

Perspective

Resolving the prefrontal mechanisms of adaptive cognitive behaviors: A cross-species perspective

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SUMMARY

The prefrontal cortex (PFC) enables a staggering variety of complex behaviors, such as planning actions, solving problems, and adapting to new situations according to external information and internal states. These higher-order abilities, collectively defined as adaptive cognitive behavior, require cellular ensembles that coordinate the tradeoff between the stability and flexibility of neural representations. While the mechanisms underlying the function of cellular ensembles are still unclear, recent experimental and theoretical studies suggest that temporal coordination dynamically binds prefrontal neurons into functional ensembles. A so far largely separate stream of research has investigated the prefrontal efferent and afferent connectivity. These two research streams have recently converged on the hypothesis that prefrontal connectivity patterns influence ensemble formation and the function of neurons within ensembles. Here, we propose a unitary concept that, leveraging a cross-species definition of prefrontal regions, explains how prefrontal ensembles adaptively regulate and efficiently coordinate multiple processes in distinct cognitive behaviors.

INTRODUCTION

We face diverse problems in our daily lives. To cope with these demands, purposeful behaviors of high complexity emerged during evolution, reaching unprecedented sophistication in mammals, above all in humans. These higher-order cognitive abilities, such as information storage and updating, planning, and making decisions according to past experiences and expectations, are enabled by the activity of billions of neurons. These neurons are distributed throughout the brain, but it is widely accepted that the prefrontal cortex (PFC) functions as a critical hub.¹ In particular, the PFC provides executive “top-down” control when the behavior must be guided by internal states (e.g., hunger, fatigue) or goals. In this context, the PFC is involved in higher-order cognitive abilities, such as attention, salience detection, working memory, strategy shifting, and inhibitory control, all of which enable adapting to varying condi-

tions.^{2,3} These abilities are defined in this study as adaptive cognitive behaviors, the impairment of which is a core symptom of several mental disorders, such as schizophrenia and autism spectrum disorders.⁴ Therefore, the prefrontal region is considered to have fundamental clinical relevance and has been labeled the “psychic” cortex.⁵ However, even after decades of research, how the higher cognitive abilities, which require the organization of information to be continually updated, arise from the activity of prefrontal neurons remains puzzling.

The reasons for this knowledge gap are manifold. The PFC is largest in humans, covering one-third of the entire cortical mantle and containing almost twice as much cortical gray matter as in macaques.⁶ However, it is in humans that our understanding of the organization and operation of the PFC is most incomplete. The neuronal networks of the human brain are not amenable to scientific investigation as they are in animals. Ethical and technical considerations severely limit opportunities to directly



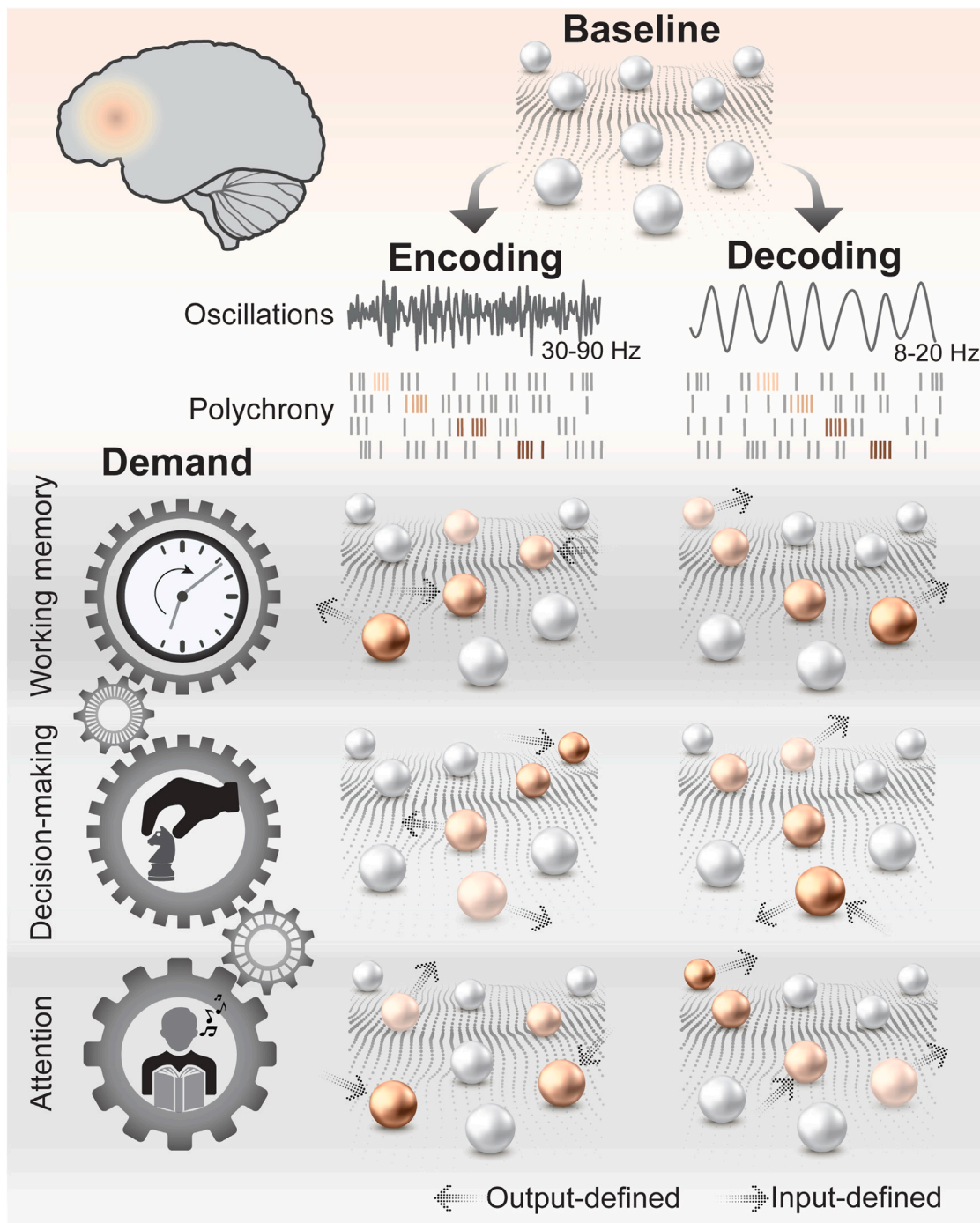


Figure 1. Assembling mechanisms of prefrontal neurons across adaptive cognitive behaviors

