FEATURE ARTICLE
The Neurobiology of Thought: The Groundbreaking Discoveries of Patricia Goldman-Rakic 1937–2003

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Patricia S. Goldman-Rakic (1937–2003) transformed the study of the prefrontal cortex (PFC) and the neural basis of mental representation, the basic building block of abstract thought. Her pioneering research first identified the dorsolateral PFC (dlPFC) region essential for spatial working memory, and the extensive circuits of spatial cognition. She discovered the cellular basis of working memory, illuminating the dlPFC microcircuitry underlying spatially tuned, persistent firing, whereby precise information can be held "in mind": persistent firing arises from recurrent excitation within glutamatergic pyramidal cell circuits in deep layer III, while tuning arises from GABAergic lateral inhibition. She was the first to discover that dopamine is essential for dlPFC function, particularly through D1 receptor actions. She applied a host of technical approaches, providing a new paradigm for scientific inquiry. Goldman-Rakic's work has allowed the perplexing complexities of mental illness to begun to be understood at the cellular level, including atrophy of the dlPFC microcircuits subserving mental representation. She correctly predicted that impairments in dlPFC working memory activity would contribute to thought disorder, a cardinal symptom of schizophrenia. Ten years following her death, we look back to see how she inspired an entire field, fundamentally changing our view of cognition and cognitive disorders.

Keywords: dopamine, mental representation, prefrontal cortex, schizophrenia, working memory

Introduction

How does the brain create thought? This weighty question has perplexed philosophers and scientists alike, and many still surmise that it is a quandary beyond the scope of scientific inquiry. How do we think about something that is not actually stimulating our senses? How does the brain generate its own activity—creating goals and visions—and how does it maintain this information despite distractions and interruptions? The brain's ability to create mental representations is the foundation of abstraction, a process that liberates us from our environment, liberates us from conditioned responses, the foot-in-the-door that is free will. It is extraordinary that this vital process has now begun to be understood at the cellular level, in large part due to the groundbreaking research of Patricia Shoer Goldman-Rakic.

Patricia Shoer was born on 22 April 1937 in Salem, Massachusetts. It was a year after the publication of the very first work to uncover the critical role of the dorsolateral prefrontal cortex (dlPFC) in the generation of thought, the research of Carlyle Jacobsen at Yale (Fig. 1). The chairman of Jacobsen's department was John Fulton, an expert primate neurosurgeon, who helped Jacobsen create lesions to different parts of the cerebral cortex. Jacobsen discovered that the monkeys with bilateral lesions to the dlPFC could solve even difficult puzzles if the information needed was present in the environment, while even a short delay that required information to be held in mind, reduced performance to chance (Jacobsen 1936). He wrote: "The animal without the frontal association area learns and retains sensory-motor habits and visual discriminations but it is unable to remember for even a few seconds under which of two cups a piece of food is concealed … It is as if 'out of sight, out of mind' were literally applicable" (Jacobsen 1936), a reference to Ferrier's generalized description of subjects with frontal lesions (Ferrier 1886). Jacobsen also speculated about the possible cellular basis for this critical ability, writing that the answer "must be supplied by the subject either through some sustained activity during the period of delay or by recall from past experience…" (Jacobsen 1936). This speculation would be supported some 40 years later when neuroscientists began to record from prefrontal neurons.

Following the interruption of World War II, there ensued an era of extraordinary lesion studies, much of which has become invisible to today's researchers, as the data were often published in books or journals not captured in PubMed, for example, in The Frontal Granular Cortex and Behavior edited by Warren and Akert and published by McGraw-Hill in 1964. Lesion studies in monkeys have become prohibitively expensive, but they reveal the essential contributions of a brain area in ways that functional imaging and even neuronal recordings do not. Functional imaging and physiology can reflect indirect activity from other, interconnected brain regions, while lesion studies reveal what is uniquely lost. These early lesion studies showed that monkeys with PFC ablations or cooling of the PFC to induce a functional lesion were easily distracted (Grueninger and Pribram 1969), inflexible, perseverative (Mishkin 1964; Butter 1968), and hyperactive (Kennard et al. 1941; Ruch and Shenkin 1943), with lesions to the orbital PFC altering emotional responses (Butter and Snyder 1972) and that to the dorsolateral aspects altering cognition (Fuster and Bauer 1974). The beginnings of circuit contributions were also apparent in lesion studies, for example, showing that the most prominent deficits on spatial working memory tasks were found with frontal lesions, but more subtle deficits could be seen following lesions to such areas as the caudate and hippocampus (Rosvold and Szwarcbart 1964).

Early in her career at the NIH, Patricia Shoer Goldman worked with Rosvold to continue the work of Jacobsen and refined the region of dlPFC necessary for visuospatial working memory. She determined that the cortex surrounding the caudal two-thirds of the principal sulcus was essential for

Timeline:
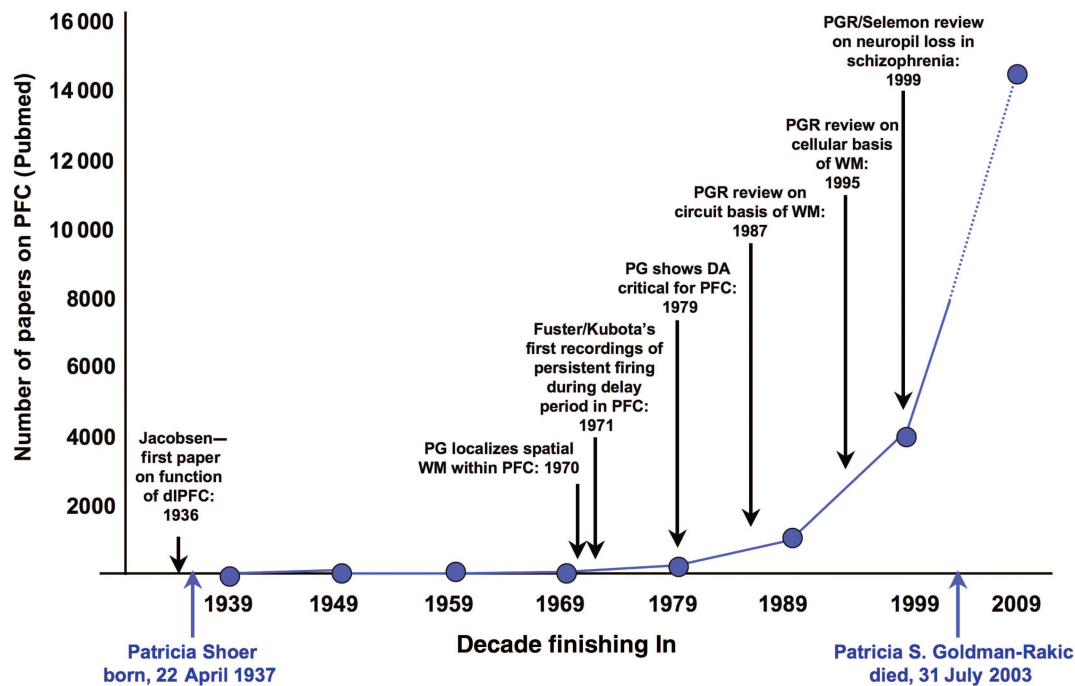## The discovery of the neurobiology of working memory (WM)

Figure 1. Timeline of the discoveries of the PFC role in working memory (WM) and the key contributions of Goldman-Rakic. The graph shows the number of papers cited on PubMed using the search term "prefrontal cortex" for each decade ending in the year noted. Key publications by Goldman-Rakic and other early pioneers are indicated.

spatial working memory, and that monkeys with principal sulcus lesions could perform visuospatial tasks that did not require memory, or perform memory tasks that did use visuospatial information, but could not perform tasks that required memory of visuospatial information (Goldman and Rosvold 1970; Goldman et al. 1971). This information not only defined the "bull's eye" for the cortex underlying spatial working memory, but also gave the first hints of the parallel organization underlying cognitive operations.

