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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 conditions.[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

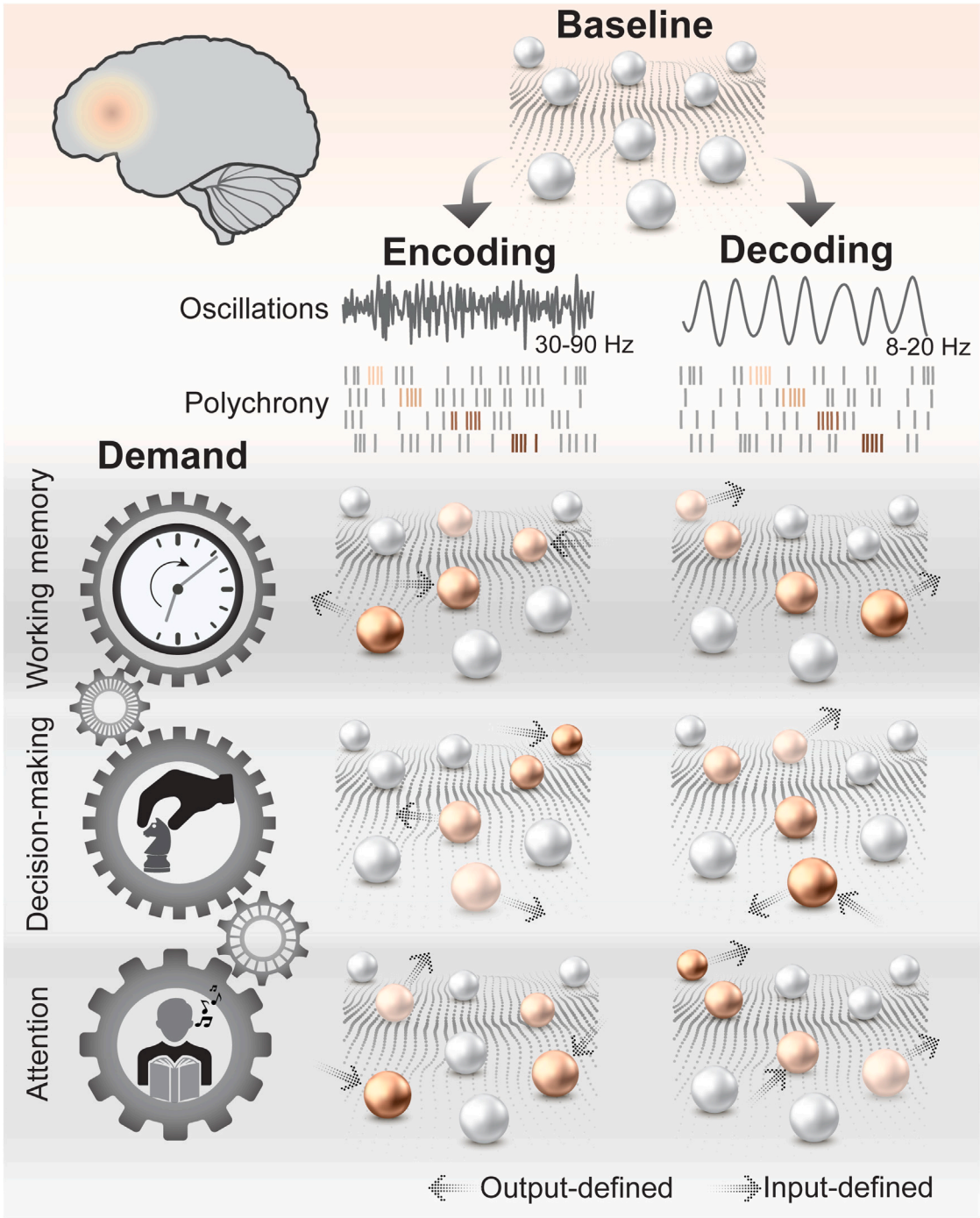

Figure 1. Assembling mechanisms of prefrontal neurons across adaptive cognitive behaviors

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 rodents[8] 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 rats[70]). We propose that within the PFC, the distinct inputs and outputs that define the PFC could give rise to anatomically mixed and dynamic neuronal ensembles. 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 principles[89] 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 patterns[92] 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 polychrony[92] 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 synapsemble 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 phototagging[120] 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,

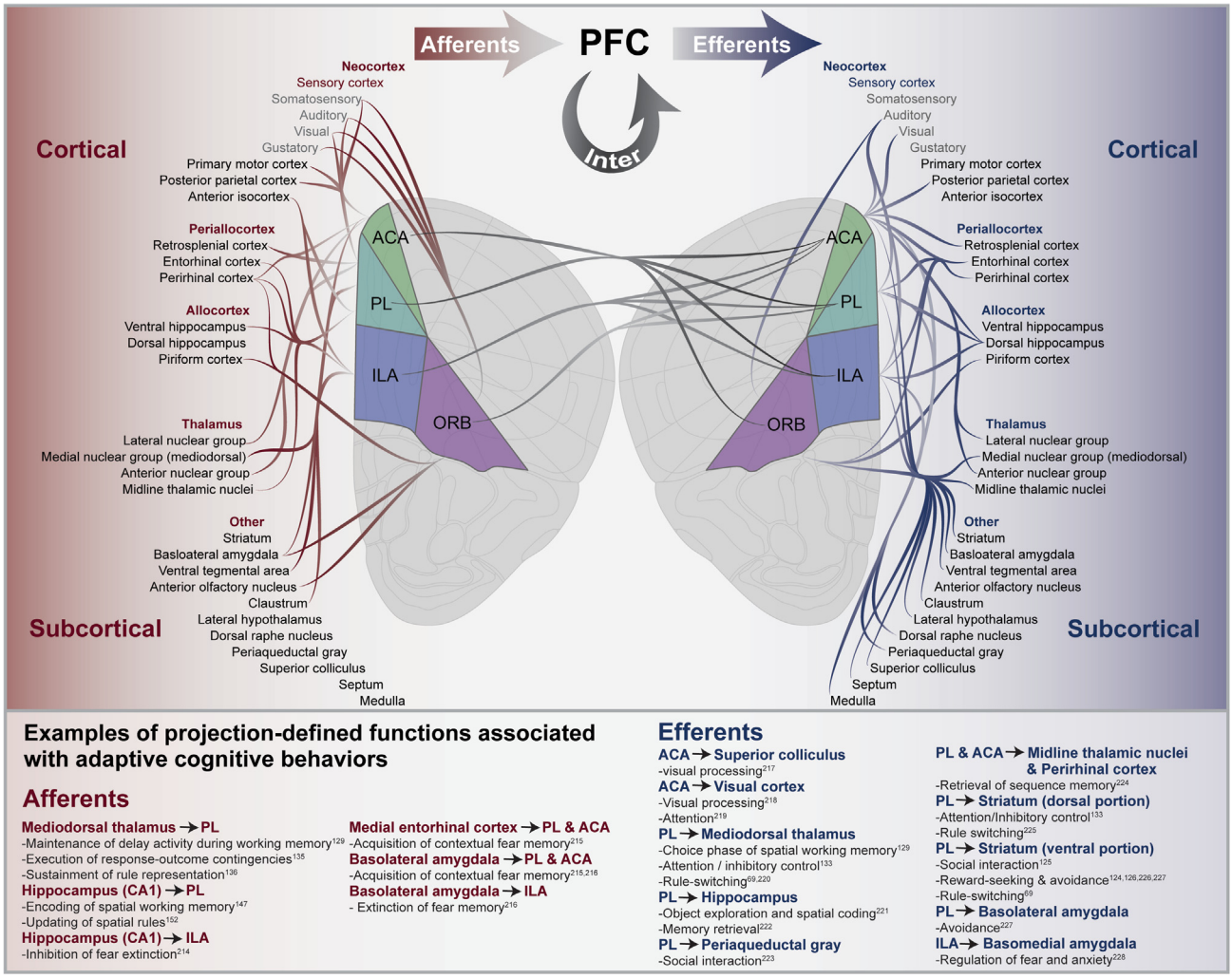

Figure 2. Overview of afferents (red) and efferents (blue) of rodent PFC in relation to behavioral relevance

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,[125] 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 task[129] 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 risk[127] 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 DNMTP 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 detection 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 plane[226]—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.