The schematic diagram exemplifies the potential mechanisms of prefrontal ensemble formation during three representative aspects of adaptive cognitive behaviors: working memory (top), decision-making (middle), and attention (bottom). During baseline activity (absence of task-related demands), prefrontal neurons lack functional coordination of activity. Upon task-related demands, temporal coordination of activity dynamically binds prefrontal neurons into functional units via oscillations and polychrony. Oscillatory phase locking occurs by predominantly bottom-up-directed gamma band (30–90 Hz), which is controlled by predominantly top-down-directed alpha-beta band (8–20 Hz). Polychrony, observed as sequences of neuronal activity, induces distinct higher-order temporal correlations. Depending on the task-related demand, flexible projection-defined (input/output) ensembles regulate multiple processes across tasks but also within tasks during stimulus encoding (left) and decoding (right). Consequently, prefrontal neurons are tuned to mixtures of multiple task-relevant aspects with a high degree of overlap. Gray and golden balls represent prefrontal neurons at baseline activity and after ensemble formation, respectively. Increasing color intensity indicates the history of the temporal sequence of coordinated activity within the same ensemble.

(legend continued on next page)

access and manipulate single neurons and their circuits in humans,⁷ emphasizing the paramount importance of fundamental research with animal models, including rodents⁸ and non-human primates.⁹ However, integrative research across animal models has been hampered by the lack of consensus on how the PFC and its subregions should be defined across species. The structural and functional similarities of a given region of the brain across mammalian species typically enable knowledge to be applied across the species. Using this approach, the advantages of each species can be leveraged. Examples of such advantages include the accessibility of rodents for genetic interventions, increased cognitive abilities and feasibility for invasive neural recordings among non-human primates, and humans who are less accessible experimentally but cognitively most advanced. This approach is less straightforward with regards to the PFC, since its connectivity patterns, parcellation, and layered structure are different in rodents, and to a lesser extent in non-human primates, than in humans.^{8,10,11} Thus, cross-species comparisons based on the “functional homology” of prefrontal regions with similar functions (although not necessarily evolutionarily homologous), offer a promising research direction.^{12,13} Many of the prefrontal functions that evolved to enable the behavioral complexity and sophistication characteristic of humans also exist in a basic form in rodents, since the ability to adapt and develop flexible strategies is crucial for their evolutionary success. For example, the medial PFC (mPFC) of rats and mice is not anatomically equivalent to the non-human primate or human dorsolateral PFC (dlPFC),^{8,14} yet it mediates similar cognitive functions such as working memory, decision-making, and attention.

Even factoring out the cross-species limitations, explaining how the PFC enables complex cognitive functions is challenging. The PFC is the best example of a brain structure that lacks stereotyped specialization. Prefrontal neuron activity is tuned to mixtures of multiple task-relevant aspects.^{15–17} As a result, the PFC differs from other cortical areas, such as those involved in sensory processing. Prefrontal neurons may be active during multiple tasks; their responses might vary even within individual tasks. On the other hand, commonalities may be apparent when a task is completed by different species.

To cope with the demands of adaptive cognitive behavior, prefrontal neurons form ensembles, traditionally defined as groups of temporally co-active neurons.¹⁸ These ensembles must be able to maintain stability over time but also express a high degree of flexibility, for example, when a behavioral change is required. The activity of prefrontal neurons within ensembles might also change with age in relation to the development of cognitive abilities.¹⁹ Prefrontal neurons respond differently in different contexts, suggesting that they can flexibly switch among different ensembles or assignments within an ensemble depending on the task demands.²⁰ Moreover, in some cases, prefrontal neurons have been reported to provide either unequal or redundant contributions to the overall activity of the ensemble.^{21,22}

Only recently, neurotechnological and neurocomputational developments have enabled the uncovering of distinct mechanisms underlying the formation of prefrontal ensembles in complex cognitive tasks. These experimental findings and theoretical models have delivered the first insights into the function of the PFC and offer a promising basis for future research and generally testable hypotheses. In this perspective, we make an initial attempt in this direction, capitalizing on data from mice, rats, non-human primates, and humans. First, we briefly review the cross-species structural and functional characteristics of the PFC and how such characteristics might relate to the construction of dynamic task-relevant ensembles. Second, we introduce strategies of temporal coordination that enable ensemble formation in diverse cognitive tasks. Third, we propose that prefrontal connectivity (i.e., outputs = efferents, inputs = afferents) might define these ensembles and review the recent experimental evidence that neurons projecting to the same region or receiving inputs from the same region build functional ensembles (Figure 1). Fourth, we elaborate on the relevance of data from studies of rodents and non-human primates for human cognitive processing. Finally, we provide a modeling-based theoretical framework of prefrontal function in complex cognitive tasks.

BASIC PFC ANATOMY, FUNCTIONALITY, CONNECTIVITY, AND PUTATIVE EVOLUTION

The term PFC refers to a range of brain regions in the frontal part of the mammalian cerebral cortex. Because distinct regions of the PFC evolved and specialized at different times in evolutionary history, and to some degree independently in different mammalian lineages,²³ there is a lack of consensus regarding what comprises the PFC in different mammalian orders.²⁴ Since rodents (mice and rats) and primates (humans and non-human primates, especially simian monkeys) currently provide the dominant model systems in neuroscience, we first sketch the organization and evolution of the frontal cerebral cortex in a comparative approach.

