Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Modulation of cortical circuits by top-down processing and arousal state in health and disease

Renata Batista-Brito[1,4], Edward Zagha[2,4], Jacob M Ratliff[1] and Martin Vinck[3,4]

In this review, we explore how contextual modulations of sensory processing are implemented within the local cortical circuit. We focus on contextual influences of global arousal state (e.g. how alert am I?), sensory predictions (e.g. which stimuli do I expect?), and top-down attention (what is relevant to me?). We review recent literature suggesting that these operations are implemented throughout sensory cortices, and are mediated by excitatory and inhibitory local circuits. By focusing on the circuit mechanisms of contextual modulation operations, we may begin to understand how mutations in GABAergic interneurons and alterations in neuromodulatory signaling lead to specific deficits of information processing in neuropsychiatric disease.

Addresses
[1] Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Rose F. Kennedy Center, 1410 Pelham Parkway South Room 203, Bronx, NY 10461, USA
[2] Department of Psychology, University of California Riverside, 900 University Avenue, Riverside, CA 92521, USA
[3] Ernst Struengmann Institute for Neuroscience in Cooperation with Max Planck Society, Deutschordenstraße 46, 60528 Frankfurt am Main, Germany

Corresponding authors:
Batista-Brito, Renata (renata.brito@einstein.yu.edu),
Zagha, Edward (ezagha@ucr.edu),
Vinck, Martin (martin.vinck@esi-frankfurt.de)
[4] Equal contribution.

Current Opinion in Neurobiology 2018, **52**:172–181

This review comes from a themed issue on **Systems neuroscience**

Edited by **Michael Long** and **Rosa Cossart**

For a complete overview see the Issue and the Editorial

Available online 29th July 2018

https://doi.org/10.1016/j.conb.2018.06.008

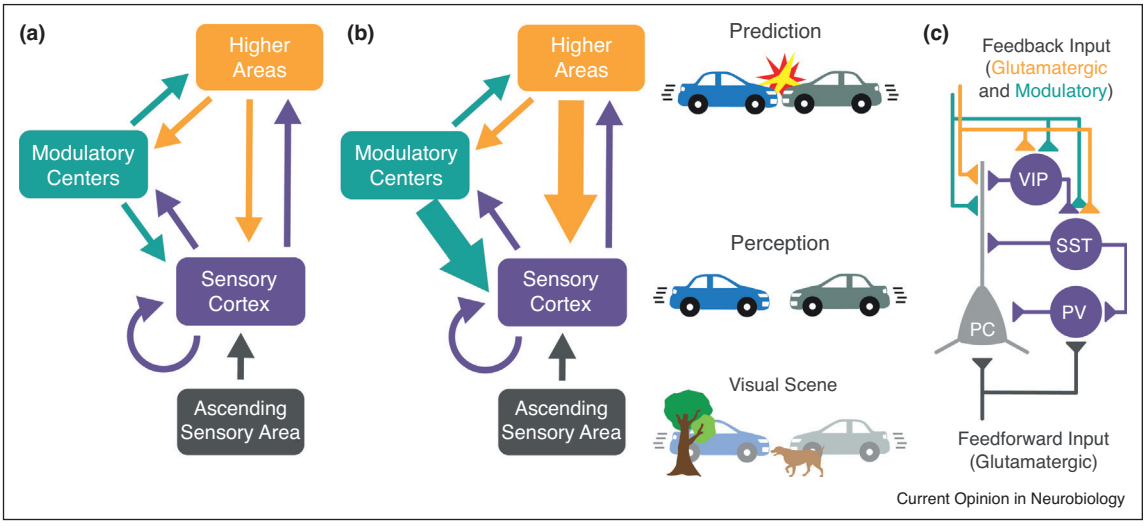
Neuronal responses to sensory stimuli depend strongly on the context. For instance, when we are driving a car, we are alert to our surroundings, continuously predicting the future trajectories of other cars, and selectively attending to traffic signs and road conditions. By contrast, the demands on our sensory systems are very different when we are listening to music or reading a book. Arousal, expectation and attention are a subset of the contextual 'knobs' that modulate sensory processing according to immediate task demands. Anatomically, contextual modulations of sensory processing can originate from cortical, glutamatergic top-down feedback and lateral connections, or subcortical pathways (Figure 1). Subcortical pathways include a variety of neuromodulatory systems utilizing dopamine, norepinephrine, histamine, serotonin and acetylcholine, which regulate global arousal [1,2]. Cortical and sub-cortical pathways converge onto GABAergic circuits within cortex (Figure 1c) whereby they modulate cortical dynamics and signaling.

Here, we discuss the mechanisms by which contextual modulation provided by arousal state, sensory predictions and top-down attention are implemented within the local cortical circuit. Arousal state entails a global modulation of neural activity and sensory encoding according to behavioral context. Sensory prediction and top-down attention are two principal types of contextual processing occurring within cortex [3,4]: Predictive coding operations encompass the differential encoding of sensory inputs depending on expectancies and priors (i.e. how likely an input is), and the emergence of neurons that encode unexpected sensory prediction errors [3]. Attention entails the modulation of neural activity depending on internal goals (i.e. how relevant an input is). Expectancy and attention may modulate neural activity in a wide variety of ways, from being complementary to opposing (Figure 1b).

GABAergic circuits underlying top-down functions

In this section, we provide a coarse overview of the properties of different GABAergic subtypes, emphasizing the vasoactive intestinal peptide (VIP) and somatostatin (SST) expressing interneuron classes, as these have recently emerged as essential mediators of contextual modulation. Cortical circuits consist of two main types of neurons, glutamatergic principal cells (PCs) and GABAergic inhibitory interneurons (INs), which together regulate information flow into and throughout the local network. GABAergic interneurons, which compose about 10–20% of cortical neurons in rodents, have different intrinsic physiological properties, morphology, synaptic targets, and molecular markers (for review see [5]). Cortical interneurons are typically subdivided into three distinct groups by using three non-overlapping markers: 1. Somatostatin (SST), 2. Serotonin receptor 3a

Figure 1



Contextual modulation of sensory processing. **(a)** Schematic representation of synaptic interactions between cortical and subcortical brain regions involved in context-dependent sensory processing. Ascending sensory information is depicted as bottom-up, from subcortical ascending sensory areas (gray) to sensory cortex (purple) to higher-order cortical areas (orange). Modulating this bottom-up processing stream are top-down glutamatergic signals from higher to lower-ordered cortices (orange arrows), neuromodulatory signals from, for example, nucleus basalis (cholinergic) and locus coeruleus (noradrenergic) (green arrows) and lateral connections within sensory cortices (purple recurrent arrow). **(b)** Example of how top-down processing and arousal can mediate predictive coding. Visual scene information is conveyed through bottom-up connections. A top-down prediction (orange arrow) is made about salient features of the image (cars passing each other). Any unexpected stimuli (impending crash) would strongly propagate to higher areas. This prediction-error, in turn, would strongly activate attentional and arousal signals (green arrow). **(c)** Basic elements of a neural circuit within sensory cortex. The local network is composed of pyramidal cells (PC in grey) and inhibitory GABAergic interneurons (purple). This circuit receives feedforward inputs from lower sensory areas, feedback signals from higher areas and neuromodulation from a variety of neuromodulatory centers. Feedforward inputs primarily target PCs and PV-INs, while glutamatergic top-down feedback and neuromodulatory inputs primarily target VIP and SST-INs. *Abbreviations*: PV, parvalbumin; IN, interneuron; VIP, vasoactive intestinal peptide; SST, somatostatin.

