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Review

Dopaminergic impact on local and global cortical circuit processing during learning

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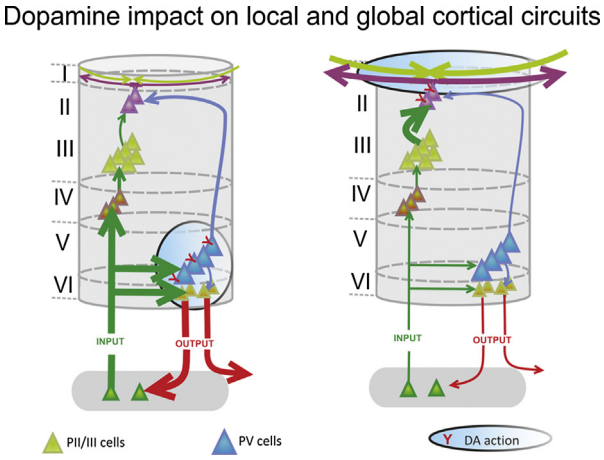
HIGHLIGHTS

- Dopamine impacts on cortical circuit processing in a layer-dependent manner.
- Dopamine-modulated corticoefferent feedback gain promotes sensory input processing.
- Local cortical dopamine actions broadcast to global corticocortical circuits.
- Such circuit functions assist the integration of bottom–up and top–down information.
- Cortical dopamine is a multifunction signal in the service of behavioral adaptation.

GRAPHICAL ABSTRACT



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ABSTRACT

We have learned to detect, predict and behaviorally respond to important changes in our environment on short and longer time scales. Therefore, brains of humans and higher animals build upon a perceptual and semantic salience stored in their memories mainly generated by associative reinforcement learning. Functionally, the brain needs to extract and amplify a small number of features of sensory input with behavioral relevance to a particular situation in order to guide behavior. In this review, I argue that dopamine action, particularly in sensory cortex, orchestrates layer-dependent local and long-range cortical circuits integrating sensory associated bottom–up and semantically relevant top–down information, respectively. Available evidence reveals that dopamine thereby controls both the selection of perceptually or semantically salient signals as well as feedback processing from higher-order areas in the brain. Sensory cortical dopamine thereby governs the integration of selected sensory information within a behavioral context. This review proposes that dopamine enfolds this function by temporally distinct actions on particular layer-dependent local and global cortical circuits underlying the integration of sensory, and non-sensory cognitive and behavioral variables.

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1. Introduction

Humans and higher animals continuously update anticipation of behaviorally relevant events and flexibly adapt to environmental changes. Mechanisms of associative reinforcement learning have been accounted to guide these processes. But how are processing and evaluation of immediate choice-outcome consequences transferred to long-term behavioral adaptation and learning? In this context, many constitutive functions including locomotor adaptation, coding of rewards and predictions, memory consolidation and retrieval have been associated with the action of the neuromodulator dopamine. Based on its architecture, cerebral cortex is most suited to integrate current experiences with existing internal representations of the world and consequently to constantly mediate and update behavioral adaptations [1,2]. In order to guide adaptive behavior, a small number of features of sensory input with behavioral relevance to a particular situation have to be selected and their neuronal representation be amplified [2,3]. But only the integration of such selected sensory bottom–up and semantically driven top-down information enables cognitive and behavioral control [4–8]. In this context, dopamine released by midbrain neurons has been extensively discussed to provide suitable instructive signals directing rewarding outcomes to distributed regions of the brain involved in stimulus processing [5,9].

A current conceptual problem of the midbrains phasic dopamine signaling (see Section 2.1) is that sensory stimuli and the outcomes that they predict are often seconds apart from each other. This problem has been described by Hull as the "distal reward problem [10]" or more recently in the reinforcement learning literature as credit assignment problem (e.g. [11]). Further, on a behavioral level dopamine affects learning and memory consolidation on longer time scales even days after its actual neuronal action [12–14].

Dopamine was identified as a neurotransmitter by Arvid Carlsson and colleagues in 1957. In spite of the long research history it is quite astonishing how far we are still from a better mechanistic circuit understanding of the plethora of dopamine functions. This is particularly true for the highly innervated networks of the cortex [15].

This review proposes a framework of successive dopamine-modulated layer-dependent processing modes of cortical areas involved in sensory stimulus processing underlying the integration of sensory, and non-sensory cognitive and behavioral variables. Current research evidences that dopamine recruits layer-specific and temporally specific cortical computational processing units. Specifically, increased dopamine levels promote salient local stimulus processing by corticoefferent recurrent feedback gain. And subsequently increased activity expatiates to persistent horizontal corticocortical activity spread in upper layers. This model of dopamine function may provide a plausible network mechanism suggesting how dopamine integrates temporally distinct sensory stimuli and internal value evaluations. Thereby, dopamine may link local and global cortical circuit systems during states of conflicts between expectations and outcome on a behavioral, cognitive level. It will be discussed how this circuit effect might impact on the conceptual problem of credit assignment in associative learning [9] and on long-term learning and memory functions (see Section 4).

2. Dopamine as a multifunctional signal in the service of goal-directed behavior

The neurotransmitter dopamine released in midbrain and cortical structures is involved in a multitude of neurophysiological processes that do not easily map to psychological and cognitive concepts [16]. In fact, neurophysiological research on the functional roles of dopamine allowed addressing the complex relationships between the action of a single neurotransmitter and various aspects of behavioral functions [17–19]. The complexity results from several facts. First, dopamine is released by different populations of neurons that are influencing distributed brain networks serving distinct functional roles [18,20]. Further, psychological concepts are formulated on the basis of different conceptual frameworks, including those addressing the discernible temporal phases of motivated behavior or qualitatively different aspects of motivated behavior [21,22]. In addition, it has been emphasized to relate dopamine functions to a-priori existing functional psychological categories on the basis of architectural principles apparently "implemented" in dopaminergic brain systems [23].

With respect to psychological constructs, an enormous amount of studies have focused on the roles of dopamine for processing of reward, expectation of reward and violation of reward expectations. A very influential framework is that of the reward prediction error (RPE) signaled by the activity of dopaminergic neurons in the midbrain and influencing widespread brain regions. In this framework of reinforcement learning, dopamine initially encodes affective properties of a reward, but rapidly transforms to code for predictions about reward [24,25]. This dopaminergic RPE signal is hence seen as a teaching signal allowing associative reinforcement

learning between stimuli in the environment and particular internal reward values and has been extensively reviewed [18,19,26].

Despite a traditional emphasis in the literature to discuss dopamine in the context of reward processing, this transmitter has also been implicated in the processing of aversive stimuli [27–30]. The aversive space in which a dopaminergic neuron operates might thereby not be a direct blueprint of its reward space [31]. However, especially in dorsal midbrain dopaminergic neurons tend to get activated by both appetitive and aversive events [28,32]. In the context of motivation by appetitive and aversive stimuli dopamine is involved in sensorimotor functions [16] and formation of goal-directed behaviors [30]. Moreover, the role of dopamine during processing of aversive signals and their predictors has been discussed in the context of formation of instrumental strategies to avoid expected aversive experiences [30]. In addition, dopamine shows several well documented related functions, including coding novel, but non-reinforcing stimuli [33,34], risk and reward uncertainty [35] and an economic updating of decision variables [36,37]. Dopamine further signals motivational salience engaging with options at times of uncertainty in order to re-establish good predictions about its own behavioral consequences [18,38]. Thereby, dopamine has a strong impact on behavioral and cognitive flexibility—viz. ignoring irrelevant events in stable environments and integration of new events in changing situations [39–41]. Together, the available evidence highlights diverse functions of dopamine in order to flexibly adapt valuable behavioral options in complex, changing environments. These dopamine functions comprise, on the one hand, the coding of the behavioral (perceptual and semantical) salience and valence of new and known environmental stimuli. On the other hand, dopamine engages an organism to actively interact with the world by increase of attention, motivation to explore and gain new information and successful learning feedback [18,22,26,42].

3. Dopamine action in sensory cortex

3.1. Map plasticity in sensory cortex underlying associative learning

Dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra are known to innervate main parts of the forebrain including sensory and motor cortex [20,43,44]. Nevertheless, research on the action of dopamine has mainly focused on midbrain, striatal and prefrontal circuits [45,46]. Hence, understanding of general circuit mechanisms of dopamine-mediated functions in the neocortex, especially in sensory cortex, are still relatively scarce. In motor cortex, dopamine action has been related, for instance, to fine motor skill learning [47]. Similarly, Bao et al. [48] paired pure tone frequency stimulation with electrical stimulation of the VTA to trigger an increase in the respective tonotopic area in rat auditory cortex. This study did not elucidate an association between the artificial reinforcement signal and the tone on a behavioral level. Nevertheless, the authors speculated that dopamine as a teaching signal would underlie representational map plasticity. Further evidence suggests that dopamine triggers learning-induced plasticity in primary sensory cortical map representations by enhancing the sensitivity to behavioral important stimuli in order to command a particular behavior [12,49–51].

