



Distributed coding in auditory thalamus and basolateral amygdala upon associative fear learning

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Associative fear learning is a fundamental learning mechanism that is crucial for an animal's survival. The amygdala's role in fear memory formation has been studied extensively and molecular, cell type and circuit-specific learning mechanisms as well as population level encoding of threatful stimuli within the amygdala are at the core of fear learning. Nevertheless, increasing evidence suggests that fear memories are acquired, stored and modulated by a distributed neuronal network across many brain areas. Here we review recent studies that particularly re-assessed the role of auditory/lateral thalamus, which is one synapse upstream of the lateral amygdala, required for fear learning and exhibits a striking functional resemblance and plasticity pattern to downstream amygdala neurons on the single cell level, yet distinct population level coding.

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Neuronal plasticity in MGB and BLA upon associative fear learning

Associative learning is a fundamental learning mechanism that allows us to match sensory stimuli with expected outcomes. One of the most famous examples of associative learning is classical Pavlovian conditioning. Outcome-associated sensory stimuli can be as complex as a multimodal, environmental context in the case of spatial learning and contextual conditioning or as minimal as brief auditory stimuli in the case of Pavlov's dog or auditory fear learning. To understand the computational principles underlying associative learning, neuroscience has undertaken the quest to map brain

areas, circuits, cell types and even molecules that are necessary for the formation and expression of associative memories. Auditory fear conditioning is a widely used associative learning paradigm due to its fast learning rates (e.g. single or few trials are sufficient to form fear memories) [1] and strong memory formation that lasts for days, weeks or months [2–4].

A large body of work has placed the amygdala at the center of fear learning and there is now an ever increasing understanding of how basolateral amygdala (BLA) activity dynamics relate to changes in fear learning, both on the single cell level [5–9] as well as the population level [10–13]. However, the amygdala is not the sole site of fear learning. Many studies examined circuit elements and brain areas that exhibit adaptive changes in fine-tuned neuronal activity and cellular function upon memory formation during fear learning, for example, medial prefrontal cortex [14], auditory cortex [15] or periventricular thalamus [16] as well as many others [17].

Memories are encoded in distributed networks across the brain [18] and it is quite unlikely that an associative memory is stored at a single site or a dedicated neuron [19,20]. Implicitly, to understand the formation of associative memories we need to study the individual sites of memory formation as well as their interaction to resolve the complex dynamics of memory encoding and expression [21]. This effort has led to the identification of many distributed brain areas and neural circuits that are crucial for fear learning and memory consolidation [for review see Refs. 2,17]. Studying the interaction of distinct large populations of individual, identified neurons simultaneously and longitudinally during memory formation and long term consolidation is a daunting and technically so far not feasible task, although recent developments of multisite recording techniques will bring us closer to this goal [22]. Nevertheless, a currently achievable approach is to unravel the interaction of smaller distributed networks to reveal the coding patterns in a distributed neural population with well-defined circuit elements.

Such a sizable network is the feedforward pathway from auditory thalamus to the amygdala. The individual elements of this network, that is, the medial geniculate body (MGB) and the basolateral amygdala (particularly the lateral amygdala) and their role in sensory processing and memory formation have been studied extensively

in now classical papers. Initially, auditory thalamus received attention for its role as an integrative site of CS and US signalling. Electrophysiological recordings in MGB revealed that particularly the higher order nuclei of the auditory thalamus and adjacent nuclei like posterior intralaminar nucleus (PIN) and supragenicular nucleus (SG) receive converging auditory as well as somatosensory information [23]. Auditory stimuli are fed-forward via the ascending auditory pathway [24], while somatosensory inputs most likely originate in the trigeminal spinal cord, periaqueductal gray and colliculus [25,26] and/or via potential (polysynaptic) top-down feedback from cortical US-processing areas [15,27]. It was thus suggested that MGB might be an ideal site for CS-US integration and neuronal plasticity in associative learning [26] and it has been shown early on that neuronal responses to auditory tones are enhanced in MGB upon auditory fear conditioning [28]. These studies demonstrated neuronal response plasticity in MGB upstream of response potentiation in the amygdala [29].