(5HT3aR), which includes VIP-expressing interneurons, and 3. Parvalbumin (PV) (Figure 1c) [6].

1 SST-interneurons primarily target the dendritic compartments of principal cells. SST-interneurons receive inhibitory inputs from VIP and PV-interneurons [7] and distance-dependent excitatory inputs from PCs [7–10]. SST-interneurons receive little direct thalamic input as compared to PV-interneurons, but instead are modulated by recurrent excitatory activity, top-down signals and neuromodulatory signals such as cholinergic and noradrenergic inputs [5,11,12]. By contrast to PV-interneurons, which generally suppress the output of a neuron by targeting somata and proximal dendrites, SST-interneurons can inhibit PCs with high specificity by co-localizing with specific excitatory synapses on PC dendrites [13]. SST-interneurons have the ability to control active dendrite properties (i.e. calcium spikes or plateau potentials), and thereby modulate the perceptual thresholds for sensory stimuli [14,15]. The two main subclasses of SST-interneurons preferentially synapse onto: (a) layer 4, which is the recipient layer for thalamic inputs and (b) the apical tufts in layer 1 (Martinotti cells) [5], which is a prominent recipient of top-down cortical feedback [16••,17,18]. The facilitatory nature of principal cell-to-SST synapses, that is, increased synaptic responses with repeated stimulation, make these cells suited to integrate synaptic inputs over a long time-windows [5]. Together, these characteristics suggest that SST-interneurons have essential roles in mediating and gating contextual signals, as well as balancing recurrent excitatory activity with feedback inhibition.

2 5HT3aR-expressing interneurons mostly reside in superficial layers. These neurons express fast-acting (ionotropic) serotonin and acetylcholine receptors, and are direct recipients of top-down glutamatergic feedback [5]. 5HT3aR-interneurons can be further divided into VIP-positive and VIP-negative interneurons [5]. In the cortex VIP-interneurons inhibit not only PCs, but also SST-interneurons. Consequently, VIP-interneuron activity leads to *disinhibition* (VIP → SST → PC) in a subset of PCs [7,19,20]. 5HT3aR-positive, VIP-negative interneurons include (but are not restricted to) neurogliaform cells, which reside mainly in layer 1. Layer 1 neurogliaform cells receive top-down feedback inputs and callosal inputs [21], target PCs and interneurons, and form gap junctions with other interneurons, through which they can exert powerful cortical inhibition (for review see [22]).

3 PV-interneurons are fast-spiking cells, meaning that they can sustain high-frequency firing in response to synaptic inputs, and preferentially target PC somata. They receive strong feedforward inputs (e.g. thalamocortical), and integrate local excitatory inputs with high temporal precision, making them ideally suited to balance feedforward excitatory inputs and stabilize the local network. PV cells also receive direct top-down projections and could play a role in several of the operations discussed below (for review see [5]). However, they will not be the focus of this review, given their primary function in network stabilization. This is supported by observations that modulations of PV-interneuron and PC activities are correlated, as required for network stabilization, in contrast to anti-correlated modulations between SST-interneurons and PCs [8,23].

In the following, we focus on the role of VIP-interneurons and SST-interneurons in mediating contextual influences. We note that although GABAergic circuits are highly conserved across cortex and species, the reviewed studies almost exclusively use genetic mouse models that allow *in vivo* access to identified GABAergic subtypes.

Arousal state

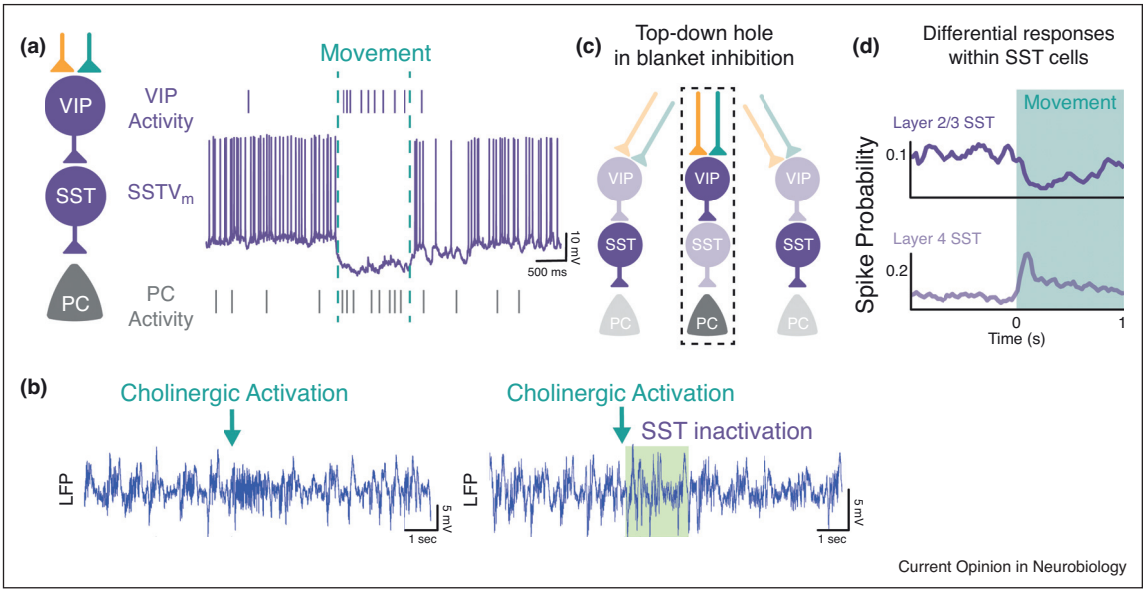
The demands for neural processing capacity change drastically from sleep to wakefulness and from quiet wakefulness to engagement [24]. Arousal states can be measured from 'low' to 'high' by the extent to which the central nervous system is globally activated. Highly active states are associated with strong cholinergic and noradrenergic activation of cortical circuits mediated by the basal forebrain and locus coeruleus, respectively [25•]. In recent years there have been major efforts in understanding how these high-arousal states influence sensory processing [26]. In rodents, pupillometry shows that active states like locomotion and whisking correspond to high-arousal states (for review see [24]). An important caveat is that many high-arousal states like locomotion can be decomposed into arousal and motor components, which can have distinct effects on neuronal activity patterns and sensory encoding [27•]. In neocortex, high arousal states are associated with the presence of fast beta or gamma waves (the 'desynchronized' or 'activated' state), whereas low arousal states are associated with synchronous fluctuations in the alpha, theta and delta frequency range (the 'synchronized' state) [27•].

