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A model of amygdala function following plastic changes at specific synapses during extinction

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A B S T R A C T

The synaptic networks in the amygdala have been the subject of intense interest in recent times, primarily because of the role of this structure in emotion. Fear and its extinction depend on the workings of these networks, with particular interest in extinction because of its potential to ameliorate adverse symptoms associated with post-traumatic stress disorder. Here we place emphasis on the extinction networks revealed by recent techniques, and on the probable plasticity properties of their synaptic connections. We use modules of neurons representing each of the principal components identified as involved in extinction. Each of these modules consists of neural networks, containing specific ratios of excitatory and specialized inhibitory neurons as well as synaptic plasticity mechanisms appropriate for the component of the amygdala they represent. While these models can produce dynamic output, here we concentrate on the equilibrium outputs and do not model the details of the plasticity mechanisms. Pavlovian fear conditioning generates a fear memory in the lateral amygdala module that leads to activation of neurons in the basal nucleus fear module but not in the basal nucleus extinction module. Extinction protocols excite infralimbic medial prefrontal cortex neurons (IL) which in turn excite so-called extinction neurons in the amygdala, leading to the release of endocannabinoids from them and an increase in efficacy of synapses formed by lateral amygdala neurons on them. The model simulations show how such a mechanism could explain experimental observations involving the role of IL as well as endocannabinoids in different temporal phases of extinction.

Author summary

The synaptic networks in the amygdala have been the subject of intense interest in recent times, primarily because of the role of this structure in emotion. Fear and its extinction depend on the workings of these networks, with extinction of particular interest in its potential to ameliorate adverse symptoms associated with post-traumatic stress disorder (PTSD). Here we place emphasis on the extinction networks revealed by recent techniques, and of the probable plasticity properties of their connections, in order to provide a parsimonious model of the function of these networks.

1. Introduction

Evidence suggests that mechanisms underlying anxiety have much in common with Pavlovian fear conditioning (Bouton et al., 2001; Bremner et al., 2008; Graham and Milad, 2011; LeDoux, 2000; Maren and Quirk, 2004; Pitman et al., 1999; Shin et al., 2006; Sullivan et al., 2003) and are conserved across species (LeDoux, 2014; Phelps and LeDoux, 2005). The Pavlovian fear response to a conditioned stimulus (CS; say a tone) in conjunction with an unconditioned stimulus (US; say a shock) leads to plasticity changes at synapses in dorsal lateral amygdala (LAd, henceforth LA) that are retained for long periods of up to years (Pape and Pare, 2010; Quirk et al., 1995; Rogan et al., 1997) following only a few US-CS pairings (Gale et al., 2004; McAllister et al., 1986). This learning involves the plasticity phenomenon of long-term potentiation (LTP) (Cho et al., 2013; McKernan and Shinnick-Gallagher, 1997; Tsvetkov et al., 2002). On the other hand extinction occurs with repeated presentations of the CS in the absence of the US, which leads to gradual decay in the fear response (Maren and Quirk, 2004; Myers and Davis, 2007; Pavlov, 1927; Rescorla, 2002). This is dependent on the establishment of an extinction memory rather than decay of the fear memory (Herry et al., 2008). There is a considerable literature implicating N-Methyl-D-Aspartate (NMDA) receptors, together with LTP, in the formation of these memories (Davis et al., 2006; Lin et al., 2003a; Ressler et al., 2004). In this work consideration is first given to the mechanisms in the amygdala involved in establishing and stabilizing this extinction memory. Existing models of these processes are next considered before a new model is presented that incorporates the most recent observations in a coherent framework.

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Definition of abbreviations used in the legends

US	unconditioned stimulus
CS	conditioned stimulus
LA	lateral amygdala
PV	parvalbumin
SOM	somatostatin
CCK	cholecystokinin
VIP	vasoactive intestinal peptide
BAF	basolateral fear
BAE	basolateral extinction
IL	infra-limbic
ITC	intercalated
CEL	lateral central nucleus
CEM	central nucleus

Fear conditioning is dependent on neural networks in the lateral nucleus (LA) and the basal nucleus (BA) of the amygdala (Maren, 2001), with mechanisms for fear learning occurring in LA (Pare et al., 2004; Sigurdsson et al., 2007) and those for fear extinction in the BA (Pare et al., 2004; Sigurdsson et al., 2007; Myers and Davis, 2002; Sotres-Bayon et al., 2004). There are two main types of neurons in LA and BA, pyramidal-like projection neurons and local circuit gamma-amino-butyric acid (GABAergic) interneurons (McDonald, 1984). The BLA (i.e. LA and BA) is like the cortex (Ehrlich et al., 2009) in as much as it possesses an abundance of excitatory as compared with inhibitory neurons (Carlsen et al., 1985; Smith and Pare, 1994). On the other hand the central nucleus of the amygdala (CE) is more like the striatum in as much as most of the neurons are inhibitory (GABAergic) (McDonald, 1984) and of medium spiny shape like those in the striatum (Ascoli et al., 2008; Markram et al., 2004; Martina et al., 1999; Schiess et al., 1999).

Amygdala networks are well-established and consist of connections between sets of neurons that we call modules, found in the LA, BA (subdivided into fear (BAF) and extinction (BAE) modules), the intercalated inhibitory module ITC (subdivided into dorsal (ITCd) and ventral (ITCv) modules) and the medial central nucleus CEM (the output module) (see, for example, Fig. 3 in Duvarci and Pare (2014)). This work is primarily concerned with the most likely inter-and intra-modular networks that subserve extinction. To that end, a description is first given, for both fear activation and extinction, of the principal inter-modular connections and the functioning of their intra-modular synapses. Next an extinction hypothesis is formulated, based on what is known of plasticity at these synapses, which at this time provides the most likely account of how extinction comes about. The plausibility of this hypothesis is then tested with numerical models that show that it could indeed account for extinction.

2. Review of the amygdala networks and an extinction hypothesis

2.1. Fear activation

2.1.1. Principal pathway modules (Fig. 1)

Three pathways leading from LA are activated following CS exciting LA neurons after CS/US conditioning and which can give rise to enhanced activity of the medial central nucleus (CEM) output from the amygdala (40) (Duvarci and Pare, 2014). A principal one of these is a direct glutamatergic input to BA neurons, called fear neurons (BAF), which projects to form glutamatergic synapses on the amygdala output CEM neurons (Fig. 1). Another important one of these involves the projection of LA neurons to dorsal-intercalated inhibitory neurons (ITCd), that in turn inhibit ventral-intercalated inhibitory neurons (ITCv), thereby disinhibiting ITCv on CEM neurons (Fig. 1). Finally, LA neurons project to inhibitory neurons in the lateral central nucleus (CEL), namely CELon neurons characterized by PKCδ$^-$ (lacking PKCδ) which in turn inhibit CELoff neurons characterized by PKCδ$^+$ (cells possessing PKCδ) and lack somatostatin expression (Ciocchi et al., 2010; Haubensak et al., 2010; Li et al., 2013); these normally inhibit the output of the CEM cells but in this case they are disinhibited (Fig. 1).

2.2. Fear memory

The LA contains neurons that are critical for the laying down of Pavlovian fear memories acquired in a classical US/CS paradigm (Quirk et al., 1995; LeDoux et al., 1990; Repa et al., 2001). CS inputs and US inputs converge on neurons at the input to the LA (LeDoux, 2000; Walker and Davis, 2000), a site known to contain neurons that are capable of sustained forms of synaptic potentiation, or plasticity (LeDoux, 2000; Blair et al., 2001; Malkani and Rosen, 2000). As a consequence of such potentiation mechanisms, overlap in activity initiated in the CS and US pathways can lead to the CS on its own providing large responses at the input to LA (Quirk et al., 1995; Blair et al., 2001). About 25% of the principal neurons in the LA increase their activity in such a way as to imply that they constitute an engram for a fearful stimulus such as a shock (Quirk et al., 1995; Repa et al., 2001;

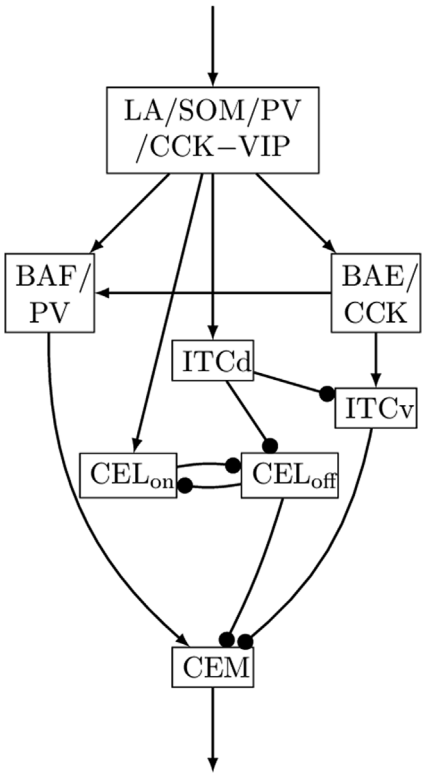

Fig. 1. The modular network of the amygdala for fear acquisition and extinction. The canonical modular network. This consists of eight modules, four with excitatory outputs (LA, BAF, BAE, CEM) and four with inhibitory outputs (ITCv, ITCd, CELon and CELoff), arranged in the pattern of connectivity shown (based largely on the circuitry given in Duvarci and Pare (2014)). Specialized inhibitory neurons are indicated in the modules as follows: in the LA module, these are SOM-, PV- and CCK-VIP- containing inhibitory (GABA) interneurons; in the BAF module they are PV - containing inhibitory interneurons; in the BAE module, CCK - containing inhibitory interneurons; in the ITC modules, ITCd and ITCv, nearly all the neurons are inhibitory; in the CEL modules, CELon and CELoff, nearly all the neurons are also inhibitory. The output module, CEM, has no specialized inhibitory interneurons.