However, amygdala's and MGB's role in neural plasticity upon fear learning was discussed diversely arguing that either site is the 'root' or 'site' of plasticity in fear learning [30,31] resulting in an auditory thalamus-centric versus a, now more common, amygdala-centric view. During the last decades, a particular focus has been placed on the individual circuit elements of the BLA and their involvement in fear learning. For example, individual interneuron subtypes like parvalbumin, somatostatin, CCK or VIP interneurons play distinct roles in the representation of conditioned and unconditioned stimuli during and across fear learning [32–34] and can thus exert distinct effects on long-range projection neurons [35] in a pathway-specific manner [36]. Furthermore, long-range projection pathways of BLA neurons are functionally diverse [7,37,38] and can have opposing effects during fear learning and fear extinction [39]. It is now widely accepted that BLA is a site of fear memory storage, harbouring networks of memory engram neurons [40,41].

Nevertheless, both, the MGB-centric and the BLA-centric view did indeed argue that the other respective site might be involved in fear learning as well and that the storage of fear memories might occur in a distributed circuit fashion [30,31]. At that time both views did point towards future studies to resolve the question whether BLA or MGB are the root of plasticity in fear learning. What additional evidence did we acquire and are we closer to answer that question?

MGB and the lateral thalamus are sites of neuronal plasticity in fear learning

MGB neurons are activated by both, the auditory tone CS and the foot shock US upon fear conditioning. Particularly neurons of higher order, extralemiscal parts of medial geniculate body (MGBm) and associated nuclei

(PIN, SG) – regions that project to the amygdala [42] – are involved in fear learning and memory formation [1,43]. Furthermore, Han *et al.* showed that phosphorylated CREB, a marker for neuronal plasticity, is specifically enhanced in higher order MGB neurons upon auditory fear learning, but not during contextual conditioning, while overexpression of CREB leads to a strengthening of fear memories [44]. In line with these experiments, inhibiting RNA-synthesis and/or protein expression in MGB reduced freezing levels after fear conditioning [45,46].

On the level of single neuron responses, higher order MGB neurons are responsive to both, the tone and the unconditioned aversive stimulus [23], rendering them an ideal site for the formation of associative memories based on CS/US pairing-dependent long-term potentiation similar to the amygdala [29,47,48]. Several types of response potentiation or plasticity have been observed in MGB neurons upon fear conditioning. For example, as one of the first observations of MGB response plasticity, Ryugo and Weinberger observed auditory stimulus response potentiation upon discriminative aversive conditioning particularly in the medial subdivision of MGB, but not in its ventral (MGBv) or dorsal subdivision (MGBd) in paralyzed cats. Additionally, US response dynamics of MGB multiunit activity were predictive of consecutive response plasticity [28]. Re-tuning of auditory receptive fields via a shift towards the conditioned CS frequency has been observed in all subdivisions of MGB during conditioning. This re-tuning involves complex dynamics, for example, potentiation of conditioned stimulus frequencies or depression of responses to non-CS frequencies. Auditory thalamus neurons are frequency-tuned in an area-specific manner and exhibit differential plasticity during associative learning. Neurons of the medial and dorsal subdivisions of MGB (as well as SG) retain their receptive field plasticity beyond conditioning, while plasticity of neurons in MGBv is more transient upon associative learning [49–51].

Initial studies on response plasticity in MGB upon associative learning were mostly conducted in head-fixed preparations and individual neurons were not tracked across days. Two recent studies recorded from genetically identified or projection-specific neurons in MGB. Calretinin-positive neurons extend through the medial part of the MGB as well as PIN and SG, sites which have recently been classified as lateral thalamus [25]. These areas harbour amygdala-projecting neurons which are by-and-large calretinin-positive [25,52]. Using a classical auditory fear conditioning paradigm, Barsy *et al.* and Taylor *et al.* show that identified amygdala-projecting neurons of MGB and PIN/SG are plastic upon fear learning in freely moving mice and can potentially drive response plasticity in downstream amygdala neurons [25,52]. Furthermore, optogenetic inhibition of

