



Published in final edited form as:

Neurobiol Learn Mem. 2020 March ; 169: 107117. doi:10.1016/j.nlm.2019.107117.

Learning-induced Intrinsic and Synaptic Plasticity in the Rodent Medial Prefrontal Cortex

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Abstract

In rodents, the anterior cingulate (ACC), prelimbic (PL), and infralimbic cortex (IL) comprise the medial prefrontal cortex (mPFC). Through extensive connections with cortical and subcortical structures, the mPFC plays a key modulatory role in the neuronal circuits underlying associative fear and reward learning. In this article, we have compiled the evidence that associative learning induces plasticity in both the intrinsic and synaptic excitability of mPFC neurons to modulate conditioned fear and cocaine seeking behavior. The literature highlights the accumulating evidence that plasticity in the intrinsic excitability of mPFC neurons represents a major cellular mechanism that interacts with synaptic changes to alter the impact of the mPFC on fear and reward circuits.

Keywords

prelimbic cortex; infralimbic cortex; intrinsic excitability; fear conditioning; cocaine

The medial prefrontal cortex (mPFC) in rodents includes the anterior cingulate, prelimbic, and infralimbic cortex. Extensive connections with both cortical and subcortical structures allow the mPFC to partake in the neuronal circuits that allow experience to modify behavior. In this review, we have compiled the evidence that associative learning of aversive and rewarding events induces plasticity in the intrinsic excitability of mPFC neurons. These intrinsic changes interact with synaptic plasticity in mPFC neurons to modulate conditioned fear and cocaine seeking behavior via changes in mPFC influence over fear and reward circuits.

Delay Fear Conditioning

The central neuronal circuit that rodents use to acquire, store, and update delay fear conditioning memories involves the amygdala, hippocampus, and mPFC (Paré et al., 2004; Giustino and Maren, 2015). During fear conditioning, incoming sensory information

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impinges on glutamatergic neurons in the lateral amygdala to induce synaptic strengthening of glutamatergic inputs from the cortex and thalamus which allows the association between the conditioned (CS) and unconditioned stimulus (US) to be stored in the amygdala circuits (Medina et al., 2002). Coincidentally, information related to the context in which the animal receives fear conditioning activates hippocampal neurons to strengthen glutamatergic synapses on CA1 pyramidal neurons (Sun et al., 2016). As discussed in depth elsewhere (Oh and Disterhoft, 2015), trace eyeblink (Moyer Jr. et al., 1996; Thompson et al., 1996), delay (Sun et al., 2016), trace (McKay et al., 2009; Song et al., 2015) and contextual fear conditioning (McKay et al., 2009) increases the intrinsic excitability of CA1 and CA3 pyramidal neurons in the dorsal hippocampus of rabbits and rats. The strengthening of synaptic and intrinsic excitability of hippocampal neurons enables them to encode information about the context related to the CS. Subsequent exposure to the CS in the appropriate context and/or when appropriate cues are presented produces a more robust firing of the hippocampal neurons that signals to the amygdala to produce a fear response. The basal amygdala and ventral hippocampus also connect with regions of the mPFC which allows higher order integration and processing of internal and external signals to generate an appropriate response. Activation of the PL tends to increase fear responses to the CS while stimulation of the IL inhibits fear response (Milad and Quirk, 2012; Giustino and Maren, 2015). On the other hand, the ACC seems to modulate remote fear recall (Frankland et al., 2004; Bergstrom, 2016).