Recent studies have revealed essential cortical circuit motifs responsible for translating neuromodulatory signals into changes in sensory processing. Notably, the same cortical circuit elements that are targeted globally during arousal also mediate top-down processing, yet at much finer spatial and temporal scales. Essential motifs that have emerged for arousal include:

1) *VIP–SST–PC disinhibition* (Figure 2a). During highly active states, like whisking and locomotion, VIP-interneuron firing is strongly enhanced [19,28••,29] by cholinergic activation [29]. VIP-interneurons strongly inhibit SST-interneurons, particularly the Martinotti cells which target layer 1 (L1) [7,16••], and weakly inhibit PCs and PV-interneurons [7]. Consequently, VIP activation results in disinhibition of the apical dendrites of PCs [16••,23]. Such disinhibition may enhance the impacts of top-down inputs [16••,17,18], which enter cortex primarily via L1, and promote permissive conditions for cortical plasticity [30–33].
2) *SST-mediated desynchronization*. SST-interneurons are directly stimulated by cholinergic and noradrenergic inputs, and may be essential mediators of the changes in temporal patterning of neuronal activity associated with high arousal states (reduced low-frequency synchronization, increased power of beta and gamma waves) [34,35,36•] (Figure 2b). This may depend on direct activation of nicotinergic and muscarinic receptors expressed on SST cells and/or a potentiation of PC-to-SST synapses through activation of pre-synaptic nAChRs [11].
3) *SST-PV-PC disinhibition*. In whisker somatosensory cortex, SST-interneurons inhibit layer IV PV-interneurons, thereby disinhibiting the propagation of thalamic input signals and firing of L4 PCs [37]. Importantly, this effect is mediated by SST-interneurons that do not have a Martinotti morphology and project strongly to PV-interneurons [37].
4) *PC gain modulation*. Neuromodulators like acetylcholine and norepinephrine can directly boost PC input resistance and synaptic activity, thereby boosting sensory response gain and signal-to-noise ratio (i.e. evoked vs. spontaneous activity) [38].
5) *VIP-negative based disinhibition*. Ongoing research efforts are aimed at understanding the roles of L1 VIP-negative 5HT3aR-interneurons. Recent studies suggest that they exert disinhibitory effects by targeting PV cells and are important for learning and plasticity [17,39].

Since the active state is characterized by desynchronization and strongly enhanced VIP-interneuron firing, it appears there is a contradiction between the dependence of desynchronization on SST-interneuron activation and the VIP–SST–PC disinhibitory motif. This may be explained by the heterogeneity in the SST-interneuron population. During whisking, a vast majority of SST-interneurons in superficial layers with Martinotti morphology are inhibited by VIP-interneurons, whereas most SST-interneurons in granular and infragranular layers are strongly activated by acetylcholine, thereby overcoming VIP-mediated inhibition [16••] (Figure 2d). Future work is needed to determine the effects that these two subgroups of SST-interneurons have on desynchronization.

Figure 2



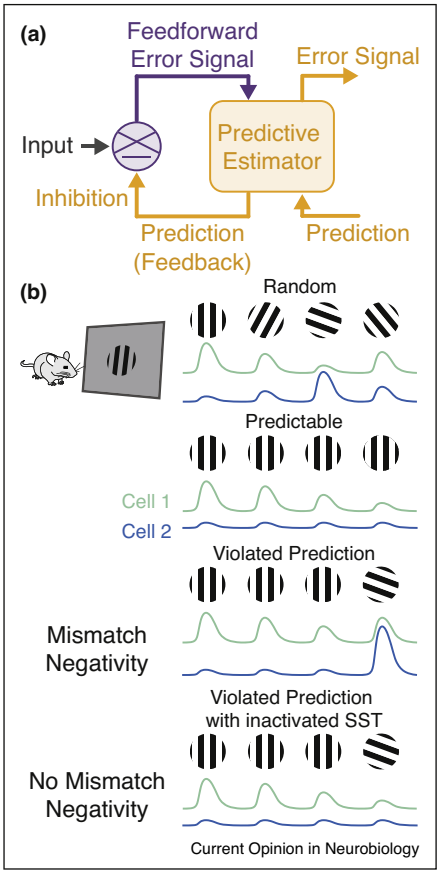
Cortical inhibitory circuits underlying top-down functions. **(a)** (Left) Schematic of the VIP-SST-PC disinhibitory circuit. VIP-INs are a major recipient of top-down glutamatergic (orange arrow) and neuromodulatoty (green arrow) inputs. During movement (such as whisking or locomotion), VIP cells are activated by cholinergic or top-down inputs. This causes the inhibition of SST-INs (brown trace, intracellular SST-IN recording [23], leading to enhanced PC activity. **(b)** (Left) Cholinergic activation leads to desynchronization of the cortical local network. (Right) This desynchronization is dependent on the activity of SST-INs [34], such that it does not occur if SST-INs are inactivated. **(c)** Specific activations of the VIP-SST-PC disinhibitory circuit may contribute to the cortical implementation of attention. According to this model, local activation of VIP-INs, through glutamatergic or cholinergic stimulation, is able to cut local 'holes' in the SST-IN mediated 'blanket of inhibition'. **(d)** Illustration of the diversity of SST-IN responses to the same context (e.g. whisking). Interestingly, SST-INs with different responses also differ in laminar position and anatomy [16••], indicating a much richer diversity of cortical interneurons than currently understood.

Modulation of neuronal activity by sensory predictions

Sensory predictions may modulate neuronal activity in different ways, including direct activation of local PCs. Here, we focus here on the 'suppressive' modulation of neuronal activity according to sensory predictions as formulated in the efficient and predictive coding frameworks. To remove redundancies among sensory representations within cortex and optimally use the available communication channels for signaling novel information, a predictive template, conveyed through lateral or top-down feedback, may be subtracted from sensory inputs to amplify those elements of the sensory input that are unexpected or salient (low probability), and to efficiently dim those elements that are redundant or expected (Figure 3a) [40]. Sensory predictions can flow from the natural statistics of an organism's environment, or from the re-afferent signals expected from an organism's own movements. Because in predictive coding operations, predictions are in the mathematical sense subtracted from the sensory input, resulting in prediction error signals [40], a natural hypothesis is that SST-interneurons or PV-interneurons instantiate this 'subtractive' operation. As explained above, SST-interneurons are an excellent candidate to mediate this kind of operation.