4. 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.
5. 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.

REFERENCES

1. Miller, E.K., and Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. *24*, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167.

2. Buschman, T.J., and Miller, E.K. (2014). Goal-direction and top-down control. Philos. Trans. R. Soc. Lond. B Biol. Sci. *369*, 20130471. https://doi.org/10.1098/RSTB.2013.0471.

3. Diamond, A. (2013). Executive functions. Annu. Rev. Psychol. *64*, 135–168. https://doi.org/10.1146/ANNUREV-PSYCH-113011-143750.

4. Meyer-Lindenberg, A. (2010). From maps to mechanisms through neuroimaging of schizophrenia. Nature *468*, 194–202. https://doi.org/10.1038/NATURE09569.

5. Goldman-Rakic, P.S. (1999). The "psychic" neuron of the cerebral cortex. Ann. N. Y. Acad. Sci. *868*, 13–26. https://doi.org/10.1111/J.1749-6632.1999.TB11270.X.

6. Donahue, C.J., Glasser, M.F., Preuss, T.M., Rilling, J.K., and Van Essen, D.C. (2018). Quantitative assessment of prefrontal cortex in humans relative to nonhuman primates. Proc. Natl. Acad. Sci. USA *115*, E5183–E5192. https://doi.org/10.1073/PNAS.1721653115.

7. Feinsinger, A., Pouratian, N., Ebadi, H., Adolphs, R., Andersen, R., Beauchamp, M.S., Chang, E.F., Crone, N.E., Collinger, J.L., Fried, I., et al. (2022). Ethical commitments, principles, and practices guiding intracranial neuroscientific research in humans. Neuron *110*, 188–194. https://doi.org/10.1016/J.NEURON.2021.11.011.

8. Carlén, M. (2017). What constitutes the prefrontal cortex? Science *358*, 478–482. https://doi.org/10.1126/SCIENCE.AAN8868.

9. Roelfsema, P.R., and Treue, S. (2014). Basic neuroscience research with nonhuman primates: a small but indispensable component of biomedical research. Neuron *82*, 1200–1204. https://doi.org/10.1016/J.NEURON.2014.06.003.

10. Fuster, J.M. (2008). The Prefrontal Cortex, Fourth Edition (Academic Press).

11. Uylings, H.B.M., Groenewegen, H.J., and Kolb, B. (2003). Do rats have a prefrontal cortex? Behav. Brain Res. *146*, 3–17. https://doi.org/10.1016/j.bbr.2003.09.028.

12. Ährlund-Richter, S., Xuan, Y., van Lunteren, J.A., Kim, H., Ortiz, C., Pollak Dorocic, I., Meletis, K., and Carlén, M. (2019). A whole-brain atlas of monosynaptic input targeting four different cell types in the medial prefrontal cortex of the mouse. Nat. Neurosci. *22*, 657–668. https://doi.org/10.1038/S41593-019-0354-Y.

13. Brown, V.J., and Bowman, E.M. (2002). Rodent models of prefrontal cortical function. Trends Neurosci. *25*, 340–343. https://doi.org/10.1016/S0166-2236(02)02164-1.

14. Preuss, T.M. (1995). Do Rats Have Prefrontal Cortex? The Rose-Woolsey-Akert Program Reconsidered. J. Cogn. Neurosci. *7*, 1–24. https://doi.org/10.1162/jocn.1995.7.1.1.

15. Rao, S.C., Rainer, G., and Miller, E.K. (1997). Integration of what and where in the primate prefrontal cortex. Science *276*, 821–824. https://doi.org/10.1126/SCIENCE.276.5313.821.

16. Funahashi, S., Bruce, C.J., and Goldman-Rakic, P.S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol. *61*, 331–349. https://doi.org/10.1152/JN.1989.61.2.331.

17. Asaad, W.F., Rainer, G., and Miller, E.K. (2000). Task-specific neural activity in the primate prefrontal cortex. J. Neurophysiol. *84*, 451–459. https://doi.org/10.1152/JN.2000.84.1.451.

18. Carrillo-Reid, L., and Yuste, R. (2020). Playing the piano with the cortex: role of neuronal ensembles and pattern completion in perception and behavior. Curr. Opin. Neurobiol. *64*, 89–95. https://doi.org/10.1016/j.conb.2020.03.014.

19. Bitzenhofer, S.H., Pöpplau, J.A., Chini, M., Marquardt, A., and Hanganu-Opatz, I.L. (2021). A transient developmental increase in prefrontal activity alters network maturation and causes cognitive dysfunction in adult mice. Neuron *109*, 1350–1364.e6. https://doi.org/10.1016/J.NEURON.2021.02.011.

20. Rigotti, M., Barak, O., Warden, M.R., Wang, X.J., Daw, N.D., Miller, E.K., and Fusi, S. (2013). The importance of mixed selectivity in complex cognitive tasks. Nature *497*, 585–590. https://doi.org/10.1038/NATURE12160.

21. Leavitt, M.L., Pieper, F., Sachs, A.J., and Martinez-Trujillo, J.C. (2017). Correlated variability modifies working memory fidelity in primate prefrontal neuronal ensembles. Proc. Natl. Acad. Sci. USA *114*, E2494–E2503. https://doi.org/10.1073/PNAS.1619949114/SUPPL_FILE/PNAS.201619949SI.PDF.

22. Meyers, E.M., Freedman, D.J., Kreiman, G., Miller, E.K., and Poggio, T. (2008). Dynamic population coding of category information in inferior temporal and prefrontal cortex. J. Neurophysiol. *100*, 1407–1419. https://doi.org/10.1152/JN.90248.2008/ASSET/IMAGES/LARGE/Z9K0080890030008.JPEG.

23. Preuss, T.M., and Wise, S.P. (2022). Evolution of prefrontal cortex. Neuropsychopharmacology *47*, 3–19. https://doi.org/10.1038/S41386-021-01076-5.

24. Laubach, M., Amarante, L.M., Swanson, K., and White, S.R. (2018). What, if anything, is rodent prefrontal cortex? eNeuro *5*. ENEURO. 0315–18.2018. https://doi.org/10.1523/ENEURO.0315-18.2018.

25. Brodmann, K. (1909). Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues/[K. Brodmann] (Wellcome Collection (Barth)).

26. Brodmann, K., and Garey, L.J. (2006). Brodmann's Localisation in the Cerebral Cortex: The Principles of Comparative Localisation in the Cerebral Cortex Based on Cytoarchitectonics (Springer US). https://doi.org/10.1007/b138298.

27. Leonard, C.M. (1969). The prefrontal cortex of the rat. I. Cortical projection of the mediodorsal nucleus. II. Efferent connections. Brain Res. *12*, 321–343. https://doi.org/10.1016/0006-8993(69)90003-1.

28. Divac, I., Mogensen, J., Petrovic-Minic, B., Zilles, K., and Regidor, J. (1993). Cortical projections of the thalamic mediodorsal nucleus in the rat. Definition of the prefrontal cortex. Acta Neurobiol. Exp. *53*, 425–429.

29. Williams, S.M., and Goldman-Rakic, P.S. (1998). Widespread origin of the primate mesofrontal dopamine system. Cereb. Cortex *8*, 321–345. https://doi.org/10.1093/CERCOR/8.4.321.