In primates (referring to non-human primates and humans), the dorsolateral anterior pole of the frontal lobe, where the neocortical layers include a compact inner granular layer 4 (which is missing for the rest of the frontal lobe), has become known as “the PFC,” “the granular frontal cortex,” “the frontal association cortex,” “the granular PFC,” or “the dorsolateral PFC.”^{25,26} Since this granular PFC is absent in rodents,^{25,26} researchers searched for other potentially defining features of the mammalian PFC. All of the features they considered, such as input from the thalamic mediodorsal nucleus (MD),^{27,28} dopamine input projections,^{29,30} or involvement in spatial-delay tasks, were found to be only approximations and ultimately proved untenable as strict defining features of the PFC.

Currently, it is generally accepted that there are three major regions of the anterior frontal lobe, which show different relationships in rodents and primates.²³ First, rodents possess a putative

Maximum color intensity represents the time point of observation. Depending on their orientation, dotted arrows exemplify distinct afferent and efferent projections that contribute to ensemble formation. The different angles of the arrows illustrate the diversity of inputs and outputs and their varying relationship to the encoding and decoding of information. Note that different, but also the same, neurons could be involved in stimulus encoding and decoding.

homolog of the agranular medial frontal cortex of primates; the anterior cingulate cortex (ACC) in primates is typically called the mPFC in rodents.²³ Second, rodents possess a putative homolog of the agranular orbitofrontal cortex (OFC) of primates, but the anterior, granular subdivisions of the primate OFC appear to be new additions.^{31,32} Third, rodents lack anatomical homologs of the granular frontal cortex (dlPFC) that constitutes the largest part of PFC in most primate species. Within the order of “primates,” an evolutionary trajectory is seen, with a small granular PFC in basal primates and an increasingly larger granular PFC in more advanced simian primates, particularly in humans. With the rise of simian primates (old-world and new-world monkeys), additional granular PFC regions emerged.³³ The number of cell-cell connections dramatically increased for prefrontal neurons, rendering human prefrontal circuits cognitively more sophisticated.³⁴

Functionally, the regions of the PFC that share a longer phylogenetic history, namely the ACC/mPFC and the OFC, are considered parts of the limbic system in humans.^{35,36} The human OFC network is generally associated with the integration of affective information with cognition.^{35,36} One essential role of the OFC is guiding value-based decision-making.³⁷ Rhesus monkeys and rats with OFC lesions show impairments in updating the value of a stimulus,^{38,39} and OFC neurons in behaving macaques and rodents signal reward/value and are involved in choice selection.^{40–43} However, the OFC may have a much broader role in cognition by representing behavior-guiding cognitive maps.^{37,44} Notably, in humans, the OFC has a role in shaping personality and psychosocial behavior.¹⁰

ACC/mPFC activity, similarly to that of OFC, reflects choice value.^{45,46} In both macaques and rats, ACC/mPFC reflects outcomes of decisions—both successes and errors—and whether such feedback indicates a need for behavioral change.^{47,48} Beyond decision-making, the ACC has also been found to be related to affective vocal communication in old- and new-world monkeys^{49,50} and prosocial behavior in mice, monkeys, and humans.^{51–53} In humans, the ACC is additionally associated with empathy-related behaviors^{54,55} and the inference of others’ mental states.^{36,56}

The dlPFC in macaques has long been implicated in cognitive control and executive functions, such as encoding and memorizing of abstract categories,^{57,58} endogenous attention,⁵⁹ spatial and object-related working memory,^{15,60} semantic associations,⁶¹ following abstract rules,⁶² planning ahead,⁶³ response selection,⁶⁴ and inhibiting inappropriate responses.⁶⁵ In rodents (mice and rats), the mPFC also accounts for executive functions, such as spatial working memory, action inhibition, and decision-making.^{66–69}

As the seat of the central executive function of the mammalian brain, the PFC requires information from the external and internal world and access to motor output. One defining feature of the primate granular PFC is that it is directly connected with secondary sensory input and premotor output structures but not with primary sensory or motor cortices (note that this holds not for agranular PFC territories and thus not for the PFC of rodents such as Sprague Dawley rats⁷⁰). We propose that within the PFC, the distinct inputs and outputs that define the PFC could give rise to anatomically mixed and dynamic neuronal ensem-

bles. As a high-level executive area operating at the apex of the cortical hierarchy, the PFC is reciprocally connected with other associative cortical regions that are themselves sites of multimodal convergence, such as the primate posterior parietal and superior temporal cortices.⁷¹ The PFC therefore receives and merges processed visual, somatosensory, and auditory information in addition to multimodal sensory information. To enable the PFC to control behavior, rich connections exist to various motor-related regions located on the lateral surface of the primate frontal lobe (such as the premotor cortex, BA 6) and in the medial wall of the frontal lobe (such as the supplementary motor area and several cingulate motor regions).⁷² These regions, in turn, send projections to the primary motor cortex and the spinal cord. In addition, the PFC sends efferent connections to the cerebellum and midbrain.⁷³ Dense connections also exist between the PFC and the basal ganglia, which projects back to the frontal lobe via the thalamus.⁷⁴ Specifically, via the orbital and medial PFC, structures related to long-term memory, but also limbic regions associated with internal (affective and motivational) states, are accessed. Among these are direct and indirect (via the mediodorsal nucleus of the thalamus) connections with the hippocampus, the amygdala, and the hypothalamus.⁷⁵

Structural and physiological input from distinct brain regions may target separate efferent projection networks that enhance or inhibit contrasting behaviors either by synapsing directly onto distinct output ensembles or by synapsing onto local excitatory or inhibitory neurons first. This suggests that different neuronal ensembles within PFC may activate a given efferent output while inhibiting the opposing efferent output.⁷⁶ We hypothesize that the modulation of distinct ensembles providing output from the PFC happens both via direct projections onto individual output ensembles and projections to the local microcircuitry within PFC. Synchronization of prefrontal firing may additionally shape task-relevant neural ensembles out of larger, overlapping circuits.⁷⁷ To decipher such heterogeneous neuronal PFC ensembles, temporally precise perturbation of individual populations of PFC neurons in combination with activity-dependent labeling or projection-specific targeting of PFC inputs and outputs is necessary. This may be difficult to achieve in primates but is promising in rodents.