In contrast to enhanced excitability found in hippocampal neurons (Kaczorowski et al., 2007; McKay et al., 2009), the initial recordings of randomly selected mPFC neurons in brain slices found that auditory fear conditioning depressed the intrinsic excitability of IL pyramidal neurons of male adolescent rats (Santini et al., 2008). The IL neurons fired fewer repetitive spikes during prolonged depolarization. The depression was learning-dependent, since neurons from the unpaired controls did not show the same depression. Furthermore, neurons in the PL were not affected indicating some regional selectivity. A subsequent study found that contextual fear conditioning was sufficient to depress the intrinsic excitability of IL neurons suggesting that the depression may be encoding contextual information perhaps via direct connections from the ventral hippocampus (Soler-Cedeño et al., 2016). However, the possibility that information related to the cue also contributes to the depression cannot be excluded. A recent paper demonstrated that auditory fear conditioning also depressed IL intrinsic excitability of juvenile, adolescent and young adult mice (Koppensteiner et al., 2019). Consistent with the slice recordings, single-unit recordings in awake behaving animals found that IL firing is suppressed during the recall of auditory fear conditioning (Giustino et al., 2016). In fact, the more depressed the IL firing was relative to PL firing in response to the CS correlated with the amount of freezing suggesting that IL suppression may drive fear expression (Giustino et al., 2016).

Since IL has direct projections to the amygdala (Vertes, 2004; Arruda-Carvalho and Clem, 2014) and the stimulation of the IL neurons or IL synapses in the amygdala reduces conditioned fear responses (Milad and Quirk, 2002; Adhikari et al., 2015), the prevailing model postulates that the IL inhibits the amygdala to reduce fear responses (Milad and Quirk, 2012; Giustino and Maren, 2015). Based on this model, the depression of IL intrinsic excitability after fear conditioning was interpreted to mean reduced inhibition of the

amygdala by IL which would aid in increasing the conditioned fear responses (Santini et al., 2008). However, given that only about 8% of IL neurons project to the amygdala (Gabbott et al., 2005), randomly sampling IL pyramidal neurons would unlikely include many neurons with projections to the amygdala (Santini et al., 2008; Soler-Cedeño et al., 2016). Therefore, a later study directly examined the intrinsic excitability of IL neurons projecting to the amygdala (Bloodgood et al., 2018). This study found IL neurons projecting to the amygdala were not depressed after delay fear conditioning. Instead delay fear conditioning depressed IL neurons with projections to the nucleus accumbens (NAc) (Bloodgood et al., 2018). Similarly, delay fear conditioning also depresses the synaptic activation of BLA neurons that project to the NAc (Namburi et al., 2015). Since the NAc plays a central role in promoting rewarding behaviors (Kauer and Malenka, 2007), this suggests that reduced IL and BLA modulation of the reward circuit may contribute to enhancing fear responses.

Relatively little is known about the cellular mechanisms that are activated by delay fear learning to depress the intrinsic excitability of mPFC neurons. Both delay and contextual fear conditioning increased the slow afterhyperpolarizing potential (sAHP) (Santini et al., 2008; Soler-Cedeño et al., 2016) which are produced by a calcium-dependent potassium current (Sah and Faber, 2002; Abel et al., 2004; Tombaugh et al., 2005). Calcium influx through voltage-gated calcium channels that open during prolonged depolarization activates this potassium current leading to inhibition of additional action potentials (Disterhoft and Oh, 2006). Reducing the sAHP in IL neurons by stimulation of β -adrenergic receptors (Mueller et al., 2008), muscarinic receptors (Santini et al., 2012), α 2-adrenergic receptors (Carr et al., 2007), or type 5 metabotropic glutamate receptors (mGluR5) (Fontanez-Nuin et al., 2011) increases their ability to fire barrages of action potentials. Therefore, the increase in sAHP could account for the depressed repetitive firing seen in IL neurons after delay fear conditioning. It is also possible that delay fear conditioning enhances M type potassium channels (Santini and Porter, 2010) or small calcium-activated (SK) potassium channels (Criado-Marrero et al., 2014) which also modulate IL repetitive firing. Although, future experiments are needed to test this possibility, reducing IL intrinsic excitability by acutely stimulating M channels did enhance the recall of conditioned fear (Santini and Porter, 2010). In contrast, stimulating SK potassium channels did not alter the fear recall (Criado-Marrero et al., 2014). M channel activation also reduced the input resistance of IL neurons, whereas SK channel stimulation did not. Therefore, increasing potassium channel opening at the resting membrane potential of IL neurons is sufficient to increase fear expression.

