and caregiver influence

Rodent studies have shown that bonding with a caregiver during early life plays a significant role in shaping fear learning mechanisms. Even from birth, pups can acquire

threat responses by observing or sensing fear in their mother. This early form of social learning is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, which, in turn, increases activity in the amygdala and other regions involved in processing stress, fear, and pain.[1,10,11] Infants and young children demonstrate high sensitivity to caregivers' emotional states, which plays a critical role in early fear learning. This responsiveness enables them to learn about potential environmental threats even before they have developed the sensory or motor capabilities needed to explore their surroundings independently. Thus, Social Fear Learning during infancy serves as an evolutionarily adaptive mechanism for acquiring essential survival information.[10]

In young rodents, Social Fear Learning is often mediated through chemosignaling pathways rather than visual or auditory cues. Notably, during early development, the anterior cingulate cortex and insular cortex are not yet fully functional. As a result, infant rodents can acquire fear responses without significant activation in these areas—suggesting that early-life Social Fear Learning relies on different neural mechanisms compared to those used in adulthood. [10,11] Social Fear Learning involves a complex network of brain regions that contribute in both distinct and overlapping ways to the processing and transmission of fear-related information. While the amygdala and anterior cingulate cortex are central to this process, especially in adults, early-life Social Fear Learning relies more heavily on caregiver interactions and alternative signaling pathways, such as chemosensory cues.[10,11] These findings highlight not only the neurobiological basis of Social Fear Learning but also its developmental significance—especially in how emotional information is transmitted within families and across generations. Future research focusing on the molecular and developmental underpinnings of these brain regions could further illuminate the mechanisms that shape fear learning and its long-term psychological impact.[10,11]

Social Fear Learning (SFL) refers to the process through which an organism learns to associate a neutral stimulus with a threat by observing fear responses in another individual, known as a demonstrator or conspecific. This mechanism has been observed across species, including rodents, primates, and humans.[1] Among the various brain regions implicated in SFL, the amygdala plays a central role, alongside the hippocampus, anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), and insular cortex, each contributing distinct functions within the broader learning network.[7]

The Lsamp protein interacts with several functionally relevant proteins involved in neural development, cell adhesion, and synaptic modulation, including NCAM1, CNTN2, GAP43, NEGR1, NRCAM. These interactions suggest that Lsamp plays a critical role in neuronal wiring, fear-related behavior, and adaptive emotional learning, particularly in social contexts.

4.5. Brain circuits and neuroanatomy of social fear learning

Alongside the amygdala, several other brain regions are involved in Social Fear Learning:

1. Anterior Cingulate Cortex (ACC): Studies in rodents have shown that the ACC is engaged in vicarious fear learning, particularly during observational tasks. Functional imaging in humans confirms this involvement, showing heightened ACC activity during exposure to socially mediated threat signals. Importantly, ACC activation appears to be more closely associated with socially derived fear learning than with direct classical conditioning.
2. Insular Cortex (AIC): The insula plays a role in interoceptive awareness and emotional salience, and is consistently recruited during social learning tasks involving empathy or distress. Human neuroimaging studies have shown co-activation of the amygdala, ACC, and insular cortex during observation-based fear learning.
3. Medial Prefrontal Cortex (mPFC) and Hippocampus: Although less directly involved in early social learning in infants, these regions contribute to contextual processing, memory consolidation, and regulation of fear responses in adult SFL paradigms.

4.6. Emotional learning in infancy and maternal transmission of fear

Social Fear Learning begins early in development. Infants and young animals rely heavily on caregiver emotional cues to assess safety and threat in their environment. This early form of learning allows them to adapt behaviorally to environmental dangers before they are capable of independent exploration. Studies have demonstrated that in rats, maternal presence and fear expressions are sufficient to elicit fear learning in pups. Mechanistically, this form of learning involves activation of the amygdala and the hypothalamic-pituitary-adrenal (HPA) axis, as well as chemosensory signals, such as alarm pheromones. One study showed that maternal fear can be transferred to offspring via alarm chemosignaling and that this transmission is entirely dependent on the functional activity of the pup's amygdala. Interestingly, during the neonatal period, this process occurs without engagement of the hippocampus or neocortical structures, which are not yet fully developed. This suggests that the amygdala is innately capable of supporting social fear learning at birth, offering a rapid, evolutionarily conserved mechanism for transmitting survival-relevant information across generations.[10]

4.7. Intergenerational transmission of fear

One of the most compelling aspects of Social Fear Learning is its role in the intergenerational transmission of trauma or fear. In both animal and human studies, offspring have been

shown to acquire threat responses not only through direct exposure but also via parental experiences.