TEMPORAL COORDINATION DEFINES DYNAMIC PREFRONTAL ENSEMBLES

Given the variety and complexity of PFC-dependent higher-order cognitive functions, there is a strong need to identify common mechanisms underlying ensemble construction across species. It is reasonable to assume that prefrontal ensembles dynamically evolve^{78,79} to fulfill behavioral demands. To form and maintain these ensembles while retaining the ability to constantly update them, it has been suggested that the online formation of ensembles of prefrontal neurons with highly diverse anatomical and neurochemical identities arises from synchronous firing.⁸⁰ The synchronous depolarization of a subset of neurons acts as a gain pattern facilitating ensemble-specific excitation along anatomical local or long-range connectivity. Here, we propose two concepts relevant to the temporal formation of prefrontal ensembles: oscillations (as macroscopic effect

of periodically occurring time windows for preferred firing) and synchrony/polychrony (as microscopic organization of spike time correlations; see Figure 1).

Coordination between spatially distinct brain oscillations is generally thought to facilitate uni- or bidirectional exchange of information, both within the same frequency band and across frequency bands via phase coherence (i.e., a consistent phase relation between oscillators).^{81,82} In line with theories of communication between brain regions, the microscopic picture underlying such coherence or synchrony gating presumes activation of target regions to be facilitated by the coincident arrival of many synaptic inputs from a source area at a specific “phase” of high excitability. It has been suggested that such interactions support cognitive functions, often depending on the precise oscillatory frequency. The predominantly bottom-up-directed gamma band (30–90 Hz) impact is controlled by the predominantly top-down-directed alpha-beta band (8–20 Hz).⁸³ Putative attentional top-down processing enables stimuli to be sampled at a 7–8 Hz theta rhythm.⁸³ It has been reported that the gamma band activity serves as a multiplicative gain of the input, and its functional relevance has been evidenced by behavioral correlates and optogenetic stimulation effects.^{84,85}

As an example, PFC-dependent working memory has been characterized as involving complex dynamics with discrete oscillatory bursts.⁸⁶ Brief bursts of gamma oscillations were found to be closely linked to informative spiking, representing the coordinated activation of an ensemble encoding a specific memory item. Beta oscillations were also found to occur in brief bursts, but this reflected a default state interrupted by processes of encoding and decoding, similar to what has been described for sensory cortices.⁸⁷ Based on their relationship to oscillatory dynamics during working memory, two principal neuronal populations can be defined.⁸⁶ One population is mainly active in stimulus encoding and decoding. Its spiking activity closely follows the gamma burst rate. A second population is active mainly during memory delays when, instead, the average beta burst rate is higher. Thus, a shift in the balance of beta and gamma burst rates could reflect different phases during working memory (WM) tasks. Gamma bursting could modulate the spiking of encoding/decoding neurons, thus allowing access to WM. Alternatively, in the absence of bursting, WM would be protected from interference from new sensory inputs.

In addition to exerting a strong drive on a postsynaptic neuron, the coincident arrival of many spikes is also understood to facilitate learning and neural plasticity.⁸⁸ This occurs both on the synaptic level via Hebbian principles⁸⁹ and on the cellular level via the homeostatic regulation of excitability.^{90,91} Synchrony-based communication typically takes the form of coincidentally arriving inputs. However, the individual presynaptic neurons, which give rise to this barrage of excitation, may connect to the postsynaptic neuron with different delays or evoke responses of different kinetics owing to variability in synaptic location or postsynaptic channel composition. Thus, coincidence detection at the location of spike generation, typically the initial axon segment, may require the temporal integration of polychronous presynaptic spike patterns⁹² in which presynaptic neurons fire at distinct relative latencies and thereby induce distinct higher-order temporal correlations.^{93,94}

Polychrony has been ubiquitously identified in cortical regions, most prominently in the hippocampus, and can often be observed as sequences of activity. Both during theta oscillations^{95–98} and sharp-waves,^{99–101} hippocampal neurons are repeatedly activated in a consistent order within a defined time window. Hippocampal sequence motifs are thereby thought to be flexibly combined^{102–104} to match task requirements. Similarly, in the PFC, fast temporal coordination of neuronal spiking has been described in the context of inter-area coordination with hippocampal rhythms, both theta^{105–108} and sharp-waves.^{109–112} More recently, similar interactions have been reported for the communication between the PFC and the striatum, with spike synchrony being modulated, according to the task, in prefrontal-striatal neuron pairs.^{113,114}

Despite the overwhelming evidence of fast cortical sequence activity and its relation to distinct behavioral features, its computational role is still unclear. On the one hand, a postsynaptic readout station might detect the specific temporal order, as suggested by the two theories of polychrony⁹² and the tempotron^{115,116} that propose a synaptic learning rule, which enables single neurons to categorize random spatiotemporal patterns. On the other hand, according to the synapse theory,¹¹⁷ defined presynaptic activity patterns occurring within a defined time window may be sufficient to drive a readout neuron independent of individual neurons’ specific temporal activation sequence. In such a scenario, temporal spike patterns could still be organized as recurring sequences, yet they would be epiphenomenal because the biophysical properties of the underlying neural networks would bias the order of activation within a presynaptic ensemble.¹¹⁸ For example, more excitable neurons tend to fire earlier than less excitable ones on simultaneous stimulation and would therefore generally be found to lead activity sequences (Figure 1).