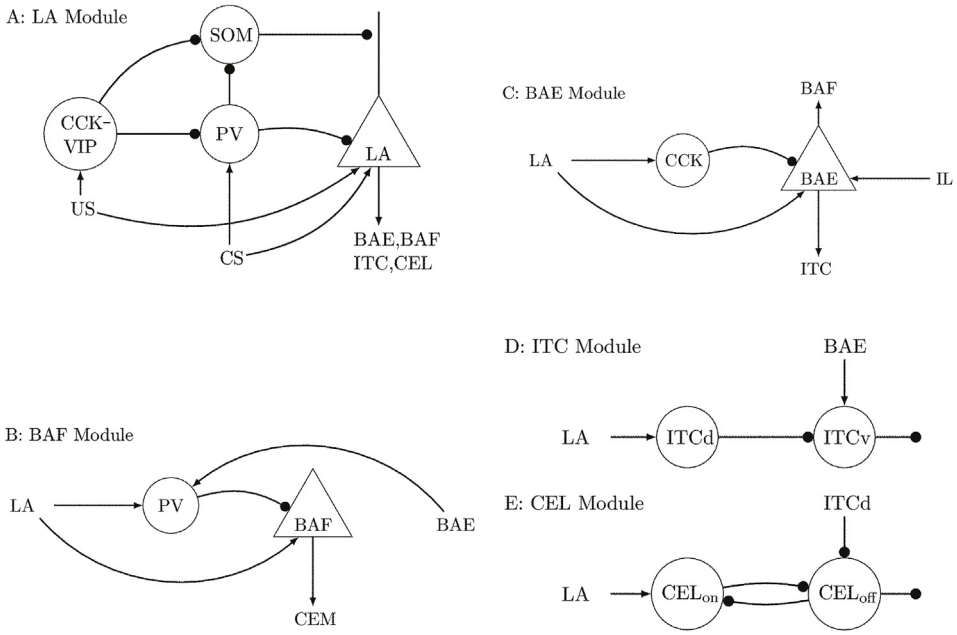

Fig. 2. Detailed neuronal connections in modules of the amygdala network. Triangles represent excitatory neurons and circles inhibitory neurons. **A.** The LA module. This consists of principal excitatory neurons (LA) that project out of the module, and which receive inputs from the US pathway, the CS pathway, as well as specialized inhibitory inputs from SOM-containing and PV-containing inhibitory interneurons as shown. The SOM neurons receive specialized inhibitory inputs from both PV- and CCK-VIP- containing inhibitory neurons; the PV neurons receive the CS input as well as inhibitory input from the CCK-VIP containing inhibitory neurons that in turn receive input from the US pathway. The specialized inhibitory neurons in this module amount to 75% of all the inhibitory neurons (the remaining 25% inhibitory neurons are not shown), that receive collateral connections from the principal excitatory neurons and which in turn synapse on these (Wolff et al., 2014). **B.** The BAF module. This consists of principal excitatory neurons (BAF) that project out of the module and which receive inhibition from specialized PV-containing inhibitory neurons. (The specialized inhibitory neurons in this module amount to 20% of all the inhibitory neuronsin the module and these receive collateral connections from the principal excitatory neurons, which in turn synapse on these (the remaining 80% inhibitory neurons are not shown)). Both the BAF and the inhibitory neurons receive inputs from the LA output neurons, as well as from the output of BAE principal excitatory neurons (Duvarci and Pare, 2014). The output from this module is mainly to the CEM module. **C.** The BAE module. This consists of principal excitatory neurons (BAE) that project out of the module and which receive inhibition from specialized CCK-containing inhibitory neurons (the specialized inhibitory neurons in this module amount to 20% of all the inhibitory neurons, which receive collateral connections from the principal excitatory neurons and which in turn synapse on these (the remaining 80% inhibitory neurons are not shown)). Both the BAE and the inhibitory neurons receive inputs from the LA output neurons. The infra-limbic cortex (IL) projects to BAE principal excitatory neurons. The output from this module is to the ITC and BAF modules. Specialized mechanisms upon which the output of this module is dependent are the strengthening of previously weak LA to BAE synapses by LTP following concomitant excitation of the BAE principal neurons by IL at the time of LA input to BAE and the release of endocannabinoids from excited BAE principal neurons to decrease the release of GABA from inhibitory interneurons of the CCK variety. Together these mechanisms can greatly increase the output of the BAE principal neurons in response to a LA input. **D.** Neurons of two ITC modules are shown. Each of these consists only of intercalated inhibitory (ITC) neurons that are distinguished on the basis of their geographical position as dorsal (ITCd) or ventral (ITCv). The neurons in the ITCd module receive input from LA (see Fig. 1) whereas those in the ITCv module receive input from both ITCd neurons and the BAE module, with the ITCv neurons then projecting to the CEM module (not shown). Each of these modules could have been represented by a separate figure, but have not to save space **E.** Neurons of two CEL modules are shown here. Each of these consists only of CEL neurons, CELon and CELoff, that mutually inhibit each others module. The CELon module exclusively receives inputs from the LA, whereas the CELoff module receives inputs from the ITCd module. The output of the CELoff module is to CEM and is of course inhibitory. The CEM module (not shown) contains principal excitatory neurons and inhibitory interneurons with recurrent collaterals as specified in the Methods.

Blair et al., 2001; Rumpel et al., 2005). Indeed those in the ventral part of the LA show long-lasting increases in firing that are sustained even in the face of extinction trials (Repa et al., 2001).

Strong evidence for an engram of randomly distributed LA neurons has come from Tonegawa's laboratory. For example, optogenetic excitement of BLA neurons, that were first excited in a context where footshocks were delivered, determined that the mice avoided the context (Redondo et al., 2014). This is almost certainly due to these neurons being recruited into the engram by the development of stronger synaptic connections, as shown by enhanced field potentials recorded in LA to the CS (Quirk et al., 1995; Rogan et al., 1997; McKernan and Shinnick-Gallagher, 1997; Goosens et al., 2003; Tye et al., 2008). Recruitment of neurons into engrams is such that engrams laid down by distinct fear conditioning events that are close in time come to share some neurons whereas those distant in time do not (Rashid et al., 2016).

The recruitment of engram neurons is dependent on LTP and the excitability of the neurons, which is in turn modulated by the release of neuromodulators, the efficacy of the synapses and the activity of the local GABAergic neurons mentioned above. These engram neurons are reactivated on remembering (retrieval) of the memory (Redondo et al., 2014; Yiu et al., 2014). The GABAergic interneurons contain either parvalbumin (PV), somatostatin (SOM) or both vasoactive intestinal peptide (VIP) and cholecystokinin (CCK) (Fig. 2A) (Mascagni and McDonald, 2003). PV neurons respond to a CS (auditory) and thereby inhibit SOM neurons mediating inhibition of dendrites of the primary excitatory neurons, thus enhancing the CS response of these (Wolff et al., 2014). On the other hand, a US (shock) inhibits both PV - and SOM - containing interneurons (Wolff et al., 2014), and this must be through the remaining interneurons about 90% of which are CCK-VIP - containing interneurons (Mascagni and McDonald, 2003) thereby enhancing the US response (Wolff et al., 2014). The size of the engram of distributed neurons laid down in LA is determined by these GABAergic neurons, in particular the PV-containing interneurons (Morrison et al., 2016).

A possible contradiction between the conceptual scheme of the engram, consisting of a random distribution of cells, and that of identifiable fear neurons, namely BAFs, has been noted in a recent review (Bocchio et al., 2017): “The random nature of the engram neuron distribution is at odds with data showing that certain neuron populations are assigned to specific behavioral outputs. For example, BLA neurons projecting to the prelimbic mPFC (medial prefrontal cortex) promote fear expression (BAF, fear neurons) whereas the axons projecting to the infralimbic region (IL) promote fear extinction (extinction neurons (BAE) (Senn et al., 2014).” However the two schemes can be reconciled, as they are in the present work, if the engram neurons are located in LA, with these distinguished from the BAFs located in BA which receive projections from the engram neurons in LA (Figs. 1 and 2B).