3.2. Representation of task-specific, cognitive processing in sensory cortex & dopamine

However, how may the described dopamine effect in primary sensory cortex relate to dopamine-mediated reward processing and behavioral adaptation? Recently, evidence accumulates that sensory cortical activity is associated with dopamine-mediated rewarding feedback in somatosensation [52], vision [53,54] and audition [55,56] across a range of several behavioral paradigms and species. For instance, multiunit activity in auditory cortex adaptively encodes the reward expectancy for an upcoming trial and the reward-size received [55]. In visual cortex, dopamine increases the response magnitude and selectivity of single cell visual responses during a target selection task [57]. These findings indicate a close relation between map plasticity of sensory cortex and the reinforcement prediction by dopaminergic input [7,9]. Furthermore, sensory cortex is involved in working memory tasks [58,59] generally associated with prefrontal dopamine release [60,61]. Together, sensory cortices substantially integrate bottom–up and top–down information and are much more dedicated to cognitive, task- and learning-relevant aspects of processing rather than working as a mere higher-order stimulus feature processing unit [6–8,49,62].

Nevertheless, adaptive behavior and learning are functions of neuronal circuits. We will only understand the integrating role of bottom–up and top–down processes ascribed to dopamine by a better picture about the functional-anatomical basis of the cortical dopamine system (see Section 5).

4. Dopamine as essential component in long-term consolidation during associative learning

4.1. Dopaminergic impact on long-term memory consolidation in cortex-dependent forms of learning

Several recent findings have illuminated the functional role of sensory cortical dopamine in the context of learning and memory. In this respect, dopamine-based signals are not only spatially broadly distributed across the brain and can become temporally dissociated from the receipt of reinforcers [20]. They further act directly and indirectly through different time-scales [22]. Dopamine impacts on long-term memory consolidation, retention and retrieval at times distant from the original experience during several different task designs and forms of learning, as for instance spatial and cued discrimination [63], novel object recognition memory [64], hippocampal-prefrontal dependent learning [65,66], and sensory cortex-dependent discrimination learning [12,50,67].

In auditory cortex the temporally distinct dopamine effects have been demonstrated by two separate technical approaches both using cortex-dependent discrimination learning of frequency-modulated (FM) sounds [68,69]. First, using brain microdialysis it has be shown that dopamine is transiently released in auditory cortex during the initial acquisition learning phase reflecting the formation of a correct go/nogo avoidance strategy. Dopamine levels returned to baseline already in phases where animals still increased their performance and during phases of retrieval [50,70]. Hence, dopamine seems to orchestrate the goal-directed formation of a behavioral strategy that builds upon the initial establishment of task-relevant associations [71]. By the same token, Schicknick et al. [12] locally injected the D1/D5 dopamine receptor agonist SKF-38393 into bilateral primary auditory cortex shortly before or after a first session of FM-tone discrimination learning [12].The increased dopaminergic transmission had no effect on the initial learning performance. However, after several training days, injected animals acquired an enhanced discrimination performance [12]. This effect could be blocked by local injection of dopamine antagonists. Injection of pharmacological agents interfering with protein biosynthesis, like anisomycin or rapamycin had the same effect [12,67]. Rapamycin is a blocker for the protein kinase mammalian target of rapamycin (mTOR)—a translational regulator of mRNAs associated with synaptic plasticity. Hence, dopamine locally acting in auditory cortex might bridge the gap

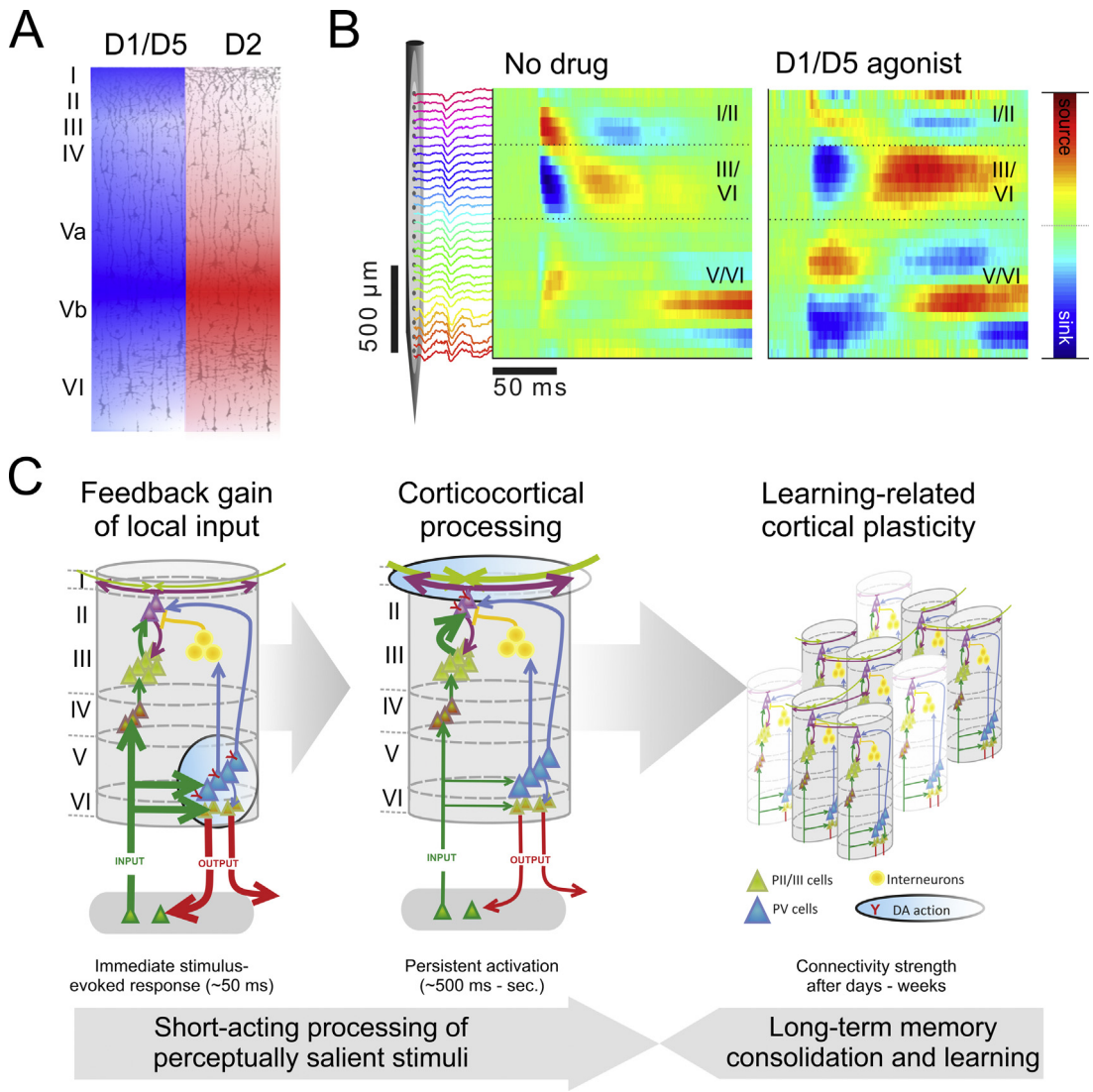

Fig. 1. Local and global impact of dopamine on cortical processing and learning. (**A**) All cortical regions show a highly layer-dependent distribution of dopamine receptor types with high levels of D1-like and D2-like receptors in infragranular layers, and higher levels of D1-recpetors in upper layer I. Modified from ref's [43,80–83]. (**B**) *Left*, Tone-evoked current-source density profiles in auditory cortex of Mongolian gerbils reveal a feedforward pattern of the spatiotemporal synaptic current flow with major early input in thalamocortical input layers III/IV [93]. *Right*, Systemic application of the D1/D5 agonist SKF38393 [12] strongly enhanced early synaptic activity in infragranular layers and subsequently prolonged cortical tone-evoked processing. Modified from ref. [51]. (**C**) Schematic overview of the short-acting impact of dopamine on cortical processing of behaviorally relevant stimuli with increased input processing by recurrent corticothalamic feedback gain (*left*) and subsequent increase in horizontal corticocortical processing (*middle*). This processing mode thereby triggers associative synaptic reorganizations of corticocortical distributed networks (*right*). Plastic reorganization of the connectivity strength between cortical circuits is symbolized by different grey shadings of the cortical columns. Such plastic processes are protein-synthesis dependent, long-lasting, and hence affect long-term memory consolidation.

between immediate stimulus-response processing and the consolidation of auditory memories required for long-term retrieval. Dopamine therefore, activates complex cell-intrinsic molecular signaling cascades strengthening or weakening the re-activated synaptic networks in a protein synthesis-dependent manner. Rather diffuse non-specific neuromodulatory value signals are thereby conveyed by the layer-dependent sensory cortical circuitry to act mainly on the connection strength of recently activated sets of synapses. This allows the temporally well-structured bottom–up inputs to encode stimulus-association pairings [9].