The Circuit Basis for Working Memory

Currently, researchers often use magnetic resonance imaging (MRI) methods to try to reveal connectivity in human brains, for example, examining the cohesion of white matter tracks, or correlations between activated areas. Many are unaware of the wealth of anatomical tracing studies of the monkey brain, some of which continue to this day. With the development of sensitive track tracing methods in the 1970's, the detailed connections between brain regions could be revealed for the first time. Pat collaborated with Walle Nauta at MIT to learn these new techniques and found the first evidence of columnar organization of cortical–cortical connections in the dlPFC, similar to what had been traced in the primary visual cortex (Goldman and Nauta 1977). These columns suggested that the methods being applied to the primary visual cortex to reveal the circuit and cellular basis of visual perception could be applied to the PFC to explore the neuronal basis of thought. This affirmation of strategy served as a talisman to Pat, as the attitude at the time (and even sometimes today) was that the processes underlying thought were beyond the scope of science, and that rigorous scientific pursuits could only be applied to sensory-motor functions. Pat's work revolutionized this view, demonstrating that

the neurobiology of cognition was tractable if approached in a manner that respected component processes and revealed the inherent neural organization.

Pat married Pasko Rakic in 1979 and they both came to Yale to create the Section of Neuroanatomy (later called the Department of Neurobiology). Goldman-Rakic and Rakic went on to found this journal, *Cerebral Cortex*, in 1991. On arriving at Yale, Goldman-Rakic performed an intensive series of anatomical tracing studies with colleagues such as Schwartz, Selemon, and Cavada, to identify the circuit basis of spatial cognition. They found that the principal sulcul PFC shared reciprocal projections with area 7a/7lip of the parietal association cortex, a region known to perform high-order processing of visuospatial information (Cavada and Goldman-Rakic 1989), as well as intensive connections across the corpus callosum with its counterpart in the opposite hemisphere (Schwartz and Goldman-Rakic 1984). These connections terminated in columns (Schwartz and Goldman-Rakic 1984), and appeared before birth (Schwartz and Goldman-Rakic 1991), establishing a genetic mediation for cortical connectivity. Remarkably, the 2 regions projected to many of the same brain areas (Selemon and Goldman-Rakic 1988), forming a complex and beautifully organized pattern of connections summarized in Figure 2. Thus, both the dlPFC and the posterior parietal cortex shared projections to a large number of cortical areas, including those involved with visuospatial processing (area 19, medial parietal cortex), auditory information and sensory integration (superior temporal cortex), motor response (premotor cortex and frontal eye fields), reward and punishment (orbital and insular PFC), memory (parahippocampal gyrus and presubiculum), and error detection (anterior cingulate cortex). Interestingly, they also interconnect with regions now considered part of the so-called "Default Network," for example, the anterior and posterior cingulate cortices and the retrosplenial cortex,

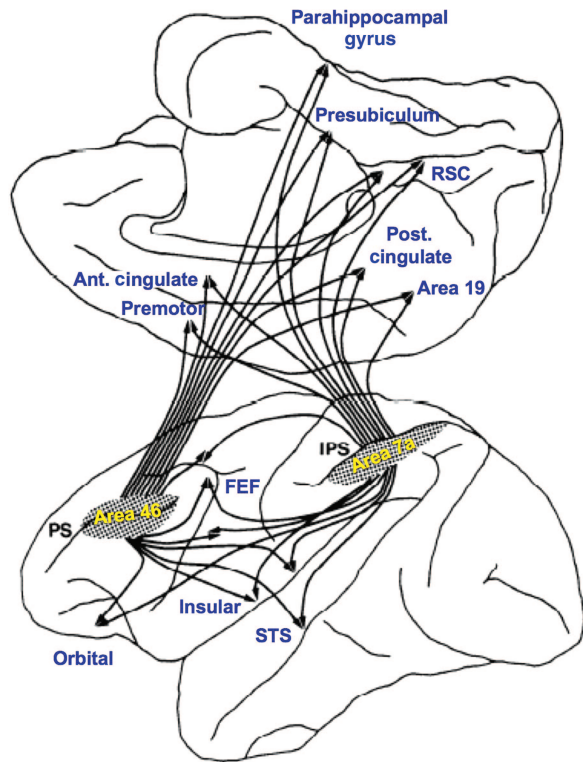## The circuitry of visuo-spatial cognition

Figure 2. The cortical circuitry for spatial cognition, based on the work of Goldman-Rakic and Selemon. Note that both the dlPFC (area 46) and parietal cortex have many shared connections to subcortical structures that are not shown in this illustration, as well as "nonshared" connections that are not included in this diagram. Figure used with the permission of L. Selemon. Ant. Cingulate: anterior cingulate; FEF: frontal eye fields; IPS: intraparietal sulcus; Post. Cingulate: posterior cingulate; PS: principal sulcus; RSC: retrosplenial cortex; STS: superior temporal sulcus.

which is involved in episodic memory, navigation, imagination, and planning for the future (Vann et al. 2009). There were also shared projections to subcortical structures that are not shown in Figure 2, including extensive projections to striatum, thalamus, and the cerebellum via the pontine nuclei (Selemon and Goldman-Rakic 1985, 1988). Thus, a picture began to build of the coordinated, long-range circuits for spatial cognition.