The BAF module consists of principal excitatory neurons (BAF) that project out of the module and which receive inhibition from specialized PV - containing inhibitory neurons. (The specialized inhibitory neurons

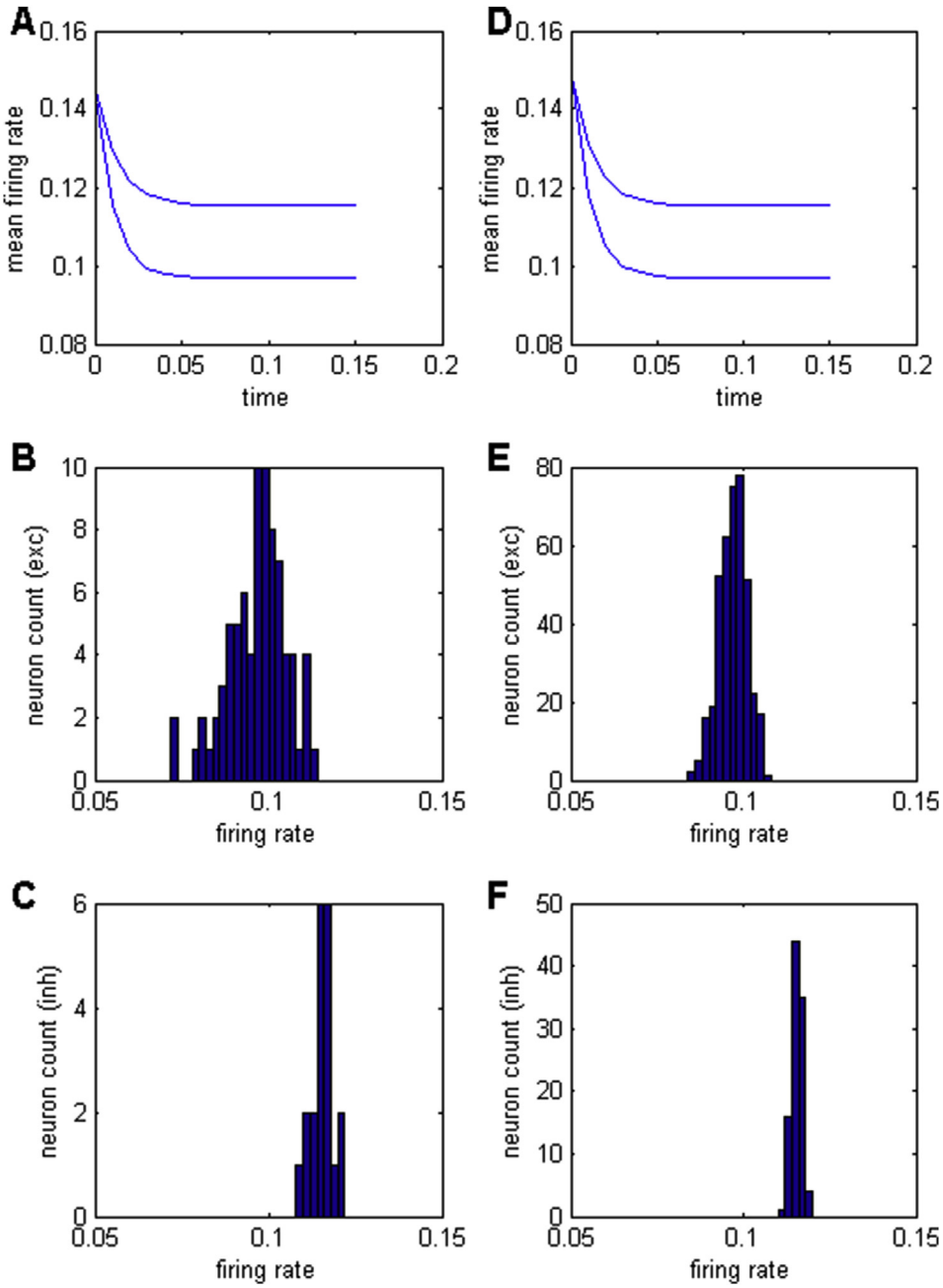

Fig. 3. Characteristics of the computational model. Fig. 3. Data produced by time-integration: (A,B,C) refer to the run with 100 neurons, (D,E,F) refer to the run with 500 neurons. Note that coupling strengths are adjusted between the two runs (to compensate for the different numbers of neurons) so that the mean firing rates are comparable. (A,D) show the rapid approach to a steady state of means for the excitatory and inhibitory compartments. (B,E) show the distribution of firing rates within the excitatory compartment. (C,F) show the distribution of firing rates within the inhibitory compartment. Even though the distributions in (B,C) are relatively broad, the mean firing rates (0.0956 and 0.1156) are close to the values (0.0968 and 0.1155) determined from a steady-state calculation.

in this module amount to 20% of all the inhibitory neurons, which receive collateral connections from the principal excitatory neurons and which in turn synapse on these (not shown).) Both the BAF and the inhibitory neurons receive inputs from the LA output neurons, as well as from the output of BAE principal excitatory neurons. The output from this module is mainly to the CEM module.

The BAF neurons receive input from local GABAergic inhibitory neurons, as do all principal excitatory neurons, and those that contain PV are of particular interest as they receive input from extinction neurons in BA, namely BAE neurons, as mentioned below. Thus the BAF module possesses BAF neurons with inputs from LA as well as from inhibitory PV-containing cells that in turn receive inputs from LA as well as from BAE (Figs. 1 and 2B).

3. Extinction activation/extinction memory

3.1. Principal pathways

One pathway leading from LA is activated following CS exciting LA neurons after conditioning, leading to decreased activity of CEM output from the amygdala (Pare and Duvarci, 2012) (Duvarci and Pare, 2014). This involves a direct glutamatergic input to BA neurons in the module BAE and these neurons project to form glutamatergic synapses on intercalated inhibitory ITCv neurons that then inhibit the amygdala output CEM neurons (Figs. 1 and 2C; the CEM neurons are not shown). The BAE neurons also change the response of BAF cells (Herry et al., 2008; Senn et al., 2014; Sierra-Mercado et al., 2011) consequent to changes in the activity of the GABAergic interneurons containing PV that control BAF cells (Pare and Duvarci, 2012)(Fig. 2B). These changes in activity contribute to a decrease in the CS fear response (Bouton and King, 1983; Quirk, 2006).

The extinction memory associated with BAE neurons decreases the activity of the BAF fear neurons (Bouton et al., 2006; Maren, 2011). Extinction is then dependent on depression of activity in BAF neurons as well as enhanced activity in ITCv inhibitory neurons. In addition there is some evidence that the LTP responsible for setting up a fear engram in LA (Bauer and LeDoux, 2004; Mahanty and Sah, 1998) is depotentiated in extinction (Hong et al., 2009; Kim et al., 2007), decreasing the drive on BAF neurons.

A number of studies suggest that a cause of inhibition of CEM in extinction experiments is direct excitation of ITCv GABAergic neurons (Amano et al., 2010; Busti et al., 2011) by principal neurons in the IL (Pavlov, 1927; Rescorla, 2002; Bouton and King, 1983; McDonald et al., 1996) during extinction training (Cho et al., 2013) (Pare and Duvarci, 2012; Quirk et al., 2003). The inhibition of CEM cells is mediated by projections of ITCv cells onto the dendrites of CEM neurons (Delaney and Sah, 2001; Royer et al., 1999). It now seems very likely from combined behavioral and *in vitro* studies that the principal extinction memory, due to an input from IL, involves BAE neurons and it is the projection from BAE neurons to ITCv that is critical in driving inhibition of the CEM amygdala output in extinction ((Amano et al., 2010); reviewed in Pare and Duvarci (2012); Bocchio et al. (2017))

The infra limbic (IL) part of the medial prefrontal cortex (mPFC) projection to some BLA neurons increases activity during extinction training that does not develop in its absence (Maren and Quirk, 2004; Quirk et al., 2000, 2003; Holmes et al., 2012; Milad et al., 2004; Morgan et al., 1993; Santini et al., 2004). Thus lesions to this part of the cortex inhibit extinction memory development (Maren and Quirk, 2004; Burgos-Robles et al., 2009). These observations indicate the existence of discrete extinction neurons in the BLA, namely BAE neurons, and this is supported by the observation that extinction memory is accompanied by an increase in excitability of about 17% of the principal neurons in the BLA, which are probably BAE neurons (Herry et al., 2008; Bouton et al., 2006; Maren, 2011; Amano et al., 2010).