30. Ott, T., and Nieder, A. (2019). Dopamine and Cognitive Control in Prefrontal Cortex. Trends Cogn. Sci. *23*, 213–234. https://doi.org/10.1016/j.tics.2018.12.006.

31. Harris, J.A., Mihalas, S., Hirokawa, K.E., Whitesell, J.D., Choi, H., Bernard, A., Bohn, P., Caldejon, S., Casal, L., Cho, A., et al. (2019). Hierarchical organization of cortical and thalamic connectivity. Nature *575*, 195–202. https://doi.org/10.1038/S41586-019-1716-Z.

32. Le Merre, P., Ährlund-Richter, S., and Carlén, M. (2021). The mouse prefrontal cortex: Unity in diversity. Neuron *109*, 1925–1944. https://doi.org/10.1016/J.NEURON.2021.03.035.

33. Preuss, T.M., and Goldman-Rakic, P.S. (1991). Ipsilateral cortical connections of granular frontal cortex in the strepsirhine primate Galago, with comparative comments on anthropoid primates. J. Comp. Neurol. *310*, 507–549. https://doi.org/10.1002/CNE.903100404.

34. Elston, G.N., Benavides-Piccione, R., Elston, A., Zietsch, B., Defelipe, J., Manger, P., Casagrande, V., and Kaas, J.H. (2006). Specializations of the granular prefrontal cortex of primates: implications for cognitive processing. Anat. Rec. A Discov. Mol. Cell. Evol. Biol. *288*, 26–35. https://doi.org/10.1002/AR.A.20278.

35. Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.K., Cipolotti, L., Shallice, T., and Dolan, R.J. (2003). Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain *126*, 2139–2152. https://doi.org/10.1093/BRAIN/AWG216.

36. Catani, M., Dell'Acqua, F., and Thiebaut de Schotten, M. (2013). A revised limbic system model for memory, emotion and behaviour. Neurosci. Biobehav. Rev. *37*, 1724–1737. https://doi.org/10.1016/J.NEUBIOREV.2013.07.001.

37. Knudsen, E.B., and Wallis, J.D. (2022). Taking stock of value in the orbitofrontal cortex. Nat. Rev. Neurosci. *23*, 428–438. https://doi.org/10.1038/S41583-022-00589-2.

38. Gallagher, M., McMahan, R.W., and Schoenbaum, G. (1999). Orbitofrontal cortex and representation of incentive value in associative learning. J. Neurosci. *19*, 6610–6614. https://doi.org/10.1523/JNEUROSCI.19-15-06610.1999.

39. Baxter, M.G., Parker, A., Lindner, C.C., Izquierdo, A.D., and Murray, E.A. (2000). Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. J. Neurosci. *20*, 4311–4319. https://doi.org/10.1523/JNEUROSCI.20-11-04311.2000.

40. Roesch, M.R., and Olson, C.R. (2004). Neuronal activity related to reward value and motivation in primate frontal cortex. Science *304*, 307–310. https://doi.org/10.1126/SCIENCE.1093223.

41. Gardner, M.P.H., Conroy, J.C., Sanchez, D.C., Zhou, J., and Schoenbaum, G. (2019). Real-Time Value Integration during Economic Choice Is Regulated by Orbitofrontal Cortex. Curr. Biol. *29*, 4315–4322.e4. https://doi.org/10.1016/J.CUB.2019.10.058.

42. Ballesta, S., Shi, W., Conen, K.E., and Padoa-Schioppa, C. (2020). Values encoded in orbitofrontal cortex are causally related to economic choices. Nature *588*, 450–453. https://doi.org/10.1038/S41586-020-2880-X.

43. Hirokawa, J., Vaughan, A., Masset, P., Ott, T., and Kepecs, A. (2019). Frontal cortex neuron types categorically encode single decision variables. Nature *576*, 446–451. https://doi.org/10.1038/S41586-019-1816-9.

44. Schuck, N.W., Cai, M.B., Wilson, R.C., and Niv, Y. (2016). Human Orbitofrontal Cortex Represents a Cognitive Map of State Space. Neuron *91*, 1402–1412. https://doi.org/10.1016/J.NEURON.2016.08.019.

45. Kennerley, S.W., Dahmubed, A.F., Lara, A.H., and Wallis, J.D. (2009). Neurons in the frontal lobe encode the value of multiple decision variables. J. Cogn. Neurosci. *21*, 1162–1178. https://doi.org/10.1162/JOCN.2009.21100.

46. Kennerley, S.W., Behrens, T.E.J., and Wallis, J.D. (2011). Double dissociation of value computations in orbitofrontal and anterior cingulate neurons. Nat. Neurosci. *14*, 1581–1589. https://doi.org/10.1038/NN.2961.

47. Ito, S., Stuphorn, V., Brown, J.W., and Schall, J.D. (2003). Performance monitoring by the anterior cingulate cortex during saccade countermanding. Science *302*, 120–122. https://doi.org/10.1126/SCIENCE.1087847.

48. Tervo, D.G.R., Proskurin, M., Manakov, M., Kabra, M., Vollmer, A., Branson, K., and Karpova, A.Y. (2014). Behavioral variability through stochastic choice and its gating by anterior cingulate cortex. Cell *159*, 21–32. https://doi.org/10.1016/J.CELL.2014.08.037.

49. Jürgens, U. (2009). The neural control of vocalization in mammals: a review. J. Voice *23*, 1–10. https://doi.org/10.1016/J.JVOICE.2007.07.005.

50. Nieder, A., and Mooney, R. (2020). The neurobiology of innate, volitional and learned vocalizations in mammals and birds. Philos. Trans. R. Soc. Lond. B Biol. Sci. *375*, 20190054. https://doi.org/10.1098/RSTB.2019.0054.

51. Sanfey, A.G., Rilling, J.K., Aronson, J.A., Nystrom, L.E., and Cohen, J.D. (2003). The neural basis of economic decision-making in the Ultimatum Game. Science *300*, 1755–1758. https://doi.org/10.1126/SCIENCE.1082976.

52. Zhou, T., Zhu, H., Fan, Z., Wang, F., Chen, Y., Liang, H., Yang, Z., Zhang, L., Lin, L., Zhan, Y., et al. (2017). History of winning remodels thalamo-PFC circuit to reinforce social dominance. Science *357*, 162–168. https://doi.org/10.1126/SCIENCE.AAK9726.

53. Ong, W.S., Madlon-Kay, S., and Platt, M.L. (2021). Neuronal correlates of strategic cooperation in monkeys. Nat. Neurosci. *24*, 116–128. https://doi.org/10.1038/s41593-020-00746-9.

54. Gu, X., Liu, X., Guise, K.G., Naidich, T.P., Hof, P.R., and Fan, J. (2010). Functional dissociation of the frontoinsular and anterior cingulate cortices in empathy for pain. J. Neurosci. *30*, 3739–3744. https://doi.org/10.1523/JNEUROSCI.4844-09.2010.

55. Lamm, C., Decety, J., and Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage *54*, 2492–2502. https://doi.org/10.1016/J.NEUROIMAGE.2010.10.014.

56. Carrington, S.J., and Bailey, A.J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. Hum. Brain Mapp. *30*, 2313–2335. https://doi.org/10.1002/HBM.20671.

57. Freedman, D.J., Riesenhuber, M., Poggio, T., and Miller, E.K. (2001). Categorical representation of visual stimuli in the primate prefrontal cortex. Science *291*, 312–316. https://doi.org/10.1126/SCIENCE.291.5502.312.

58. Nieder, A., Freedman, D.J., and Miller, E.K. (2002). Representation of the quantity of visual items in the primate prefrontal cortex. Science *297*, 1708–1711. https://doi.org/10.1126/SCIENCE.1072493.