4.2. *Specificity of sensory cortical dopamine during cortex-dependent learning*

Short-acting phasic dopamine signals novelty and salience of events rendering these as behaviorally important. Particular long-term dopamine effects implicated in learning-induced plasticity allow a specific association of external events and behavioral needs [5]. These two temporal functions of dopamine are highly interacting rather than display exclusive subfunctions and allow us to actively integrate our consequences of action over a long time scale (Fig. 1C, *right*). A model process that allows investigating this integrative function of dopamine is reversal learning. During reversal learning, the tendency to stick to a particular choice independent of contrary evidence or outcome is called perseverative behavior. Contrary, the ability to reverse behavioral preferences of previously reward-based, learned choices has been related to dopaminergic functions in different species and brain regions [70,72–74]. In this respect, Stark et al. [70] studied strategy change performance of Mongolian gerbils by confronting them with a reversal of already learned choice-outcome contingency in an auditory learning task. In parallel they performed microdialysis-based measurements of individual prefrontal dopamine levels. Trained animals were separated into two groups by their individual low or high prefrontal

dopamine release during the first reversal session, respectively. Interestingly, the performance in the first reversal session was independent of the coinciding prefrontal dopamine levels of both groups. In later sessions, however, only animals of the group with initial high dopamine levels were rapidly relearning the new task contingency, while dopamine levels in both groups were already equal again. Hence, the initial formation of associations for a new goal-directed behavioral strategy is accompanied by prefrontal dopamine release [70]. It has been supposed that the initial prefrontal dopamine release activates working memory capacities [60,75]. This may be necessary for solving complex relearning demands by supporting cognitive aspects as for instance comparison and comprehension of previous events and experiences. Such cognitive states might then allow the protein-synthesis dependent long-term synaptic adaptations underling the subsequent performance improvement [12,70]. Thereby, these studies implicate the particular cooperative function of early and late dopamine effects. The attenuation of the dopamine release while the behavioral performance still increases might reflect the reduced demand on working memory capacities at more advanced stages of the learning process [66,71]. Also other studies have linked quantitative variations of dopamine levels in the striatum to individual variability of reward-based learning performance [76,77]. Dopamine levels in individual animals, hence, predict their task performance.

A further aspect highlighting the task specificity of dopamine action is its potential role in novelty coding [18,33]. Principally, novel stimuli may contain new, behaviorally relevant aspects that are profitable to be integrated into a behavioral context. In this context, Rothe et al. [71] presented novel tone stimuli within a comparable auditory relearning context of rising and falling FM tones or without any context. The authors found a profound dopamine response to novel stimuli mainly in the first, but not the latter situation [71]. Hence, mere occurrence of novel stimuli might not per se play an essential role for the formation of new associations [78]. Novel or ambiguous stimuli that are presented simultaneously with task- or strategy-relevant events induce memory-relevant dopamine release that may promote the formation of new task-relevant re-associations. Finally, individual dopamine levels thereby relate to the cognitive demand balancing to use choice policies implemented in previous comparable situations [22,77] or the formation of new task-relevant associations [50,70]. Due to the highly individual, motivational, situation-related and task-specific functions of dopamine, it should not be understood as a homogenous reinforcement signal [22].

5. Dopaminergic impact on local and global circuit processing in cortex

So far, this review outlined particular roles of dopamine in reward-based learning and long-term memory consolidation. The remainder of this review will now consider the specific action of dopamine on neuronal processing in sensory neocortex on the circuit level assisting the aforementioned functions. The following paragraph will start the discussion by reviewing some principles of functional circuit organization in sensory neocortex and considering the effect of local dopamine release in sensory cortical circuits.

5.1. Layer-dependent dopaminergic inputs to cortical areas

An important feature to relate dopaminergic action to specific cortical processing modes is the pronounced and unique layer-dependent distribution of dopamine receptors and terminals in cortical areas (see Fig. 1A). Dopaminergic terminals and D1/D5-like as well as D2-like receptors are most abundant in infragranular output layers V and VI in visual cortex [57,79], auditory cortex [12,43], somatosensory cortex [80], motor cortex [47], prefrontal and several other cortices [81–84]. Additional to strong infragranular dopaminergic innervation, particularly cortical layer I receives dopaminergic inputs and displays a high expression of mainly D1- and to a lesser degree of D2-like receptors [43,81,83,85,86]. However, note the cooperative activity of superficial D1- and D2-receptors outlined below [87].

5.2. The cortical column as a functional unit

The outlined laminar distribution of dopaminergic receptor types indicate that dopamine may serve specific circuit functions in the cerebral cortex. At this point it is hence applicable to briefly outline current concepts of the functional cortical circuitry, as they are discussed in detail elsewhere [2,3,88]. Sensory inputs from primary thalamocortical projections most densely target granular input layer IV as well as the border of layer V/VI via collaterals [44,89,90]. These afferent inputs are integrated by diverse sets of cortical cell types [2]. Microcircuits of layers II/III can amplify afferent inputs manifold by local recurrent excitation [91–94]. Intracortical circuits then route the information across distributed corticocortical circuits including higher-order areas [2]. This leads to a strong convergence of local and distal inputs in supragranular output layers receiving main parts of horizontal corticocortical inputs at a cortical patch [2,95–97]. By terminating on both pyramidal neurons and interneurons, supragranular inputs shape the accurate columnar processing [98]. Such architecture may allow the integration of different sensory, as well as non-sensory long-range inputs with a high temporal precision underlying particularly associative plasticity [1,48,93,99,100]. Infragranular layers accommodate principle cells in layers V and VI, which comprise at least two subclasses, respectively. Large subcerebral projections neurons (SPN) in layer V receive various synaptic inputs across their dendrites spanning all cortical layers [1]. The other class of layer V intratelencephalic neurons (ITN) provides local inputs to layers II/III in opposite to SPNs that only provide minor local inputs [101]. However, SPN output of even primary sensory areas project to a large portion of first-order and higher-order subcortical and cortical targets via direct or transthalamic pathways [2,102–104]. Layer VI harbors as well two classes of mainly intracortical and corticothalamic projecting neurons. These cell types have been implicated in more modulatory than driving impact on subcortical first-order relays [105], intracortical gain control and translaminar inhibition [106]. The different corticoefferent feedback and feedforward processing systems originating in infragranular output layers integrate information from the complete cortical column. The information is then broadcasted to several distant target regions. These regions have further been assigned to diverse functions as sensory gating, working memory load by persistent activity and initiation of movement and behavior [102,107–109].

5.3. Dopaminergic impact on corticoefferent feedback and input processing

Interestingly, the infragranular hotspot of transforming stimulus-processing into action-selection is the main target region of dopaminergic inputs to the cerebral cortex [81,82]. For instance, infragranular pyramidal neurons in mouse frontal cortex expressing D2 receptors have strong corticothalamic projections [103]. This implies a potential dopamine-modulation of corticoefferent feedback processing [79]—a mechanism that has been proposed for persistent prefrontal cortex (PFC) activation before [107]; see also Section 6.1.

In a recent study we could further elucidate such a role of dopamine in primary auditory cortical circuits of Mongolian ger-

bils. We combined recording of the tone-evoked laminar current source density (CSD) distribution with pharmacological manipulation of dopaminergic neurotransmission by application of the D1/D5-agonist SKF-38393 (see Fig. 1B; cf. [51]). In this study, we utilized the previously developed analysis of the relative residuum of the CSD as a quantitative measure of activity relayed via horizontal corticocortical projections [93]. Specifically, we found that dopamine impacts on cortical processing in a two-phase mode of first local (this paragraph) and second global (next paragraph) influence on cortical processing. In the first, local phase, dopamine boosted early thalamocortical inputs particularly terminating in infragranular layers. This activated a recurrent feedback circuit originating in the corticoefferent output layers that subsequently amplified and prolonged thalamic inputs in granular layers (Fig. 1C, *left*; [79]). Synaptic delays of positive feedback from infragranular to granular layers were in the range of 6 ms which favors extracortical routing via corticothalamo-cortical circuits [110]. In addition, a constantly low CSD residuum in this early phase suggests that the dopamine-mediated amplification of afferent inputs is relayed specifically by intracolumnar and local corticoefferent circuits. Such response enhancement between granular and infragranular layers in the sense of salient input processing has also been observed in auditory cortex of sound-attending monkeys [111]. Dopamine-modulated corticoefferent output could further regulate more wide-spread higher-order cortical and various subcortical structures via transthalamic pathways [112]. Thereby, other sensory, motor, limbic, and higher cognitive processes involved in the functions of cortical dopamine are potentially coordinated. Investigation of such multisite circuit interactions will be an exciting direction in future research.