An extinction memory in the BLA, dependent on BAE neurons, involves plastic changes, including the activation of NMDA receptors (Baker and Azorlosa, 1996; Bauer et al., 2002; Falls et al., 1992; Huang et al., 1994; Lin et al., 2003b; Santini et al., 2001) as would be expected if it is LTP dependent. Hence modeling the extinction process mediated by BAE neurons at the synaptic level requires consideration of calcium influx through NMDA channels triggering a cascade of intracellular changes leading to short and/or long term forms of LTP (Ball et al., 2012; Li et al., 2009; Shouval et al., 2002a). Long -LTP is dependent on protein synthesis (Huang et al., 1994; Huang and Kandel, 1998; Nguyen and Kandel, 1996). Another plastic change involves excited BAE neurons releasing endocannabinoids onto receptors (CB1R) located on local GABAergic (CCK containing) interneurons (Fig. 2C), so blocking their activity and the inhibition of BAE neurons (Lafenetre et al., 2007); for a review see (Bennett et al., 2017).

The mechanisms of synaptic plasticity at a synapse have been explored using phenomenological (Clopath and Gerstner, 2010; El Boustani et al., 2012; Pfister and Gerstner, 2006), functional (Clopath and Gerstner, 2010; El Boustani et al., 2012; Pfister and Gerstner, 2006; Pool and Mato, 2011; Sprekeler et al., 2007) and biophysical (Shouval et al., 2002a, 2002b; Artola and Singer, 1993; Lisman, 1989) approaches. These have been used to explore models concerning the changes in the LA that might be involved in establishing a fear engram there (see for instance (Ball et al., 2012; Li et al., 2009)). Details of the biochemical pathways that support these plasticity mechanisms have been recently reviewed for both relatively short-lasting changes in synaptic efficacy arising from plasticity (Bennett et al., 2017) as well as for very long changes lasting years (Hsieh et al., 2017). Given the emphasis on LTP plasticity in establishing the extinction memory involving BAE, which has been highlighted as a possible focus for investigations on how to prevent the decline of extinction, it is important to consider plasticity mechanisms, as given below.

The distribution of synaptic efficacies over synapses in a population is skewed, with relatively high numbers of low-efficacy synapses (Leen and Friel, 2012; Loewenstein et al., 2011; van Rossum et al., 2000; Zheng et al., 2013), a condition that should hold for energy conservation, among other considerations (Krieg and Triesch, 2014). Such a distribution of low efficacy synapses is also important in order for synaptic plasticity mechanisms to encode a fear engram (Hromadka et al., 2008; Olshausen and Field, 1996) resulting from associative fear learning (e.g. (Rogan et al., 1997; Nabavi et al., 2014). However there are a variety of plasticity mechanism at different synapses, such as those dependent on the timing of presynaptic and postsynaptic action potentials (Artola and Singer, 1993; Artola et al., 1990; Gerstner et al., 1996; Markram et al., 1997), on the frequency of these action potentials (Bliss and Lømo, 1973; Sjostrom et al., 2001), as well as on previous synaptic activity (Bienenstock et al., 1982; Wang and Wagner, 1999) and the extent of synaptic efficacy before the plasticity is engendered as noted above (Ngezahayo et al., 2000). At this time it is not clear which of these are required for plasticity at the different synapses in the amygdala.

Wilson-Cowan representations of different pyramidal-neuron types in the BLA ((Wilson and Cowan, 1972); (Destexhe and Sejnowski, 2009)), characterized by their action potential firing patterns, together with Hebbian calcium mechanisms for LTP according to Cooper and his colleagues (Shouval et al., 2002a, 2002b), have been used to provide a general network of the amygdala during fear learning. However this work does not take into account the different neuron types classified on the basis of their known function and connectivity (Ball et al., 2012); (Li et al., 2009).

3.2. The extinction hypothesis

These various plastic changes involving BAE neurons, together with the dependence of extinction on input from IL (Adhikari et al., 2015), suggests the following hypothesis for extinction (see Fig. 2C): BAE neurons are weakly excited by input from fear engram neurons in LA, while GABA (CCK - containing) local inhibitory interneurons are strongly excited by the LA input, all in the absence of an input from IL; subsequently, during extinction training, the excited IL input to BAE neurons, concomitantly with the CS input mediated by CS excited engram cells in LA, leads through LTP to the strengthening of the LA input to BAE principal neurons; this is accompanied by the enhanced release of endocannabinoids from the excited BAE neurons, and so to their disinhibition as a consequence of the endocannabinoids decreasing GABA release from the CCK - containing inhibitory interneurons. BAE neurons are now engaged each time a CS is presented at the input to LA, providing an extinction memory. The extinction memory outlined here is separate from the fear engram and does not erase the fear engram; indeed it depends on it in order to be established, (Pavlov, 1927; Rescorla, 2002; Bouton and King, 1983). The plausibility of this extinction hypothesis is examined here using recurrent neural networks to represent each of the interconnected modules described above and thus determining the changes in the steady-state output of the modules, especially that of CEM, conditional on the excitability of BAE determined by the various plastic changes at the synapses on BAE neurons.

A number of studies suggest that a cause of inhibition of CEM in extinction experiments is direct excitation of ITCv GABAergic neurons (Amano et al., 2010; Busti et al., 2011) by principal neurons in the IL (Pavlov, 1927; Rescorla, 2002; Bouton and King, 1983; McDonald et al., 1996) during extinction training (Cho et al., 2013) (Pare and Duvarci, 2012; Quirk et al., 2003). The inhibition of CEM cells is mediated by projections of ITCv cells onto the dendrites of CEM neurons (Delaney and Sah, 2001; Royer et al., 1999). It now seems very likely from combined behavioral and *in vitro* studies that the principal extinction memory, due to an input from IL, involves BAE neurons and it is the projection from BAE neurons to ITCv that is critical in driving inhibition of the CEM amygdala output in extinction ((Amano et al., 2010);

reviewed in Pare and Duvarci (2012); Bocchio et al. (2017)).

4. Method

The computational model used is an adaptation of one due to Abbott, Rajan and Sompolinsky (Abbott et al., 2011). Their model is a generic one, designed to investigate the relation between intrinsic and stimulus-evoked activity in a neural network, and not oriented towards any particular physiological system. We have previous used this formalism in a network study of synapse loss in schizophrenia (Bennett, Farnell, Gibson: Fiber Pathway Pathology, Synapse Loss and Decline of Cortical Function in Schizophrenia, *PLOS One*, **8** (2013), no. 4, (e60518).) We choose to use it here, in a simplified version, as it provides a middle path that avoids unnecessary complexity but still retains the essential features required for the current investigation.

In the model each neuron has a firing rate r_i in the range 0 to R_{max} where R_{max} is taken as 1. The firing rate is related to an "activation parameter" x_i, which is defined so that when x_i is zero r_i is equal to the background firing rate R_0, which is taken as 0.1:

$$r_i = R_0 + (R_{max} - R_0)tanh\left(\frac{x_i}{R_{max} - R_0}\right) \quad x_i > 0 \tag{1a}$$

$$r_i = R_0 + R_0 tanh\left(\frac{x_i}{R_0}\right), \quad x_i < 0 \tag{1b}$$

The primary quantities in the equations for time-development are the activation parameters which evolve according to:

$$\tau\frac{dx_i}{dt} = -x_i + g\sum_j J_{ij}r_j + I_i \tag{2}$$

Here, τ is a time constant, J_{ij} is the coupling strength by which firing in neuron j stimulates activity in neuron i, g is a global coupling constant, and I_i is an external input peculiar to each neuron. In the original model (Abbott et al., 2011) the connection strengths J_{ij} are randomly and independently chosen from a Gaussian distribution and this may lead to chaotic spontaneous activity in an isolated network. We have simplified this by using a fixed connection strength between pair of neurons of the same type, e.g. LA excitatory to SOM inhibitory. The complete set of neurons of a given type form a compartment (e.g. excitatory) within a module (e.g. LA). We make the further assumption that only 20% of the possible connections between two compartments are active, so that the connection strength for the remainder may be taken as zero. The 20% which are active are chosen randomly. These modifications have the effect that the time-evolution is no longer chaotic but rather the system rapidly approaches a steady state. This is illustrated for a module with a total of 100 neurons (Fig. 3, left column) or 500 neurons (Fig. 3, right column) split into two compartments (excitatory and inhibitory). The distribution of firing rates for each compartment (Fig. 3) are narrower for the module with a larger number of neurons; this is a consequence of the smaller standard deviation of the binomial distribution of active connections to the various neurons. It therefore makes sense to compute the mean firing rates directly using a steady-state calculation, instead of time-integrating a large number of neurons. Doing this for the 500 neuron two-compartment model gives 0.0970 (excitatory compartment) and 0.1156 (inhibitory compartment) compared with 0.0970 and 0.1155 obtained from the time-integration.