Three types of contextual response modulation have been interpreted from the predictive coding framework, namely surround inhibition, repetition suppression/mismatch negativity and visual–motor integration. Evidence suggests that SST-interneurons are targeted by PCs residing in other columns through lateral connections and play an important role in mediating surround suppression of PCs [[36•]] (but see [41]). Consistent with this scenario, SST-interneurons contribute to the emergence of gamma-frequency (30–80 Hz) oscillations [36•] which have been theorized to play an important function in predictive surround signaling [42]. However, given that V1 gamma in carnivores and primates can operate at much higher frequencies (up to 70 Hz) it is possible that in these species PV-interneurons rather than SST-interneurons mediate predictive surround signaling [34,43], consistent with elevated rates of FS cells with surround modulation in cats [44]. SST-interneurons also mediate suppression of V1 PC responses to repeated (predicted) stimuli and mismatch negativity error signals (Figure 3b) [45••]. Predictions of sensory events are also derived from self-induced movements. For instance, locomotion makes specific visual flow predictions that might be 'subtracted' from the sensory input, creating mismatch signals. The error signals of 'mismatch' in PCs depend on SST-interneuron activity [46••]. Altogether, these studies

Figure 3



Modulation of neuronal activity by sensory predictions. **(a)** Hierarchical predictive coding model modified from Rao and Ballard [40]. In this model, prediction signals (feedback) are subtracted from sensory signals (input), and the difference is propagated (feedforward) as a prediction error. This process may be implemented along the feedforward and feedback cortical processing streams. **(b)** Experimental set up: an awake mouse is presented with sequential visual stimuli (gratings), while monitoring neural activity in visual cortex. Below each grating is the simulated activity of two pyramidal neurons with different preferred orientations. Top, four randomly-oriented stimulus patterns, driving responses in each neuron according to its orientation tuning. Second row, presenting the same stimulus repeatedly causes response adaptation, particularly for the optimally tuned neuron. Third row, a mismatch paradigm in which the repetition is violated, causing increased responses (mismatched negativity signal). Bottom, with SST inactivation the mismatched negativity signal is abolished, suggesting that SST-INs are essential mediators of this response [45••].

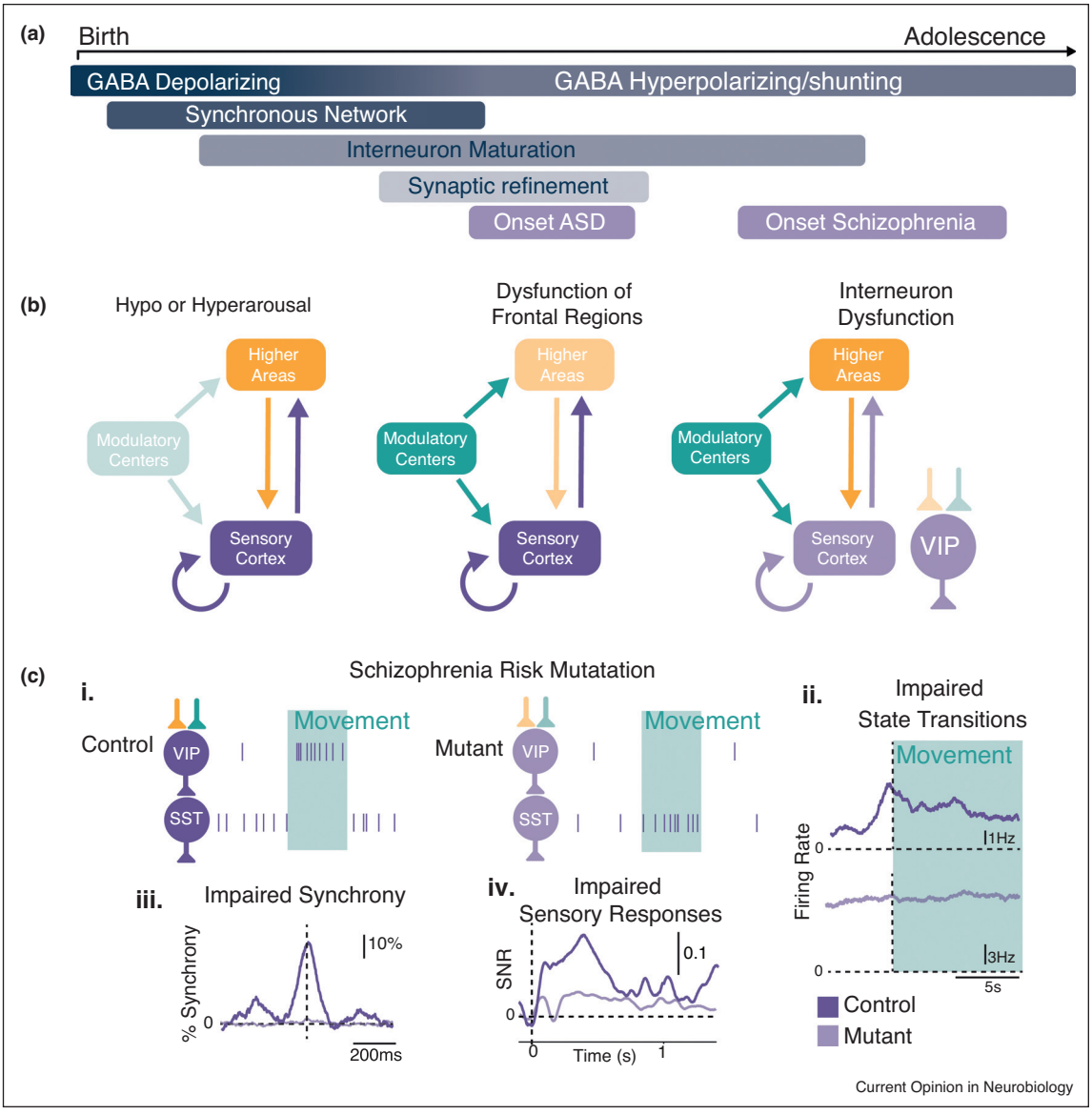
demonstrate strong evidence for SST-interneurons in regulating PC firing according to input predictions. The extent to which these functions depend on lateral and top-down connections, and VIP activation or suppression, are currently unknown. Furthermore, top-down connections may not only convey sensory prediction signals, but could also convey error signals that drive learning in the lower area, analogous to backpropagation in artificial neuronal nets. Such learning mechanisms may be implemented by the non-linear properties of PC apical dendrites, and their gating by SST-interneurons, such that hyper-activity or hypo-activity of SST-interneurons may lead to learningdeficits [35] (Figure 4).

Mechanisms of top-down, selective attention

Selective attention enhances certain sensory processing streams while suppressing others in order to improve the neural representation and propagation of goal-relevant stimuli. Top-down (selective) attention differs from arousal in the sense that it is not a global activation of cortex, but can be highly selective for specific retinotopic locations or features. Studies on selective attention in non-human primates have revealed two key effects on local network activity: (1) Gain modulation of sensory responses [47], (2) A reduction in low-frequency synchronization [48] and 'noise' correlations [49]. The local circuit mechanisms that mediate selective attentional modulations remain largely unknown. A major impediment to this research is the lack of a selective attention paradigm in a genetic model system such as mouse, limiting the ability to resolve specific neural populations during behavior.