5.4. Dopamine modulation of corticocortical feedforward processing

Of further particular interest is how dopaminergic transmission affects processing in supragranular layers via the less frequent and densely limited receptor distribution in mainly layer I [81,113]. Supragranular layers are the main origin of feedforward connections and the termination zone of main parts of long-range horizontal inputs to a cortical column. Only around 10% of inputs to layer I stem from nearby neurons [3]. Upper layers show neuronal synchronization and spike-coherence predominantly in higher (gamma) frequency ranges implicated in feedforward processing [114], which are indeed altered by dopaminergic transmission [48]. Especially the coordination of long-range networks across the brain via oscillatory rhythms may regulate the neural communication underlying specific behaviors and learning [4,115,116]. Hence, dopamine-modulated synaptic processing might impact on the reliable and temporally precise integration of distal inputs and local processing in upper layers which may effectively alter the feedforward output mode [93,100]. Wu and Hablitz [87], for instance, described a dopamine-induced depolarization of layer I interneurons by cooperative activation of superficial D1 and D2 receptors. The authors hypothesized that dopamine thereby induces translaminar inhibition in layers II/III [87]. Further, electric stimulation of the VTA inducing dopamine release in auditory cortex [117] is not only mediating tonotopic map plasticity, but increases strong long-range coherence of activity between primary and secondary auditory cortical fields [48]. Such dopaminergic innervation of supragranular circuit elements might serve comparable functions as cholinergic disinhibition of layer I interneurons in auditory cortex during associate fear conditioning [118]. This is in agreement with our recent findings about dopamine effects on late tone-evoked synaptic input activity in supragranular auditory cortex. The previous paragraph described the first phase of intracolumnar feedback gain amplification of sensory input (see Section 5.3). We found that this locally amplified thalamocortical input was transferred to later supragranular synaptic processing. This increase of supragranular synaptic activity coincided with an increase in spread of horizontal long-range activity across cortical columns (Fig. 1C, *middle*). We could further show that this two-phase mode of layer-dependent dopaminergic cortical processing is involved in salient detection of behaviorally relevant stimuli in a detection task [51]. Therefore, the two subsequent phases of dopamine action in sensory cortex are as follows: (1) dopamine locally promotes a salient processing of behaviorally relevant bottom–up stimuli. And (2), subsequently dopamine enhanced later, more global activity in supragranular horizontal networks. The latter might promote associative synaptic plasticity underlying the readout of task-relevant information (Fig. 1C, *left and middle*).

Together, dopamine can potentially strengthen distal corticocortical connections in accordance with salient sensory processing during active behavioral states [119] via translaminar interactions [120]. Indeed, infragranular pyramidal neurons, as a main cortical target of dopaminergic input, assemble synaptic inputs of both supragranular and infragranular circuits along their dendritic tufts. Thereby they might display a cellular entity of such associative synaptic plasticity of bottom–up and top–down information [1].

6. Functional circuit mechanisms of cortical dopamine

It should be acknowledged that due to complex receptor-type interactions dopamine has diverse and often opposing cellular effects on both pyramidal neurons and interneurons (for the details that go far beyond the scope of this review, see references: [45,85,121]). The following paragraph focusses on findings in support of the aforementioned cortical network effects of dopamine.

6.1. Local recurrent excitation, gating and synaptic cooperative plasticity

In sensory cortex, dopamine has been shown to operate as neuromodulator acting on glutamatergic inputs [122] or by co-release of glutamate from dopaminergic terminals [117,123]. By modulating recurrent excitation, dopamine can increase and prolong the spiking probability of neurons to a given stimulus [124], presumably via ionotropic glutamatergic transmission [117,125]. In simulations of recurrent networks dopamine enhanced sustained synaptic inputs and stabilized persistent modes of activation [126,127]. Thereby, reinforced synaptic processes evoked by brief stimuli are maintained for long enough to interact with subsequent sensory input and later-arriving top-down feedback from higher-order regions. Such maintenance of internal representations during delay periods of a task has been described for many subcortical and cortical regions including sensory cortex [108] and prefrontal cortex [128]. Strengthening of sensory representations has further been related to regulate complex context-dependent behaviors [127].

Dopaminergic impact on sensory stimulus processing has been investigated most accurately in primate PFC, where it sustains synaptic inputs and maintains persistent modes of activation [127]. Dopamine exerts this effect by specific action on different cell classes: Dopamine increased the excitability of a particular cell class gating sensory inputs to PFC by an enhanced signal-to-noise ratio. In another set of neurons dopamine has been shown to strengthen the persistent representation of sensory signals which hence may allow to adapt behavior in response to changes in the sensory environment [128]. Similarly, dopamine-dependent gating of thalamocortical synapses in sensory cortex [51,129] might indeed play a fundamental role for learning- or experience-dependent plasticity in the adult brain. Temporally organized co-release of

glutamate and dopamine at eligible target synapses can modulate the postsynaptic gain and short-term dependent plasticity of presynaptic inputs. This has been discussed as mechanism of plastic strengthening of individual synaptic communication [130,131]. In general, structural plasticity of thalamocortical synapses is limited to the critical periods of the developing cortex. Learning about behaviorally important sensory cues in the adult brain is instead mainly attributed to intracortical synapses (e.g. [132]). Nevertheless, dopamine-dependent presynaptic gating mechanisms of early sensory input on thalamocortical synapses may contribute to associative learning in sensory cortex when a particular sensory event is becoming behaviorally relevant [129]. The laminar distribution of dopamine receptors in sensory cortices further implies that this would account mainly for thalamocortical collaterals in infragranular, rather than inputs in granular layers, which is in accordance with recent data [51]. Such layer-dependent modulation of thalamocortical synapses might explain the effects on early glutamate-mediated sensory input processing found in auditory cortex after systemic dopaminergic application (Fig. 1B). Thereby, dopamine might exert a layer-dependent division of labor of deeper and upper layer thalamic input systems emphasizing their individual and presumably different processing roles in the cortical circuitry [133].

6.2. Recruitment of long-range corticocortical feedback processing via locally enhanced activity

Recurrent feedback gain can enhance cortical inputs overcoming local inhibition [92] yielding long-range corticocortical spread of activity during later stages of processing [4,51,123]. Thereby, dopamine promotes internal corticocortical representations [75,134]. Corticocortical processing has been shown to serve the selection of distributed task-related neuronal ensembles underlying the readout of behaviorally relevant information [97,119,135]. It has further been implicated in triggering orienting responses, eliciting attention, stimulus assessment and detection as well as delayed internal evaluation processes [18,116].

In this respect, several studies have shown that dopamine strongly controls oscillatory activity implicated in corticocortical processing in a number of different cortical regions. In auditory cortex, dopaminergic modulation for instance impacts on the regulation of high-frequency oscillatory interactions between primary and secondary fields [48]. In rodent anterior cingulate cortex dopamine promotes high-frequency synchronized activity in the beta band underlying information transfer, fast selection and binding of distributed neuronal responses [136]. And in primate prefrontal cortex dopamine facilitated beta power related to increased long-range neuronal communication [137], working memory function [138] and signal-to-noise ratio. This may serve the formation of learning-related distributed neuronal ensembles [137,139]. Further insights into the impact of dopamine on corticocortical processing are coming from neurological malfunctions. In patients suffering from Parkinson's disease it has been shown that dopamine replacement modulates the coupling in the gamma range between premotor and motor areas [140]. This is indicative for a significantly strengthened feedback processing by dopamine correlating with improved motor function in these patients. Further evidence for a columnar circuit effect of early infragranular recurrent feedback gain on persistent upper layer oscillations is coming from the Alzheimer's disease mouse model 5xFAD. In 5xFAD mice, a functional plaque-induced impairment of the aforementioned infragranular recurrent feedback gain circuitry yields a maladaptive supragranular oscillatory pattern [141]. The described network dysfunction reflects a disruption of feedforward and feedback processing in sensory cortex—a function that is supported by dopamine in the healthy brain. Further, this pattern of maldapated laminar processing coincided in time with deficits in contextual fear memory in these mice. This study therefore might contribute to the currently debated role of dopamine in Alzheimer-related cognitive deficits [142].