59. Bichot, N.P., Heard, M.T., DeGennaro, E.M., and Desimone, R. (2015). A Source for Feature-Based Attention in the Prefrontal Cortex. Neuron *88*, 832–844. https://doi.org/10.1016/J.NEURON.2015.10.001.

60. Fuster, J.M., and Alexander, G.E. (1971). Neuron activity related to short-term memory. Science *173*, 652–654. https://doi.org/10.1126/SCIENCE.173.3997.652.

61. Diester, I., and Nieder, A. (2007). Semantic associations between signs and numerical categories in the prefrontal cortex. PLoS Biol. *5*, e294–e2695. https://doi.org/10.1371/JOURNAL.PBIO.0050294.

62. Bongard, S., and Nieder, A. (2010). Basic mathematical rules are encoded by primate prefrontal cortex neurons. Proc. Natl. Acad. Sci. USA *107*, 2277–2282. https://doi.org/10.1073/PNAS.0909180107.

63. Mushiake, H., Saito, N., Sakamoto, K., Itoyama, Y., and Tanji, J. (2006). Activity in the lateral prefrontal cortex reflects multiple steps of future events in action plans. Neuron *50*, 631–641. https://doi.org/10.1016/J.NEURON.2006.03.045.

64. Hoshi, E., Shima, K., and Tanji, J. (2000). Neuronal activity in the primate prefrontal cortex in the process of motor selection based on two behavioral rules. J. Neurophysiol. *83*, 2355–2373. https://doi.org/10.1152/JN.2000.83.4.2355.

65. Munoz, D.P., and Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. Nat. Rev. Neurosci. *5*, 218–228. https://doi.org/10.1038/NRN1345.

66. Seamans, J.K., Floresco, S.B., and Phillips, A.G. (1995). Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. Behav. Neurosci. *109*, 1063–1073. https://doi.org/10.1037//0735-7044.109.6.1063.

67. Kellendonk, C., Simpson, E.H., Polan, H.J., Malleret, G., Vronskaya, S., Winiger, V., Moore, H., and Kandel, E.R. (2006). Transient and Selective Overexpression of Dopamine D2 Receptors in the Striatum Causes Persistent Abnormalities in Prefrontal Cortex Functioning. Neuron *49*, 603–615. https://doi.org/10.1016/J.NEURON.2006.01.023.

68. Jercog, D., Winke, N., Sung, K., Fernandez, M.M., Francioni, C., Rajot, D., Courtin, J., Chaudun, F., Jercog, P.E., Valerio, S., and Herry, C. (2021). Dynamical prefrontal population coding during defensive behaviours. Nature *595*, 690–694. https://doi.org/10.1038/S41586-021-03726-6.

69. Spellman, T., Svei, M., Kaminsky, J., Manzano-Nieves, G., and Liston, C. (2021). Prefrontal deep projection neurons enable cognitive flexibility via persistent feedback monitoring. Cell *184*, 2750–2766.e17. https://doi.org/10.1016/J.CELL.2021.03.047.

70. Bedwell, S.A., Billett, E.E., Crofts, J.J., and Tinsley, C.J. (2014). The topology of connections between rat prefrontal, motor and sensory cortices. Front. Syst. Neurosci. *8*, 177. https://doi.org/10.3389/fnsys.2014.00177.

71. Cavada, C., and Goldman-Rakic, P.S. (1989). Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. J. Comp. Neurol. *287*, 422–445. https://doi.org/10.1002/CNE.902870403.

72. Dum, R.P., and Strick, P.L. (2002). Motor areas in the frontal lobe of the primate. Physiol. Behav. *77*, 677–682.

73. Schmahmann, J.D., and Pandya, D.N. (1997). Anatomic organization of the basilar pontine projections from prefrontal cortices in rhesus monkey. J. Neurosci. *17*, 438–458. https://doi.org/10.1523/JNEUROSCI.17-01-00438.1997.

74. Alexander, G.E., DeLong, M.R., and Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. *9*, 357–381. https://doi.org/10.1146/ANNUREV.NE.09.030186.002041.

75. Barbas, H. (2015). General cortical and special prefrontal connections: principles from structure to function. Annu. Rev. Neurosci. *38*, 269–289. https://doi.org/10.1146/ANNUREV-NEURO-071714-033936.

76. Nett, K.E., and LaLumiere, R.T. (2021). Infralimbic cortex functioning across motivated behaviors: Can the differences be reconciled? Neurosci. Biobehav. Rev. *131*, 704–721. https://doi.org/10.1016/J.NEUBIOREV.2021.10.002.

77. Buschman, T.J., Siegel, M., Roy, J.E., and Miller, E.K. (2011). Neural substrates of cognitive capacity limitations. Proc. Natl. Acad. Sci. USA *108*, 11252–11255. https://doi.org/10.1073/PNAS.1104666108/-/DCSUPPLEMENTAL/PNAS.201104666SI.PDF.

78. Hopfield, J.J., and Herz, A.V. (1995). Rapid local synchronization of action potentials: Toward computation with coupled integrate-and-fire neurons. Proc. Natl. Acad. Sci. USA *92*, 6655–6662. https://doi.org/10.1073/pnas.92.15.6655.

79. Izhikevich, E.M. (1999). Weakly pulse-coupled oscillators, FM interactions, synchronization, and oscillatory associative memory. IEEE Trans. Neural Netw. *10*, 508–526. https://doi.org/10.1109/72.761708.

80. Womelsdorf, T., Schoffelen, J.M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., and Fries, P. (2007). Modulation of neuronal interactions through neuronal synchronization. Science *316*, 1609–1612. https://doi.org/10.1126/SCIENCE.1139597.

81. Axmacher, N., Henseler, M.M., Jensen, O., Weinreich, I., Elger, C.E., and Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. Proc. Natl. Acad. Sci. USA *107*, 3228–3233. https://doi.org/10.1073/PNAS.0911531107.

82. Pesaran, B., Vinck, M., Einevoll, G.T., Sirota, A., Fries, P., Siegel, M., Truccolo, W., Schroeder, C.E., and Srinivasan, R. (2018). Investigating large-scale brain dynamics using field potential recordings: analysis and interpretation. Nat. Neurosci. *21*, 903–919. https://doi.org/10.1038/S41593-018-0171-8.

83. Fries, P. (2015). Rhythms for Cognition: Communication through Coherence. Neuron *88*, 220–235. https://doi.org/10.1016/J.NEURON.2015.09.034.

84. Lewis, C.M., Ni, J., Wunderle, T., Jendritza, P., Lazar, A., Diester, I., and Fries, P. (2021). Cortical gamma-band resonance preferentially transmits coherent input. Cell Rep. *35*, 109083. https://doi.org/10.1016/J.CELREP.2021.109083.

85. Ni, J., Wunderle, T., Lewis, C.M., Desimone, R., Diester, I., and Fries, P. (2016). Gamma-Rhythmic Gain Modulation. Neuron *92*, 240–251. https://doi.org/10.1016/J.NEURON.2016.09.003.

86. Lundqvist, M., Rose, J., Herman, P., Brincat, S.L., Buschman, T.J., and Miller, E.K. (2016). Gamma and Beta Bursts Underlie Working Memory. Neuron *90*, 152–164. https://doi.org/10.1016/J.NEURON.2016.02.028.

87. Karvat, G., Alyahyay, M., and Diester, I. (2021). Spontaneous activity competes with externally evoked responses in sensory cortex. Proc. Natl. Acad. Sci. USA *118*. e2023286118. https://doi.org/10.1073/PNAS.2023286118/-/DCSUPPLEMENTAL.

88. Axmacher, N., Mormann, F., Fernández, G., Elger, C.E., and Fell, J. (2006). Memory formation by neuronal synchronization. Brain Res. Rev. *52*, 170–182. https://doi.org/10.1016/J.BRAINRESREV.2006.01.007.