Adopting this procedure, the neurons in our model are grouped in modules (Fig. 1) each with at least two compartments, one containing only excitatory neurons and one only inhibitory neurons; additional compartments are represented by further Neuron Fractions in the table of parameters (Table 1). The aim is compute a mean firing rate for each compartment, the compartment being the primary entity in the calculation. Compartments are grouped into modules because within a particular module the compartments are connected bidirectionally and thus need to be solved together, whereas connections between modules are (nearly all) one-way so that the modules can be solved successively. The global (g) and specific (J_{ij}) strengths are amalgamated in a set of values, each of which is a property of a particular pair of compartments, e.g. $g_{SOM\text{-}CCK}$ which is used from CCK to SOM. The effect of using 20% active connections is just to multiply each strength by 0.2.

Since the neurons in a given compartment have the same parameters, it is not necessary to sum over individual neurons. Instead the count of neurons is represented by the neuron fractions v_j, being the relative number of neurons in each compartment. Thus the final equations only require a sum over compartments. Removing the time-derivative we arrive at

$$0 = -x_i + \sum_j g_{ij}v_j r_j + I_i \tag{3}$$

where the summation is now over compartments. This equation may be solved iteratively by starting from appropriate values of x_i, computing the related r_i, and determining improved values for xi using the equation rewritten in the form

$$x_i = \sum_j g_{ij}v_j r_j + I_i \tag{4}$$

this being repeated till the results are self-consistent.

The external inputs I_i may include (a) conditioned and unconditioned stimuli; (b) cortical inputs; (c) intermodular inputs, which are constructed with fixed coupling constants analogous to the intra-modular couplings. Provided that the modules are solved in the appropriate order, these are mostly known quantities. This is not true for the CEL modules, which are coupled bidirectionally, so an extra level of iteration is required to make their firing rates consistent.

In order to illustrate the output from BAE resulting from simultaneous inputs from CCK and LA, a a much simplified model has been used, in which the output is related to the input by

$$BAE_{out} = \tanh(2\,BAE_{in}) + 0.1 \tag{5}$$

Table 1
Parameters for LA system.

Neuron Fractions		
LA excitatory	v_{LAe}	0.80
LA inhibitory	v_{LAi}	0.05
SOM	v_{SOM}	0.05
CCK	$v_{CCK(LA)}$	0.05
PV	$v_{PV(LA)}$	0.05
Connection Strengths		
LA excitatory to itself	$g_{LAe\text{-}LAe}$	1
LA excitatory to inhibitory	$g_{LAi\text{-}LAe}$	1
LA excitatory to SOM	$g_{SOM\text{-}LAe}$	1
LA excitatory to CCK	$g_{CCK(LA)\text{-}LAe}$	1
LA excitatory to PV	$g_{PV(LA)\text{-}LAe}$	1
LA inhibitory to excitatory	$g_{LAe\text{-}LAi}$	−1
CCK to SOM	$g_{SOM\text{-}CCK}$	−1
CCK to PV	$g_{PV\text{-}CCK}$	−1
PV to SOM	$g_{SOM\text{-}PV}$	−1
SOM to LA excitatory	$g_{LAe\text{-}SOM}$	−1
PV to LA excitatory	$g_{LAe\text{-}PV}$	−1
SOM to LA inhibitory	$g_{LAi\text{-}SOM}$	−1
PV to LA inhibitory	$g_{LAi\text{-}PV}$	−1
Stimuli		
Conditioned stimulus	r_{CS}	0
Unconditioned stimulus	r_{US}	0
Stimulus Coupling Strengths		
CS to PV	$g_{PV(LA)\text{-}CS}$	2
CS to LA excitatory	$g_{E(LA)\text{-}CS}$	2
US to CCK	$g_{CCK(LA)\text{-}US}$	2
US to LA excitatory	$g_{E(LA)\text{-}US}$	2
Connection Strengths (from LA excitatory) to Downstream Modules		
to PV	$g_{PV(BAF)\text{-}LAe}$	1
to CCK	$g_{CCK(BAE)\text{-}LAe}$	1
to BAE excitatory	gBAEe-LAe	0.1; 0.7–1.5
to CELon inhibitory	$g_{CEL12i\text{-}LAe}$	1
to ITCd inhibitory	$g_{ITCDi\text{-}LAe}$	1

which gives an output starting at 0.1 for zero input and asymptoting to 1.1 for large input (see Fig. 6A).

4.1. Parameter values

Unless otherwise specified, the parameters used are as listed in Tables 1–5 below. If a possible parameter is not listed, it should be taken as 0. CCK to BAE excitatory is −5 in the default condition, and sometimes varied from −21 to 0. (Table 2). LA to BAE excitatory is 0.1 in the default condition, but may be varied over the range 0.7–1.5 (Table 1); the low default condition is to ensure that BAEexcitatory does not fire unless the LTP/endocannabinoid mechanisms are brought into play as a consequence of simulating an IL input.

5. Aims of the model

The aim of this work is to provide a future testable mechanism, summarized in Fig. 1, for the dependence of an early phase of extinction memory on endocannabinoids and a later phase on LTP. Specifically it seeks to provide insights into recent experimental results on this subject (Plendl and Wotjak, 2010a). It is argued that a plausible mechanism for the early phase is the transient release of endocannabinoids from BAE neurons on their being excited by an IL input triggered by the extinction protocol. The later and enduring phase of extinction is due to the IL input increasing the efficacy of LA-BAE connections through LTP, which builds up slowly as the endocannabinoid effect wanes, as illustrated in Fig. 6A. It is then the IL input to BAE that is the critical driver of extinction in this model, as is now shown in detail below.

6. Results

During a US (say a foot-shock) both PV-containing and SOM-containing GABAergic interneurons are inhibited by CCK-VIP-containing GABAergic interneurons, thus inhibiting both SOM as well as PV inhibition of principal excitatory neurons, and so enhancing the foot shock response (Rashid et al., 2016) (Fig. 4A); in contrast, during a CS (say auditory cue) there is excitation of PV-containing GABAergic interneurons that in turn disinhibit SOM-containing GABAergic interneurons which normally inhibit inputs to dendrites, so enhancing the major CS (auditory) input to these dendrites (Fig. 4B), resulting in auditory cue-foot shock associations.

BAF neurons, besides receiving inputs from LA, also receive inputs from local PV containing GABAergic interneurons, which in turn are innervated by BAE neurons (Fig. 2B). Increases in the LA input to the BAF module give rise to substantial increases in the firing of BAF excitatory neurons (Fig. 5A), despite the input to these neurons from inhibitory interneurons, in particular those driven by the BAE. This is because BAE neurons, besides receiving weak inputs from LA, also receive strong inputs from CCK-containing GABAergic interneurons, which in turn are innervated by LA neurons and BAE neurons (Fig. 2C) (Duvarci and Pare, 2014; Duvarci SP, 2014). The consequences of this is that the concomitant LA input to the BAE module, with that of LA to the BAF module, has little effect on increasing the activity of BAE principal neurons (Fig. 5A), so there is little effect of the BAE module on the BAF principal neuron firing in these circumstances. The increase in BAF firing with that of LA firing then leads to very substantial increases in the output of the amygdala, CEM (Fig. 5B). It follows that increases in LA activity give rise to increases in CEM activity, as shown in Fig. 5C.

As noted above, increased LA input to the BAE module (Fig. 2C) gives only marginal increases in BAE output (see Fig. 5A) due to the normal low efficacy of LA to BAE synapses and the inhibition of BAE neurons by CCK-containing interneurons. This can be overcome by boosting the efficacy of LA to BAE synapses with concomitant firing of LA to BAE synapses and of synapses between infra-limbic (IL) neurons and BAE principal neurons through the mechanism of NMDA-mediated LTP. However the anticipated increase in excitability of BAE principal neurons will be considerably dampened by the inhibitory CCK-containing interneurons. As also noted above, endocannabinoids released following increased excitation of principal BAE neurons leads to disinhibition of these cells through block of GABA release from the CCK-containing interneurons through the action of the endocannabinoids (see (Lafenetre et al., 2007)).