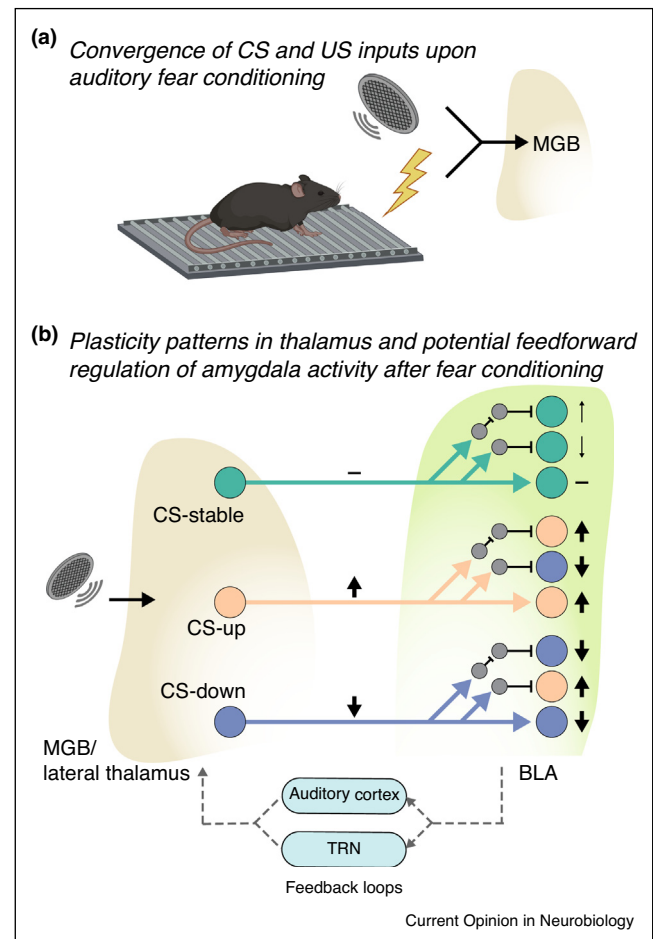
amygdala-projecting neurons in MGB and PIN/SG prevented fear learning indicating the necessary role of CS/US-driven activity in MGB and PIN/SG to facilitate fear memory formation. Calretinin-negative neurons exhibit distinct anatomical connectivity and CS/US responsiveness when compared to amygdala-projection neurons suggesting distinct functions in integration and learning-dependent plasticity of these two cell types in higher order thalamus [25].

Plasticity in MGB upon fear learning is diverse and not exclusively limited to short term potentiation or depotentiation of individual neurons. Across a four-day fear conditioning and fear extinction paradigm, MGB neurons exhibited response plasticity depending on the behavioural state of the animal [52]. For example, individual neurons were potentiated after fear learning when the animal was in a high fear state [25,52], while another set of distinct neurons was potentiated after fear extinction, when the animal was in a low fear state. These two functional neuronal classes in MGB are similar to previously described fear (potentiated after fear conditioning) and extinction (potentiated after fear extinction) neurons that were first identified downstream in the amygdala [7]. Additionally, MGB also exhibits neurons with less stereotypic plasticity across fear learning (e.g. CS down cells, fear down cells, extinction down cells etc.) [52], which resembles the diversity of response plasticity types that was recently described in the amygdala [10,11]. Besides conditioned stimulus coding, amygdala-projecting MGB neurons exhibit a large diversity and short term plasticity of adaptive US coding similar to downstream amygdala neurons rendering MGB a site of CS-US integration, coincidence detection or teaching signals, depending on the response type of a given neuron [52]. Future studies will have to determine how a neuron's US response type contributes to CS plasticity in MGB and if and how this information is used for the expression of plasticity in downstream areas like the amygdala or auditory cortex (Figure 1).

Besides auditory fear learning, amygdala-projecting neurons from MGB and PIN/SG are also involved in the formation of contextual fear memories indicating their role in higher order multisensory processing during associative learning that goes beyond cued fear conditioning [25]. Along these lines, a recent study demonstrated that MGB response plasticity is also observed in an instrumental learning paradigm, where mice had to report a decision based on an auditory discrimination task. In addition to response plasticity to the rewarded stimulus, MGB neurons also encoded the choice of the mouse, which revealed an unexpected cognitive function of auditory thalamus [53] [see also Refs. 54,55].

Together, previous and recent studies indicate that higher order auditory thalamus and the surrounding

Figure 1



Auditory/lateral thalamus plasticity upon fear learning.