Mechanisms of intergenerational transmission may include:

1. Prenatal exposure to stress hormones
2. Altered maternal care during early postnatal life
3. Epigenetic changes in gametes
4. Chemosensory communication (e.g., pheromones)

These processes may shape the developing brain, particularly the amygdala and related networks, predisposing offspring to heightened emotional reactivity and fear sensitivity. Importantly, such transmission may contribute to the development of pathological fears, anxiety disorders, or altered social behavior later in life.[7,10]

4.8. Functional implications and disorders

Deficits in amygdala circuits—particularly the LA-MeA pathway—have been linked to social dysfunction, including traits observed in autism spectrum disorders (ASD). The inability to interpret or respond appropriately to social signals may stem from disruptions in these pathways, as evidenced by both animal gene knockout models and human clinical data.

Furthermore, the unique developmental timeline of Social Fear Learning, beginning in early infancy and shaped heavily by caregiver interactions, underscores its dual potential: while it supports adaptive learning and survival, it also forms the basis for maladaptive fear and anxiety when disrupted or exaggerated.[7,10]

Social Fear Learning relies on a specialized network of brain regions, with the amygdala at its core. The intra-amygdala circuit between the lateral and medial nuclei is crucial for processing social cues and generating appropriate emotional responses. This mechanism is not only essential for individual learning but also plays a significant role in transgenerational transmission of fear and risk-related behaviors. Understanding the neurobiological and developmental underpinnings of SFL provides insight into normal emotional development, the origins of anxiety disorders, and potential pathways for therapeutic intervention in conditions marked by social dysfunction. Continued research in this field holds promise for uncovering targeted strategies to mitigate the effects of maladaptive social learning in both clinical and educational settings.[7]

4.9. Regenerative medicine in social fear learning

Regenerative medicine is a field that focuses on restoring or replacing tissues and organs damaged by injury, disease, or aging. This is achieved through a variety of advanced biomedical approaches, including the use of stem cells, gene therapy, biocompatible materials, and targeted neuroregenerative techniques.

In the context of the brain, regenerative strategies are being actively investigated for their potential to:

1. Repair neural damage caused by conditions such as stroke, traumatic brain injury, or neurodegenerative diseases like Parkinson's disease.
2. Enhance neural plasticity, allowing for the reorganization and strengthening of brain circuits that support learning, memory, and emotional regulation.
3. Support recovery from psychiatric and neurodevelopmental disorders, where disruptions in brain connectivity and function contribute to cognitive and emotional impairments.

These approaches hold promise for not only healing damaged neural tissues but also for restoring critical functions involved in mood, behavior, and cognition.[6]

1. Neuroregeneration after trauma
    a. Individuals with chronic social fear or trauma (e.g., PTSD) show neural atrophy or dysfunctional circuits, especially in the amygdala and hippocampus.
    b. By understanding the genes dysregulated during SFL (like *Lsamp* or *ADAR3*), regenerative therapies can target these areas using:
    c. Gene therapy to modulate expression.
2. Targeted Brain Repair via Molecular Insights
    a. Regenerative medicine can use SFL molecular markers to guide precise repair:
    b. For example, if *CREBRF* is downregulated in the hippocampus in stress-induced fear, upregulating it with gene-editing tools or small molecules may restore normal function.
3. Preventing or Reversing Maladaptive Social Fear Learning
    a. Regenerative therapies could be designed to "reprogram" maladaptive fear responses at the molecular level.
    b. This could involve epigenetic modulation (e.g., histone acetylation) to reverse chronic fear-based learning.
    c. Rejuvenation of glial cells and support systems (astrocytes, microglia) involved in SFL-related inflammation and neurodegeneration.
4. Modeling and Repairing Social Cognition in Disorders
    a. In disorders like autism spectrum disorder (ASD) or social anxiety, abnormal SFL is common.