Fig. 6A shows the result of the interaction between these two mechanisms controlling BAE excitation using a simple model (as described in the Methods): increases in the efficacy of LA to BAE synapses through LTP (0–0.5), enhances BAE excitation in the presence of relatively low levels of BAE release of endocannabinoids onto the CCK neurons (at a level of – 0.5 in Fig. 6A), but increases substantially as the endocannabinoids increasingly block the inhibitory influence of CCK neurons (towards zero in Fig. 6A). This is shown in Fig. 6B, using the full computational model: BAE firing increases with LTP-enhanced efficacy of LA to BAE synapses (at a fixed level of endocannabinoid-mediated disinhibition of BAE neurons); BAE firing increases, but to a lesser extent, with decrease in the endocannabinoid-mediated inhibition of CCK-interneurons; and the action of both these mechanisms together leads to the greatest increase in BAE excitation. This increase in BAE firing then leads to substantial increases in the excitation of intercalated inhibitory neurons, ITCv (Fig. 6C). The result is decreases in the activity of the output of the amygdala, CEM (Fig. 7A). On the other hand, increases in the endocannabinoid-mediated inhibition of CCK-interneurons enhances BAE firing further, increasing ITCd activity

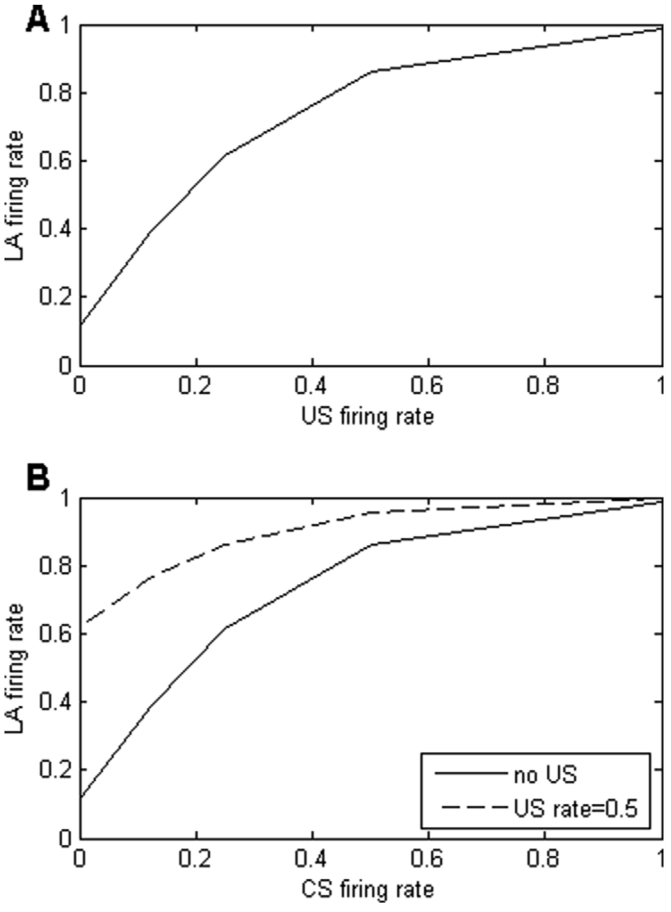

Fig. 4. Lateral amygdala (LA) module output. A, gives the output (LA) for different unconditioned stimuli (r_{US}, see Fig. 2A) in the absence of a conditioning stimulus (r_{CS} = 0). **B, g**ives the output (LA) for different conditioning stimuli (r_{CS}) to the module, in the absence of the unconditioned stimulus (r_{US} = 0, continuous line) or in its presence (r_{US} = 0.5, broken line). The LA firing rates are given for the excitatory neurons only. Default parameter values for this module are given in Table 1.

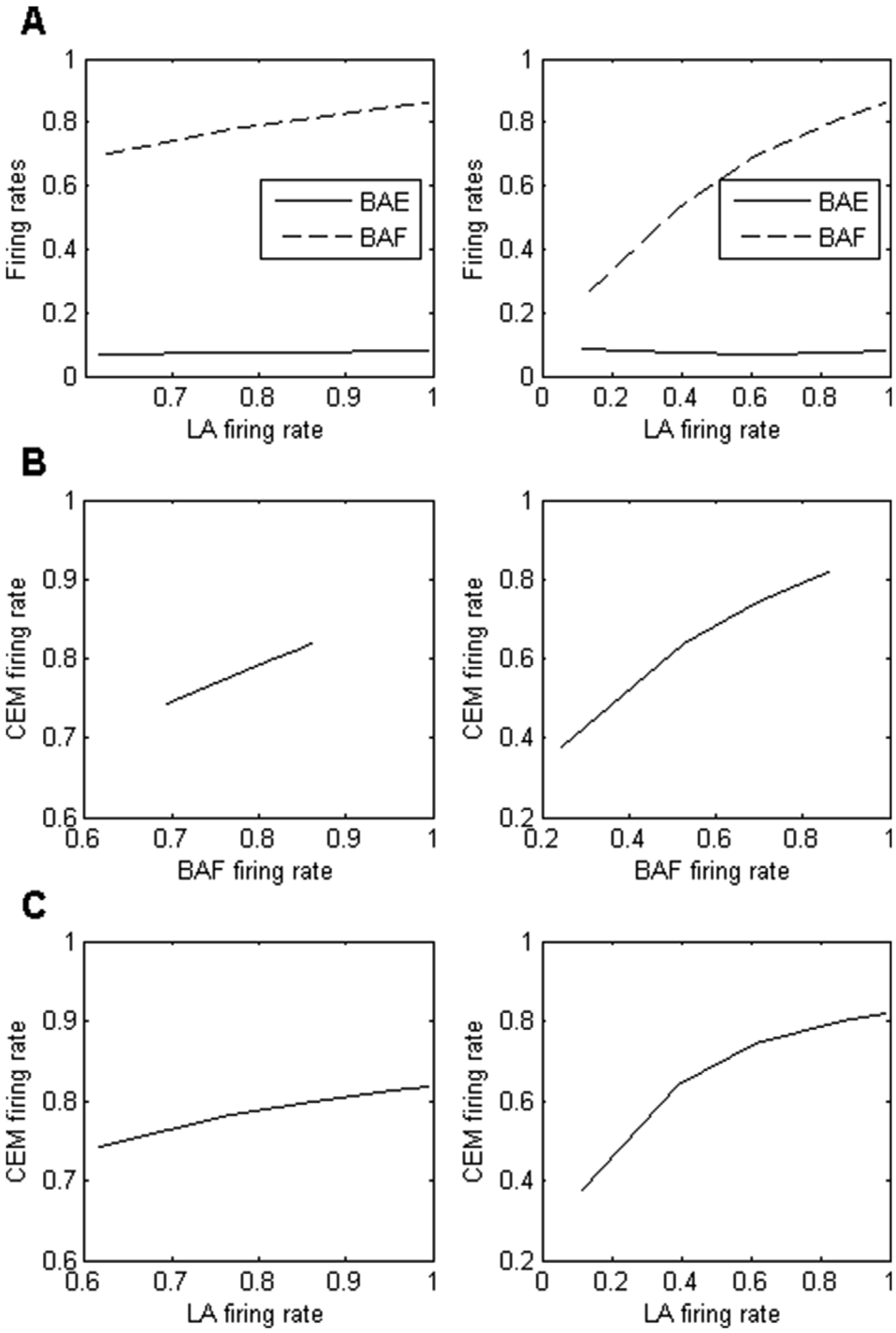

Fig. 5. Output of the amygdala (CEM) for different LA module inputs to the fear module (BAF); the left-hand column is for a r_{US} = 0.5 and the right-hand column for r_{US} = 0 **. A,** increase in output of the fear module (BAF, broken line) and extinction module (BAE, continuous line) for different LA inputs. Parameter values for the BAF and BAE modules given in Tables 2 and 3 Note the very small increase in BAE output (continuous line, due to low efficacy of the LA-BAE synapse). **B,** large increases in the amygdala output CEM, with increases in the output of the fear module BAF given in A. **C,** changes in the amygdala output, CEM, with changes in the output of the lateral amygdala; the increase in output of CEM with LA follows directly from the strong input delivered by the BAF module and the very low activity in the BAE module. The BAE, BAF and CEM firing rates are given for the excitatory neurons only. Default parameter values for this module given are given in Table 5.

and so reducing CEM output (Fig. 7B).