To disentangle the roles of oscillations and synchrony/polychrony in the PFC for encoding, interareal communication, and memory maintenance,¹¹⁹ continuously improving optogenetic labeling and phototagging¹²⁰ and novel data analysis techniques offer promising avenues to investigate both output- (defined by common targets) and input- (defined by their common, potentially coherent input) specific neuronal ensembles. Combined with population analysis techniques for detecting ensembles as recurring sequences inspired by machine learning and real-time feedback methods that allow online interference and, hence, behavioral manipulations, this approach will allow a detailed dissection of the role of temporal synchronization within prefrontal ensembles for cognitive performance. Moreover, recent data have provided initial insights into the dynamic structure of prefrontal ensembles, identifying a shift from the contribution of fewer neurons with high impact on the ensemble activity to that of larger populations with proportionally smaller contributions when the behavior changes from flexibility to routine.¹²¹

OUTPUT-DEFINED PREFRONTAL ENSEMBLES

The PFC projects to a large number of cortical and subcortical regions with strikingly diverse functions.^{10,122–126} These include regions involved in sensory processing (auditory and visual cortex), declarative memory and spatial processing (hippocampus,

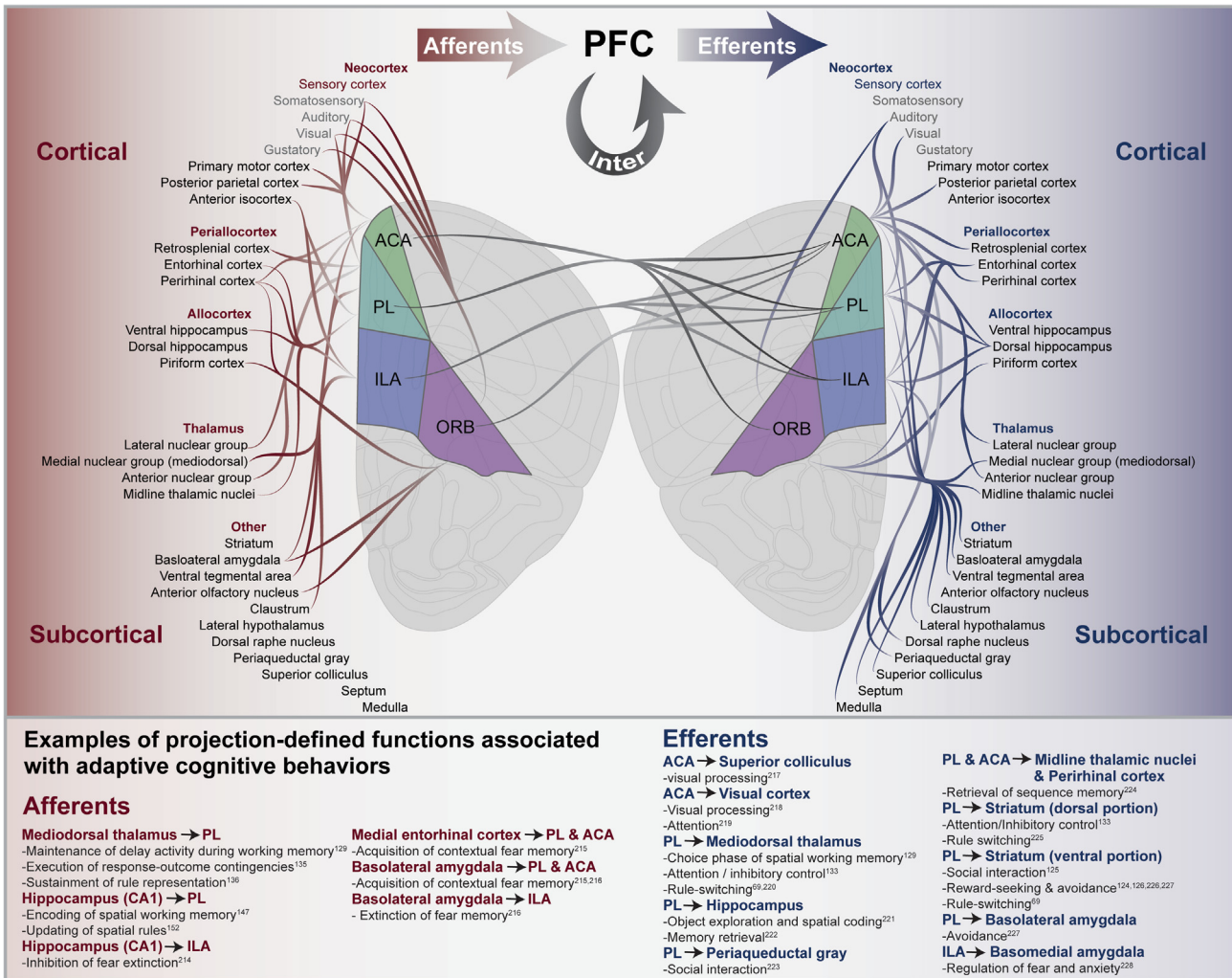


Figure 2. Overview of afferents (red) and efferents (blue) of rodent PFC in relation to behavioral relevance

The PFC is connected with cortical and subcortical structures. Often the very same PFC cell projects to, or receives inputs from, more than one brain area, thus requiring the dynamical formation of functional neuronal ensembles based on inputs and outputs. ACA, anterior cingulate cortex; PL, prelimbic cortex; ILA, infralimbic cortex; ORB, orbitofrontal cortex. The diagram summarizes the knowledge about the rat/mouse connectivity. For reference, see Spellman et al.⁶⁹ and refs.^{127–150}.

entorhinal cortex, retrosplenial cortex), goal-directed behavior (dorsomedial striatum), reward learning (nucleus accumbens [NAc], ventral tegmental area), emotional processing (amygdala, periaqueductal gray), motor planning (premotor cortex), and regions involved in instinctive behaviors and homeostatic regulation (hypothalamus, medulla; Figure 2). Through these diverse projections, the PFC is ideally positioned to adaptively regulate and coordinate multiple neuronal processes in distinct cognitive tasks. Understanding the relationship between task-dependent dynamic ensembles and prefrontal projection targets is, therefore, an important step toward elucidating the role of PFC in higher-order cognitive processing. This will require understanding what information is relayed by individual prefrontal projections to their downstream targets, how these projections influence activity in their target regions, and, ultimately, how they control behavioral output. Within the PFC, these functions

could be mediated by “output-defined” ensembles: groups of PFC neurons sharing common projection targets that temporally coordinate their activity. Below we discuss how thinking in terms of such output-defined ensembles can aid in our understanding of the PFC.