But what about working memory for other sensory modalities? The work of Haxby, Ungerleider, and colleagues had identified parallel processing streams for the processing of visual space versus visual features (Haxby et al. 1991). Goldman-Rakic saw that these streams remained in parallel as they projected into distinct subregions of the dlPFC (Goldman-Rakic 1987; Fig. 3). Further work showed that these parallels extended to auditory processing as well, creating a dorsal zone for spatial aspects of working memory, and a more ventral zone for working memory of sensory features (Romanski et al. 1999). As with the posterior cortical streams, these areas are extensively interconnected (Barbas and Pandya 1989), thus providing a cohesive experience of reality. In contrast to the sensory projections to the dlPFC, affective and interoceptive information projected into the orbital and medial PFC, which, in turn, projected to limbic structures such as the amygdala, hypothalamus, and brainstem (Price et al. 1996; Ghashghaei and Barbas 2002). Thus, there is a topographic organization to the circuitry, and therefore the functions, of the primate PFC.
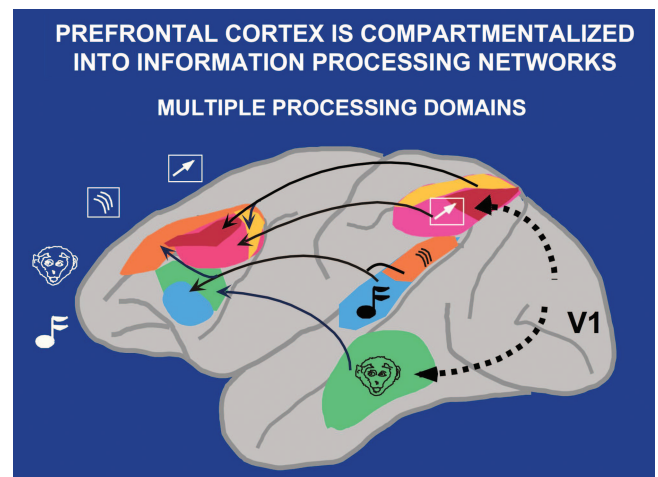

Figure 3. The parallel cortical circuits for space versus features in the visual and auditory domains. Parallel visual pathways for the processing of visual space and visual features emerge from the primary visual cortex, area V1. These pathways remain in parallel as they project into the PFC. Similar parallel projections were observed for the auditory spatial and feature streams. The visuospatial circuit is shown in pink/red/yellow; the auditory spatial circuit in orange; the visual feature circuit is shown in green, and the auditory feature circuit is shown in blue. Figure from a Goldman-Rakic presentation for Yale undergraduates with the permission of P. Rakic. Note that projections from the PFC back to the sensory cortex are not illustrated in this figure, but likely play an important role in top-down regulation of attention and sensory processing.

The Cellular Basis of Working Memory

Fuster (Fuster and Alexander 1971; Fuster 1973) and Kubota (Kubota and Niki 1971) were the first to record from neurons in the dlPFC as monkeys performed working memory tasks. They used classical, manual versions of these tasks and discovered neurons with a variety of properties: Those that responded to the sensory cue, many that responded in anticipation of or during the motor response, and most intriguingly, neurons that were able to maintain persistent firing across the delay period, the sustained neural activity that was predicted by Jacobsen years before. Fuster (Fuster 1985, 2008) realized that, with these "memory cells" he had captured that foot-in-the-door, the neural process that integrated perception with action, the temporal bridge that wedded the past to the future: "the bridging of cross-temporal contingencies of behavior, in other words, the adjustment of the actions of the organism to temporally distant events and objectives" thus generating "short-term memory, preparatory set, and control of interference" (Fuster 1985).

Pat built on this work with Funahashi and Bruce, adapting a delayed saccade task (Hikosaka and Wurtz 1983) that allowed precise knowledge of the retinotopic position of 8 spatial cues. These recordings revealed that the persistent firing across the delay period in the spatial working memory task was spatially tuned (Funahashi et al. 1989), representing a specific portion of the visual field (Fig. $4A_1$). Thus, a "Delay cell" will show elevated firing across the delay period for the memory of one particular location (usually in the contralateral visual field), and actually inhibit its firing during the delay period for other directions, creating a so-called "memory field" (Fig. $4A_2$). The location of a neuron's memory field is stable day-to-day (Fig. $4B$), as would be needed for mental representation. Furthermore, tiny lesions within this area of dlPFC produced "mnemonic scotomas," impairments in remembering just that specific area of visual space, with no effect on visually guided
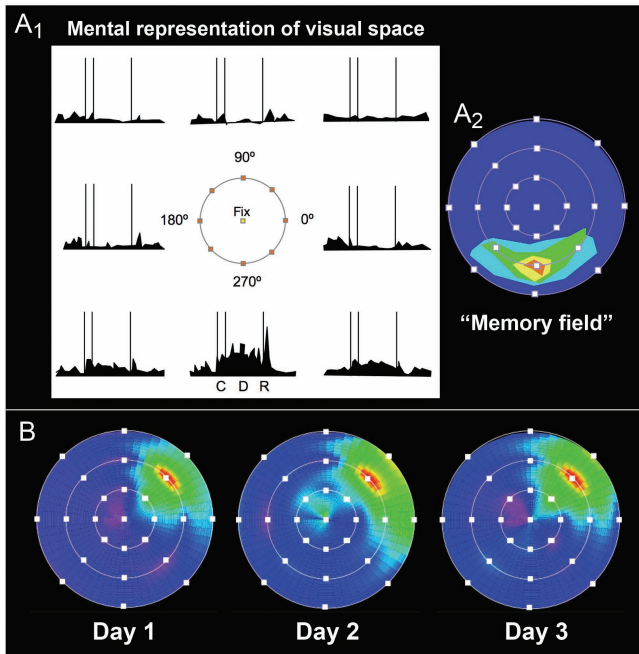
Figure 4. The physiology of mental representation in dlPFC. (A_1) A schematic representation of a neuron with spatially tuned, persistent firing during the oculomotor delayed-response task. The possible spatial locations for cues are shown in the center of this figure, with the fixation point indicated in yellow. This neuron has persistent firing for the memory of a cue at 270°, but has less persistent firing for the memory of nearby locations, and actually inhibits firing during the delay period following cues distant to the neuron's "preferred location." Goldman-Rakic considered this the cellular representation of visual space, the fundamental building block of mental representation. C: cue period; D: delay period; R: signal for saccadic response. (A_2) The neuronal firing patterns of the neuron depicted in (A_1) shown as a "memory field," where dark blue represents low levels of firing during the delay period and brighter colors signify progressively higher firing rates. This method provides a more intuitive process for depicting the strength and precision of a neuron's spatial tuning. (B) The same neuron recorded on 3 separate days shows stable spatial tuning for 45°, as would be needed for the mental representation of visual space. This figure is from a Goldman-Rakic presentation for Yale undergraduates with the permission of P. Rakic; the data are from O'Scalaidhe and Goldman-Rakic, unpublished.

eye movements (Funahashi, Bruce, et al. 1993). Neurons representing visual features, for example faces, could be found more ventrally in the area of PFC that receives information from the ventral stream (Wilson et al. 1993; O'Scalaidhe et al. 1997). Taken together, these findings had uncovered the cellular basis for mental representation: "I have maintained that the prefrontal neuron's capacity for sustained activation in the absence of external stimulation is the cellular basis of mental representation and the essential building block for information processing systems in the human brain. This is the neural mechanism presumably disrupted in the condition: 'out of sight-out of mind' that Sir John Ferrier used to describe monkeys with prefrontal lesions (Ferrier 1886) and so often been used to describe patients with prefrontal lesions" (Goldman-Rakic 2002).