Together, cortical dopamine regulates the distributed internal representation of sensory signals that are required for perceptual or behavioral decisions [51,128,136], as well as precede and give rise to memory function [6,12,46]. On a functional level, dopamine allows for the gating of relevant sensory signals and subsequent strengthening and prolongation of internal representation as fundamental computational network mechanism. Furthermore, laminar dopamine effects match with oscillatory patterns in corticocortical and cortico-subcortical circuits associated with feedforward and feedback processing between sensory and higher cortical areas and subcortical structures [143]. Hence, sensory cortical dopamine not only orchestrates top-down processing via prefrontal circuits, but also regulates sensory bottom–up representations. Thereby, dopamine function contrasts with effects described for cholinergic/norepinephrinic modulation that mainly enhances local afferent input and feedforward processing while suppressing persistent activity and feedback pathways in sensory cortex [144–146].

The described circuit effect of cortical dopamine may be one important feature to explain the temporal and spatial specificity of the rather broad and unspecific dopamine signal. Namely, diffuse dopamine modulates eligible circuit sites, as for instance infragranular thalamocortical recipient neurons, that allow a highly local and temporally precise integration of bottom–up representations yielding specificity. Thereby, dopamine may preserve recently activated synaptic sets reflecting stimulus–stimulus or stimulus-response associations across seconds. Such synaptic circuit effects might hence help to better understand how the brain might resolve the problem of credit assignment [10,11].

7. Cortical dopamine during learning: local integration of information from global neuronal interactions

Dopamine engages an organism in an active and self-related manner with behaviorally relevant environmental conditions and allows learning from them. Learning sojourns when appropriate behavioral adaptations lead to context-adequate outcomes.

This review has outlined a dopamine-modulated circuit loop function within cortical circuits and with higher and lower-level target regions. The described dopaminergic network functions potentially account for the effects in both short-term encoding of associations and dynamic updating of long-term memory reconsolidation [8,22]. Thereby, particularly sensory cortex with its local and global processing modes might serve the organization of distributed networks that incorporate old associations and behaviorally relevant processing of new stimuli. Cortical dopamine hence assists to implement context-dependent individual behavioral choices that built on previously established, learned behaviors (Fig. 1C, [51,70]).

In essence, dopamine thereby provides an instruction signal independent of primary rewards (food, drink, sex and so on) but rather reinforces the acquisition or the adaptation of our "behavioral constituents". These are mandatory to generate novel sequences of autonomous goal-directed actions during states of conflicts of expectation and outcome: (1) Phasic short-term dopamine responses coding for stimulus salience, motivational salience and task-relevant predictions (even at the level of sensory cortex). This promotes (2) sustained activity in several brain areas allowing the integration of feedback information from a recent trial into actual decisions, as for instance the testing of contingencies by higher working memory capacity [70,147]. Such context-adequate

feedback information from the past trial history could be perceived as success eliciting an internal reward [42]. Thereby, we may experience solving conflicts or problems as a sense of achievement by our own, planned actions. This further leads to (3) the long-term re-formation of associative synaptic plasticity based on molecular cascades within neurons engaged in the re-activated networks. Such plastic processes are fundamental for (4) individual long-term memory reconsolidation, id est triggers and updates the learning processes necessary to interact with our ever changing environment [6,22].

8. Concluding remarks

This review has focused on dopamine functions in cortical circuits with a particular emphasize on sensory areas. It should be acknowledged that the impact of dopamine on other circuit systems, as for instance in the corticostriatal system, has been largely elided. In any case, the emerging picture of dopamine functions on a neural circuit level will have strong translational implications for the challenging development of new therapeutic strategies interacting with the dopaminergic system. For instance, dopamine-modulated sensory gain modulation might be a potential pharmacological target in the context of developmental sensory-processing disorders. It may help to better understand effects of dopaminergic drugs as treatment for dyslexia or learning disabilities in school children [148], attention deficit disorder [149], or antipsychotic treatment of sensory hallucinations for instance during schizophrenia [150].

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References

[1] M. Larkum, A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex, Trends Neurosci. 36 (2013) 141–151.
[2] K.D. Harris, T.D. Mrsic-Flogel, Cortical connectivity and sensory coding, Nature 503 (2013) 51–58.
[3] R.J. Douglas, K.A.C. Martin, Neuronal circuits of the neocortex, Annu. Rev. Neurosci. 27 (2004) 419–451.
[4] V.a.F. Lamme, H. Supèr, H. Spekreijse, Feedforward, horizontal, and feedback processing in the visual cortex, Curr. Opin. Neurobiol. 8 (1998) 529–535.
[5] P.R. Roelfsema, O. van, A. oyen, T. Watanabe, Perceptual learning rules based on reinforcers and attention, Trends Cogn. Sci. 14 (2010) 64–71.
[6] H. Scheich, A. Brechmann, M. Brosch, E. Budinger, F.W. Ohl, The cognitive auditory cortex: task-specificity of stimulus representations, Hear. Res. 229 (2007) 213–224.
[7] F.W. Ohl, H. Scheich, Learning-induced plasticity in animal and human auditory cortex, Curr. Opin. Neurobiol. 15 (2005) 470–477.
[8] F.W. Ohl, Role of cortical neurodynamics for understanding the neural basis of motivated behavior-lessons from auditory category learning, Curr. Opin. Neurobiol. 31 (2015) 88–94.
[9] T.H.B. FitzGerald, K.J. Friston, R.J. Dolan, Characterising reward outcome signals in sensory cortex, Neuroimage 83 (2013) 329–334.
[10] C.L. Hull, Principles of Behavior, Appleton-Century, New York, 1943.
[11] F. Wörgötter, B. Porr, Temporal sequence learning, prediction, and control: a review of different models and their relation to biological mechanisms, Neural Comput. 17 (2005) 245–319.
[12] H. Schicknick, B.H. Schott, E. Budinger, K.-H. Smalla, A. Riedel, C.I. Seidenbecher, H. Scheich, E.D. Gundelfinger, W. Tischmeyer, Dopaminergic modulation of auditory cortex-dependent memory consolidation through mTOR, Cereb. Cortex 18 (2008) 2646–2658.
[13] N. Reichenbach, U. Herrmann, T. Kähne, H. Schicknick, R. Pielot, M. Naumann, D.C. Dieterich, E.D. Gundelfinger, K.-H. Smalla, W. Tischmeyer, Differential effects of dopamine signalling on long-term memory formation and consolidation in rodent brain, Proteome Sci. 13 (2015) 1–17.
[14] I. Balderas, P. Moreno-Castilla, F. Bermudez-Rattoni, Dopamine D1 receptor activity modulates object recognition memory consolidation in the perirhinal cortex but not in the hippocampus, Hippocampus 23 (2013) 873–878.
[15] S.D. Iversen, L.L. Iversen, Dopamine: 50 years in perspective, Trends Neurosci. (2007) 188–193.
[16] J.D. Salamone, Complex motor and sensorimotor functions of striatal and accumbens dopamine: involvement in instrumental behavior processes, Psychopharmacology (Berl) 107 (1992) 160–174.
[17] S.N. Haber, T.E.J. Behrens, The neural network underlying incentive-based learning: implications for interpreting circuit disruptions in psychiatric disorders, Neuron 83 (2014) 1019–1039.
[18] E.S. Bromberg-Martin, M. Matsumoto, O. Hikosaka, Dopamine in motivational control: rewarding, aversive, and alerting, Neuron 68 (2010) 815–834.
[19] W. Schultz, Behavioral dopamine signals, Trends Neurosci. 30 (2007) 203–210.
[20] T.J. Vickery, M.M. Chun, D. Lee, Ubiquity and specificity of reinforcement signals throughout the human brain, Neuron 72 (2011) 166–177.
[21] J.D. Salamone, M. Correa, The mysterious motivational functions of mesolimbic dopamine, Neuron 76 (2012) 470–485.
[22] M. Baudonnat, A. Huber, V. David, M.E. Walton, Heads for learning, tails for memory: reward, reinforcement and a role of dopamine in determining behavioral relevance across multiple timescales, Front. Neurosci. 7 (2013) 1–14, 7 OCT.
[23] S. Hong, Dopamine system: manager of neural pathways, Front. Hum. Neurosci. 7 (854) (2013).
[24] W. Schultz, P. Dayan, P.R. Montague, A neural substrate of prediction and reward, Science 275 (1997) 1593–1599 (80-).
[25] J. Mirenowicz, W. Schultz, Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli, Nature 379 (1996) 449–451.
[26] W. Schultz, Neuronal reward and decision signals: from theories to data, Physiol. Rev. 95 (2015) 853–951.
[27] B. Sorg, P.W. Kalivas, Effects of cocaine and footshock stress on extracellular dopamine levels in the medial prefrontal cortex, Neuroscience 53 (1991) 695–703.
[28] M. Matsumoto, O. Hikosaka, Two types of dopamine neuron distinctly convey positive and negative motivational signals, Nature 459 (2009) 837–841.
[29] E.D. Abercrombie, K.a. Keefe, D.S. DiFrischia, M.J. Zigmond, Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex, J. Neurochem. 52 (1989) 1655–1658.
[30] A. Ilango, W. Wetzel, H. Scheich, F.W. Ohl, The combination of appetitive and aversive reinforcers and the nature of their interaction during auditory learning, Neuroscience 166 (2010) 752–762.
[31] C.D. Fiorillo, Two dimensions of value: dopamine neurons represent reward but not aversiveness, Science 341 (2013) 546–549.
[32] J.C. Horvitz, Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events, Neuroscience 96 (2000) 651–656.
[33] J.C. Horvitz, T. Stewart, B.L. Jacobs, Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat, Brain Res. 759 (1997) 251–258.
[34] G.V. Rebec, Real-time assessments of dopamine function during behavior: single-unit recording, iontophoresis, and fast-scan cyclic voltammetry in awake, unrestrained rats, Alcohol. Exp. Res. 22 (1998) 32–40.
[35] C.D. Fiorillo, P.N. Tobler, W. Schultz, Discrete coding of reward probability and uncertainty by dopamine neurons, Science 299 (2003) 1898–1902.
[36] A. Lak, W.R. Stauffer, W. Schultz, Dopamine prediction error responses integrate subjective value from different reward dimensions, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 2343–2348.
[37] W.R. Stauffer, A. Lak, W. Schultz, Dopamine reward prediction error responses reflect marginal utility, Curr. Biol. 24 (2014) 2491–2500.
[38] G. Jocham, T.A. Klein, M. Ullsperger, Dopamine-mediated reinforcement learning signals in the striatum and ventromedial prefrontal cortex underlie value-based choices, J. Neurosci. 31 (2011) 1606–1613.
[39] L.S. Colzato, F. Waszak, S. Nieuwenhuis, D. Posthuma, B. Hommel, The flexible mind is associated with the catechol-O-methyltransferase (COMT) Val158Met polymorphism: Evidence for a role of dopamine in the control of task-switching, Neuropsychologia 48 (2010) 2764–2768.
[40] H.E.M. den Ouden, N.D. Daw, G. Fernandez, J.a. Elshout, M. Rijpkema, M. Hoogman, B. Franke, R. Cools, Dissociable effects of dopamine and serotonin on reversal learning, Neuron 80 (2013) 1090–1100.
[41] M. Ullsperger, C. Danielmeier, G. Jocham, Neurophysiology of performance monitoring and adaptive behavior, Physiol. Rev. 94 (2014) 35–79.
[42] H. Scheich, A. Brechmann, M. Brosch, E. Budinger, F.W. Ohl, E. Selezneva, H. Stark, W. Tischmeyer, W. Wetzel, Behavioral semantics of learning and crossmodal processing in auditory cortex: the semantic processor concept, Hear. Res. 271 (2011) 3–15.
[43] M.J. Campbell, D.A. Lewis, S.L. Foote, J.H. Morrison, Distribution of choline acetyltransferase-, serotonin-, dopamine-beta-hydroxylase-, tyrosine hydroxylase-immunoreactive fibers in monkey primary auditory cortex, J. Comp. Neurol. 261 (1987) 209–220.
[44] E. Budinger, A. Laszcz, H. Lison, H. Scheich, F.W. Ohl, Non-sensory cortical and subcortical connections of the primary auditory cortex in Mongolian gerbils: bottom–up and top–down processing of neuronal information via field AI, Brain Res. 1220 (2008) 2–32.
[45] N.X. Tritsch, B.L. Sabatini, Dopaminergic modulation of synaptic transmission in cortex and striatum, Neuron 76 (1) (2012) 33–50.