Given that the PFC projects to multiple brain regions, a fundamental question is how these projections arise at the level of individual PFC neurons. Specifically, does each prefrontal neuron project to one brain area (“one-to-one” connectivity) or multiple regions (“one-to-many” connectivity)? To address this question, injections of retrograde tracers into two projection targets of the PFC in the same animal, followed by quantification of the number of prefrontal neurons labeled by both tracers (and thus projecting to both regions) proved instrumental. Studies using this approach in rats and mice have consistently reported low numbers of single PFC neurons projecting to two brain

regions.^{69,123,127–129,151} Although these results seem to provide strong evidence for dominant one-to-one projections between PFC neurons and their target regions, they should be interpreted with caution. Because retrograde labeling studies typically label neurons from only two target regions, they likely underestimate the extent of one-to-many projections. Indeed, analysis of the bulk axonal projections of retrogradely labeled neurons strongly suggests that they also project to regions other than those in which the tracer is injected.⁶⁹ Estimating the full extent of such divergent projections at the single-cell level, however, requires tracing the axons and axon collaterals of individual PFC neurons. Although this has traditionally been a labor-intensive task, advances in imaging and computational methods have now made this feasible at a large scale. In a recent study,¹²⁹ the axons of more than 6,000 mouse PFC neurons were reconstructed. Based on their pattern of axonal arborization, 64 subtypes of projection neurons were identified, the majority of which projected to multiple cortical and subcortical brain regions. Furthermore, one-to-many projections of individual PFC neurons often preferentially targeted specific groups of functionally related brain regions.¹⁵² Although the functional role of such one-to-many projections is unclear, they theoretically enable PFC neurons to build ensembles that influence multiple brain regions in a coordinated fashion, which is likely critical for adaptive behavior. Furthermore, the results of Gao et al.¹²⁵ suggest that projection-defined prefrontal ensembles are better characterized by their pattern of projections to multiple regions rather than their projection to any single brain region. Finally, whether neurons belonging to a projection-defined ensemble are also preferentially connected with each other, which could boost their temporal coordination, remains an open question.

If PFC neurons are organized into projection-defined ensembles, might such ensembles also have different functional roles? It is well established from studies in rodents and primates that the PFC interacts with its projection targets through synchronous neuronal oscillations, which are flexibly modulated depending on task demands.^{119,130,153–155} Furthermore, optogenetic manipulations have demonstrated that different projections of prefrontal neurons make distinct causal contributions to behavior.^{129–131} (see also Figure 2). Recently, studies in mice have also begun to compare the activity patterns of different projection-defined prefrontal ensembles during behavioral tasks. For example, recordings from prefrontal neurons projecting to the NAc and the paraventricular thalamus (PVT) during an auditory go/no-go task¹²⁹ showed that NAc-projecting neurons were predominantly excited by the cue predicting reward, whereas the same cue primarily caused inhibition in PVT-projecting neurons. Other studies have revealed how the activation of prefrontal neurons by behavioral choices and reward context,¹⁵⁶ inhibitory control,¹³¹ or reward-seeking during risk¹²⁷ partially depends on their projection target. It is important to emphasize, however, that these studies also revealed considerable overlap in the activity of different projection-defined ensembles and sometimes even no differences between these ensembles.⁶⁹ Likewise, considerable heterogeneity in responses can be observed among prefrontal neurons projecting to the same brain region. However, as noted above, because each PFC neuron may project to multiple brain regions, it is likely that ensembles

defined based on their projection to a single area (e.g. “NAc-projecting”), as was done in the studies mentioned above, may in fact contain multiple subpopulations displaying different projection patterns and functional properties. It should also be emphasized that relatively few studies have examined the activity of projection-defined PFC ensembles, and the activity patterns of many prefrontal projections are yet to be determined. Nonetheless, the studies performed to date collectively support the view that projection-defined prefrontal ensembles are functionally specialized to relay different as well as shared task-related signals to their downstream projection targets.

INPUT-DEFINED PREFRONTAL ENSEMBLES

Besides projecting to a variety of brain regions, the PFC has been shown to be the target of numerous axonal projections (Figure 2). These long-range excitatory inputs influence the activity of the PFC during diverse tasks and, therefore, most likely decisively contribute to the emergence of coordinated prefrontal activity in dynamic task-related ensembles. In particular, projections from two brain regions, the MD and the hippocampus, have been identified as providing instructive signals coordinating prefrontal ensembles during different aspects of adaptive cognitive behavior.

Using chemogenetic silencing of MD cells and optogenetic inhibition of MD terminals in the mouse mPFC, it has been shown that MD-to-PFC projections support a variety of behaviors. For example, MD afferents are important for the maintenance phase in a delayed-non-match-to-place (DNMTP) working memory task (i.e., for retaining information about the current goal arm for subsequent choice), but not for the encoding or choice phase of the task.¹³⁰ Prefrontal activity during the delay phase is diminished when input from the MD is silenced. In contrast, blocking hippocampal inputs does not impair delay activity,¹³⁰ suggesting that MD afferents are particularly relevant for maintaining the activity of prefrontal ensembles. Similarly, silencing MD neurons projecting to the prelimbic cortex impaired the ability of rats to execute previously learned response-outcome contingencies, further underscoring the critical role of MD inputs to guide behavioral choice in the absence of external cues.¹³² Mechanistic insight into how MD might shape ensemble activity in PFC during decision-making has been obtained from simultaneous recordings from both structures during a two-alternative forced choice task.¹³³ Following an instructive rule signal, mice had to attend to visual or auditory cues to obtain a reward. While MD neurons increased their activity during task engagement, as did fast-spiking interneurons, similar results were not found for pyramidal cells in the prelimbic cortex.¹³³ These data are consistent with the hypothesis that MD afferents predominantly innervate prefrontal inhibitory interneurons.^{157,158} Constant spike rates of pyramidal neurons in the face of enhanced MD-driven inhibition can be explained by increased functional connectivity among prefrontal pyramidal neurons, in particular during the delay period between the rule and the cue signal.¹³³ A boost in functional connectivity among pyramidal cells requires MD-mediated recruitment of vasoactive intestinal polypeptide (VIP)-expressing interneurons, suggesting that input amplification among

prefrontal pyramidal cells is caused through VIP interneuron-driven disinhibition.¹⁵⁹ Indeed, suppression of VIP interneurons eliminates this MD effect.¹⁵⁹ Thus, MD inputs represent a crucial afferent system controlling the activity of prefrontal ensembles involved in maintaining relevant information about external variables that guide decision-making.