(a) Auditory thalamus and adjacent nuclei are sites of convergence of auditory tones (CS) and foot shocks (US) during auditory fear conditioning [23,25,31,52]. (b) Examples of CS plastic neurons after fear conditioning in amygdala-projecting neurons of auditory/lateral thalamus. These plasticity patterns potentially impose diverse plasticity in BLA neurons after fear conditioning via direct feed forward excitation, inhibition or disinhibition leading to complex BLA output (green: no change; orange: response potentiation; blue: response suppression, grey: inhibitory interneurons; thick arrows indicate neurons with plastic changes). Note that this feedforward-driven single cell plasticity in BLA will be substantially more complex due to additional local synaptic plasticity mechanisms in BLA and plastic input from auditory cortex and other brain areas. Furthermore, auditory/lateral thalamus activity is prone to be modulated by BLA feedback via auditory cortex and the thalamic reticular nuclei (TRN) [56,57].

PIN/SG areas are sites of multisensory integration, stimulus association and learning-dependent plasticity that go beyond a classical sensory relay function. Nevertheless, the interaction of sensory signalling and plasticity between MGB and the amygdala and the distributed population coding in both areas remains unknown.

Population coding in auditory thalamus and basolateral amygdala

Single cell response patterns and plasticity of defined neuronal circuits has been widely studied in associative learning and fear conditioning, particularly in the BLA. However, in the central nervous system, sensory stimuli and their behavioural consequences are most likely encoded as a higher dimensional signal across a large population of neurons [58–61]. In light of large single cell response variances to identical repetitive stimuli across trials and days, population signals have proven to be stable encoders of sensory inputs [62,63]. However, in mice, access to large numbers of identified individual neurons was so far limited to cortical rain areas, while deeper brain areas like the amygdala or auditory thalamus were inaccessible. Novel imaging techniques based on gradient refractive index lenses and miniaturized microscopes now allow the measurement of simultaneous activity of large numbers of individual neurons in deep brain areas of freely moving animals [64].

By following large populations of amygdala neurons across a fear conditioning paradigm, Grewe *et al.* demonstrated that the population of BLA projection neurons reliably encodes an auditory CS tone across repetitive stimulations and days [10]. However, upon fear conditioning, the population representation of the CS response changes towards the US and the population decoder across days breaks down, while the higher dimensional (number of dimensions equals the number of recorded neurons) population representation of the CS becomes more similar to the US. This shift is enhanced with increasing numbers of pairings during fear conditioning and consolidated overnight, that is, the CS representation in the amygdala becomes even more similar to the US without additional numbers of pairings or CS presentation. Furthermore, this shift is a population level representation of post-conditioning memory consolidation given that the magnitude of the shift in the amygdala was predictive of the strength of freezing during fear recall. This population level representation of consolidated associative memories is valence-unspecific in BLA and occurs also during appetitive learning [13].

A similar shift of the conditioned stimulus response towards the aversive foot shock can be observed in the population of MGB projection neurons that are upstream of the BLA or auditory cortex. The representation of the shock predicting CS becomes more similar to the US. However, and in contrast to the observations in the BLA, this shift is neither amplified nor conserved overnight. This suggests that the population level change in MGB during conditioning is not consolidated and the population level representation in MGB is not predictive of the aversive outcome. Using a population decoding approach across days as an alternative method revealed that CS signals can be reliably decoded from the MGB, both from

the total population as well as from amygdala-projecting MGB neurons. This suggests that the population level encoding of auditory conditioned stimuli is stable across days in auditory thalamus and that MGB does not get biased towards an aversive representation or ‘fear hijack’ [52].

Nevertheless, this does not exclude that plasticity of population encoding of MGB neurons is necessary for fear learning. For example, upon fear learning, changes in the MGB population representation of the CS that make it more similar to the US could be crucial to drive downstream changes in population activity of amygdala neurons that could not be achieved by single cell plasticity. An enhanced recruitment of MGB neurons to this ‘population trace’ of within session learning and a broad transmission of this signal to the amygdala could be necessary to cross a detection threshold to drive BLA population plasticity [10,13]. Similar to a map expansion/normalization model [65], transient MGB population plasticity and recruitment of a large fraction of MGB neurons with divergent downstream targets in BLA, could drive learning but is not necessary to ‘hold’ the memory. Once a stable fear memory is formed (e.g. overnight), MGB population coding can normalize back to a default state to ensure reliable sensory representation and to instruct the future acquisition of a new stimulus association. On the other hand, BLA maximizes stimulus association on the population level for enhanced stimulus-dependent threat detection [10,13,66]. To understand how MGB population representations affects plasticity of population coding in the amygdala, it will be crucial to test how MGB and BLA coding changes upon specific manipulations of MGB → BLA neurons, for example, by using novel circuit neuroscience tools like all-optical simultaneous imaging and manipulation approaches [67].