Delay fear conditioning does not induce a global change in glutamatergic inputs onto IL neurons (Pattwell et al., 2012; Sepulveda-Orengo et al., 2013) or in IL synapses onto amygdala neurons (Arruda-Carvalho and Clem, 2014). However, more subtle synaptic changes do occur. Optogenetic stimulation in brain slices found that delay fear conditioning reduces NMDA receptor currents at ventral hippocampal synapses onto randomly selected IL pyramidal neurons (Soler-Cedeño et al., 2019). Since NMDA receptors prolong the duration of the EPSPs, facilitate bursts of action potentials, and increase Ca^{2+} in the dendritic spines (Paoletti et al., 2013), this suggests that delay fear conditioning reduces ventral hippocampal activation of IL pyramidal neurons. Furthermore, ventral hippocampal projections produce a robust feedforward inhibition in IL (Marek et al., 2018) and delay fear

conditioning did not affect GABAergic synapses onto IL neurons (Koppensteiner et al., 2019). Taken together, these findings suggest that the intrinsic and synaptic plasticity produced by delay fear conditioning would result in ventral hippocampal inhibition of IL projections during the recall of conditioned fear. In addition, the current literature suggests that delay fear conditioning induces projection-specific depression of intrinsic excitability with synapse-specific reductions in synaptic input to reduce IL activation of rewarding circuits relative to aversive circuits (Figure 1A).

Similar to the initial report (Santini et al., 2008), PL neurons projecting to the NAc or amygdala did not show intrinsic changes after delay fear conditioning (Bloodgood et al., 2018). However, delay fear conditioning strengthens glutamatergic synapses onto PL neurons (Pattwell et al., 2012) and enhances PL synapses on to amygdala neurons (Arruda-Carvalho and Clem, 2014). Together these findings suggest that enhanced synaptic input is the primary driver of increased PL activity during recall of delay fear conditioning.

Extinction of Delay Fear Conditioning

Although extinction does not erase the fear memory (Quirk et al., 2006), extinction does tend to reverse the conditioning-induced changes at the cellular level. Extinction of delay fear conditioning reversed the conditioning-induced depression of IL neuronal firing in juvenile, mid-adolescent, and adults (Santini et al., 2008; Koppensteiner et al., 2019). Extinction also reversed the enhanced sAHP induced by delay fear conditioning (Santini et al., 2008). The repetitive firing of IL neurons did not reverse until four hours after extinction training suggesting that the reversal was important for consolidation of the extinction memory (Cruz et al., 2014). In support of this interpretation, early adolescent rats that fail to recall their extinction memory also fail to reverse their depressed IL intrinsic excitability (Koppensteiner et al., 2019). Similar to acquisition of delay fear conditioning, extinction induced projection-specific changes in intrinsic excitability. The conditioning-induced depression of IL neurons with projections to the NAc was reversed by extinction suggesting a return of IL modulation of reward circuits (Bloodgood et al., 2018). Therefore, extinction reverses the depression of repetitive firing induced by delay fear conditioning during the consolidation phase.

In addition to reversing the effects of delay fear conditioning, extinction also induces some specific intrinsic changes. In unidentified IL projections, extinction reduces the fast afterhyperpolarization (fAHP) between sequential spikes (Santini et al., 2008; Cruz et al., 2014) and increased burst firing (Santini et al., 2008). The reduction in the fAHP effectively reduces the time between spikes and may underlie the increase in bursting of IL neurons in vivo that is needed for consolidation of the extinction memory (Burgos-Robles et al., 2007). Although delay fear conditioning did not affect the intrinsic excitability of IL-to-BLA projecting neurons, extinction did enhance repetitive firing of IL-to-BLA projecting neurons immediately after extinction training (Bloodgood et al., 2018) suggesting that activity of this projection contributes to reduced fear after extinction. Consistent with this, chemogenic inhibition of IL projections to BLA reduces recall of fear extinction (Bloodgood et al., 2018).