89. Artola, A., and Singer, W. (1993). Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. Trends Neurosci. *16*, 480–487. https://doi.org/10.1016/0166-2236(93)90081-V.

90. Burrone, J., O'Byrne, M., and Murthy, V.N. (2002). Multiple forms of synaptic plasticity triggered by selective suppression of activity in individual neurons. Nature *420*, 414–418. https://doi.org/10.1038/NATURE01242.

91. Keck, T., Toyoizumi, T., Chen, L., Doiron, B., Feldman, D.E., Fox, K., Gerstner, W., Haydon, P.G., Hübener, M., Lee, H.K., et al. (2017). Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions. Philos. Trans. R. Soc. Lond. B Biol. Sci. *372*, 20160158. https://doi.org/10.1098/RSTB.2016.0158.

92. Izhikevich, E.M. (2006). Polychronization: computation with spikes. Neural Comput. *18*, 245–282. https://doi.org/10.1162/089976606775093882.

93. Martignon, L., Von Hasseln, H., Grün, S., Aertsen, A., and Palm, G. (1995). Detecting higher-order interactions among the spiking events in a group of neurons. Biol. Cybern. *73*, 69–81. https://doi.org/10.1007/BF00199057.

94. Stella, A., Bouss, P., Palm, G., and Grün, S. (2022). Comparing Surrogates to Evaluate Precisely Timed Higher-Order Spike Correlations. eNeuro *9*. ENEURO.0505–21.2022. https://doi.org/10.1523/ENEURO.0505-21.2022.

95. Dragoi, G., and Buzsáki, G. (2006). Temporal encoding of place sequences by hippocampal cell assemblies. Neuron *50*, 145–157. https://doi.org/10.1016/J.NEURON.2006.02.023.

96. Feng, T., Silva, D., and Foster, D.J. (2015). Dissociation between the experience-dependent development of hippocampal theta sequences and single-trial phase precession. J. Neurosci. *35*, 4890–4902. https://doi.org/10.1523/JNEUROSCI.2614-14.2015.

97. Foster, D.J., and Wilson, M.A. (2007). Hippocampal theta sequences. Hippocampus *17*, 1093–1099. https://doi.org/10.1002/HIPO.20345.

98. Yiu, Y.H., Leutgeb, J.K., and Leibold, C. (2022). Directional Tuning of Phase Precession Properties in the Hippocampus. J. Neurosci. *42*, 2282–2297. https://doi.org/10.1523/JNEUROSCI.1569-21.2021.

99. Berners-Lee, A., Feng, T., Silva, D., Wu, X., Ambrose, E.R., Pfeiffer, B.E., and Foster, D.J. (2022). Hippocampal replays appear after a single experience and incorporate greater detail with more experience. Neuron *110*, 1829–1842.e5. https://doi.org/10.1016/J.NEURON.2022.03.010.

100. Lee, A.K., and Wilson, M.A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. Neuron *36*, 1183–1194. https://doi.org/10.1016/S0896-6273(02)01096-6.

101. Chenani, A., Sabariego, M., Schlesiger, M.I., Leutgeb, J.K., Leutgeb, S., and Leibold, C. (2019). Hippocampal CA1 replay becomes less prominent but more rigid without inputs from medial entorhinal cortex. Nat. Commun. *10*, 1341. https://doi.org/10.1038/S41467-019-09280-0.

102. Liu, J., Fu, T.M., Cheng, Z., Hong, G., Zhou, T., Jin, L., Duvvuri, M., Jiang, Z., Kruskal, P., Xie, C., et al. (2015). Syringe-injectable electronics. Nat. Nanotechnol. *10*, 629–636. https://doi.org/10.1038/nnano.2015.115.

103. Liu, K., Sibille, J., and Dragoi, G. (2021). Orientation selectivity enhances context generalization and generative predictive coding in the hippocampus. Neuron *109*, 3688–3698.e6. https://doi.org/10.1016/J.NEURON.2021.08.013.

104. Widloski, J., and Foster, D.J. (2022). Flexible rerouting of hippocampal replay sequences around changing barriers in the absence of global place field remapping. Neuron *110*, 1547–1558.e8. https://doi.org/10.1016/J.NEURON.2022.02.002.

105. Battaglia, F.P., Benchenane, K., Sirota, A., Pennartz, C.M.A., and Wiener, S.I. (2011). The hippocampus: hub of brain network communication for memory. Trends Cogn. Sci. *15*, 310–318. https://doi.org/10.1016/J.TICS.2011.05.008.

106. Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P.L., Gioanni, Y., Battaglia, F.P., and Wiener, S.I. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. Neuron *66*, 921–936. https://doi.org/10.1016/J.NEURON.2010.05.013.

107. Euston, D.R., Tatsuno, M., and McNaughton, B.L. (2007). Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. Science *318*, 1147–1150. https://doi.org/10.1126/SCIENCE.1148979.

108. Jones, M.W., and Wilson, M.A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol. *3*, 1–13. https://doi.org/10.1371/JOURNAL.PBIO.0030402.

109. Berners-Lee, A., Wu, X., and Foster, D.J. (2021). Prefrontal cortical neurons are selective for non-local hippocampal representations during replay and behavior. J. Neurosci. *41*, 5894–5908. https://doi.org/10.1523/JNEUROSCI.1158-20.2021.

110. Klee, J.L., Souza, B.C., and Battaglia, F.P. (2021). Learning differentially shapes prefrontal and hippocampal activity during classical conditioning. Elife *10*, e65456. https://doi.org/10.7554/ELIFE.65456.

111. Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S.I., and Battaglia, F.P. (2009). Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nat. Neurosci. *12*, 919–926. https://doi.org/10.1038/NN.2337.

112. Tang, W., Shin, J.D., Frank, L.M., and Jadhav, S.P. (2017). Hippocampal-Prefrontal Reactivation during Learning Is Stronger in Awake Compared with Sleep States. J. Neurosci. *37*, 11789–11805. https://doi.org/10.1523/JNEUROSCI.2291-17.2017.

113. Handa, T., Harukuni, R., and Fukai, T. (2021). Concomitant Processing of Choice and Outcome in Frontal Corticostriatal Ensembles Correlates with Performance of Rats. Cereb. Cortex *31*, 4357–4375. https://doi.org/10.1093/CERCOR/BHAB091.

114. Oberto, V.J., Boucly, C.J., Gao, H., Todorova, R., Zugaro, M.B., and Wiener, S.I. (2022). Distributed cell assemblies spanning prefrontal cortex and striatum. Curr. Biol. *32*, 1–13.e6. https://doi.org/10.1016/J.CUB.2021.10.007.

115. Gütig, R. (2016). Spiking neurons can discover predictive features by aggregate-label learning. Science *351*, aab4113. https://doi.org/10.1126/SCIENCE.AAB4113.

116. Gütig, R., and Sompolinsky, H. (2006). The tempotron: a neuron that learns spike timing-based decisions. Nat. Neurosci. *9*, 420–428. https://doi.org/10.1038/NN1643.

117. Buzsáki, G. (2010). Neural syntax: cell assemblies, synapsembles, and readers. Neuron *68*, 362–385. https://doi.org/10.1016/J.NEURON.2010.09.023.

118. Luczak, A., Barthó, P., and Harris, K.D. (2009). Spontaneous events outline the realm of possible sensory responses in neocortical populations. Neuron *62*, 413–425. https://doi.org/10.1016/J.NEURON.2009.03.014.

119. Jacob, S.N., Hähnke, D., and Nieder, A. (2018). Structuring of Abstract Working Memory Content by Fronto-parietal Synchrony in Primate Cortex. Neuron *99*, 588–597.e5. https://doi.org/10.1016/J.NEURON.2018.07.025.