As noted, increasing LA input to the BAE module gives only marginal increases in BAE output (see Fig. 5A) due to the normal low efficacy of LA-BAE synapses and the inhibition of BAE neurons by interneurons. This can be overcome by boosting the efficacy of LA-BAE synapses with LTP due to concomitant firing of LA-BAE and IL-BAE synapses, with the increase in firing of the BAE neurons providing the added advantage of releasing endocannabinoids that inhibit the release of inhibitory transmitter from CCK inhibitory interneurons. **A**. A simple qualitative model illustrating the dual effect of LTP and endocannabinoid release on the output of the BAE module following IL activity. The output from LA is constant at 0.5 and the output from IL steps from 0 to 0.3 at the start of the simulation. CCK and BAE are each modelled as single units with a hyperbolic tangent activation function (See Methods, Eq (Maren and Quirk, 2004)). The decrease in CCK to BAE synaptic strength due to endocannabinoid release is given by $x = -0.5 + 0.01z$ and the concomitant increase in LA to BAE strength due to LTP is given by $y = 0.01z$ where z is the activity in BAE. The solid line on the surface shows a possible path of BAE activity, with the endocannabinoids dominating initially and then LTP providing the major contribution. Note that the scaling here is in arbitrary units. **B.** Modeling of the changes in BAE output for a given LA input using the full model. These are due to LTP of the BAE-LA synapse (increasing values of $g_{BAEe\text{-}LAe}$) and/or decreases in the CCK-BAE synaptic efficacy ($g_{BAEe\text{-}CCK(BAE)}$) due to endocannabinoids; shown are changes due to both LTP and endocannabinoids (dot-dash; $g_{BAEe\text{-}CCK(BAE)}$ and $g_{BAEe\text{-}}$

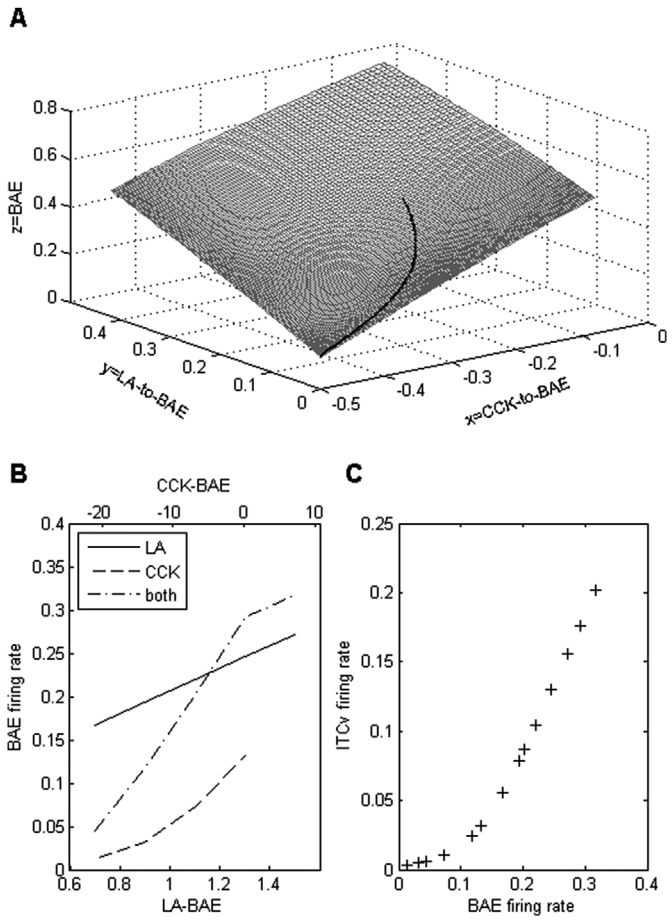

Fig. 6. Infra-limbic cortex (IL) control of the extinction module (BAE) function.

Table 2
Parameters for BAE system.

Neuron Fractions		
BAE excitatory	ν_{BAEe}	0.80
BAE inhibitory	ν_{BAEi}	0.04
CCK	$\nu_{CCK(BAE)}$	0.16
Connection Strengths		
Excitatory to itself	$g_{BAEe\text{-}BAEe}$	1
Excitatory to inhibitory	$g_{BAEi\text{-}BAEe}$	1
Inhibitory to excitatory	$g_{BAEe\text{-}BAEi}$	−1
Excitatory to CCK	$g_{CCK(BAE)\text{-}BAEe}$	1
CCK to excitatory*	$g_{BAEe\text{-}CCK(BAE)}$	−5; −21 to 0
Connection Strengths (from BAE excitatory) to Downstream Modules		
to ITCV inhibitory	$g_{ITCVi\text{-}BAEe}$	1
to BAF excitatory	$g_{BAFe\text{-}BAEe}$	1
to PV (in BAF system)	$g_{PV(BAF)\text{-}BAEe}$	1

* This parameter is fixed at −5 in all simulations, except those illustrated in Figs. 6 and 7, in which it is varied from −21 to 0.

$_{LAe}$)), changes due only to the endocannabinoids (broken line; $g_{BAEe\text{-}CCK(BAE)}$) with BAE-LA constant at 0.1, and changes in LTP (continuous line; $g_{BAEe\text{-}LAe}$) with the endocannabinoid effect held constant at $g_{BAEe\text{-}CCK(BAE)} = -5$. **C, i**ncreases in inhibitory output of the ITC module following boosting of the output of the BAE module with LTP and endocannabinoids. The firing rates are for the inhibitory neurons only. All parameter baseline values as in Tables 1 and 2

Observations suggest that the increased CS responsiveness of CEM output neurons after fear conditioning depends on parallel mechanisms: CS presentations excite LA neurons leading to the recruitment of ITCd neurons and a subset of CEL cells, likely PKCδ$^-$ (CELon) cells, which in turn inhibit PKCδ$^+$ (CELoff) cells so disinhibiting CEM neurons; recruited ITCd neurons also inhibit ITCv cells, so disinhibiting CEM neurons. The activation of LA neurons by the CS causes BAF neurons to fire that directly excite CEM neurons. During such LA presentations, BAE extinction neurons are inhibited through local GABAergic interneurons directly excited by the BAF neurons.

Observations also suggest that the reduced CS responsiveness of CEM neurons during extinction conditioning depends on increased feed-forward inhibition by ITCv neurons and disfacilitation of glutamatergic BAF inputs to CEM. This disfacilitation most likely arises from inhibitory inputs from local GABAergic-PV-containing neurons consequent on their excitation by BAE neurons. The feed-forward inhibition of CEM neurons by ITCv neurons can be instigated by direct inputs to ITCv from IL neurons in the mPFC but more importantly from BAE neurons consequent on their disinhibition by local GABAergic interneurons, through the action of endocannabinoids released from excited BAE neurons due to their also receiving input from IL neurons.

7. Discussion

In the present model extinction memories are laid down in BLA, through IL induced LTP of LA synapses on BAE neurons located in BLA, so forming an engram for extinction in the BLA. We favor this site over the alternative, namely at the IL input to ITCv neurons, since on present evidence IL-enhanced activity is required for extinction training but not for extinction retrieval (Do-Monte et al., 2015). Once the extinction engram is established through the action of IL in conjunction with LA synapses, IL is no longer required in the process of retrieving an extinction memory. The possibility that inhibitory neurons form engrams (Barron et al., 2017) in the amygdala has not been entertained here, so the only mechanism open for IL's action on ITCv neurons is to potentiate synaptic transmission from BAE neurons to ITCv neurons.

The most important consideration in the present model is that it provides a mechanistic explanation for observations on the role of endocannabinoids in the dissociation of within- and between-session extinction of conditioned fear (Plendl and Wotjak, 2010b). The authors Plendl and Wotjak (2010b), found that the release of endocannabinoids was essential for within session extinction over an experimental day but not for retention of the extinction the subsequent day (see their Fig. 5). The present model suggests that this may come about by endocannabinoids being the primary agent for the increased excitability of primary BAE neurons during the period of within session extinction, as illustrated by the black line in Fig. 6A,. During this period there is not much contribution from the increase in efficacy of LA to BAE neurons consequent on their LTP due to concomitant firing of IL to BAE neurons. But the chemical pathways mediating LTP, mentioned above, ensure that this builds up so that it becomes the significant determinant of increased excitability in subsequent extinction sessions. Thus according to this scheme then it is not endocannabinoids that are the critical factor in sustaining extinction over long periods but the LTP of LA to BAE neurons (see the locus of the black line in Fig. 6A). As Plendl and Wotjak (2010b) stress, the inhibitory learning process is likely to be independent of endocannabinoid signaling, so that within-session fear reduction will not predict therapy success. This, we suggest, is determined by the extent of LTP at LA to BAE synapses that is governed by the chemical machinery underlying LTP, following initiation by combined LA and IL activity.

Modeling of the fear engram in LA has been carried out by Kim, Pare and colleagues (Kim et al., 2013a) using a biophysical computational model using a large number of principal excitatory neurons, each with one of three different classes of excitability characterized by different spike frequency adaptations as well as inhibitory interneurons, the connections between these capable of undergoing changes in Hebbian plasticity (Kim et al., 2013a); (Feng et al., 2016). This model showed that inhibition (between inhibitory neurons and principal neurons) is a dominant factor in LA determining which principal neurons with high intrinsic excitability are grouped together through their collateral excitatory connections to form an engram (Feng et al., 2016). These

Table 3
Parameters for BAF system.

Neuron Fractions		
BAF excitatory	ν_{BAFe}	0.80
BAF inhibitory	ν_{BAFi}	0.16
PV	$\nu_{PV(BAE)}$	0.04
Connection Strengths		
Excitatory to itself	$g_{BAFe\text{-}BAFe}$	1
Excitatory to inhibitory	$g_{BAFi\text{-}BAFe}$	1
Inhibitory to excitatory	$g_{BAFe\text{-}BAFi}$	−1
Excitatory to PV	$g_{PV(BAE)\text{-}BAEe}$	1
PV to excitatory	$g_{BAEe\text{-}PV(BAE)}$	−1
Connection Strengths to Downstream Modules		
BAF excitatory to CEM excitatory	$g_{CEMe\text{-}BAFe}$	1

Table 4
Parameters for inhibitory modules (ITCv, ITCd, CELon, CELoff).