Several findings suggest that the extinction-induced changes in IL intrinsic excitability contribute to the extinction memory. First, animals which fail to recall extinction memory also fail to alter the repetitive firing of IL neurons (Koppensteiner et al., 2019). This extinction failure occurred in early adolescent mice (P27) but not in preadolescent (P24) or adult mice suggesting that the mechanisms responsible for reversing the depressed IL firing is impaired during early adolescence. Second, impairing extinction memory by blocking mGluR5 receptors also prevents the intrinsic excitability changes in IL (Sepulveda-Orengo et al., 2013). Third, the repetitive firing of IL neurons reverses with the spontaneous return of fear after extinction leaving the IL neurons depressed relative to age-matched controls (Cruz et al., 2014).

Extinction of delay fear conditioning also induces synaptic plasticity in IL neurons (Pattwell et al., 2012; Sepulveda-Orengo et al., 2013). Electrical stimulation found evidence for an increase in rectifying AMPA receptor current at synapses in IL suggesting that extinction induced the insertion of calcium-permeable AMPA receptors (Pattwell et al., 2012; Sepulveda-Orengo et al., 2013). Similar to the intrinsic plasticity these synaptic changes also required mGluR5 activation (Sepulveda-Orengo et al., 2013) suggesting that both intrinsic and synaptic plasticity share a common mechanism in IL. In addition, fear extinction also reversed the reduced NMDA receptor currents at ventral hippocampal synapses in IL pyramidal neurons (Soler-Cedeño et al., 2019). Extinction of Delay fear conditioning did not affect GABAergic synapses onto IL neurons (Koppensteiner et al., 2019). Overall, the current literature suggests that extinction of delay fear conditioning enhances the intrinsic and synaptic excitability of IL pyramidal neurons through projection- and synapse-specific mechanisms to increase IL modulation of rewarding and aversive circuits (Figure 1B).

Trace Fear Conditioning and Extinction

In trace fear conditioning the CS and US do not overlap in time as in delay fear conditioning. The temporal separation of the CS and US reduces the dependency of the learning on the amygdala while maintaining the importance of the hippocampus and mPFC (Gilmartin and Helmstetter, 2010; Raybuck and Lattal, 2011, 2014; Kwapis et al., 2014). Consistent with the differences between delay and trace fear conditioning, trace fear conditioning has different effects on IL intrinsic excitability. In contrast to delay fear conditioning (Bloodgood et al., 2018), trace fear conditioning increased the intrinsic excitability of IL-to-amygdala projecting neurons by reducing spike threshold and increasing HCN currents (Song et al., 2015). Based on the evidence that IL inhibits the amygdala (Quirk et al., 2003; Amano et al., 2010), this suggests that IL may inhibit the amygdala after trace fear conditioning which should reduce fear expression. However, trace fear conditioning and extinction can occur independent of the amygdala (Raybuck and Lattal, 2011; Kwapis et al., 2014), so the behavioral relevance of increased IL inputs to the amygdala for trace fear conditioning is unclear. Trace fear conditioning increased the intrinsic excitability of PL bursting neurons by increasing input resistance, while depressing the intrinsic excitability of PL regular firing neurons by reducing input resistance (Song et al., 2015). These findings suggest that regular spiking and bursting PL neurons may activate different amygdala circuits. Extinction reversed the intrinsic plasticity induced by trace fear conditioning in both IL and PL neurons projecting to the amygdala (Song et al., 2015).

Overall, this study suggests that trace fear conditioning increases IL and decrease PL modulation of the amygdala. After extinction, the intrinsic changes are reversed leading to a relative decrease in IL and a relative increase in PL influences on the amygdala.

Drug Seeking Behavior

Similar to fear conditioning, substances of abuse also induce neuroadaptations in the mPFC, which modifies its influence on the reward circuitry that includes the NAc, ventral tegmental area (VTA), and hippocampus. These neuroadaptations lead to dysregulated communication between regions of the reward circuitry that contributes to the development of substance use disorders.

Clinical and preclinical studies show that the direction of change in neuronal firing in the mPFC depends on the stage of drug addiction under investigation (i.e. drug consumption, withdrawal, or relapse/reinstatement). For example, human studies found that drug intake or presentation of drug-related cues activates the ACC region of the mPFC (Goldstein and Volkow, 2002). On the other hand, ACC hypoactivity is observed during drug abstinence and cognitive task performance in human addicts (Goldstein and Volkow, 2002, 2011). Below, we discuss the effects of cocaine and opiates on the intrinsic excitability (firing rate) of the mPFC neurons during the development of substance use disorder.