120. De La Crompe, B., Coulon, P., and Diester, I. (2020). Functional interrogation of neural circuits with virally transmitted optogenetic tools. J. Neurosci. Methods *345*, 108905. https://doi.org/10.1016/j.jneumeth.2020.108905.

121. Chiang, F.K., Wallis, J.D., and Rich, E.L. (2022). Cognitive strategies shift information from single neurons to populations in prefrontal cortex. Neuron *110*, 709–721.e4. https://doi.org/10.1016/j.neuron.2021.11.021.

122. Collins, D.P., Anastasiades, P.G., Marlin, J.J., and Carter, A.G. (2018). Reciprocal Circuits Linking the Prefrontal Cortex with Dorsal and Ventral Thalamic Nuclei. Neuron *98*, 366–379.e4. https://doi.org/10.1016/J.NEURON.2018.03.024.

123. Gabbott, P.L.A., Warner, T.A., Jays, P.R.L., Salway, P., and Busby, S.J. (2005). Prefrontal cortex in the rat: Projections to subcortical autonomic, motor, and limbic centers. J. Comp. Neurol. *492*, 145–177. https://doi.org/10.1002/cne.20738.

124. Heidbreder, C.A., and Groenewegen, H.J. (2003). The medial prefrontal cortex in the rat: Evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. Neurosci. Biobehav. Rev. *27*, 555–579. https://doi.org/10.1016/j.neubiorev.2003.09.003.

125. Gao, L., Liu, S., Gou, L., Hu, Y., Liu, Y., Deng, L., Ma, D., Wang, H., Yang, Q., Chen, Z., et al. (2022). Single-neuron projectome of mouse prefrontal cortex. Nat. Neurosci. *25*, 515–529. https://doi.org/10.1038/S41593-022-01041-5.

126. Ongür, D., and Price, J.L. (2000). The Organization of Networks within the Orbital and Medial Prefrontal Cortex of Rats, Monkeys and Humans. Cereb. Cortex *10*, 206–219. https://doi.org/10.1093/cercor/10.3.206.

127. Kim, C.K., Ye, L., Jennings, J.H., Pichamoorthy, N., Tang, D.D., Yoo, A.C.W., Ramakrishnan, C., and Deisseroth, K. (2017). Molecular and Circuit-Dynamical Identification of Top-Down Neural Mechanisms for Restraint of Reward Seeking. Cell *170*, 1013–1027.e14. https://doi.org/10.1016/J.CELL.2017.07.020.

128. Murugan, M., Jang, H.J., Park, M., Miller, E.M., Cox, J., Taliaferro, J.P., Parker, N.F., Bhave, V., Hur, H., Liang, Y., et al. (2017). Combined Social and Spatial Coding in a Descending Projection from the Prefrontal Cortex. Cell *171*, 1663–1677.e16. https://doi.org/10.1016/J.CELL.2017.11.002.

129. Otis, J.M., Namboodiri, V.M.K., Matan, A.M., Voets, E.S., Mohorn, E.P., Kosyk, O., McHenry, J.A., Robinson, J.E., Resendez, S.L., Rossi, M.A., and Stuber, G.D. (2017). Prefrontal cortex output circuits guide reward seeking through divergent cue encoding. Nature *543*, 103–107. https://doi.org/10.1038/NATURE21376.

130. Bolkan, S.S., Stujenske, J.M., Parnaudeau, S., Spellman, T.J., Rauffenbart, C., Abbas, A.I., Harris, A.Z., Gordon, J.A., and Kellendonk, C. (2017). Thalamic projections sustain prefrontal activity during working memory maintenance. Nat. Neurosci. *20*, 987–996. https://doi.org/10.1038/nn.4568.

131. de Kloet, S.F., Bruinsma, B., Terra, H., Heistek, T.S., Passchier, E.M.J., van den Berg, A.R., Luchicchi, A., Min, R., Pattij, T., and Mansvelder, H.D. (2021). Bi-directional regulation of cognitive control by distinct prefrontal cortical output neurons to thalamus and striatum. Nat. Commun. *12*, 1994. https://doi.org/10.1038/S41467-021-22260-7.

132. Alcaraz, F., Fresno, V., Marchand, A.R., Kremer, E.J., Coutureau, E., and Wolff, M. (2018). Thalamocortical and corticothalamic pathways differentially contribute to goal-directed behaviors in the rat. Elife *7*, e32517. https://doi.org/10.7554/ELIFE.32517.

133. Schmitt, L.I., Wimmer, R.D., Nakajima, M., Happ, M., Mofakham, S., and Halassa, M.M. (2017). Thalamic amplification of cortical connectivity sustains attentional control. Nature *545*, 219–223. https://doi.org/10.1038/NATURE22073.

134. Spellman, T., Rigotti, M., Ahmari, S.E., Fusi, S., Gogos, J.A., and Gordon, J.A. (2015). Hippocampal-prefrontal input supports spatial encoding in working memory. Nature *522*, 309–314. https://doi.org/10.1038/NATURE14445.

135. Park, A.J., Harris, A.Z., Martyniuk, K.M., Chang, C.Y., Abbas, A.I., Lowes, D.C., Kellendonk, C., Gogos, J.A., and Gordon, J.A. (2021). Reset of hippocampal–prefrontal circuitry facilitates learning. Nature *591*, 615–619. https://doi.org/10.1038/s41586-021-03272-1.

136. Marek, R., Jin, J., Goode, T.D., Giustino, T.F., Wang, Q., Acca, G.M., Holehonnur, R., Ploski, J.E., Fitzgerald, P.J., Lynagh, T., et al. (2018). Hippocampus-driven feed-forward inhibition of the prefrontal cortex mediates relapse of extinguished fear. Nat. Neurosci. *21*, 384–392. https://doi.org/10.1038/S41593-018-0073-9.

137. Kitamura, T., Ogawa, S.K., Roy, D.S., Okuyama, T., Morrissey, M.D., Smith, L.M., Redondo, R.L., and Tonegawa, S. (2017). Engrams and circuits crucial for systems consolidation of a memory. Science *356*, 73–78. https://doi.org/10.1126/SCIENCE.AAM6808.

138. Senn, V., Wolff, S.B.E., Herry, C., Grenier, F., Ehrlich, I., Gründemann, J., Fadok, J.P., Müller, C., Letzkus, J.J., and Lüthi, A. (2014). Long-range connectivity defines behavioral specificity of amygdala neurons. Neuron *81*, 428–437. https://doi.org/10.1016/J.NEURON.2013.11.006.

139. Zhang, S., Xu, M., Kamigaki, T., Hoang Do, J.P., Chang, W.C., Jenvay, S., Miyamichi, K., Luo, L., and Dan, Y. (2014). Selective attention. Long-range and local circuits for top-down modulation of visual cortex processing. Science *345*, 660–665. https://doi.org/10.1126/SCIENCE.1254126.

140. Hu, F., Kamigaki, T., Zhang, Z., Zhang, S., Dan, U., and Dan, Y. (2019). Prefrontal Corticotectal Neurons Enhance Visual Processing through the Superior Colliculus and Pulvinar Thalamus. Neuron *104*, 1141–1152.e4. https://doi.org/10.1016/J.NEURON.2019.09.019.

141. Norman, K.J., Riceberg, J.S., Koike, H., Bateh, J., McCraney, S.E., Caro, K., Kato, D., Liang, A., Yamamuro, K., Flanigan, M.E., et al. (2021). Post-error recruitment of frontal sensory cortical projections promotes attention in mice. Neuron *109*, 1202–1213.e5. https://doi.org/10.1016/J.NEURON.2021.02.001.