In addition to afferents from MD, projections of ventral hippocampal CA1 (vCA1) neurons have been shown to control the emergence of behaviorally relevant prefrontal ensembles during adaptive behavior.^{160–166} Optogenetic silencing of vCA1 terminals in the mouse mPFC revealed that monosynaptic projections from the hippocampus are required for the encoding phase of spatial working memory.¹³⁴ Prefrontal neurons fire phase-locked to hippocampal theta oscillations,^{108,167} thereby forming oscillation-entrained ensembles. Both theta coherence between PFC and CA1 and phase-locking of prefrontal spikes to theta are maximal when rats or mice are required to maintain information about past and current spatial position to guide their behavior.^{106,108,168–170} Hippocampal afferents thus comprise a crucial input signal organizing prefrontal activity into neuronal ensembles while encoding and maintaining spatial information. A recent study, moreover, identified a crucial role of hippocampal afferents to the PFC in controlling the updating of rules. When mice had to switch from a free arm choice to a DNMT protocol in a T-maze, brief exposure to a novel arena between the sessions facilitated learning of the new rule. Intriguingly, novelty decreased communication between vCA1 and PFC, which was followed by increased hippocampal-PFC coupling upon learning. These results suggest a model where hippocampal afferents provide spatial rule information to the PFC, which enables optimal flexibility when existing CA1-PFC connections carrying “old rule” information are weakened.¹³⁵ Further evidence for the role of vCA1 afferents in rule updating comes from the analysis of prefrontal “replay.” Studies conducted in rats and mice suggest that neurons across prefrontal regions display spatially tuned firing responses.^{171–176} Spatial trajectories are replayed by prefrontal neurons of an ensemble during sleep and immobile periods in spatial memory and rule-switching tasks.^{107,111,175} During rule switching, such replay events represent generalized trajectories to target locations, and the frequency at which replay events occur correlates with the animals’ performance in an upcoming rule switch. It was thus hypothesized that awake prefrontal replay might recapitulate the general task structure in neuronal ensembles, a process that might support the flexible updating of the currently relevant rule.¹⁷⁵ The replay coincides with hippocampal sharp-wave-ripple events, suggesting an instructive role of hippocampal inputs for the temporal coordination of prefrontal replay.

Projections from the MD and CA1 to the PFC thus support the emergence of local neuronal ensembles in a behavior-dependent manner. MD inputs seem to provide an excitatory drive that is crucial for ensembles carrying relevant information concerning the currently valid rule. Hippocampal afferents bring contextual information that appears to modulate the updating of (spatial) rules upon learning and support the emergence of neuronal ensembles that express paths to goal locations. However, it is still unclear how the temporal and spatial organization

of distinct inputs, including those from upstream regions other than the MD and the hippocampus (Figure 2), contribute to the selection of active prefrontal ensembles during different aspects of adaptive cognitive behaviors.

TOWARDS NEURONAL ENSEMBLES IN HUMAN (PRE) FRONTAL CORTEX

The knowledge gained from animal studies and theoretical approaches is crucial for a better understanding of the functions and dysfunctions of prefrontal ensembles in humans. In addition, interdisciplinary collaborations between clinicians (neurologists and neurosurgeons) and neuroscientists (neurophysiologists) can open up unique direct windows into the human mind through invasive intracranial measurements of the extracellular activity of populations of individual neurons. Such studies are most frequently performed in patients with medically intractable epilepsy that are semi-chronically implanted with depth electrodes for diagnostic purposes. Because epilepsy dictates the site of electrode implantation, most unit recordings in epilepsy patients have been obtained in the medial temporal lobe (MTL)^{177–179} and, therefore, mainly address the neuronal correlates of human (long-term) memory and spatial cognition. Very little is known, in comparison, about the cellular and microcircuit basis of cognitive functions that are supported by other brain regions. In recent years, however, reports of intracranial unit recordings outside of the MTL have emerged. In some epilepsy patients, electrodes are placed in the frontal lobe and target the medial wall of the frontal cortex (MFC).^{180–182} In patients undergoing deep brain stimulation (DBS), electrodes are passed through the dorsal PFC to reach subcortical structures.^{183,184} Both settings have produced novel insights into the neuronal mechanisms governing crucial constituent prefrontal functions.

The devices currently available for human intracranial recordings do not allow for simultaneous measurements of large ensembles of neurons, meaning that most studies have traditionally emphasized exploring the firing patterns of individual units. The introduction of devices for large-scale single-unit recordings, such as microelectrode arrays or Neuropixels probes, which have already shown great potential in animal models,¹⁸⁵ into the neurosurgical operating theater promises to significantly improve our ability to monitor human brain functions at the cellular level.^{186,187} Many technical challenges remain, but cross-species comparisons performed with data recorded from the same brain region and with the same spatial resolution^{188,189} are within reach. Genuine translation will be achieved when a mechanistic understanding of the neuronal underpinnings of human prefrontal cognition results in improvements in diagnostic and therapeutic tools for a wide range of neurological and psychiatric diseases.¹⁹⁰

To gain insights into the mechanisms of ensemble formation, a large number of studies have explored the role of rhythmic neuronal activity in human higher cognition, in particular, working memory. Working memory lends itself well to studying oscillatory neuronal dynamics because its distributed nature requires precise long-range coordination of multiple regions in the fronto-temporo-parietal association cortex.^{119,191,192} Reminiscent of the findings in animal studies, where phase-locking of single-unit

spiking activity to specific frequencies of local field potential oscillations (LFPs) is observed (see above), task-correlated electroencephalogram (EEG) activity in different frequency bands is characteristic of human working memory maintenance. Theta frequencies have been strongly associated with top-down frontoparietal and frontotemporal communication in the working memory network.^{191,193} Recent studies have therefore probed the causality of this association by providing phase-synchronized transcranial electrical or magnetic stimulation in the theta frequency range (5–6 Hz) to the PFC. Supporting the hypothesis that rhythmic synchrony in human association cortical circuits is essential for working memory, these experiments demonstrated increased visual working memory capacity and enhanced holistic working memory performance in both young^{194,195} and older adults.¹⁹⁶