This "essential building block" can be seen contributing to other PFC executive operations in recordings from monkeys performing related tasks. For example, spatially tuned persistent firing underlies behavioral inhibition, in which the monkey has to look away from a remembered stimulus (Funahashi, Chafee, et al. 1993). Similarly, it is essential for goal-directed attention and resistance to distraction. For example, dlPFC neurons can maintain persistent firing across the delay

period despite distractions, in contrast to more posterior cortices where distraction interrupts firing (Miller et al. 1996). How do PFC circuits generate this robust, highly specific, persistent firing to represent events and goals for action?

The dlPFC Microcircuits That Generate Mental Representations

Goldman-Rakic combined anatomical tracing methods with multiple electrode recordings to reveal the circuitry underlying spatially tuned, persistent firing by dlPFC Delay cells.

Persistent Firing

Kritzer and Goldman-Rakic (1995) examined the intrinsic circuitry of the dlPFC by making very small injections of a retrograde tracer within a distinct layer. They found that neurons in deep layer IIIc had the most extensive horizontal connections, consistent with recurrent excitatory connections in this sublayer (Fig. 5A). These horizontal connections extended 2–7 mm and terminated in a series of columns in deep layer III. There was also evidence of horizontal connections between neurons in the superficial part of layer V (Va), connecting with both layer III and superficial layer V cells. In contrast, the other layers and sublayers showed more typical, vertical labeling. The depiction of deep layer III horizontal, recurrent excitatory connections is schematically illustrated by Goldman-Rakic in Figure 5B. The finding of extensive horizontal projections with a columnar pattern within deep layer III fits with the previous data, showing columnar inputs of visuospatial information from the parietal association cortex (Schwartz and Goldman-Rakic 1984) and also with subsequent physiological recordings showing clusters of neurons with similar spatial tuning and timing consistent with monosynaptic excitatory connections (Constantinidis et al. 2001). Pyramidal cells intersynapse onto dendritic spines, and our more recent data have shown very long and thin spines in deep layer III (Arnsten et al. 2012; Paspalas et al. 2012). We have also shown that the persistent firing of Delay cells depends on glutamate stimulation of *N*-methyl-D-aspartic acid (NMDA) receptors with slow, NR2B subunits that can be found in the postsynaptic density on spines in deep layer III (Wang et al. 2013). Thus, the persistent firing needed to sustain a mental representation without sensory stimulation arises from recurrent glutamate NMDAR pyramidal cell excitation, likely in deep layer III and possibly superficial layer V.

Spatial Tuning

The circuit basis for the spatial tuning of dlPFC Delay cells arises from the lateral inhibition provided by fast-spiking, parvalbumin-containing, GABAergic interneurons (basket and chandelier cells), for example, the basket cell seen in Figure 6A (Rao et al. 1999; Constantinidis and Goldman-Rakic 2002). A schematic illustration of this lateral inhibition is portrayed in Figure 5B, where the 90° pyramidal cells activate an interneuron (represented in blue) to inhibit the firing of the 270° pyramidal cells, and vice versa. An example of simultaneous, multiple electrode recordings from a fast-spiking neuron (presumed parvalbumin-containing GABAergic interneurons) and a regular-spiking neuron (presumed pyramidal cells) is shown in Figure 6; note that the spatial tuning of the presumed pyramidal cell (Fig. $6C_1$) is opposite to that of the presumed GABAergic interneuron (Fig. $6B_1$), and that the pyramidal cell increased its firing (Fig. $6C_2$) as the interneuron reduced its
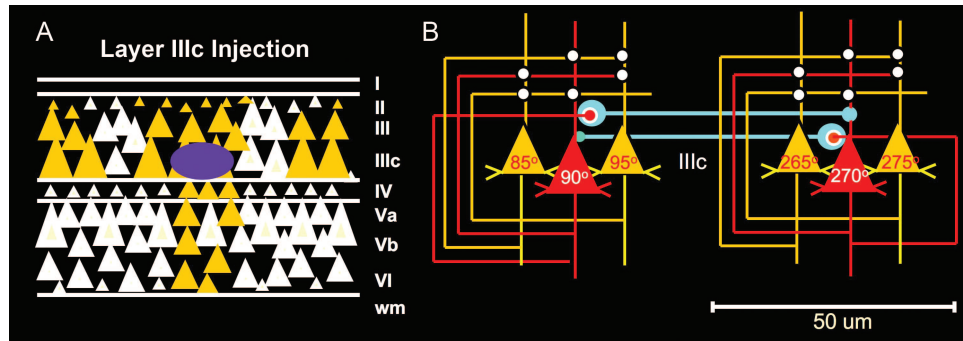
Figure 5. The dlPFC microcircuits underlying mental representation. (*A*) Microinjections of an anatomical tracer (purple) into layer IIIc of the primate dlPFC-labeled horizontal connections (gold) consistent with recurrent excitation between pyramidal cells. (*B*) Goldman-Rakic's schematic depiction of the primate layer IIIc microcircuits that provide the cellular basis for mental representation. Pyramidal cells are depicted by triangles; they excite each other through glutamatergic synapses on spines (white circles). GABAergic interneurons providing lateral inhibition are shown in blue. Note that although connections between pyramidal cells are depicted on the apical dendrites for the sake of clarity, they are likely most concentrated on the basal dendrites. Figures from a Goldman-Rakic presentation for Yale undergraduates with the permission of P. Rakic.
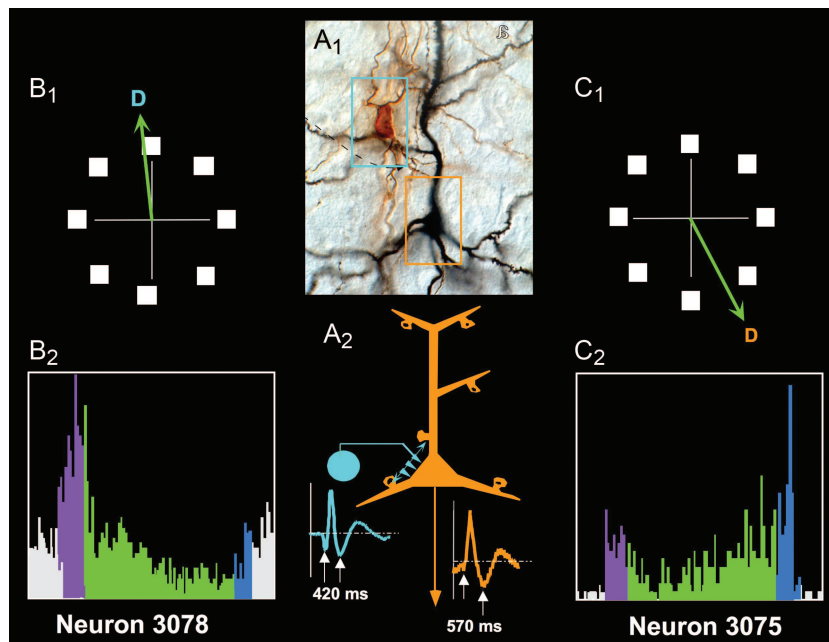

