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A disinhibitory circuit motif and flexible information routing in the brain

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In the mammalian neocortex, an area typically receives inputs from, and projects to, dozens of other areas. Mechanisms are needed to flexibly route information to the right place at the right time, which we term 'pathway gating'. For instance, a region in your brain that receives signals from both visual and auditory pathways may want to 'gate in' the visual pathway while 'gating out' the auditory pathway when you try to read a book surrounded by people in a noisy café. In this review, we marshall experimental and computational evidence in support of a circuit mechanism for flexible pathway gating realized by a disinhibitory motif. Moreover, recent work shows an increasing preponderance of this disinhibitory motif from sensory areas to association areas of the mammalian cortex. Pathway input gating is briefly compared with alternative or complementary gating mechanisms. Predictions and open questions for future research on this puzzle about the complex brain system will be discussed.

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Introduction

Recent years have witnessed substantial progress in the neuroscience of large-scale brain circuits. Notably, a series of papers reported high-quality directed and weighted inter-areal connectivity of cortex in macaque monkey [1–3] and mouse [4,5]. These datasets provided an anatomical foundation for the development of computational models of the global cortical dynamics [6–8]. With this advance, a new set of questions have gained urgency, one of which is concerned with gating in the brain. In the mammalian neocortex, an area typically receives inputs from several dozens of other areas, and projects to similarly numerous areas downstream. Mechanisms are needed to flexibly route information to the right place at the right time, which we term 'pathway gating'.

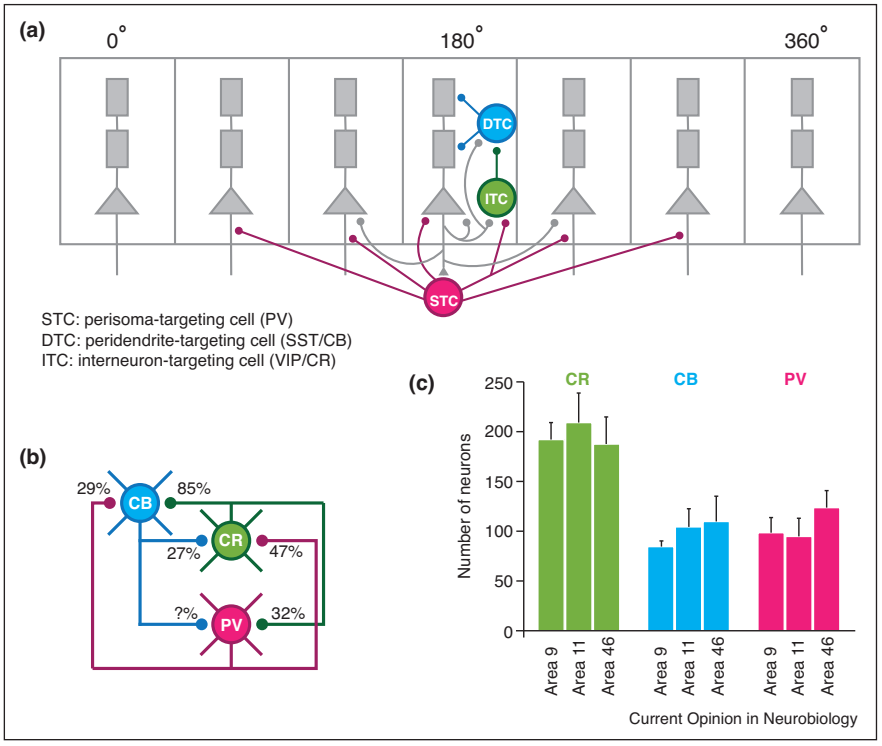
A parallel development in recent years is a dramatic increase in our knowledge about a diversity of GABAergic inhibitory neurons in the cortex. Thanks to the availability of genetic tools, researchers can label specific subtypes of GABAergic cells, quantify their molecular fingerprints, measure their morphological and physiological properties, record their activity from behaving animals and assess their functional role by optogenetic manipulations. Whereas classification of GABAergic interneurons continues to be refined and debated, a consensus has emerged with regard to a canonical disinhibitory motif that involves three non-overlapping subclasses of interneurons, in empirical support of a model prediction [9]. A first type of parvalbumin (PV) positive interneurons target perisomatic regions of excitatory pyramidal (P) cells and control their spiking outputs; a second type of somatostatin (SST) positive interneurons target pyramidal dendrites and are in an ideal position to control their inputs; a third type of interneurons express vasoactive intestinal peptide (VIP) and preferentially target SST cells. When VIP neurons are activated, they inhibit SST cells, thereby disinhibiting pyramidal dendrites. Following the initial breakthroughs (for a review of the work prior to 2015, see [10]), our knowledge about these different inhibitory cell types [11–14], their interactions [15••,16] and their functions in behaving mice [14,17–20,21•,22–25] continue to grow over the last few years.