Neuron Fractions		
Excitatory	ν_e	0.10
Inhibitory	ν_i	0.90
Connection Strengths		
Excitatory to itself	g_E	1
Excitatory to inhibitory	g_{IE}	1
Inhibitory to excitatory	g_{EIi}	−1
Intermodular Connection Strengths		
Inhibition of CEM inhibitory (by CELoff, ITCv)	$g_{CEMi\text{-}I}$	−1
Inhibition of CEM excitatory (by CELoff, ITCv)	$g_{CEMe\text{-}I}$	−1
Inhibition of other inhibitory modules	$g_{Xe\text{-}I}$	−1
(both excitatory and inhibitory targets)	$g_{Xi\text{-}I}$	−1

Table 5
Parameters for CEM module.

Neuron Fractions		
Excitatory	ν_{CEMe}	0.80
Inhibitory	ν_{CEMi}	0.20
Connection Strengths		
Excitatory to itself	$g_{CEMe\text{-}CEMe}$	1
Excitatory to inhibitory	$g_{CEMi\text{-}CEMe}$	1
Inhibitory to excitatory	$g_{CEMe\text{-}CEMi}$	−1

authors, Feng et al. (2016), show the essential role of plasticity at the synapses both from the thalamic input to LA and between the principal neurons in LA (Kim et al., 2013b).

The above considerations do not incorporate mechanisms that account for contextual clues involved in fear and extinction learning. Such clues are incorporated in the model of Carrere and Alexandre (2015). After US/CS fear-learning in the LA, following sensory inputs from the thalamus and cortex concerning the US (foot-shock) and the CS (tone), BAF and CELon cells are directly excited leading to enhanced activity of CEM as in the present model. But in addition, BAF neurons receive inputs from the hippocampus relaying information about the context of the conditioning. A projection of BAF neurons to CELon cells or of BAE neurons to CELoff cells, and mutual inhibition of CELon and CELoff cells can be incorporated. These authors, Carrere and Alexandre (2015), replicated a number of animal experiments concerning Pavlovian conditioning in different contexts.

Hippocampal inputs carrying contextual information, as well as the plasticity of synapses mediating US/CS and context-specific inputs, were emphasized in an early model which showed that two populations of BA excitatory neurons could be recruited during conditioning and extinction (Vlachos et al., 2011). These presumably can be identified as BAF and BAE neurons, which the later literature has emphasized. The importance of neuromodulators, such as noradrenaline are also emphasized in this work.

Some models place emphasis on the neurons in the BLA (BAF neurons) that directly excite the CEM output neurons of the amygdala. This is in contrast to ventral mPFC (infra limbic (IL) neurons) projections to

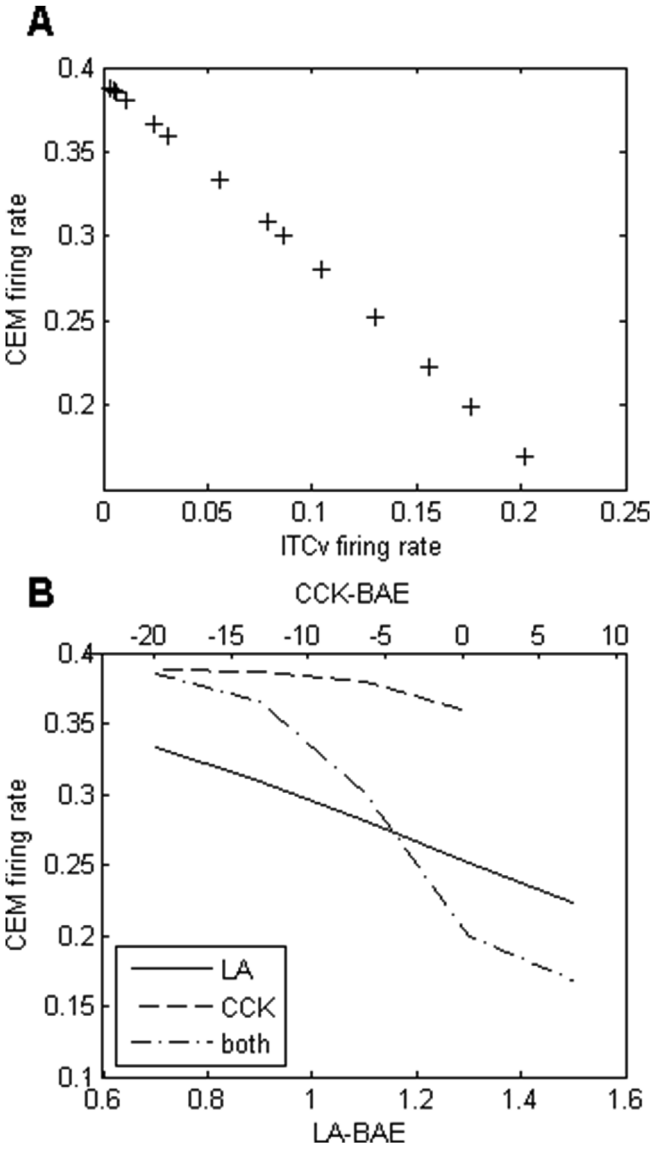

Fig. 7. Output of the amygdala (CEM) following extinction of conditioned fear. The CEM output increases rapidly with LA following US/CS fear acquisition. **A,** in extinction, the increase in efficacy of LA-BAE synapses due to infralimbic cortex input (IL), for a given LA, greatly enhances the activity of the intercalated inhibitory neurons (ITC) as in Fig. 6C, decreasing the enhanced activity due to firing in the fear pathway (from BAF) and hence CEM (crosses; derived from the same runs as in Fig. 6). **B,** shows the extent of LTP/endocannabinoid effects in the BAE module, for a given LA, decreasing the CEM output generated by the fear pathway, as a consequence of elevating ITCv activity. Curves are: dot-dash, changes due to LTP and endocannabinoids; broken line, changes due to endocannabinoids alone; continuous line, changes due to LTP alone. All parameter baseline values as in Tables 1–5

ITC inhibitory neurons that in turn directly inhibit CEM. Context is then accounted for by hippocampal neuron projections to both ventral mPFC and BLA (BAF neurons) (Moustafa et al., 2013). In this case account is not made of the more specific circuitry of the amygdala, such as that involving BAE and CEL (on or off) neurons. More particularly, consideration of the IL projections to BAE as perhaps the most important pathway mediating extinction (not IL to ITC) is not canvassed.

As noted above, the release of endocannabinoids in the BLA is required for extinction, and this involves their release from excited BAE neurons onto the terminals of GABAergic cholecystokinin containing interneurons in order to block the release of the inhibitory transmitter (for a review, see (Bennett et al., 2017)). This mechanism has been

incorporated into a model of connectivity between different amygdala nuclei (Duvarci and Pare, 2014), (Anastasio, 2013). Using a computational approach, the model was used to indicate that the endocannabinoid-mediated depression of the GABAergic synapses could lead to changes in synaptic efficacy that might support extinction.

The results of the modeling in this paper supports the idea that the most likely site at which failure to retrieve extinction occurs, such as in the failure of treatment for patients with post-traumatic stress disorder, is at the synapses of LA neurons on BAE neurons, following their potentiation during extinction training by IL through synapses of IL neurons on BAE neurons. This, it is argued, should be the site requiring detailed study in the context of the failure of extinction memory.

Supplementary Material

The output data for the various simulations is now provided together with the code in Supplementary Material

Critical tests of the model

The present work provides a model for sustained extinction, based on the LTP of LA inputs on BAE neurons by IL inputs. However, although it is known that the IL input to BLA is critical for extinction (for recent observations see (Bloodgood et al., 2018)), it is not known if this input is to BAE neurons that receive input from LA. If this is the case then it has also to be shown that the synapses formed by LA undergo LTP due to the IL input during extinction. Finally, this LTP of LA projections to BAE neurons has to build up slowly, allowing endocannabinoids to dominate in early extinction, as is shown in Fig. 6A. If any of these three tests, all focused on the existence and properties of LTP at LA-BAE synapses, fail then the model fails.

Limitations

The following limitations of the model should be noted: it is assumed that neuron types within each module behave identically; although the model is capable of offering dynamic solutions only static ones are considered that satisfy the known constraints; the actual firing rates in the model's modules are not compared with those recorded.

A particular limitation is that the details of the plasticity mechanisms have not been modelled. Rather our principal focus in the modeling has been to make explicit the hypothesis presented that extinction arises as a consequence of the release of endocannabinoids from BAE neurons in the short term and their extinction by IL neurons to generate LTP in the long term. Utilizing these cellular processes was necessary to show the plausibility of the hypothesis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2019.100159.

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