Cocaine

Human studies show that cocaine intake activates the ACC, while withdrawal induces hypofunction that correlates with more craving symptoms (Jentsch and Taylor, 1999; Goldstein and Volkow, 2011). Milella and colleagues found increased dopamine release in frontal and striatal regions when cocaine-dependent participants were exposed to drug-related cues (Milella et al., 2016). Similarly, preclinical studies also showed that cocaine stimulates dopaminergic projections from the VTA to the mPFC which increase extracellular dopamine in the mPFC to subsequently enhance glutamatergic signaling from the mPFC to other regions (Cornish and Kalivas, 2000, 2001; Kalivas et al., 2003, 2009; McFarland et al., 2003). Dopaminergic projections innervate mPFC neurons (Goldman-Rakic et al., 1989; Carr and Sesack, 1996). Moreover, pyramidal neurons and GABAergic interneurons contain D1 and D2 dopamine receptors, which suggests that mPFC neuronal properties are modulated during the development of cocaine addiction (Le Moine and Gaspar, 1998; Xu and Yao, 2010).

Cocaine exposure affects the intrinsic excitability of mPFC neurons. Chen and colleagues observed a decrease of intrinsic excitability in the PL pyramidal neurons in rats exposed to prolonged (two months) cocaine self-administration combined with punishment (shocks) on the last 4 days (Chen et al., 2013). Rats that continued to self-administer high levels of cocaine despite the shocks showed more depressed repetitive firing than those that reduced their cocaine intake in the presence of the shocks. However, PL pyramidal neurons from both groups were severely depressed compared to rats that never received cocaine (Chen et al., 2013). In the rats that resisted the punishment, a reduction in input resistance caused the depressed excitability. In this study, the animals were not exposed to withdrawal. In contrast,

moderate exposure to cocaine (two weeks or less) with a withdrawal period increased the intrinsic excitability of the PL pyramidal neurons (Dong et al., 2005; Nasif et al., 2005a, 2005b; Sepulveda-Orengo et al., 2018). Taken together, these findings suggest the possibility that prolonged self-administration of cocaine depresses PL repetitive firing and during withdrawal PL excitability increases. However, it is also possible that the duration of cocaine self-administration or the addition of punishment induces the depression of PL intrinsic excitability (Chen et al., 2013).

Several findings suggest that the changes in PL intrinsic excitability contribute to the cocaine-induced memories. Pharmacological reversal of the intrinsic changes prevents the cocaine-induced memories (Chen et al., 2013; Otis et al., 2018; Parrilla-Carrero et al., 2018; Sepulveda-Orengo et al., 2018). Furthermore, Parrilla-Carrero and colleagues found that PL pyramidal neurons from rats trained to self-administer cocaine show increased intrinsic excitability relative to the cocaine-yoked group, suggesting that the increased excitability is caused by associative learning (lever presses paired with cues), as opposed to being a direct effect of cocaine (Parrilla-Carrero et al., 2018). In addition, rats which fail to retrieve cocaine conditioned place preference also fail to show enhanced PL intrinsic excitability (Otis et al., 2018).

Moderate cocaine exposure also produced opposite physiological effects on pyramidal neurons from the PL and IL cortices (Dong et al., 2005; Nasif et al., 2005b; Gipson et al., 2013; Hearing et al., 2013; Otis et al., 2018; Parrilla-Carrero et al., 2018; Sepulveda-Orengo et al., 2018). Cocaine self-administration followed by extinction enhanced the intrinsic excitability of PL and depressed IL neurons (Sepulveda-Orengo et al., 2018). Sepulveda-Orengo and colleagues showed that the increased intrinsic excitability in PL neurons results from a reduction in the fAHP, which is largely regulated by voltage-gated and Ca²⁺-dependent potassium channels (Oh et al., 2010). On the other hand, the fAHP was not affected in IL, suggesting a different cellular mechanism depressed IL repetitive firing.