Built on the new barrage of experimental data, a computational model was developed to test the hypothesis that the canonical disinhibitory motif provides a circuit substrate for pathway gating [26••]. In this short review, we first summarize recent experimental research on this canonical disinhibitory motif. Then, we will discuss requirements and supporting evidence for this circuit motif to implement pathway gating. Finally, we will contrast this mechanism with other, potentially complimentary, gating scenarios within cortex and involving subcortical structures, and suggest open questions for future research on the dynamical operation and flexible functions of the cell-type specific large-scale brain systems.

A disinhibitory motif

One of the cognitive functions that depend on input gating is working memory, the brain's ability to internally store and manipulate information in the absence of

Figure 1



A disinhibitory circuit motif. **(a)** A neural circuit model for working memory with three types of inhibitory neurons, that is perisoma targeting, peridendrite-targeting, and interneuron-targeting neurons. Dendrite-targeting inhibitory neurons (blue) control the resistance to distractors (adapted from [9]). **(b)** The circuit diagram of PV, CB, and CR neurons. The connection probabilities between different types of neurons are measured in inferior temporal cortex of macaque monkey (adapted from [32]). **(c)** Number of CR, CB, and PV neurons in three subregions of the macaque monkey prefrontal cortex, showing that PV are not predominant among the three interneuron types in the prefrontal cortex (adapted from [33]).

sensory stimulation. A cardinal requirement for a working memory circuit to function properly is that only behavioral relevant stimuli are 'gated in' while irrelevant distractors are filtered out and ignored. Computational considerations of this problem have led to the publication, in 2004, of a biologically based local circuit model endowed with three subtypes of inhibitory neurons (Figure 1a) [9]. The model was inspired by three lines of anatomical evidence. First, a subpopulation of GABAergic cells labeled by VIP or calcium-binding protein calretinin (CR) preferentially target other interneurons rather than pyramidal cells in the hippocampus [27], as well as neocortex of rodents [28,29] and monkeys [30–32]. Second, statistically, VIP and CR cells preferentially target dendrite-targeting inhibitory neurons expressing calbindin (CB) or SST, rather than PV cells (Figure 1b) [32]. Third, unlike primary sensory areas where PV cells are the majority of GABAergic neurons, CB and CR interneurons are predominant in the prefrontal cortex which plays a central role in working memory (Figure 1c) [33]. The model has several predictions. In particular, dendrite-targeting interneurons should have a significant spontaneous activity, which was later supported by empirical data [34]. Moreover, these cells display an 'inverted tuning', that is a decrease in activity for specific stimulus features, which was found in single-unit recording from behaving monkeys [9]. More direct support came recently in a mice experiment showing that activation of VIP or SST neurons of dorsomedial frontal cortex, respectively enhanced or impaired working memory retention and behavioral performance [25].

Although the theoretical proposal of a disinhibitory microcircuit motif was originally motivated by the need of gating for a working memory network, the local circuit organization (Figure 1a) is in principle general for all cortical areas. Note that it appears that PV, CB and CR positive interneurons do not have significant overlap in macaque monkey; whereas the overlaps are more substantial in mice, for which PV, SST and VIP are better markers of non-overlapping interneuron subpopulations. Importantly, Wang *et al.* explicitly stated that 'We emphasize that the three interneuron types in our model should be more appropriately interpreted according to their synaptic targets rather than calcium-binding protein expressions' [9].