Given their involvement in global cortical activation, SST-interneurons and VIP-interneurons are important candidates to implement selective attention mechanisms, or, at minimum, strongly modulate attentional processing. In primates, attentional gain modulation of firing rates is highly similar between fast spiking cells (putative PV-interneurons) and PCs, suggesting that selective attention is not mediated by a release from perisomatic inhibition [43,50]. One view is that the cortex is continuously flooded by a 'blanket of inhibition' mediated by SST-interneurons and that local activation of VIP-interneurons is able to cut local 'holes' in this 'blanket' by selectively inhibiting SST-interneurons [18,51] (Figure 2c). This would open the gate for excitatory feedback inputs arriving in L1, and ultimately increasing the firing rates of PCs representing the attended stimulus. Signal propagation and plasticity of pyramidal cell's dendritic tufts in L1 depends strongly on the generation of NMDA-R-dependent spikes or plateau potentials [21,52]. Consistent with the purported role of L1 signaling, it has been shown that figure-ground modulation and selective attentional modulations depend on the NMDA-R [53]. Attention-associated reductions in low-frequency synchronization and noise correlations also strongly resemble global cortical activation due to arousal [43,54]. Following the discussion in the arousal section above, this could be mediated by activation of a subpopulation of SST-interneurons, especially those disinhibiting layer 4, together with the suppression of L2/3 Martinotti SST-interneurons mediated by VIP-interneurons, thereby opening the gate for specific L1 inputs.

Figure 4



Cortical circuits in health and disease. **(a)** Cortical circuit development follows a specific trajectory, which involves the integration and maturation of GABAergic interneurons. Deviations from this developmental trajectory result in abnormal cortical circuit function. The onset of neurodevelopmental disorders such as autism spectrum disorders (ASD) and schizophrenia are tightly linked to major landmarks for the development of GABAergic inhibition, suggesting that altered GABAergic maturation may lead to neuropsychiatric disease. **(b)** Abnormal contextual processing may be the consequence primary deficits in modulatory centers (left), higher-order frontal cortex (middle) or specific neural elements within sensory cortex (right). In this illustration, the primary deficits (persistent increases or decreases) are indicated by lighter shading, whereas secondary effects on cortical signaling are indicated by dashed arrows. **(c)** Recent studies have identified VIP-INs as critical for translating modulatory inputs into changes in cortical dynamics and sensory processing. Shown are example data of circuit-level alterations caused by removing schizophrenia risk gene ErbB4 selectively from VIP-INs in sensory cortex during early childhood [28••]. This mutation resulted in (i) lack of VIP-IN activation and SST-IN suppression with movement, (ii) impaired cortical state transitions with movement, (iii), impaired network synchrony, and (iv) reduced sensory responses.

Modulations by selective attention are, at least in part, mediated by glutamatergic top-down feedback projections from frontal cortex [55,56]. This assertion is supported by optogenetics studies demonstrating that activation of glutamatergic top-down feedback can drive local and rapid low-frequency desynchronization [57] and enhance behavioral performance via activation of VIP-interneurons [18]. Although modulations by selective attention depend on cholinergic activation of muscarinic receptors [58], it is difficult to envisage how cholinergic modulation alone would implement spatially and feature specific attention, given the lack of ACh-releasing

neurons in the cortex of non-human primates [59], the relatively diffuse nature of basal forebrain projections, and the relatively slow action of the muscarinic ACh receptor [60,61]. Instead, top-down glutamatergic feedback may mimick the effect that neuromodulators have on local circuits, by modulating the activity of VIP and SST-interneurons in highly synergistic and coordinated ways.

Interactions between arousal state and top-down processing

If arousal and top-down processing converge onto the same neural elements, we should expect circuit-level interactions between these processes, and a strong dependence of 'high-level' processes like top-down attention and predictive coding on a 'low-level' process like arousal. We predict moderate levels of arousal to drive moderate SST-mediated desynchronization and partial VIP–SST—PC-mediated 'ungating' of layer 1 inputs. This may establish a permissive set of initial conditions upon which top-down and lateral inputs can further modulate according to immediate task demands. In particular, global cholinergic activation may be highly conductive in facilitating top-down modulations of neuronal activity. Cholinergic but not noradrenergic agonists boost global attention [38,62], which may reflect the bias for cholinergic inputs to engage the VIP–SST–PC circuit and disinhibit layer 1, whereas noradrenergic inputs preferentially stimulate SST-interneurons [5] and suppress L1 top-down signals.

Several pieces of evidence indicate that top-down processes indeed depend on arousal state. Gamma-band synchronization, which is functionally implicated in predictive coding operations [42] and selective attention [48], depends strongly on arousal state mediated by the cholinergic system [63]. Similarly, surround suppression is abolished by isoflurane anesthesia, likely due to the lack of basal cholinergic drive onto SST cells [8]. Furthermore, the modulation of neuronal activity by spatial attention is enhanced and suppressed by agonists and antagonists of the muscarinic cholinergic receptors, respectively [53]. This may not necessarily indicate that top-down attention is directly mediated by cholinergic mechanisms (as discussed in previous section), but could alternatively be explained by the purported role of SST-interneurons in mediating selective attention modulations. Future work should further address the precise sites of convergence of top-down and arousal pathways, to better understand how these different processes interact.

Contextual modulations linking GABAergic interneuron dysfunction and neuropsychiatric disease

All major GABAergic interneuron cell-types have been implicated in neuropsychiatric disease [64]. However, we have yet to identify the circuit-level alterations that underlie abnormal behavioral and cognitive disease phenotypes. The current framework proposes that GABAergic interneuron dysfunction causes neuropsychiatric disease due to a disruption of excitation–inhibition (E–I) balance [65–67]. We, and others [68], find this framework limiting for three reasons. (1) Given the diversity of GABAergic interneurons and related circuits as described above, there is no singular 'E–I balance' in cortex. (2) For most neuropsychiatric conditions, effective medications target neuromodulatory systems (e.g. dopamine, serotonin, norepinephrine) which have complicated effects on levels of excitation and inhibition. (Notable exceptions are anxiety, seizure and alcohol withdrawal, which are managed by directly increasing the strength of GABAergic inhibition [69–71]). (3) A focus on contextual modulations, in contrast to E–I balance, provides direct, testable hypotheses for linking cellular dysfunction with behavior and neuropsychiatric disease (see below).

Deficits of contextual modulation are prominent components of neuropsychiatric disease. Attention is highly compromised in schizophrenia and ADHD [72,73]. Altered arousal is a hallmark of mood and anxiety disorders [74–76]. Altered predictive coding, as assessed by repetition suppression and mismatch negativity, is prominent in schizophrenia and autism [77,78]. Given the roles of GABAergic interneurons in contextual modulation and their dysfunction in disease, we propose that components of neuropsychiatric disease can be understood as deficits in GABAergic interneuron-mediated contextual modulation.