Other proposed cellular mechanisms that mediate the increase in intrinsic excitability of the mPFC after cocaine withdrawal include enhanced protein kinase A (PKA) activation of voltage-sensitive Ca²⁺ influx through high-voltage activated L-type channels, reduced potassium inward rectifiers (Kir), and reduced voltage-gated K⁺ currents (Dong et al., 2005; Nasif et al., 2005b; Hu, 2007; Ford et al., 2009). Other studies suggest that cocaine enhances the intrinsic excitability of PL neurons by potentiating the inhibition of Kv7 ion channels produced by dopamine released from VTA projections in the mPFC (Buchta et al., 2017; Parrilla-Carrero et al., 2018). Also, bath application of dopamine with or without cocaine, optogenetic activation of VTA projections, or bath application of clozapine-N-oxide (CNO) to activate VTA-Gq-DREADDs reduced the sAHP to increase repetitive firing of PL neurons (Buchta et al., 2017). Although most studies did not determine the projections of the PL pyramidal neurons, cocaine does increase the excitability of PL projections to NAc (Hearing et al., 2013).

In addition to enhancing PL intrinsic excitability, cocaine conditioned place preference also potentiates synaptic stimulation of PL pyramidal neurons (Otis et al., 2018). Otis and Mueller showed that retrieval of cocaine-induced memory increases spontaneous excitatory

postsynaptic currents and AMPA/NMDA ratio in PL pyramidal neurons. Inhibition of noradrenergic/cAMP-dependent signaling pathway prevents the increase of AMPA/NMDA ratio in PL neurons and reduces cocaine seeking behavior (Otis et al., 2018). Therefore, cocaine-induced learning also increases glutamatergic activation of PL pyramidal neurons.

Cocaine conditioned place preference also increases GABAergic synapses onto fast-spiking inhibitory interneurons leading to reduced GABAergic inhibition of PL pyramidal neurons (Slaker et al., 2015, 2018). These findings suggest that reduced inhibition of PL pyramidal neurons contributes to their increased excitability after cocaine exposure (Hearing et al., 2013; Slaker et al., 2015). In addition, higher concentrations of dopamine in the mPFC activate D2 dopamine receptors which decrease IPSCs (Trantham-Davidson et al., 2004; Xu and Yao, 2010). These studies suggest that cocaine activates dopamine receptors to depress GABAergic interneuron activity and subsequently increase the intrinsic excitability of PL pyramidal neurons, leading to enhanced glutamatergic transmission of PL projections in the NAc to modulate cocaine-seeking behavior (McFarland and Kalivas, 2001; McLaughlin and See, 2003; McFarland et al., 2004; Ma et al., 2013; Suska et al., 2013). In other words, increased glutamate release in the NAc core by cocaine exposure is partially due to increase activation in PL neurons (McFarland et al., 2003, 2004). In support of this, inactivation of PL prevents cue-induced reinstatement, as well as the increase of glutamate release and AMPA/NMDA ratio in the NAc (Gipson et al., 2013).

Overall, the majority of the literature suggests that cocaine-induced learning enhances the intrinsic excitability of PL pyramidal neurons while also increasing synaptic excitation and reducing synaptic inhibition. Figure 2 shows a proposed model for the mechanisms by which cocaine-induced learning alters the intrinsic excitability of mPFC neurons. However, how cocaine induces the cellular changes that regulate the intrinsic excitability in the mPFC, and in turn affect synaptic transmission in other regions of the reward circuitry remains unclear and needs to be further examined.

Future Directions

In conclusion, the accumulating evidence summarized in Table 1 suggest that aversive and appetitive learning induces plasticity in mPFC intrinsic excitability often in parallel with synaptic changes. The literature also supports the conclusion that intrinsic and synaptic plasticity in the mPFC contributes to the learned behavioral modifications. However, many unanswered questions remain. First, most if not all studies examined only male rats. Therefore, we do not know whether female rats show similar intrinsic and synaptic plasticity in response to learning. Second, although many receptors modulate the intrinsic excitability of mPFC neurons, very little is known about which receptors mediate associative learning-induced changes in mPFC neuronal excitability. Third, given the evidence of projection-specific changes in intrinsic excitability, it will be critical to evaluate learning-induced changes in the different projections to better understand how learning alters mPFC interactions with other structures. Fourth, to facilitate translation to the genetically diverse human population, we need to consider the contribution of different genetic backgrounds to the identified intrinsic and synaptic changes. For example, since the role of the mPFC in fear extinction depends on the strain of rats (Chang and Maren, 2010; Chang et al., 2010), the