By mapping which genes or neural circuits are disrupted (e.g., intra-amygdala circuits involving *Lsamp* or *Kif2a*), brain organoids or in vitro neural models can be used to test regenerative interventions.

4.10. Gene mutations and their effects on fear expression

Epigenetic processes that regulate gene expression to create enduring transformations in cellular activity could aid in the

development of fear memories associated with PTSD. Various epigenetic mechanisms have been related to the formation of long-term memory, such as histone acetylation,[16] phosphorylation,[18] and methylation,[15] as well as DNA methylation[19] and nucleosome remodeling.[17] These epigenetic changes associated with learning may persist in the cell's state long after the learning event, resulting in durable and resilient behavior. In the case of fear memory, this indicates that epigenetic modifications might influence the enduring actions related to PTSD, such as reliving the event, steering clear of reminders that evoke trauma memories, and ongoing hyperarousal. Epigenetic processes play a role in all stages of fear memory, encompassing initial consolidation through to extinction. These mechanisms, which generate fairly consistent alterations in cellular function, could serve as an excellent target for addressing PTSD and other anxiety disorders, as they can be adjusted to reduce the intensity of fear memory development or render current fear memories less distressing.[13] Anxiety disorder rank among the most common and debilitating mental health conditions, shaped by a complicated interaction of genetic, environmental, and neurobiological elements. Recent progress in gene regulation studies provides a novel understanding of the causes, co-occurrence, gender differences, and inheritance of anxiety disorders.[14]

5. Future Directions

1. Tailored regenerative treatments grounded in unique gene expression patterns within SFL-associated pathways.
2. AI integration to forecast which molecular alterations from SFL might be reversible through regenerative methods.
3. Creation of biomarkers (e.g., gene expression of Hpcal4) to monitor treatment efficacy.

6. Conclusion

It became evident that specific brain regions are critically involved in the regulation of Social Fear Learning (SFL). These regions include the Amygdala, Hippocampus, Prefrontal Cortex, Anterior Cingulate Cortex (ACC), Anterior Insular Cortex (AIC), Inferior Parietal Lobule, and the Temporoparietal Junction (TPJ). Each of these areas plays a distinct role in processing socially acquired fear, integrating emotional, contextual, and social information. Within these brain structures, several key genes were identified as being actively involved in the regulation of Social Fear Learning. In particular, the Amygdala—notably its lateral and basal nuclei—expresses genes such as Lsamp (*Limbic System-Associated Membrane Protein*), Hpcal4 (*Hippocalcin-like 4*), Kif2a (*Kinesin Family Member 2A*), Nsf (*N-ethylmaleimide Sensitive Factor*), and Ppid (*Peptidylprolyl Isomerase D*), all of which are implicated in synaptic function, neural signaling, and plasticity associated with fear conditioning. Similarly, in the Hippocampus, two genes—ADAR3 (*Adenosine Deaminase Acting on RNA 3*) and CREBRF (*CREB3 Regulatory Factor*)—were found to be active during fear learning. These genes are associated with RNA processing, memory formation, and cellular stress responses, highlighting the molecular complexity underlying the encoding of socially transmitted fear. Thus, Regenerative Medicine emerge as an evolutionary field to target all the therapeutic areas to provide constructive therapeutic approaches towards Social Fear learning by targeting those particular brain areas and associated genes dysregulated during Social Fear Learning.

Together, these findings emphasize the interconnected roles of specific brain regions and gene networks in shaping how organisms learn about threats through social cues, offering a foundation for future molecular and behavioral research in fear and anxiety-related disorders.

7. Author Contribution

Harshita Sharma: Conceptualization, Methodology, Analysis, Writing

Rakesh Pandit: Literature Search, Interpretation

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9. Conflict of Interest

None.

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