Figure 6. An example of the reciprocal relationship between pyramidal cells and GABAergic interneurons in the dlPFC. (A_1) Photograph of a GABAergic basket cell (within blue rectangle) and a pyramidal cell (within orange rectangle) in the primate dlPFC. (A_2) A schematic diagram of the likely connections between these neurons, whereby the basket cell (blue, fast-spiking with thin waveform) inhibits the pyramidal cell (orange, regular-spiking with longer waveform) through connections on the soma (shown) and proximal primary dendrites (not shown). (B_1) The preferred direction of the presumed GABAergic interneuron during the delay period. (B_2) The firing pattern of a fast-spiking, presumed GABAergic interneuron during the initial fixation (gray), cue presentation (purple), delay period (green), and response epochs (blue). (C_1) The preferred direction of the regular-spiking, presumed pyramidal cell during the delay period. Note that it is opposite to the preferred direction of the interneuron. (C_2) The firing pattern of the presumed pyramidal cell during the initial fixation (gray), cue presentation (purple), delay period (green), and response epochs (blue). Note that the firing of the pyramidal cell increases as the firing of the GABAergic interneuron decreases. Figures from a Goldman-Rakic presentation for Yale undergraduates with the permission of P. Rakic.

firing (Fig. 6B_2). Furthermore, local application of a gamma-aminobutyric acid (GABA) antagonist eroded the spatial tuning of dlPFC Delay cells (Rao et al. 2000), consistent with this working model. Thus, lateral inhibition from GABAergic interneurons is important for enhancing contrast and allowing more precise information to be held in working memory stores.

Recordings down the depth of the principal sulcus (Fig. 7), as well as from the surface of the dlPFC (Constantinidis et al. 2001), showed the progressive representation of the visual field as the electrode advanced. These extensive physiological assessments of the dlPFC revealed a microcolumnar architecture, as schematically depicted in Figure 5B and described by Goldman-Rakic in 2002:

"Thus, using multiple electrodes in vivo, we have shown that neurons that lie in close proximity to each other not only are likely to have shared spatial tuning, i.e., to be iso-directionally related (Constantinidis et al. 2001), but also to be monosynaptically connected (Constantinidis et al. 2000). In contrast, neurons at wider distances, e.g., within 200–300 µm of each other, are more likely to have wide disparities in their spatial
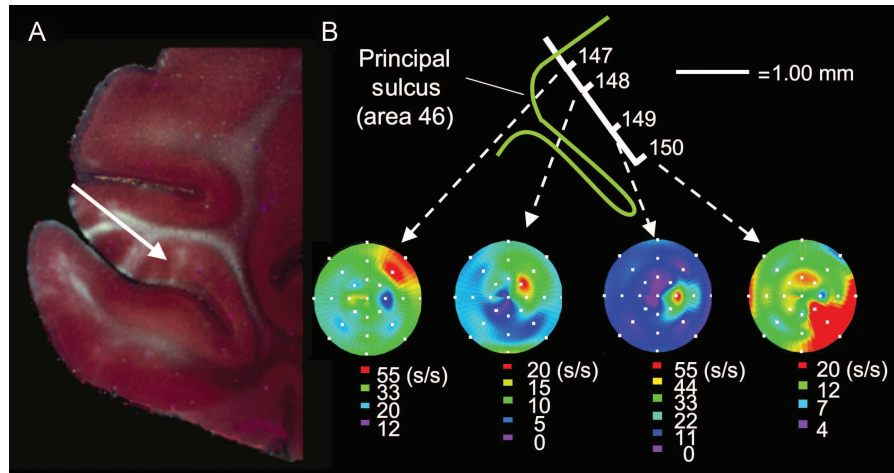
Figure 7. Representation of the visual field in principal sulcal dlPFC. (*A*) An image of the rostral principal sulcus that Goldman-Rakic used to illustrate the concept of progressive recordings down the sulcus as indicated by the white arrow. The autoradiographic image of the dlPFC is from an earlier anatomical study with Nauta showing columns of labeling from connections with the contralateral dlPFC. The actual recordings were performed in a more caudal region of the principal sulcal cortex. (*B*) Recordings by O'Scalaidhe and Goldman-Rakic (unpublished) down the length of the caudal principal sulcal cortex show progressive changes in the preferred direction of each neuron, thus providing comprehensive representation of the entire, contralateral visual field. Figures from a Goldman-Rakic presentation for Yale undergraduates with the permission of P. Rakic.

tuning and to be cross-directionally tuned, suggestive of a modular organization for visuo-spatial information processing. The striking local circuit and functional arrangements between adjacent and separated pyramidal and fast-spiking interneurons support a microcolumnar functional architecture in the dorsolateral prefrontal cortex for spatial memory fields and hence for psychic functions, similar to that found in other areas of cortex for sensory receptive fields." (Goldman-Rakic 2002)

Thus, Goldman-Rakic revealed the basic microcircuitry for mental representation in the dlPFC. This building block of cognition can be used to construct ever-higher functions—representations of representations—the foundation of abstract thought.

The Key Role of Dopamine and Neuromodulation

The higher cognitive functioning of the dlPFC is especially sensitive to its neuromodulatory environment, a finding discovered by Pat in 1979. In her groundbreaking study with Brozoski et al. (1979), Pat showed that depletion of catcholamines from the monkey dlPFC was as devastating to spatial working memory performance as removing the cortex itself. This work has served as a beacon for all subsequent studies on the neuromodulation of dlPFC, illuminating the critical importance of molecular state to higher cognitive function, and helping to explain both the etiology of cognitive disorders and possibilities for their treatment.

It is remarkable that the finding of dopamine's importance to the primate dlPFC was published in 1979, years before parallel cognitive studies were performed in rodents (Bubser and Schmidt 1990). The dopamine innervation of the rat cortex was first mapped in the 1970's, showing a selective projection of dopamine fibers to the PFC but not other cortical areas (Berger et al. 1976). Pat and Roger Brown were the first to measure monoamine concentrations in the primate cortex, and found that dopamine levels and synthesis were very high in