LINKING THEORIES OF ADAPTIVE MECHANISMS IN THE PREFRONTAL CORTEX WITH NEURONAL ENSEMBLES AND PROJECTIONS

Historically, most early models of prefrontal function were developed to better understand working memory and decision-making. Using single-cell recordings of decision-making in sensory regions,¹⁹⁷ working memory in the PFC was modeled in small neuronal networks in which the dynamics were largely explained by the neuronal firing rates.^{198–201} These network models were mostly used in a non-oscillatory regime and thereby inherently assume that task parameters (e.g., time in delay period or the decision) are mapped to continuous neuronal activity, which does not intuitively give rise to the notion of ensembles and synchrony. Nevertheless, this rate-based framework has successfully yielded mechanistic hypotheses. For example, it was suggested that working memory and decision-making result from the dynamical reconfiguration of point attractor states in a simple competition network.^{202,203} Similar successes were achieved for event timing and temporal predictions^{204,205} and rule learning.²⁰⁶

With the recent development of high-density electrode recordings and calcium imaging, these rate-based theories now face critical tests. Dynamical patterns can be assessed at scale. For the reconstruction of nonlinear dynamical systems from time series data, machine learning techniques, such as recurrent neural networks (RNNs) need to be employed.^{207–212} RNNs are dynamically universal, i.e., they can implement any other dynamical system^{213,214} and can be trained on physiological recordings to provide a data-based model of the system dynamics underlying experimental observations.^{207,209–211,215} In other words, unlike other methodological tools used previously to assess dynamics in neuroscience (e.g., state space models or Gaussian process factor analysis),^{216,217} RNNs trained on physiological data provide generative models that behave dynamically identically to the physiological substrate they are trained on. These powerful new methods make it possible to unravel the specific dynamical mechanisms at work in a given cognitive task.^{210,218,219} However, RNN-based models—as mostly used up to now—still often refer to firing rates and in this form provide no straightforward solution to the identification of ensembles. Straightforward for ensemble detection are spike pattern detec-

tion methods, which either take into account temporal correlations,^{220,221} sequence ordering,^{101,222} or both.²²³ While these methods were not necessarily developed in the context of PFC recordings, they have yielded appropriate results on PFC data.^{224,225}

Quantitative methods for exploring population activity—be they rate-based or spike-based—will not only allow us to understand PFC activity in terms of information processing and as a dynamical system but are also indispensable for relating the PFC code to input and output regions. Only if ensembles—or in the language of dynamical systems, the informative regions in the phase plane²²⁶—are identified will temporal and causal correlations to other brain regions be possible beyond the single-cell level.¹⁰⁹

OPEN QUESTIONS AND FUTURE RESEARCH DIRECTIONS

While the methodological, experimental, and analytical progress of recent years has provided important knowledge regarding the prefrontal function for cognitive processing, major questions remain.

1. How do prefrontal ensembles emerge, and how are they refined over the lifespan to ensure the development of cognitive strategies? Almost all adaptive cognitive abilities emerge during late childhood and peak in adulthood. It has been shown that, long before the emergence of these abilities, coordinated activity patterns are present in the PFC of rodents and humans^{227,228} and are critical for cognitive performance later in life.¹⁹ However, the mechanisms by which the prefrontal units of coordinated activity are transformed into task-related functional ensembles are still largely unknown.
2. How do we dissect spatially intermingled neurons with different functional roles within projection-defined ensembles? Ensembles can be defined either by temporal coordination or based on their projection to a single area (e.g., NAc-projecting). New computational tools allow predictions regarding functionally defined subpopulations within projection- or temporally defined ensembles,²²⁹ while optogenetic 2-photon holography is perfectly suited to validate these predictions.²³⁰ The combination of these two techniques has the potential to advance our understanding of the link between prefrontal inputs and outputs and dynamic ensemble formation.
3. How do neuronal ensembles change across contexts? To address this question, researchers have started to train individual subjects in several behavioral tasks.¹⁰³ Here, the language abilities of humans and their cognitive flexibility combined with the introduction of devices for large-scale single-unit recordings, such as microelectrode arrays or Neuropixels probes, in humans offer a promising pathway to fully exploring this question. Training animals (mainly rodents) in multiple, less complex tasks in combination with state-of-the-art techniques to monitor and manipulate neuronal activity will complement this research.

- How are decisions and abrupt switches of strategy manifest in prefrontal activity? Here, neurocomputational approaches applied to simultaneous recordings of the activity of multiple neurons led to an unprecedented advance.²¹⁸ However, the link between the theoretical concepts and the enormous multitude of neurons, the interplay of distinct neuronal cell types, and the specific synaptic input and output connections remain significant challenges.
- How are abrupt switches of strategy communicated to the output regions of the PFC? In particular, it remains unclear how the necessary response and instructions are communicated, timed, and precisely orchestrated across multiple output regions receiving information from the prefrontal networks during tasks with changing cognitive demands. Studies combining optogenetic identification of long-range synaptic connectivity with neuronal activity recordings will provide novel insights into this open question.

The technological and conceptual advances of the last years place the neuroscientific community in a unique position to address these questions and thereby unravel the neuronal underpinnings of prefrontal ensemble formation and the role of inputs and outputs of the PFC in this process. We propose that the combination of frequency-dependent coupling of neurons and input- and output-defined ensembles markedly increases the ability of individual neurons to multiplex across behaviors.²³¹ This enormously extends the range of dynamically forming task-specific ensembles, thereby enabling adaptive cognitive behaviors.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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