On the single cell level, MGB exhibits across-day-plasticity to the conditioned stimulus. Despite this single cell plasticity MGB population level coding of CS representations is stable across fear learning. This phenomenon might be similar to cortical populations, which have been shown to reliably encode sensory stimuli on the population level despite single cell response variability [62,63]. Nevertheless, changes in response patterns of individual MGB neurons could be a strong driver of plasticity downstream in the amygdala. For example, besides direct feedforward activation of BLA neurons, convergent inputs to inhibitory BLA networks could drive wide-ranging changes in population representations of the CS and US in BLA neurons, depending on the area within BLA [68], the specific interneuron subpopulation they impinge on [32,34,35] or on the plasticity type (e.g. potentiated or depotentiated neurons, see Figure 1) of the individual MGB neurons [25,52].

Furthermore, those different MGB plasticity types could activate distinct, and potentially opposing BLA subnetworks [38,69] that could enhance population level encoding of threat predicting stimuli or behavioural state representations during fear learning or fear extinction [see also Ref. 70] via feedforward or lateral inhibition [71]. Future experiments need to reveal if and how functional subtypes of MGB neurons impinge on distinct downstream BLA cell types or subnetworks to understand if and how MGB induces or maintains plasticity in downstream amygdala circuits.

Conclusions and outlook

Despite many early seminal papers that investigated the role of the auditory thalamus → amygdala network during fear learning, we are only starting to understand the circuit basis, functional diversity and computational principles that underlie the neuronal plasticity in this crucial pathway for threat learning. Multisite activity and plasticity in auditory thalamus and the basolateral amygdala upon fear learning might be required for precise memory formation and recall as well as the induction of appropriate, defensive behaviours, which goes beyond the notion of a simple feed-forward relay pathway and single-site information integration and storage. Distributing sensory integration and plasticity upon fear learning between thalamus and amygdala would allow for area-specific representations of environmental features and local state-dependent modulation enhancing the information content of sensory representations and memories for downstream brain regions that receive converging inputs from both areas. Furthermore, distinct auditory thalamus → amygdala projections could act as labelled lines on the microcircuit level to recruit different amygdala subnetworks or memory engrams and the activity balance of those lines could in turn determine behavioural outcomes in response to environmental stimuli. Learning-dependent plasticity in MGB might then shift this balance to strengthen appropriate behavioural responses via the recruitment of specific amygdala subnetworks, while state-dependent activity within the amygdala might lead to additional behavioural modulations, valence assignment and updating-feedback to thalamus via auditory cortex or the thalamic reticular nucleus. In addition to the wealth of amygdala circuit research, it will be crucial to understand how MGB interacts with other cortical and subcortical areas and the impact of these projections on behavioural, autonomous or cognitive functions to reveal if and how a distributed code across amygdala and auditory/lateral thalamus leads to a sharpening of memory formation and behavioural gains.

Testing these hypotheses will require a detailed description of the cell-type-specific synaptic connectivity between auditory thalamus and amygdala, simultaneous recordings of population coding during learning as well as cell-specific and network-specific targeted manipulations

to test interdependencies between the two areas as well as their downstream brain areas during fear learning. Unravelling the neuronal population and circuit plasticity principles in this network using a fast and efficient paradigm will not only help us to understand the basis of associative aversive learning, but could reveal the computational principles of distributed encoding of behaviourally relevant sensory information upon learning as well as the potential transfer of these codes between brain areas during memory consolidation. The modern neuroscience toolbox will make these experiments now possible.

Conflict of interest statement

Nothing declared.

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Grewe *et al.* use a miniature microscope imaging approach to study the activity of large populations of amygdala neurons. This novel approach reveals increased as well as decreased CS response patterns of individual BLA neurons, which is independent of their US activity upon fear learning. Using this large-scale approach, the authors identify that the population representation of the CS becomes more similar to the US during fear conditioning. The magnitude of this ensemble level shift is predictive of the strength of memory formation.

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