the primate PFC, but that unlike the rodent, dopamine was also prevalent in other cortical areas as well (Brown et al. 1979). Working with Brozoski, they examined the functional contribution of dopamine to the primate dlPFC by infusing the catecholamine neurotoxin, 6-OHDA, into the dlPFC, with or without desmethylimipramine (DMI), supposed to protect noradrenergic fibers. DMI was not very effective in protecting norepinephrine, but it did facilitate uptake into dopaminergic fibers to enhance depletion. Thus, they created lesions with very large dopaminergic (and large noradrenergic) depletions restricted to the dlPFC. These lesions markedly impaired spatial working memory performance, similar to that seen with dlPFC ablations. Performance was improved by catecholaminergic drugs: The catecholamine precursor L-3,4-dihydroxyphenylalanine, the dopamine D2 receptor agonist, apomorphine, and (in a footnote), the α2 noradrenergic agonist, clonidine. Since noradrenergic depletion with minimal dopamine depletion had little effect on working memory performance, the authors concluded that dopamine was the key factor. However, it is now known that both dopamine and norepinephrine are critical for dlPFC function, and it is likely that one can substitute for the other in long-term lesion studies such as the one performed by Brozoski et al. Indeed, that footnote on clonidine led to studies showing that noradrenergic stimulation of postsynaptic, α2 adrenergic receptors is essential to dlPFC function (Arnsten and Goldman-Rakic 1985) via functional strengthening of pyramidal cell circuits (Wang et al. 2007), and α2A receptor agonists such as guanfacine are now in widespread clinical use to treat PFC cognitive disorders (Hunt et al. 1995; Scahill et al. 2001, 2006; Biederman et al. 2008; McAllister et al. 2011; Connor et al. 2013). Goldman-Rakic also began to explore other modulatory influences on dlPFC, including serotonin (e.g. Lidow et al. 1989; Williams et al. 2002); and acetylcholine (e.g. Mrzljak et al. 1993). But her primary focus remained on dopamine. She worked with Mark Williams to identify the midbrain source of dopamine to the PFC (Williams and Goldman-Rakic 1998), and to map the dopaminergic fibers innervating the frontal lobe

(Williams and Goldman-Rakic 1993). The dopamine-containing fibers in the dlPFC are actually rather sparse (Fig. 8A), emphasizing that quantity does not always correlate with efficacy.

D1 versus D2 Receptor Actions

The advent of selective D1 versus D2 receptor antagonists allowed the exploration of dopamine's actions at these differing receptor families. The D1 receptor family (D1 and D5) was most prevalent in the dlPFC, with dense binding in superficial and deep layers, whereas D2 receptor binding was sparse and concentrated in layer V (Goldman-Rakic et al. 1990; Lidow et al. 1991). These findings were later confirmed by in situ hybridization histochemistry, where mRNA for D2 receptors was again focused in layer V neurons (Lidow et al. 1998), and by immunoelectron microscopy, where D1 receptors were most prevalent on dendritic spines (Smiley et al. 1994).

D1 Receptor Beneficial Actions

Given the extensive D1 receptor binding in the dlPFC, Goldman-Rakic's initial studies focused on D1 receptor actions. Working with Sawaguchi, she found that infusion of a D1 receptor antagonist into the dlPFC impaired spatial working memory performance, but had no effect on visually guided saccades (Sawaguchi and Goldman-Rakic 1991, 1994). Infusion of a D2 receptor antagonist had no effect on spatial working memory, although this may have been due to the fact that ceiling effects precluded improvements in performance. The impairment following D1 receptor antagonist infusion was consistent with the subsequent physiological data, showing that iontophoretic application of a high dose of D1 receptor antagonist onto dlPFC Delay neurons markedly reduced neuronal firing (Williams and Goldman-Rakic 1995). Taken together, these data showed that dopamine has an important beneficial influence on dlPFC spatial working memory function through D1 receptor actions.

The Discovery of the D1 Receptor "inverted-U" Dose–Response

Although the research had emphasized the beneficial influences of dopamine, behavioral data provided the first indication that high levels of dopamine release, such as occurs during stress exposure (Deutch and Roth 1990), could be detrimental to dlPFC function through excessive stimulation of D1 receptors (Arnsten and Goldman-Rakic 1990, 1998; Arnsten et al. 1994; Murphy et al. 1996; Arnsten 1998). This was also the first evidence that exposure to uncontrollable stress could impair PFC function (Arnsten and Goldman-Rakic 1990, 1998; Murphy et al. 1996; Arnsten 1998), a finding of immediate relevance to the etiology of mental illness. With the advent of dopamine D1 receptor agonists, the inverted-U D1 receptor dose–response was confirmed (Arnsten et al. 1994; Zahrt et al. 1997). The inverted-U was also seen at the physiological level, where either too little or too much dopamine D1 receptor stimulation reduced neuronal firing (schematically illustrated in Fig. 8B; Williams and Goldman-Rakic 1995; Vijayraghavan et al. 2007). At optimal levels of D1 receptor stimulation, D1 receptors reduce "noise," that is, neuronal firing for the memory of nonpreferred spatial inputs, while low doses of D1 receptor antagonist produce the converse pattern of increased firing for
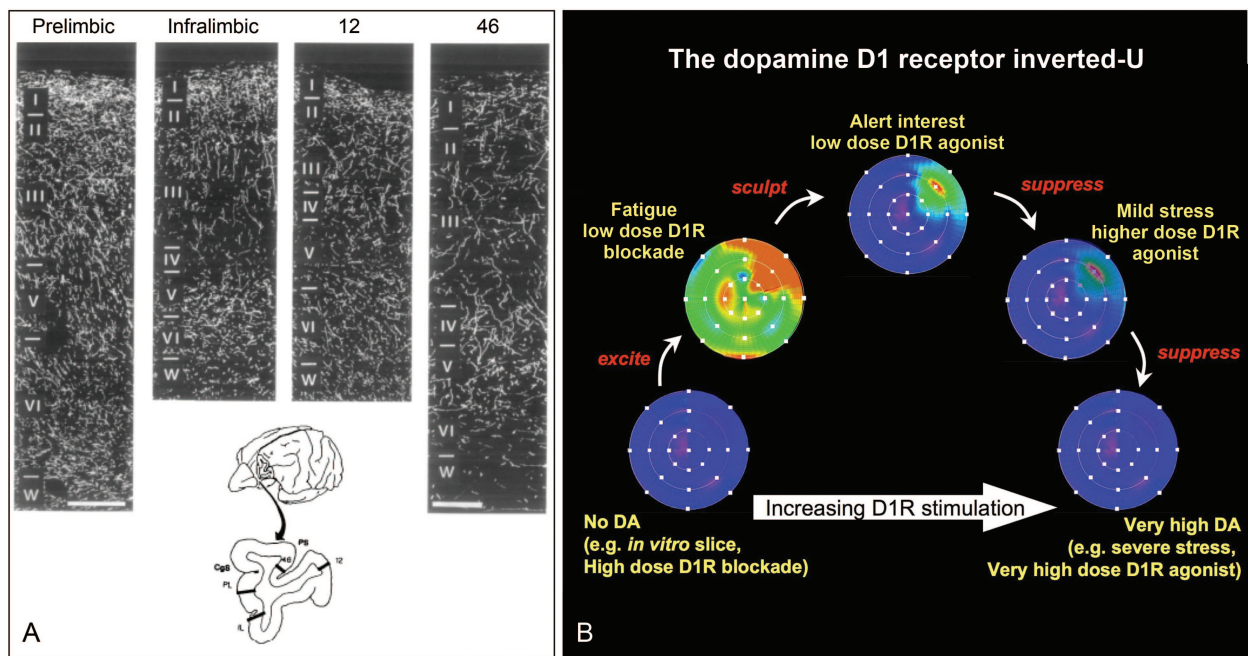
Figure 8. The key role of dopamine in the primate dlPFC. (A) The dopaminergic innervation of the primate PFC, including the dlPFC area 46, as visualized using an antibody directed against dopamine. Note the relatively sparse labeling in the dlPFC, a region that critically depends on dopamine actions. (From Williams and Goldman-Rakic 1993.) (B) A schematic illustration of the dopamine D1 receptor inverted-U influence on the pattern of Delay cell firing in the dlPFC. The memory fields of dlPFC neurons are shown under conditions of increasing levels of D1 receptor stimulation. Either very low or very high levels of D1 receptor stimulation markedly reduce delay-related firing. Low levels of D1 receptor stimulation are associated with noisy neuronal representations of visual space, while optimal levels reduce noise and enhance spatial tuning. The high levels of D1 receptor stimulation during stress exposure would reduce delay-related firing for all directions. Brighter colors indicate higher firing rates during the delay period. This figure is a schematic illustration of the physiological data presented in Williams and Goldman-Rakic (1995); Vijayraghavan et al. (2007); and Arnsten et al. (2009) and is consistent with the behavioral data from Arnsten et al. (1994); Murphy et al. (1996); Zahrt et al. (1997); and Arnsten and Goldman-Rakic (1998).