corresponding intrinsic and synaptic changes may also vary with the genetic background of the animals. Fifth, we need to understand how the effects of aging on the intrinsic excitability of mPFC neurons contributes to impaired learning in aged animals (Kaczorowski et al., 2012). Finally, it remains to be determined whether deficits in mPFC intrinsic and synaptic changes contribute to human mental disorders.

Acknowledgements

This work was supported by the RCMI BRAIN and MAGIC Cores (NIMHHD G12 MD007579-27) and R15 MH116345 from the National Institutes of Health and the Catalyzer Research Grant Program (CRG-2020-00114) from the Puerto Rico Science, Technology and Research Trust.

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Highlights

1. We compiled the evidence that associative learning induces plasticity in both the intrinsic and synaptic excitability of mPFC neurons to modulate conditioned fear and cocaine seeking behavior.
2. Plasticity in the intrinsic excitability of mPFC neurons represents a major cellular mechanism that interacts with synaptic changes to alter the impact of the mPFC on fear and reward circuits.

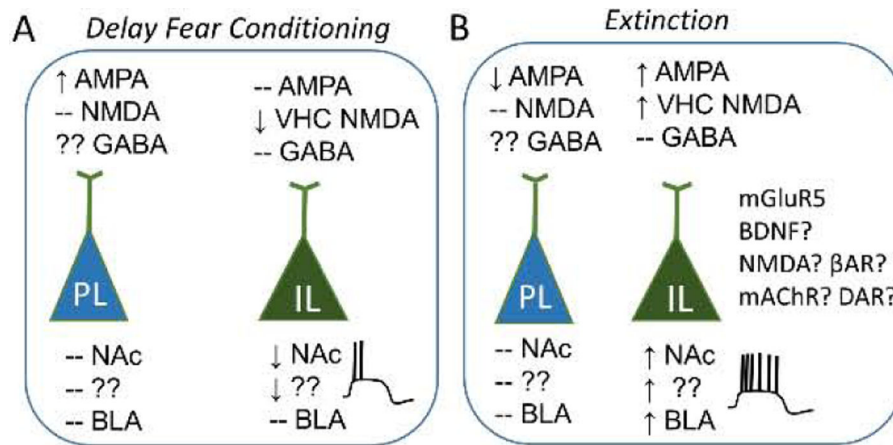


Figure 1.

This model depicts the intrinsic and synaptic plasticity induced in PL and IL neurons by delay fear conditioning (A) and extinction (B). No observed changes are indicated by -- and undetermined changes or projections are indicated by question marks.

Cocaine Seeking Behavior

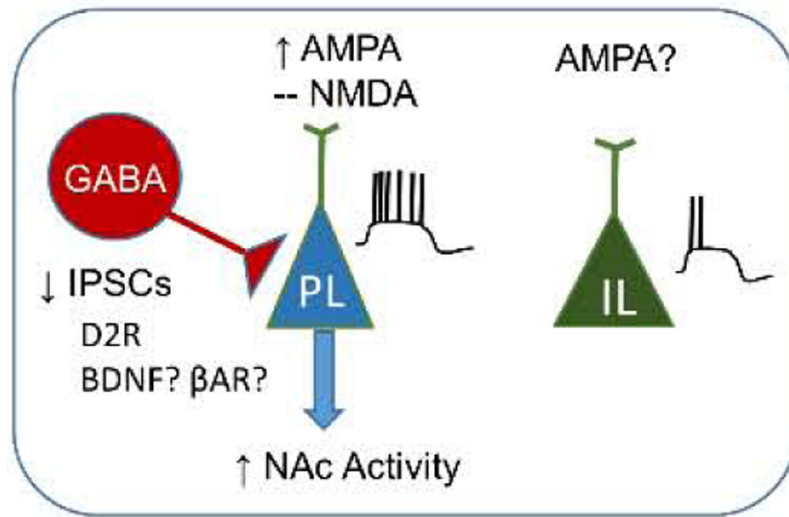


Figure 2. This model depicts the intrinsic and synaptic plasticity induced in PL and IL neurons by moderate exposure to cocaine. No observed changes are indicated by - and undetermined changes are indicated by question marks.