142. Marton, T.F., Seifikar, H., Luongo, F.J., Lee, A.T., and Sohal, V.S. (2018). Roles of Prefrontal Cortex and Mediodorsal Thalamus in Task Engagement and Behavioral Flexibility. J. Neurosci. *38*, 2569–2578. https://doi.org/10.1523/JNEUROSCI.1728-17.2018.

143. Malik, R., Li, Y., Schamiloglu, S., and Sohal, V.S. (2022). Top-down control of hippocampal signal-to-noise by prefrontal long-range inhibition. Cell *185*, 1602–1617.e17. https://doi.org/10.1016/J.CELL.2022.04.001.

144. Rajasethupathy, P., Sankaran, S., Marshel, J.H., Kim, C.K., Ferenczi, E., Lee, S.Y., Berndt, A., Ramakrishnan, C., Jaffe, A., Lo, M., et al. (2015). Projections from neocortex mediate top-down control of memory retrieval. Nature *526*, 653–659. https://doi.org/10.1038/nature15389.

145. Franklin, T.B., Silva, B.A., Perova, Z., Marrone, L., Masferrer, M.E., Zhan, Y., Kaplan, A., Greetham, L., Verrechia, V., Halman, A., et al. (2017). Prefrontal cortical control of a brainstem social behavior circuit. Nat. Neurosci. *20*, 260–270. https://doi.org/10.1038/nn.4470.

146. Jayachandran, M., Linley, S.B., Schlecht, M., Mahler, S.V., Vertes, R.P., and Allen, T.A. (2019). Prefrontal Pathways Provide Top-Down Control of Memory for Sequences of Events. Cell Rep. *28*, 640–654.e6. https://doi.org/10.1016/J.CELREP.2019.06.053.

147. Nakayama, H., Ibañez-Tallon, I., and Heintz, N. (2018). Cell-Type-Specific Contributions of Medial Prefrontal Neurons to Flexible Behaviors. J. Neurosci. *38*, 4490–4504. https://doi.org/10.1523/JNEUROSCI.3537-17.2018.

148. Lee, A.T., Vogt, D., Rubenstein, J.L., and Sohal, V.S. (2014). A class of GABAergic neurons in the prefrontal cortex sends long-range projections to the nucleus accumbens and elicits acute avoidance behavior. J. Neurosci. *34*, 11519–11525. https://doi.org/10.1523/JNEUROSCI.1157-14.2014.

149. Diehl, M.M., Iravedra-Garcia, J.M., Morán-Sierra, J., Rojas-Bowe, G., Gonzalez-Diaz, F.N., Valentín-Valentín, V.P., and Quirk, G.J. (2020). Divergent projections of the prelimbic cortex bidirectionally regulate active avoidance. Elife *9*, 1–13. https://doi.org/10.7554/ELIFE.59281.

150. Adhikari, A., Lerner, T.N., Finkelstein, J., Pak, S., Jennings, J.H., Davidson, T.J., Ferenczi, E., Gunaydin, L.A., Mirzabekov, J.J., Ye, L., et al. (2015). Basomedial amygdala mediates top-down control of anxiety and fear. Nature *527*, 179–185. https://doi.org/10.1038/NATURE15698.

151. Pinto, A., and Sesack, S.R. (2000). Limited collateralization of neurons in the rat prefrontal cortex that project to the nucleus accumbens. Neuroscience *97*, 635–642. https://doi.org/10.1016/S0306-4522(00)00042-7.

152. Zingg, B., Hintiryan, H., Gou, L., Song, M.Y., Bay, M., Bienkowski, M.S., Foster, N.N., Yamashita, S., Bowman, I., Toga, A.W., and Dong, H.W. (2014). Neural networks of the mouse neocortex. Cell *156*, 1096–1111. https://doi.org/10.1016/J.CELL.2014.02.023.

153. Carus-Cadavieco, M., Gorbati, M., Ye, L., Bender, F., Van Der Veldt, S., Kosse, C., Börgers, C., Lee, S.Y., Ramakrishnan, C., Hu, Y., et al. (2017). Gamma oscillations organize top-down signalling to hypothalamus and enable food seeking. Nature *542*, 232–236. https://doi.org/10.1038/NATURE21066.

154. Duvarci, S., Simpson, E.H., Schneider, G., Kandel, E.R., Roeper, J., and Sigurdsson, T. (2018). Impaired recruitment of dopamine neurons during working memory in mice with striatal D2 receptor overexpression. Nat. Commun. *9*, 2822. https://doi.org/10.1038/S41467-018-05214-4.

155. Likhtik, E., Stujenske, J.M., Topiwala, M.A., Harris, A.Z., and Gordon, J.A. (2014). Prefrontal entrainment of amygdala activity signals safety in learned fear and innate anxiety. Nat. Neurosci. *17*, 106–113. https://doi.org/10.1038/NN.3582.

156. Lui, J.H., Nguyen, N.D., Grutzner, S.M., Darmanis, S., Peixoto, D., Wagner, M.J., Allen, W.E., Kebschull, J.M., Richman, E.B., Ren, J., et al. (2021). Differential encoding in prefrontal cortex projection neuron classes across cognitive tasks. Cell *184*, 489–506.e26. https://doi.org/10.1016/J.CELL.2020.11.046.

157. Anastasiades, P.G., Collins, D.P., and Carter, A.G. (2021). Mediodorsal and Ventromedial Thalamus Engage Distinct L1 Circuits in the Prefrontal Cortex. Neuron *109*, 314–330.e4. https://doi.org/10.1016/J.NEURON.2020.10.031.

158. Delevich, K., Tucciarone, J., Huang, Z.J., and Li, B. (2015). The mediodorsal thalamus drives feedforward inhibition in the anterior cingulate cortex via parvalbumin interneurons. J. Neurosci. *35*, 5743–5753. https://doi.org/10.1523/JNEUROSCI.4565-14.2015.

159. Mukherjee, A., Lam, N.H., Wimmer, R.D., and Halassa, M.M. (2021). Thalamic circuits for independent control of prefrontal signal and noise. Nature *600*, 100–104. https://doi.org/10.1038/S41586-021-04056-3.

160. Ahlbeck, J., Song, L., Chini, M., Bitzenhofer, S.H., and Hanganu-Opatz, I.L. (2018). Glutamatergic drive along the septo-temporal axis of hippocampus boosts prelimbic oscillations in the neonatal mouse. Elife *7*, e33158. https://doi.org/10.7554/ELIFE.33158.

161. Cenquizca, L.A., and Swanson, L.W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. Brain Res. Rev. *56*, 1–26. https://doi.org/10.1016/J.BRAINRESREV.2007.05.002.

162. Condé, F., Maire-lepoivre, E., Audinat, E., and Crépel, F. (1995). Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. J. Comp. Neurol. *352*, 567–593. https://doi.org/10.1002/CNE.903520407.

163. Eichenbaum, H. (2017). Prefrontal-hippocampal interactions in episodic memory. Nat. Rev. Neurosci. *18*, 547–558. https://doi.org/10.1038/NRN.2017.74.

164. Jay, T.M., and Witter, M.P. (1991). Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. J. Comp. Neurol. *313*, 574–586. https://doi.org/10.1002/CNE.903130404.

165. Liu, X., and Carter, A.G. (2018). Ventral Hippocampal Inputs Preferentially Drive Corticocortical Neurons in the Infralimbic Prefrontal Cortex. J. Neurosci. *38*, 7351–7363. https://doi.org/10.1523/JNEUROSCI.0378-18.2018.

166. Xu, X., Song, L., and Hanganu-Opatz, I.L. (2021). Knock-Down of Hippocampal DISC1 in Immune-Challenged Mice Impairs the Prefrontal-Hippocampal Coupling and the Cognitive Performance Throughout Development. Cereb. Cortex *31*, 1240–1258. https://doi.org/10.1093/CERCOR/BHAA291.