nonpreferred inputs (Vijayraghavan et al. 2007; Fig. 8*B*). Currently available D1 receptor agonists have high affinity for D1 receptors, and it is likely that compounds that better mimic dopamine's gentler interactions with the D1 receptor will be needed to visualize dopamine's excitatory actions in vivo, as has been documented in vitro where bath application allows more rapid removal of drug (Seamans et al. 2001; Seong and Carter 2012).

In contrast to most biological systems where the inverted-U is seen at the extremes of physiological conditions, the D1 inverted-U occurs within a normal, relatively narrow range of physiological conditions, that is, within the parameters of daily life (e.g. fatigue and mild stress). The D1 inverted-U has translated well to humans, where it has helped to explain cognitive variations in humans based on the COMT genotype (e.g. Egan et al. 2001; Meyer-Lindenberg et al. 2005; Bertolino et al. 2006; Williams-Gray et al. 2007; Papaleo et al. 2008; Jacobs and D'Esposito 2011), and in response to dopamine drugs (e.g. Gibbs and D'Esposito 2006), thus explaining otherwise perplexing findings.

The D2 Receptor Family

The D2 receptor family (D2, D3, and D4) is also of great interest, especially in regard to the etiology and treatment of schizophrenia. Immunoelectron microscopy has revealed D2 receptors concentrated on the dendritic shafts of pyramidal cells but not on spines (Paspalas et al. 2006), while D4 receptors are enriched on GABAergic interneurons (Mrzljak et al. 1996). Just before she died, Goldman-Rakic completed a study with Wang and Vijayraghavan showing that D2 receptor stimulation increases the firing of dlPFC Response cells, with no effect on Delay cell firing (Wang et al. 2004). These data are consistent with the idea that Response cells likely reside in layer V, the site of the greatest D2 receptor mRNA, and the neurons that project most strongly to the caudate nucleus (Yeterian and Pandya 1994). Intriguingly, many of the Response cells influenced by D2 receptor stimulation fired during or after the saccadic response, suggesting that D2 receptor stimulation may be altering corollary discharge (also called "efference copy"), the mental tag that tracks and provides feedback about an internal response. Reduced corollary discharge from the dlPFC has been associated with auditory hallucinations in patients with schizophrenia (Ford et al. 2002), suggesting a potential link between altered Response cell modulation and the positive symptoms of schizophrenia.

The Neurobiological Foundations of Schizophrenia

The cognitive deficits of schizophrenia involve profound dysfunction of the dlPFC, including deficits in working memory (Weinberger et al. 1986; Park and Holzman 1992; Barch et al. 2001; Keefe et al. 2006; Barch and Ceaser 2012). Goldman-Rakic collaborated with Driesen and Krystal to adapt a spatial working memory task to human functional MRI (fMRI) imaging and found that patients with schizophrenia had reduced dlPFC activation during the delay epoch when information was held in mind (Driesen et al. 2008). Importantly, fMRI studies had also shown that working memory deficits and reduced activation of the dlPFC correlate with symptoms of thought disorder in patients with schizophrenia, thus linking cognitive impairment to a classic symptom of the illness (Perlstein et al. 2001).

Goldman-Rakic had predicted this finding in her earlier writings (Goldman-Rakic 1991), saying "a defect in working memory—the ability to guide behavior by representations—may be the fundamental impairment leading to schizophrenic thought disorder" (Goldman-Rakic 1994).

Insults to dlPFC Microcircuitry

Neuropathological studies of the brains of patients with schizophrenia have demonstrated marked atrophy in the dlPFC microcircuits needed for mental representation. Selemon, Rajkowska, and Goldman-Rakic discovered increased neuronal density corresponding to a loss of neuropil in the dlPFC (Fig. 9; Selemon et al. 1995, 1998), and overall smaller PFC gray matter volume (Selemon et al. 2002). Consonant findings were observed by the Lewis lab, which found reduced numbers of dendritic spines specifically in deep layer IIIc of the dlPFC, but not in the primary visual cortex or more superficial layers of the dlPFC (Glantz and Lewis 2000; Glausier and Lewis 2012). Based on what we have learned from Goldman-Rakic's studies in monkeys, loss of spines in layer IIIc pyramidal cell microcircuits should decrease persistent firing and weaken the ability to maintain information "in mind." The Lewis lab has also found that layer III dlPFC microcircuits show signs of weakened GABAergic function (Gonzalez-Burgos et al. 2010), which may be a compensation for a loss of excitatory pyramidal cell drive (Lewis and Gonzalez-Burgos 2006). Much of the field has focused on the consequences of weaker GABA leading to disruptions in network oscillations and cortical timing (Gonzalez-Burgos et al. 2010). However, the Goldman-Rakic data suggest that weaker GABA would also lead to weaker lateral inhibition and, thus, less precise representations of the information held in working memory. Overall, the loss of spines and weaker GABA would lead to poor maintenance of unclear information, eroding the basic building block of mentation. Layer V pyramidal cells in the dlPFC also seem to be affected, having smaller basilar dendrites (Black et al. 2004). We do not know if these are Delay cells (e.g. ramp-up Delay cells that likely inform motor structures of the goal for action) and/or Response cells, but the findings suggest that the output from and/or feedback to the dlPFC is likely impaired as well. Thus, the circuits needed to represent information in memory stores and to provide guidance for actions are especially altered in schizophrenia (Fig. 9). The work of Goldman-Rakic allowed this most complex and devastating of cognitive disorders to begin to be understood at the cellular level.