Mouse models of neuropsychiatric disease enable the examination of cellular, circuit and behavioral properties preceding and during the development of overt disease-related phenotypes. Perturbations of cortical GABAergic circuits during development have been shown to disrupt cognitive processes (such as cognitive flexibility and sensory perception) [28••,79], demonstrating that alteration of inhibition may be a common early signature of disease. A recent study selectively altered cortical VIP-INs during early postnatal development and tracked the emergence of dysfunctions in cortical dynamics and contextual modulation [28••]. Specifically, VIP-IN mutations abolished locomotion-induced modulations in SST-interneurons and PCs, reduced cortical responses to sensory stimuli and impaired sensory perception [28••]. Interestingly, these alterations emerged only during adolescence, demonstrating that disease-related phenotypes can arise from developmental dysfunction of the VIP-SST circuit motif [28••]. Such studies will provide mechanistic insights into the pathophysiology of neuropsychiatric disease, and hopefully inspire new approaches to therapeutic intervention.

To summarize, progress in development of genetic mouse model systems has made possible the study of

distinct classes of cortical GABAergic interneurons in behaving animals. In this review, we focused on the emerging roles of SST and VIP cortical interneurons in mediating contextual modulations. These contextual modulations are central mechanisms of healthy cortical functioning, and likely to be critical to cortical dysfunctions in neuropsychiatric disease.

Conflict of interest statement

Nothing declared.

Acknowledgments

We would like to thank Adam Kohn, Jose Luis Pena, Luke Sjulson, Wolf Singer and Alina Peter for critically reading this manuscript. EZ is supported by Whitehall Foundation Research Grant 2017-05-71.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as

- • of special interest
- •• of outstanding interest

1. Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ: **Model of thalamocortical slow-wave sleep oscillations and transitions to activated states**. *J Neurosci* 2002, **22**:8691-8704.

2. Steriade M, McCormick DA, Sejnowski TJ: **Thalamocortical oscillations in the sleeping and aroused brain**. *Science* 1993, **262**:679-685.

3. Parr T, Rees G, Friston KJ: **Computational neuropsychology and bayesian inference**. *Front Hum Neurosci* 2018, **12**:61.

4. Summerfield C, de Lange FP: **Expectation in perceptual decision making: neural and computational mechanisms**. *Nat Rev Neurosci* 2014, **15**:745-756.

5. Tremblay R, Lee S, Rudy B: **GABAergic interneurons in the neocortex: from cellular properties to circuits**. *Neuron* 2016, **91**:260-292.

6. Rudy B, Fishell G, Lee S, Hjerling-Leffler J: **Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons**. *Dev Neurobiol* 2011, **71**:45-61.

7. Pfeffer CK, Xue M, He M, Huang ZJ, Scanziani M: **Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons**. *Nat Neurosci* 2013, **16**:1068-1076.

8. Adesnik H, Bruns W, Taniguchi H, Huang ZJ, Scanziani M: **A neural circuit for spatial summation in visual cortex**. *Nature* 2012, **490**:226-231.

9. Kwan AC, Dan Y: **Dissection of cortical microcircuits by single-neuron stimulation in vivo**. *Curr Biol* 2012, **22**:1459-1467.

10. Silberberg G, Markram H: **Disynaptic inhibition between neocortical pyramidal cells mediated by Martinotti cells**. *Neuron* 2007, **53**:735-746.

11. Urban-Ciecko J, Jouhanneau JS, Myal SE, Poulet JFA, Barth AL: **Precisely timed nicotinic activation drives SST inhibition in neocortical circuits**. *Neuron* 2018, **97**:611-625 e615.

12. Yavorska I, Wehr M: **Somatostatin-expressing inhibitory interneurons in cortical circuits**. *Front Neural Circuits* 2016, **10**:76.

13. Chiu CQ, Lur G, Morse TM, Carnevale NT, Ellis-Davies GC, Higley MJ: **Compartmentalization of GABAergic inhibition by dendritic spines**. *Science* 2013, **340**:759-762.

14. Murayama M, Perez-Garci E, Nevian T, Bock T, Senn W, Larkum ME: **Dendritic encoding of sensory stimuli controlled by deep cortical interneurons**. *Nature* 2009, **457**:1137-1141.

15. Takahashi N, Oertner TG, Hegemann P, Larkum ME: **Active cortical dendrites modulate perception**. *Science* 2016, **354**:1587-1590.

16. •• Munoz W, Tremblay R, Levenstein D, Rudy B: **Layer-specific modulation of neocortical dendritic inhibition during active wakefulness**. *Science* 2017, **355**:954-959.
This study provides an extremely rich characterization of the way in which different SST-IN subtypes are modulated by behavioral state in the barrel cortex of mice. SST-interneurons were recorded from all cortical layers using cell-attached recordings and opto-tagging, followed by morphological reconstruction, and their responses were compared between whisking and non-whisking epochs. Consistent with previous findings [23], the study finds a strong suppression of SST-interneurons with Martinotti morphology in L2/3. However, responses of SST-interneurons in deeper layers could be either suppressed or enhanced. Using optogenetics and pharmacology, it is shown that the suppression of SST-IN firing depended on the activation of VIP interneurons, whereas the enhancement of SST-IN firing depended on cholinergic activation.

17. Takesian AE, Bogart LJ, Lichtman JW, Hensch TK: **Inhibitory circuit gating of auditory critical-period plasticity**. *Nat Neurosci* 2018, **21**:218-227.

18. Zhang S, Xu M, Kamigaki T, Hoang Do JP, Chang WC, Jenvay S, Miyamichi K, Luo L, Dan Y: **Selective attention. Long-range and local circuits for top-down modulation of visual cortex processing**. *Science* 2014, **345**:660-665.

19. Lee S, Kruglikov I, Huang ZJ, Fishell G, Rudy B: **A disinhibitory circuit mediates motor integration in the somatosensory cortex**. *Nat Neurosci* 2013, **16**:1662-1670.

20. Pi HJ, Hangya B, Kvitsiani D, Sanders JI, Huang ZJ, Kepecs A: **Cortical interneurons that specialize in disinhibitory control**. *Nature* 2013, **503**:521-524.

21. Palmer LM, Schulz JM, Murphy SC, Ledergerber D, Murayama M, Larkum ME: **The cellular basis of GABA(B)-mediated interhemispheric inhibition**. *Science* 2012, **335**:989-993.

22. van Versendaal D, Levelt CN: **Inhibitory interneurons in visual cortical plasticity**. *Cell Mol Life Sci* 2016, **73**:3677-3691.

23. Gentet LJ, Kremer Y, Taniguchi H, Huang ZJ, Staiger JF, Petersen CC: **Unique functional properties of somatostatin-expressing GABAergic neurons in mouse barrel cortex**. *Nat Neurosci* 2012, **15**:607-612.

24. McGinley MJ, Vinck M, Reimer J, Batista-Brito R, Zagha E, Cadwell CR, Tolias AS, Cardin JA, McCormick DA: **Waking state: rapid variations modulate neural and behavioral responses**. *Neuron* 2015, **87**:1143-1161.