Table 1.

Intrinsic plasticity of mPFC neurons related to conditioned fear and cocaine seeking behavior.

Behavior	Intrinsic Plasticity of Pyramidal Neurons	Mechanisms	References
Fear Conditioning <ul style="list-style-type: none"> • Delay • Contextual • Trace 	<ul style="list-style-type: none"> • Depressed firing IL neurons/ No effect on PL neurons • Depressed firing IL neurons • Depressed firing IL-to-NAc neurons No affect on firing IL-to-BLA, PL-to-BLA or PL-to-NAc neurons • Depressed firing IL neurons • Increased firing IL-to-BLA neurons • Depressed firing PL-to-BLA neurons 	<ul style="list-style-type: none"> • Increased sAHP • Decreased input resistance • Undetermined • Increased sAHP • Decreased spike threshold • Decreased input resistance 	<ul style="list-style-type: none"> • Santini et al., 2008 • Koppensteiner et al., 2019 • Bloodgood et al., 2018 • Soler-Cedeno et al., 2016 • Song et al., 2015
Fear Extinction <ul style="list-style-type: none"> • Delay • Spontaneous recovery of fear • Trace 	<ul style="list-style-type: none"> • Increased firing IL neurons • Increased firing IL neurons • Increased firing IL-to-NAc neurons Increased firing IL-to-BLA neurons • Increased firing of IL neurons 4 hrs after extinction • Depressed firing IL neurons • Depressed firing IL-to-BLA neurons • Increased firing PL-to-BLA neurons 	<ul style="list-style-type: none"> • Decreased sAHP/ increased fAHP • Undetermined • Undetermined • Increased fAHP • Decreased fAHP • Increased spike threshold • Increased input resistance 	<ul style="list-style-type: none"> • Santini et al., 2008 • Koppensteiner et al., 2019 • Bloodgood et al., 2018 • Cruz et al., 2014 • Cruz et al., 2014 • Song et al., 2015
Cocaine <ul style="list-style-type: none"> • 1 or 5 days of i.p.cocaine injections • 3 days withdrawal from cocaine i.p. injections (5 days) • 3 days withdrawal from cocaine i.p. injections (5 days) • 2 days after CPP (8 days) 	<ul style="list-style-type: none"> • Depressed firing PL GABAergic fast-spiking interneurons • Increased firing PL neurons • Increased firing PL neurons • Increased firing PL neurons • Increased firing PL neurons/ Depressed firing IL neurons • Increase firing PL neurons 	<ul style="list-style-type: none"> • Decreased resting membrane potential and threshold • Decreased K⁺ inward rectifiers (Kir) and voltage-gated K⁺ current • Reduced voltage-gated K⁺ currents • Increased L-type calcium channel conductance • Decreased fAHP in PL/ fAHP was not affected in IL 	<ul style="list-style-type: none"> • Slaker et al., 2015 • Nasif et al., 2005b • Dong et al., 2015 • Otis et al., 2018 • Sepulveda-Orengo et al., 2018 • Parrilla-Carrero et al., 2018 • Chen et al., 2013

Behavior	Intrinsic Plasticity of Pyramidal Neurons	Mechanisms	References
<ul style="list-style-type: none"> • 16 days of extinction from self-admin.(10 days) • 1 day after self-admin. (14 days) • 2 months self-admin. 4 days of shock sessions 	<ul style="list-style-type: none"> • Depressed firing PL neurons 	<ul style="list-style-type: none"> • Reduced spike frequency adaptation, AHP, and Kv7 channels • Decreased input resistance/ increased spike threshold 	

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