Interestingly, the loss of spines and dendrites in the dlPFC of patients with schizophrenia is mimicked by amphetamine sensitization in monkeys (Selemon et al. 2007), which also recreates some of the symptoms of schizophrenia (Castner and Goldman-Rakic 1999). Amphetamine increases both norepinephrine and dopamine in the PFC (Berridge et al. 2006; Berridge and Devilbiss 2011), similar to what is seen with stress exposure (Deutch and Roth 1990; Finlay et al. 1995; Miner et al. 2006). As stress can also cause spine loss and dendritic atrophy of PFC neurons (Cook and Wellman 2004; Radley et al. 2006, 2008), it is possible that dysregulation of the catecholamine stress response may contribute to dlPFC atrophy in schizophrenia. In this regard, it is of interest that a D1 antagonist reversed dendritic atrophy caused by amphetamine sensitization (Selemon et al. 2010).
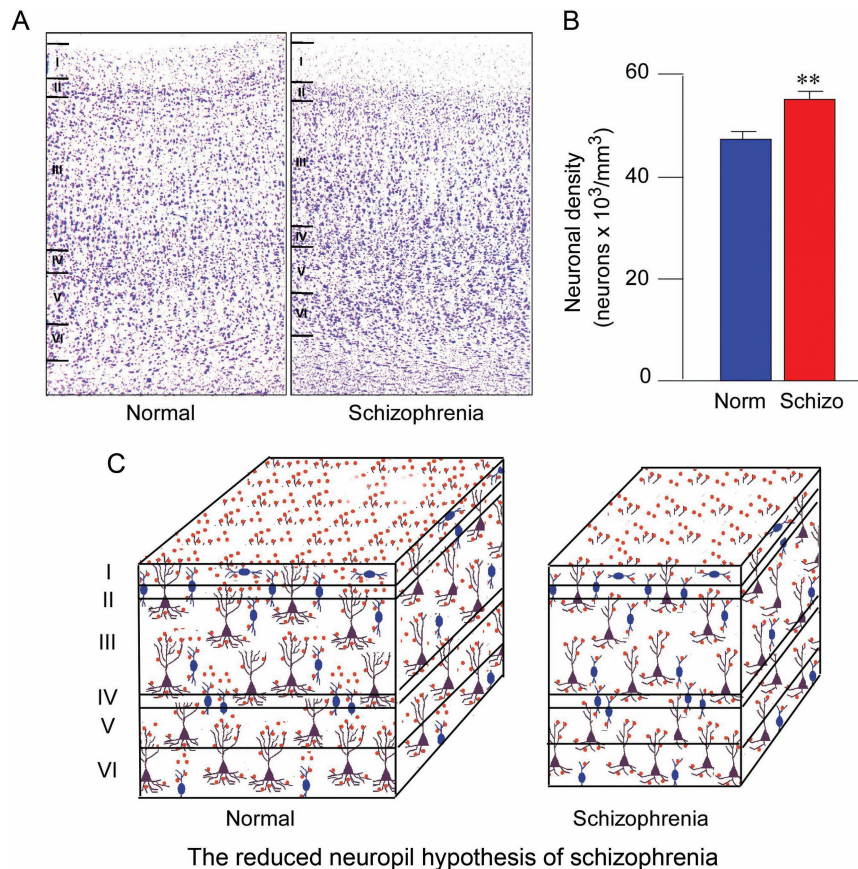
Figure 9. Reduced neuropil in the dlPFC in the brains of patients with schizophrenia. (*A*) Examples of Nissl-stained coronal sections of the dlPFC from a normal control subject and a subject with schizophrenia. (*B*) Neuronal density measured across all cortical layers is greater in the dlPFC in patients with schizophrenia. (*C*) Schematic illustration of greater cell packing in schizophrenia, that is, the same number of neurons is present in a smaller volume, suggesting that the intervening space containing neuropil is diminished. Reduced neuropil in the cortex of patients with schizophrenia suggests that impoverished connectivity of the dlPFC is a neuropathologic correlate of the disease. Figure generously provided by L. Selemon.

Dopamine and Schizophrenia

How is dopamine altered in the dlPFC of patients with schizophrenia? This is a surprisingly difficult question to answer, as the dopamine innervation of PFC is too delicate for reliable imaging in vivo. This contrasts with studies of dopamine in the heavily innervated striatum, where there is strong evidence of increased dopamine release in schizophrenia (Laruelle et al. 1996). Postmortem studies of the dlPFC from patients with schizophrenia show reduced tyrosine hydroxylase staining, which is a likely an indication of reduced dopamine levels (Akil et al. 1999), but could also be a sign of reduced tyrosine hydroxylase expression due to excessive dopamine creating negative feedback on its synthetic enzyme. Data from monkeys show that there is a hyperinnervation by dopamine of layer III in adolescence (Rosenberg and Lewis 1994, 1995), but it is not known if this also occurs in humans. If so, a hyperdopaminergic state in adolescence could promote a psychotic break and loss of spines, which could be followed by a deficit state as the disease progresses. There has been more success with imaging D1 receptors in the dlPFC. These studies show an increase in D1 receptor expression in the dlPFC early in the disease, prior to medication (Abi-Dargham et al. 2002, 2012). This may reflect a needed compensation for reduced dopamine, and/or may magnify the stress response.

Pat's great hope was that D1 agonists would help normalize cognition in patients with schizophrenia. Studies in monkeys encourage this possibility: The cognitive deficits induced by the NMDA antagonist, ketamine, were ameliorated by D1 agonist treatment (Roberts et al. 2010; Nakako et al. 2013). D1 agonists are currently being tested in patients with schizophrenia and those with schizotypal symptoms. Thus, we will soon learn whether this hope will be realized.

The Enduring Influence of Patricia Goldman-Rakic

Goldman-Rakic sparked a revolution in the study and appreciation of the PFC. Prior to her work, there were few studies published on the PFC; now, it has become a major focus on Neuroscience and Neuropsychiatry (Fig. 1). She eloquently explained why prefrontal mental representations were fundamental to cognition, and illuminated the cellular basis for this elemental function, inspiring many others to pursue the next generations of ideas. Goldman-Rakic also inspired a new "top-down" strategy for research in general, where one first asks an important scientific question and then finds multiple, appropriate techniques to try to integrate an answer, rather than finding a question to fit one's established technique. (Clearly, this expert on the PFC had remarkable prefrontal function!) But challenges remain. Goldman-Rakic's discoveries are still not taught in many medical schools, despite their immediate relevance to serious cognitive disorders such as schizophrenia. Thus, many psychiatrists are still unaware of

her work, and the neural basis of the disorders they treat. As time goes by, the ever-expanding accumulation of human imaging studies and molecular studies in mice has also obscured her groundbreaking work in primates, with many still not knowing that key aspects of cortical neural connectivity have already been discovered. Goldman-Rakic showed us that the most perplexing and clinically important questions were open to scientific inquiry, and revealed the roadmap of cognition. "'We're at the edge,' Goldman-Rakic said, 'making discoveries that are of great moment for understanding humans'" (Horgan 1999).

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Notes

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