25. • Reimer J, Froudarakis E, Cadwell CR, Yatsenko D, Denfield GH, Tolias AS: **Pupil fluctuations track fast switching of cortical states during quiet wakefulness**. *Neuron* 2014, **84**:355-362.
This study examines, using two-photon imaging, how the activity of noradrenergic (NE) and cholinergic (ACh) axons correlates with locomotion speed and pupil diameter, a marker of arousal state, in the primary visual cortex of mice. The study finds strong correlations between NE and ACh axonal activity and pupil diameter, with NE and ACh activity preceding pupil dilation in time. Locomotion led to a more phasic increase in NE activity, and a more sustained increase in ACh activity.

26. Busse L, Cardin JA, Chiappe ME, Halassa MM, McGinley MJ, Yamashita T, Saleem AB: **Sensation during active behaviors**. *J Neurosci* 2017, **37**:10826-10834.

27. • Vinck M, Batista-Brito R, Knoblich U, Cardin JA: **Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding**. *Neuron* 2015, **86**:740-754.
This study examines the relationships among locomotor activity, pupil diameter, temporal patterning of neuronal activity and visual encoding, using electrophysiological recordings in the primary visual cortex of mice. The authors show that locomotor activity leads to a strong increase in the spontaneous firing of V1 (fast spiking and pyramidal cells) neurons in anticipation to locomotion onset. Yet, arousal alone, in the absence of locomotor activity, for example, as induced by an air puff, leads to a decrease in spontaneous firing. Increases in signal-to-noise ratio of sensory responses, reductions in noise correlations of sensory responses, and low-frequency desynchronization correlate very strongly with pupil diameter and weakly with locomotor activity.

28. •• Batista-Brito R, Vinck M, Ferguson KA, Chang JT, Laubender D, Lur G, Mossner JM, Hernandez VG, Ramakrishnan C, Deisseroth K *et al.*: **Developmental dysfunction of vip interneurons impairs cortical circuits**. *Neuron* 2017, **95** 884–895.e889.
This study investigates how a developmental dysfunction of VIP interneurons affects network activity in primary visual cortex of mice, using a conditional deletion of a key developmental gene, ERBB4, for interneuron maturation, which is associated with schizophrenia. This deletion leads to a remarkable change of network activity in primary visual cortex: It abolishes synchronization among principal cells, abolishes modulation by behavioral state in principal cells and SST-interneurons, strongly reduces visual responses of principal cells and reduces their orientation selectivity and bias, and leads to deficits in sensory learning. These effects arise only during adolescence, between P15–18 and P25–28, and can be rescued by a local insertion of the ERBB4 gene into primary visual cortex, showing its high spatial specificity.

29. Fu Y, Tucciarone JM, Espinosa JS, Sheng N, Darcy DP, Nicoll RA, Huang ZJ, Stryker MP: **A cortical circuit for gain control by behavioral state**. *Cell* 2014, **156**:1139-1152.

30. Chen SX, Kim AN, Peters AJ, Komiyama T: **Subtype-specific plasticity of inhibitory circuits in motor cortex during motor learning**. *Nat Neurosci* 2015, **18**:1109-1115.

31. Cichon J, Gan WB: **Branch-specific dendritic Ca(2+) spikes cause persistent synaptic plasticity**. *Nature* 2015, **520**:180-185.

32. Fu Y, Kaneko M, Tang Y, Alvarez-Buylla A, Stryker MP: **A cortical disinhibitory circuit for enhancing adult plasticity**. *Elife* 2015, **4**: e05558.

33. Gambino F, Holtmaat A: **Spike-timing-dependent potentiation of sensory surround in the somatosensory cortex is facilitated by deprivation-mediated disinhibition**. *Neuron* 2012, **75**:490-502.

34. Chen N, Sugihara H, Sur M: **An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity**. *Nat Neurosci* 2015, **18**:892-902.

35. Chen G, Zhang Y, Li X, Zhao X, Ye Q, Lin Y, Tao HW, Rasch MJ, Zhang X: **Distinct inhibitory circuits orchestrate cortical beta and gamma band oscillations**. *Neuron* 2017, **96**:1403-1418 e1406.

36. • Veit J, Hakim R, Jadi MP, Sejnowski TJ, Adesnik H: **Cortical gamma band synchronization through somatostatin interneurons**. *Nat Neurosci* 2017, **20**:951-959.
This study examines how ~30 Hz gamma oscillations depend on the activity of SST-interneurons in primary visual cortex of mice, using a combination of electrophysiology with optogenetics. These fast gamma oscillations have been previously postulated to play a key role in routing contextual predictions. Using optogenetics, the study shows that V1 gamma oscillations depend on the activity of SST-interneurons, but not PV-interneurons.

37. Xu H, Jeong HY, Tremblay R, Rudy B: **Neocortical somatostatin-expressing GABAergic interneurons disinhibit the thalamorecipient layer 4**. *Neuron* 2013, **77**:155-167.

38. Noudoost B, Moore T: **The role of neuromodulators in selective attention**. *Trends Cogn Sci* 2011, **15**:585-591.

39. Ibrahim LA, Mesik L, Ji XY, Fang Q, Li HF, Li YT, Zingg B, Zhang LI, Tao HW: **Cross-modality sharpening of visual cortical processing through layer-1-mediated inhibition and disinhibition**. *Neuron* 2016, **89**:1031-1045.

40. Rao RP, Ballard DH: **Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects**. *Nat Neurosci* 1999, **2**:79-87.

41. Dipoppa M, Ranson A, Krumin M, Pachitariu M, Carandini M, Harris KD: **Vision and locomotion shape the interactions between neuron types in mouse visual cortex**. *Neuron* 2018.

42. Vinck M, Bosman CA: **More gamma more predictions: gamma-synchronization as a key mechanism for efficient integration of classical receptive field inputs with surround predictions**. *Front Syst Neurosci* 2016, **10**:35.

43. Vinck M, Womelsdorf T, Buffalo EA, Desimone R, Fries P: **Attentional modulation of cell-class-specific gamma-band synchronization in awake monkey area v4**. *Neuron* 2013, **80**:1077-1089.

44. Haider B, McCormick DA: **Rapid neocortical dynamics: cellular and network mechanisms**. *Neuron* 2009, **62**:171-189.

45. •• Hamm JP, Yuste R: **Somatostatin interneurons control a key component of mismatch negativity in mouse visual cortex**. *Cell Rep* 2016, **16**:597-604.
This study investigates local circuit mechanisms underlying the phenomena of repetition suppression and mismatch negativity in primary visual cortex of mice. Laminar electrophysiological and two-photon imaging recordings show that repeated presentation of the same stimulus leads to reduced responses in Principal cells, whereas the presentation of an unexpected 'deviant' stimulus leads to an enhanced response in comparison to the repeated or control stimulus. Using chemogenetics (DREADDS), it is shown that the elevated response to the deviant stimulus depends on the activity of SST-interneurons.