[46] M.V. Puig, E.G. Antzoulatos, E.K. Miller, Prefrontal dopamine in associative learning and memory, Neuroscience 282 (2014) 217–229.
[47] C. Vitrac, S. Péron, I. Frappé, P.-O. Fernagut, M. Jaber, A. Gaillard, M. Benoit-Marand, Dopamine control of pyramidal neuron activity in the primary motor cortex via D2 receptors, Front. Neural Circuits 8 (2) (2014) 13.
[48] S. Bao, V.T. Chan, M.M. Merzenich, Cortical remodelling induced by activity of ventral tegmental dopamine neurons, Nature 412 (2001) 79–83.
[49] N.M. Weinberger, Specific long-term memory traces in primary auditory cortex, Nat. Rev. Neurosci. 5 (2004) 279–290.
[50] H. Stark, H. Scheich, Dopaminergic and serotonergic neurotransmission systems are differentially involved in auditory cortex learning: a long-term microdialysis study of metabolites, J. Neurochem. 68 (1997) 691–697.
[51] M.F.K. Happel, M. Deliano, J. Handschuh, F.W. Ohl, Dopamine-modulated recurrent corticoefferent feedback in primary sensory cortex promotes detection of behaviorally relevant stimuli, J. Neurosci. 34 (2014) 1234–1247.
[52] B. Pleger, C.C. Ruff, F. Blankenburg, S. Klöppel, J. Driver, R.J. Dolan, Influence of dopaminergically mediated reward on somatosensory decision-making, PLoS Biol. 7 (2009) e1000164.
[53] J.T. Arsenault, K. Nelissen, B. Jarraya, W. Vanduffel, Dopaminergic reward signals selectively decrease fMRI activity in primate visual cortex, Neuron 77 (2013) 1174–1186.
[54] R.S. Weil, N. Furl, C.C. Ruff, M. Symmonds, G. Flandin, R.J. Dolan, J. Driver, G. Rees, Rewarding feedback after correct visual discriminations has both general and specific influences on visual cortex, J. Neurophysiol. 104 (2010) 1746–1757.
[55] M. Brosch, E. Selezneva, H. Scheich, Representation of reward feedback in primate auditory cortex, Front. Syst. Neurosci. 5 (2) (2011) 5.
[56] T. Weis, A. Brechmann, S. Puschmann, C.M. Thiel, Feedback that confirms reward expectation triggers auditory cortex activity, J. Neurophysiol. 110 (2013) 1860–1868.
[57] B. Noudoost, T. Moore, Control of visual cortical signals by prefrontal dopamine, Nature 474 (2011) 372–375.
[58] J. Fritz, S. Shamma, M. Elhilali, D. Klein, Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex, Nat. Neurosci. 6 (2003) 1216–1223.
[59] H. Stark, T. Rothe, M. Deliano, H. Scheich, Theta activity attenuation correlates with avoidance learning progress in gerbils, NeuroReport 18 (2007) 549–552.
[60] T. Sawaguchi, P.S. Goldman-Rakic, D1 dopamine receptors in prefrontal cortex: involvement in working memory, Science 251 (1991) 947–950.
[61] G.V. Williams, P.S. Goldman-Rakic, Modulation of memory fields by dopamine D1 receptors in prefrontal cortex, Nature 376 (6541) (1995) 572–575.
[62] M.F.K. Happel, H. Niekisch, R. Castiblanco, L.L. ivera, F.W. Ohl, M. Deliano, R. Frischknecht, Enhanced cognitive flexibility in reversal learning induced by removal of the extracellular matrix in auditory cortex, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 2800–2805.
[63] M.G. Packard, J.L. McGaugh, Quinpirole and D-amphetamine administration posttraining enhances memory on spatial and cued discriminations in a water maze, Psychobiology 22 (1994) 54–60.
[64] M.N.M. de Lima, J. Presti-Torres, A. Dornelles, F. Siciliani Scalco, R. Roesler, V.A. Garcia, N. Schröder, Modulatory influence of dopamine receptors on consolidation of object recognition memory, Neurobiol. Learn. Mem. 95 (2011) 305–310.
[65] Y. Goto, A.A. Grace, Dopamine modulation of hippocampal-prefrontal cortical interaction drives memory-guided behavior, Cereb. Cortex 18 (2008) 1407–1414.
[66] Y. Yamamuro, K. Hori, H. Iwano, M. Nomura, The relationship between learning performance and dopamine in the prefrontal cortex of the rat, Neurosci. Lett. 177 (1994) 83–86.
[67] H. Schicknick, N. Reichenbach, K.-H. Smalla, H. Scheich, E.D. Gundelfinger, W. Tischmeyer, Dopamine modulates memory consolidation of discrimination learning in the auditory cortex, Eur. J. Neurosci. 35 (2012) 763–774.
[68] W. Wetzel, T. Wagner, F.W. Ohl, H. Scheich, Categorical discrimination of direction in frequency-modulated tones by Mongolian gerbils, Behav. Brain Res. 91 (1998) 29–39.
[69] F.W. Ohl, W. Wetzel, T. Wagner, A. Rech, H. Scheich, Bilateral ablation of auditory cortex in Mongolian gerbil affects discrimination of frequency modulated tones but not of pure tones, Learn. Mem. 6 (1999) 347–362.
[70] H. Stark, T. Rothe, T. Wagner, H. Scheich, Learning a new behavioral strategy in the shuttle-box increases prefrontal dopamine, Neuroscience 126 (2004) 21–29.
[71] T. Rothe, M. Deliano, H. Scheich, H. Stark, Segregation of task-relevant conditioned stimuli from background stimuli by associative learning, Brain Res. 1297 (2009) 143–159.
[72] R. Cools, M.J. Frank, S.E. Gibbs, A. Miyakawa, W. Jagust, M. D'Esposito, Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration, J. Neurosci. 29 (2009) 1538–1543.
[73] B. Diekamp, T. Kalt, A. Ruhm, M. Koch, O. Güntürkün, Impairment in a discrimination reversal task after D1 receptor blockade in the pigeon prefrontal cortex, Behav. Neurosci. 114 (2000) 1145–1155.
[74] A.G. Roberge, C. Boisvert, J. Everett, Monoamine roles in retention and reversal of delayed response in cats, Pharmacol. Biochem. Behav. 12 (7) (1980) 229–234.