46. •• Attinger A, Wang B, Keller GB: **Visuomotor coupling shapes the functional development of mouse visual cortex**. *Cell* 2017, **169**:1291-1302 e1214.
This study examines how the responses of Principal cells to a mismatch between locomotion signals and visual flow signals depends on development and SST-IN activity. The study shows that the development of visuomotor mismatch signals in primary visual cortex of mice depends on experience and results from a balance among inhibition mediated by SST-interneurons and excitatory motor-related signals.

47. McAdams CJ, Maunsell JH: **Effects of attention on the reliability of individual neurons in monkey visual cortex**. *Neuron* 1999, **23**:765-773.

48. Fries P, Reynolds JH, Rorie AE, Desimone R: **Modulation of oscillatory neuronal synchronization by selective visual attention**. *Science* 2001, **291**:1560-1563.

49. Cohen MR, Maunsell JH: **Using neuronal populations to study the mechanisms underlying spatial and feature attention**. *Neuron* 2011, **70**:1192-1204.

50. Mitchell JF, Sundberg KA, Reynolds JH: **Spatial attention decorrelates intrinsic activity fluctuations in macaque area V4**. *Neuron* 2009, **63**:879-888.

51. Karnani MM, Agetsuma M, Yuste R: **A blanket of inhibition: functional inferences from dense inhibitory connectivity**. *Curr Opin Neurobiol* 2014, **26**:96-102.

52. Gambino F, Pages S, Kehayas V, Baptista D, Tatti R, Carleton A, Holtmaat A: **Sensory-evoked LTP driven by dendritic plateau potentials in vivo**. *Nature* 2014, **515**:116-119.

53. Herrero JL, Gieselmann MA, Sanayei M, Thiele A: **Attention-induced variance and noise correlation reduction in macaque V1 is mediated by NMDA receptors**. *Neuron* 2013, **78**:729-739.

54. Harris KD, Thiele A: **Cortical state and attention**. *Nat Rev Neurosci* 2011, **12**:509-523.

55. Gregoriou GG, Rossi AF, Ungerleider LG, Desimone R: **Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4**. *Nat Neurosci* 2014, **17**:1003-1011.

56. Moore T, Fallah M: **Microstimulation of the frontal eye field and its effects on covert spatial attention**. *J Neurophysiol* 2004, **91**:152-162.

57. Zagha E, Casale AE, Sachdev RN, McGinley MJ, McCormick DA: **Motor cortex feedback influences sensory processing by modulating network state**. *Neuron* 2013, **79**:567-578.

58. Herrero JL, Roberts MJ, Delicato LS, Gieselmann MA, Dayan P, Thiele A: **Acetylcholine contributes through muscarinic receptors to attentional modulation in V1**. *Nature* 2008, **454**:1110-1114.

59. Consonni S, Leone S, Becchetti A, Amadeo A: **Developmental and neurochemical features of cholinergic neurons in the murine cerebral cortex**. *BMC Neurosci* 2009, **10**:18.

60. Luchicchi A, Bloem B, Viana JN, Mansvelder HD, Role LW: **Illuminating the role of cholinergic signaling in circuits of attention and emotionally salient behaviors**. *Front Synaptic Neurosci* 2014, **6**:24.

61. Picciotto MR, Higley MJ, Mineur YS: **Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior**. *Neuron* 2012, **76**:116-129.

62. Gratton C, Yousef S, Aarts E, Wallace DL, D'Esposito M, Silver MA: **Cholinergic, but not dopaminergic or noradrenergic, enhancement sharpens visual spatial perception in humans**. *J Neurosci* 2017, **37**:4405-4415.

63. Herculano-Houzel S, Munk MH, Neuenschwander S, Singer W: **Precisely synchronized oscillatory firing patterns require electroencephalographic activation**. *J Neurosci* 1999, **19**:3992-4010.

64. Hattori R, Kuchibhotla KV, Froemke RC, Komiyama T: **Functions and dysfunctions of neocortical inhibitory neuron subtypes**. *Nat Neurosci* 2017, **20**:1199-1208.

65. Canitano R, Pallagrosi M: **Autism spectrum disorders and schizophrenia spectrum disorders: excitation/inhibition imbalance and developmental trajectories**. *Front Psychiatry* 2017, **8**:69.

66. Rubenstein JL, Merzenich MM: **Model of autism: increased ratio of excitation/inhibition in key neural systems**. *Genes Brain Behav* 2003, **2**:255-267.

67. Selten M, van Bokhoven H, Nadif Kasri N: **Inhibitory control of the excitatory/inhibitory balance in psychiatric disorders**. *F1000Res* 2018, **7**:23.

68. O'Donnell C, Goncalves JT, Portera-Cailliau C, Sejnowski TJ: **Beyond excitation/inhibition imbalance in multidimensional models of neural circuit changes in brain disorders**. *Elife* 2017, **6**.

69. Amato L, Minozzi S, Vecchi S, Davoli M: **Benzodiazepines for alcohol withdrawal**. *Cochrane Database Syst Rev* 2010: CD005063.

70. Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C: **Antidepressants and benzodiazepines for panic disorder in adults**. *Cochrane Database Syst Rev* 2016, **9**:CD011567.

71. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K: **Anticonvulsant therapy for status epilepticus**. *Cochrane Database Syst Rev* 2014:CD003723.

72. Lansbergen MM, Kenemans JL, van Engeland H: **Stroop interference and attention-deficit/hyperactivity disorder: a review and meta-analysis**. *Neuropsychology* 2007, **21**:251-262.

73. Luck SJ, Gold JM: **The construct of attention in schizophrenia**. *Biol Psychiatry* 2008, **64**:34-39.

74. Cox RC, Olatunji BO: **A systematic review of sleep disturbance in anxiety and related disorders**. *J Anxiety Disord* 2016, **37**:104-129.

75. Hasler G, Drevets WC, Manji HK, Charney DS: **Discovering endophenotypes for major depression**. *Neuropsychopharmacology* 2004, **29**:1765-1781.

76. Rumble ME, White KH, Benca RM: **Sleep disturbances in mood disorders**. *Psychiatr Clin North Am* 2015, **38**:743-759.

77. Ewbank MP, Rhodes G, von dem Hagen EA, Powell TE, Bright N, Stoyanova RS, Baron-Cohen S, Calder AJ: **Repetition suppression in ventral visual cortex is diminished as a function of increasing autistic traits**. *Cereb Cortex* 2015, **25**:3381-3393.

78. Rentzsch J, Shen C, Jockers-Scherubl MC, Gallinat J, Neuhaus AH: **Auditory mismatch negativity and repetition suppression deficits in schizophrenia explained by irregular computation of prediction error**. *PLoS One* 2015, **10**:e0126775.

79. Cho KK, Hoch R, Lee AT, Patel T, Rubenstein JL, Sohal VS: **Gamma rhythms link prefrontal interneuron dysfunction with cognitive inflexibility in Dlx5/6(+/−) mice**. *Neuron* 2015, **85**:1332-1343.