[75] M. Watanabe, T. Kodama, K. Hikosaka, Increase of extracellular dopamine in primate prefrontal cortex during a working memory task, J. Neurophysiol. 78 (1997) 2795–2798.
[76] T. Schönberg, N.D. Daw, D. Joel, J.P. O'Doherty, Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making, J. Neurosci. 27 (2007) 12860–12867.
[77] M. Klanker, T. Sandberg, R. Joosten, I. Willuhn, M. Feenstra, D. Denys, Phasic dopamine release induced by positive feedback predicts individual differences in reversal learning, Neurobiol. Learn. Mem. 125 (2015) 135–145.
[78] M.G.P. Feenstra, G. Teske, M.H.A. Botterblom, J.P.C. De Bruin, Dopamine and noradrenaline release in the prefrontal cortex of rats during classical aversive and appetitive conditioning to a contextual stimulus: Interference by novelty effects, Neurosci. Lett. 272 (1999) 179–182.
[79] O.T. Phillipson, I.C. Kilpatrick, M.W. Jones, Dopaminergic innervation of the primary visual cortex in the rat, and some correlations with human cortex, Brain Res. Bull. 18 (1987) 621–633.
[80] M.S. Lidow, D1- and D2 dopaminergic receptors in the developing cerebral cortex of macaque monkey: a film autoradiographic study, Neuroscience 65 (1995) 439–452.
[81] M.S. Lidow, P.S. Goldman-Rakic, D.W. Gallager, P. Rakic, Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]SCH23390, Neuroscience 40 (1991) 657–671.
[82] L.S. Krimer, R.L. Jakab, P.S. Goldman-Rakic, Quantitative three-dimensional analysis of the catecholaminergic innervation of identified neurons in the macaque prefrontal cortex, J. Neurosci. 17 (1997) 7450–7461.
[83] P.S. Goldman-Rakic, M.S. Lidow, D.W. Gallager, Overlap of dopaminergic, adrenergic, and serotoninergic receptors and complementarity of their subtypes in primate prefrontal cortex, J. Neurosci. 10 (1990) 2125–2138.
[84] S.M. Williams, P.S. Goldman-Rakic, Characterization of the dopaminergic innervation of the primate frontal cortex using a dopamine-specific antibody, Cereb. Cortex 3 (1993) 199–222.
[85] J. de Almeida, J.M. Palacios, G. Mengod, Distribution of 5-HT and DA receptors in primate prefrontal cortex: implications for pathophysiology and treatment, Prog. Brain Res. 172 (2008) 101–115.
[86] D.A. Lewis, D.S. Melchitzky, S.R. Sesack, R.E. Whitehead, S. Auh, A. Sampson, Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization, J. Comp. Neurol. 432 (2001) 119–136.
[87] J. Wu, J.J. Hablitz, Cooperative activation of D1 and D2 dopamine receptors enhances a hyperpolarization-activated inward current in layer I interneurons, J. Neurosci. 25 (2005) 6322–6328.
[88] A.P. Bannister, Inter- and intra-laminar connections of pyramidal cells in the neocortex, Neurosci. Res. 53 (2) (2005) 95–103.
[89] J.A. Winer, L.M. Miller, C.C. Lee, C.E. Schreiner, Auditory thalamocortical transformation: structure and function, Trends Neurosci. 28 (5) (2005) 255–263.
[90] C.M. Constantinople, R.M. Bruno, Effects and mechanisms of wakefulness on local cortical networks, Neuron 69 (2011) 1061–1068.
[91] R.M. Bruno, B. Sakmann, Cortex is driven by weak but synchronously active thalamocortical synapses, Science 312 (2006) 1622–1627.
[92] B. Liu, G.K. Wu, R. Arbuckle, H.W. Tao, L.I. Zhang, Defining cortical frequency tuning with recurrent excitatory circuitry, Nat. Neurosci. 10 (2007) 1594–1600.
[93] M.F.K. Happel, M. Jeschke, F.W. Ohl, Spectral integration in primary auditory cortex attributable to temporally precise convergence of thalamocortical and intracortical input, J. Neurosci. 30 (2010) 11114–11127.
[94] R.J. Douglas, K.A.C. Martin, Recurrent neuronal circuits in the neocortex, Curr. Biol. 17 (2004) 496–500.
[95] C.K. Moeller, S. Kurt, M.F.K. Happel, H. Schulze, Long-range effects of GABAergic inhibition in gerbil primary auditory cortex, Eur. J. Neurosci. 31 (2010) 49–59.
[96] S. Kurt, A. Deutscher, J.M. Crook, F.W. Ohl, E. Budinger, C.K. Moeller, H. Scheich, H. Schulze, Auditory cortical contrast enhancing by global winner-take-all inhibitory interactions, PLoS One 3 (3) (2008) e1735.
[97] P.W. Hickmott, M.M. Merzenich, Single-cell correlates of a representational boundary in rat somatosensory cortex, J. Neurosci. 18 (1998) 4403–4416.
[98] J.L. Dantzker, E.M. Callaway, Laminar sources of synaptic input to cortical inhibitory interneurons and pyramidal neurons, Nat. Neurosci. 3 (2000) 701–707.
[99] M. Deliano, H. Scheich, F.W. Ohl, Auditory cortical activity after intracortical microstimulation and its role for sensory processing and learning, J. Neurosci. 29 (2009) 15898–15909.
[100] C. Boucsein, M.P. Nawrot, P. Schnepel, A. Aertsen, Beyond the cortical column: abundance and physiology of horizontal connections imply a strong role for inputs from the surround, Front. Neurosci. 5 (2011) 1–13, APR.
[101] S.P. Brown, S. Hestrin, Intracortical circuits of pyramidal neurons reflect their long-range axonal targets, Nature 457 (2009) 1133–1136.
[102] S.M. Sherman, Thalamocortical interactions, Curr. Opin. Neurobiol. 22 (2012) 575–579.
[103] S. Gee, I. Ellwood, T. Patel, F. Luongo, K. Deisseroth, V.S. Sohal, Synaptic activity unmasks dopamine D2 receptor modulation of a specific class of layer V pyramidal neurons in prefrontal cortex, J. Neurosci. 32 (14) (2012) 4959–4971.
[104] K. Saldeitis, M.F.K. Happel, F.W. Ohl, H. Scheich, E. Budinger, Anatomy of the auditory thalamocortical system in the mongolian gerbil: nuclear origins

and cortical field-, layer-, and frequency-specificities, J. Comp. Neurol. 522 (2014) 2397–2430.
[105] R.W. Guillery, S.M. Sherman, Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system, Neuron 33 (2) (2002) 163–175.
[106] S.R. Olsen, D.S. Bortone, H. Adesnik, M. Scanziani, Gain control by layer six in cortical circuits of vision, Nature 483 (7387) (2012) 47–52.
[107] Y. Watanabe, S. Funahashi, Thalamic mediodorsal nucleus and working memory, Neurosci. Biobehav. Rev. 36 (1) (2012) 134–142.
[108] C.E. Curtis, D. Lee, Beyond working memory: the role of persistent activity in decision making, Trends Cognit. Sci. 14 (5) (2010) 216–222.
[109] I.M. Andolina, H.E. Jones, W. Wang, A.M. Sillito, Corticothalamic feedback enhances stimulus response precision in the visual system, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 1685–1690.
[110] F. Briggs, W.M. Usrey, A fast, reciprocal pathway between the lateral geniculate nucleus and visual cortex in the macaque monkey, J. Neurosci. 27 (2007) 5431–5436.
[111] M.N.O. Connell, A. Barczak, C.E. Schroeder, P. Lakatos, Layer specific sharpening of frequency tuning by selective attention in primary auditory cortex, J. Neurosci. 34 (2014) 16496–16508.
[112] B.B. Theyel, D.a. Llano, S.M. Sherman, The corticothalamocortical circuit drives higher-order cortex in the mouse, Nat. Neurosci. 13 (2010) 84–88.
[113] S.R. Sesack, C.L. Snyder, D.A. Lewis, Axon terminals immunolabeled for dopamine or tyrosine hydroxylase synapse on GABA-immunoreactive dendrites in rat and monkey cortex, J. Comp. Neurol. 363 (1995) 264–280.
[114] C.a. Bosman, J.M. Schoffelen, N. Brunet, R. Oostenveld, A.M. Bastos, T. Womelsdorf, B. Rubehn, T. Stieglitz, P. De Weerd, P. Fries, Attentional stimulus selection through selective synchronization between monkey visual areas, Neuron 75 (2012) 875–888.
[115] G. Buzsáki, N. Logothetis, W. Singer, Scaling brain size, keeping timing: evolutionary preservation of brain rhythms, Neuron 80 (3) (2013) 751–764.
[116] K.D. Harris, A. Thiele, Cortical state and attention, Nat. Rev. Neurosci. 12 (2011) 509–523.
[117] J. Mylius, M.F.K. Happel, A.G. Gorkin, Y. Huang, H. Scheich, M. Brosch, Fast transmission from the dopaminergic ventral midbrain to the sensory cortex of awake primates, Brain Struct. Funct. 220 (6) (2014) 3273–3294 (July 2015).
[118] J.J. Letzkus, S.B.E. Wolff, E.M.M. Meyer, P. Tovote, J. Courtin, C. Herry, A. Lüthi, A disinhibitory microcircuit for associative fear learning in the auditory cortex, Nature 480 (2011) 331–335.
[119] H. Adesnik, M. Scanziani, Lateral competition for cortical space by layer-specific horizontal circuits, Nature 464 (2010) 1155–1160.
[120] M. Zhou, F. Liang, X.R. Xiong, L. Li, H. Li, Z. Xiao, H.W. Tao, L.I. Zhang, Scaling down of balanced excitation and inhibition by active behavioral states in auditory cortex, Nat. Neurosci. 17 (2014) 841–850.
[121] B. Zhang, A. Albaker, B. Plouffe, C. Lefebvre, M. Tiberi, Constitutive activities and inverse agonism in dopamine receptors, Adv. Pharmacol. 70 (2014) 175–214.
[122] M. Atzori, P.O. Kanold, J.C. Pineda, J. Flores-Hernandez, R.D. Paz, Dopamine prevents muscarinic-induced decrease of glutamate release in the auditory cortex, Neuroscience 134 (2005) 1153–1165.
[123] A. Lavin, L. Nogueira, C.C. Lapish, R.M. Wightman, P.E.M. Phillips, J.K. Seamans, Mesocortical dopamine neurons operate in distinct temporal domains using multimodal signaling, J. Neurosci. 25 (2005) 5013–5023.
[124] S.-P. Onn, X.-B. Wang, M. Lin, A.A. Grace, Dopamine D1 and D4 receptor subtypes differentially modulate recurrent excitatory synapses in prefrontal cortical pyramidal neurons, Neuropsychopharm 31 (2006) 318–338.
[125] H.J. Seong, A.G. Carter, D1 Receptor modulation of action potential firing in a subpopulation of layer 5 pyramidal neurons in the prefrontal cortex, J. Neurosci. 32 (31) (2012) 10516–10521.
[126] D. Durstewitz, J.K. Seamans, T.J. Sejnowski, Neurocomputational models of working memory, Nat. Neurosci. 3 (2000) 1184–1191.
[127] F.G. Ashby, M.B. Casale, A model of dopamine modulated cortical activation, Neural Netw. 16 (2003) 973–984.
[128] S.N. Jacob, T. Ott, A. Nieder, Dopamine regulates two classes of primate prefrontal neurons that represent sensory signals, J. Neurosci. 33 (2013) 13724–13734.
[129] J.a. Blundon, S.S. Zakharenko, Presynaptic gating of postsynaptic synaptic plasticity: a plasticity filter in the adult auditory cortex, Neuroscientist 19 (2013) 465–478.
[130] H. Feldman, K.J. Friston, Attention, uncertainty, and free-energy, Front. Hum. Neurosci. 4 (2010) 215.
[131] E.M. Izhikevich, Solving the distal reward problem through linkage of STDP and dopamine signaling, Cereb. Cortex 17 (2007) 2443–2452.
[132] R.C. Froemke, M.M. Merzenich, C.E. Schreiner, A synaptic memory trace for cortical receptive field plasticity, Nature 450 (2007) 425–429.
[133] C.M. Constantinople, R.M. Bruno, Deep cortical layers are activated directly by thalamus, Science 340 (2013) 1591–1594.
[134] J.K. Seamans, D. Durstewitz, B.R. Christie, C.F. Stevens, T.J. Sejnowski, Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 301–306.
[135] M. Sakai, N. Suga, Centripetal and centrifugal reorganizations of frequency map of auditory cortex in gerbils, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 7108–7112.
[136] P. Steullet, J.-H. Cabungcal, M. Cuenod, K.Q. Do, Fast oscillatory activity in the anterior cingulate cortex: dopaminergic modulation and effect of perineuronal net loss, Front. Cell. Neurosci. 8 (2014) 1–10.
[137] M.V. Puig, E.K. Miller, The role of prefrontal dopamine D1 receptors in the neural mechanisms of associative learning, Neuron 74 (2012) 874–886.
[138] S. Kobayashi, K. Nomoto, M. Watanabe, O. Hikosaka, W. Schultz, M. Sakagami, Influences of rewarding and aversive outcomes on activity in macaque lateral prefrontal cortex, Neuron 51 (2006) 861–870.
[139] A.F.T. Arnsten, M.J. Wang, C.D. Paspalas, Neuromodulation of thought: flexibilities and vulnerabilities in prefrontal cortical network synapses, Neuron 76 (2012) 223–239.
[140] D.M. Herz, E. Florin, M.S. Christensen, C. Reck, M.T. Barbe, M.K. Tscheuschler, M. Tittgemeyer, H.R. Siebner, L. Timmermann, Dopamine replacement modulates oscillatory coupling between premotor and motor cortical areas in parkinson's disease, Cereb. Cortex 11 (2013) 1–11.
[141] H. Lison, M.F.K. Happel, F. Schneider, K. Baldauf, S. Kerbstat, B. Seelbinder, J. Schneeberg, M. Zappe, J. Goldschmidt, E. Budinger, U.H. Schröder, F.W. Ohl, S. Schilling, H.-U. Demuth, H. Scheich, K.G. Reymann, R. Rönicke, Disrupted cross-laminar cortical processing in β amyloid pathology precedes cell death, Neurobiol. Dis. 63C (2013) 62–73.
[142] A. Martorana, G. Koch, Is dopamine involved in Alzheimer's disease, Front. Aging Neurosci. 6 (2014) 1–6.
[143] A.M. Bastos, W.M. Usrey, R.a. Adams, G.R. Mangun, P. Fries, K.J. Friston, Canonical microcircuits for predictive coding, Neuron 76 (2012) 695–711.
[144] M.E. Hasselmo, Neuromodulation and cortical function: modeling the physiological basis of behavior, Behav. Brain Res. 67 (1) (1995) 1–27.
[145] H. Kawai, R. Lazar, R. Metherate, Nicotinic control of axon excitability regulates thalamocortical transmission, Nat. Neurosci. 10 (2007) 1168–1175.
[146] J.-M. Edeline, Beyond traditional approaches to understanding the functional role of neuromodulators in sensory cortices, Front. Behav. Neurosci. 6 (2012) 1–14.
[147] B.W. Balleine, A. Dickinson, Goal-directed instrumental action: contingency and incentive learning and their cortical substrates, Neuropharmacology 37 (4-5) (1998) 407–419.
[148] P.L. Davies, W.-P. Chang, W.J. Gavin, Maturation of sensory gating performance in children with and without sensory processing disorders, Int. J. Psychophysiol. 72 (2009) 187–197.
[149] A. Schonwald, E. Lechner, Attention deficit/hyperactivity disorder: complexities and controversies, Curr. Opin. Pediatr. 18 (2006) 189–195.
[150] J.C. Badcock, The cognitive neuropsychology of auditory hallucinations: a parallel auditory pathways framework, Schizophr. Bull. 36 (3) (2010) 576–584.