167. Siapas, A.G., Lubenov, E.V., and Wilson, M.A. (2005). Prefrontal phase locking to hippocampal theta oscillations. Neuron *46*, 141–151. https://doi.org/10.1016/J.NEURON.2005.02.028.

168. Lagler, M., Ozdemir, A.T., Lagoun, S., Malagon-Vina, H., Borhegyi, Z., Hauer, R., Jelem, A., and Klausberger, T. (2016). Divisions of Identified Parvalbumin-Expressing Basket Cells during Working Memory-Guided Decision Making. Neuron *91*, 1390–1401. https://doi.org/10.1016/J.NEURON.2016.08.010.

169. O'Neill, P.K., Gordon, J.A., and Sigurdsson, T. (2013). Theta oscillations in the medial prefrontal cortex are modulated by spatial working memory and synchronize with the hippocampus through its ventral subregion. J. Neurosci. *33*, 14211–14224. https://doi.org/10.1523/JNEUROSCI.2378-13.2013.

170. Sigurdsson, T., Stark, K.L., Karayiorgou, M., Gogos, J.A., and Gordon, J.A. (2010). Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Nature *464*, 763–767. https://doi.org/10.1038/NATURE08855.

171. Zielinski, M.C., Shin, J.D., and Jadhav, S.P. (2019). Coherent Coding of Spatial Position Mediated by Theta Oscillations in the Hippocampus and Prefrontal Cortex. J. Neurosci. *39*, 4550–4565. https://doi.org/10.1523/JNEUROSCI.0106-19.2019.

172. Fujisawa, S., Amarasingham, A., Harrison, M.T., and Buzsáki, G. (2008). Behavior-dependent short-term assembly dynamics in the medial prefrontal cortex. Nat. Neurosci. *11*, 823–833. https://doi.org/10.1038/NN.2134.

173. Jung, M.W., Qin, Y., McNaughton, B.L., and Barnes, C.A. (1998). Firing characteristics of deep layer neurons in prefrontal cortex in rats performing spatial working memory tasks. Cereb. Cortex *8*, 437–450. https://doi.org/10.1093/CERCOR/8.5.437.

174. Ito, H.T., Zhang, S.J., Witter, M.P., Moser, E.I., and Moser, M.B. (2015). A prefrontal-thalamo-hippocampal circuit for goal-directed spatial navigation. Nature *522*, 50–55. https://doi.org/10.1038/NATURE14396.

175. Kaefer, K., Nardin, M., Blahna, K., and Csicsvari, J. (2020). Replay of Behavioral Sequences in the Medial Prefrontal Cortex during Rule Switching. Neuron *106*, 154–165.e6. https://doi.org/10.1016/J.NEURON.2020.01.015.

176. Sauer, J.F., Folschweiller, S., and Bartos, M. (2022). Topographically organized representation of space and context in the medial prefrontal cortex. Proc. Natl. Acad. Sci. USA *119*. e2117300119. https://doi.org/10.1073/PNAS.2117300119/-/DCSUPPLEMENTAL.

177. Kutter, E.F., Bostroem, J., Elger, C.E., Mormann, F., and Nieder, A. (2018). Single Neurons in the Human Brain Encode Numbers. Neuron *100*, 753–761.e4. https://doi.org/10.1016/J.NEURON.2018.08.036.

178. Quiroga, R.Q., Reddy, L., Kreiman, G., Koch, C., and Fried, I. (2005). Invariant visual representation by single neurons in the human brain. Nature *435*, 1102–1107. https://doi.org/10.1038/NATURE03687.

179. Rutishauser, U., Ross, I.B., Mamelak, A.N., and Schuman, E.M. (2010). Human memory strength is predicted by theta-frequency phase-locking of single neurons. Nature *464*, 903–907. https://doi.org/10.1038/NATURE08860.

180. Fu, Z., Beam, D., Chung, J.M., Reed, C.M., Mamelak, A.N., Adolphs, R., and Rutishauser, U. (2022). The geometry of domain-general performance monitoring in the human medial frontal cortex. Science *376*, eabm9922. https://doi.org/10.1126/SCIENCE.ABM9922.

181. Kamiński, J., Sullivan, S., Chung, J.M., Ross, I.B., Mamelak, A.N., and Rutishauser, U. (2017). Persistently active neurons in human medial frontal and medial temporal lobe support working memory. Nat. Neurosci. *20*, 590–601. https://doi.org/10.1038/NN.4509.

182. Minxha, J., Adolphs, R., Fusi, S., Mamelak, A.N., and Rutishauser, U. (2020). Flexible recruitment of memory-based choice representations by the human medial frontal cortex. Science *368*, eaba3313. https://doi.org/10.1126/SCIENCE.ABA3313.

183. Jamali, M., Grannan, B.L., Fedorenko, E., Saxe, R., Báez-Mendoza, R., and Williams, Z.M. (2021). Single-neuronal predictions of others' beliefs in humans. Nature *591*, 610–614. https://doi.org/10.1038/S41586-021-03184-0.

184. Jamali, M., Grannan, B., Haroush, K., Moses, Z.B., Eskandar, E.N., Herrington, T., Patel, S., and Williams, Z.M. (2019). Dorsolateral prefrontal neurons mediate subjective decisions and their variation in humans. Nat. Neurosci. *22*, 1010–1020. https://doi.org/10.1038/S41593-019-0378-3.

185. Jun, J.J., Steinmetz, N.A., Siegle, J.H., Denman, D.J., Bauza, M., Barbarits, B., Lee, A.K., Anastassiou, C.A., Andrei, A., Aydın, Ç., et al. (2017). Fully integrated silicon probes for high-density recording of neural activity. Nature *551*, 232–236. https://doi.org/10.1038/NATURE24636.

186. Chung, J.E., Sellers, K.K., Leonard, M.K., Gwilliams, L., Xu, D., Dougherty, M.E., Kharazia, V., Metzger, S.L., Welkenhuysen, M., Dutta, B., and Chang, E.F. (2022). High-density single-unit human cortical recordings using the Neuropixels probe. Neuron *110*, 2409–2421.e3. https://doi.org/10.1016/J.NEURON.2022.05.007.

187. Paulk, A.C., Kfir, Y., Khanna, A.R., Mustroph, M.L., Trautmann, E.M., Soper, D.J., Stavisky, S.D., Welkenhuysen, M., Dutta, B., Shenoy, K.V., et al. (2022). Large-scale neural recordings with single neuron resolution using Neuropixels probes in human cortex. Nat. Neurosci. *25*, 252–263. https://doi.org/10.1038/S41593-021-00997-0.

188. Pryluk, R., Kfir, Y., Gelbard-Sagiv, H., Fried, I., and Paz, R. (2019). A Tradeoff in the Neural Code across Regions and Species. Cell *176*, 597–609.e18. https://doi.org/10.1016/J.CELL.2018.12.032.

189. Narayanan, N.S., Cavanagh, J.F., Frank, M.J., and Laubach, M. (2013). Common medial frontal mechanisms of adaptive control in humans and rodents. Nat. Neurosci. *16*, 1888–1895. https://doi.org/10.1038/nn.3549.

190. Cash, S.S., and Hochberg, L.R. (2015). The emergence of single neurons in clinical neurology. Neuron *86*, 79–91. https://doi.org/10.1016/J.NEURON.2015.03.058.

191. Johnson, E.L., Dewar, C.D., Solbakk, A.K., Endestad, T., Meling, T.R., and Knight, R.T. (2017). Bidirectional Frontoparietal Oscillatory Systems Support Working Memory. Curr. Biol. *27*, 1829–1835.e4. https://doi.org/10.1016/J.CUB.2017.05.046.

192. Salazar, R.F., Dotson, N.M., Bressler, S.L., and Gray, C.M. (2012). Content-specific fronto-parietal synchronization during visual working

memory. Science *338*, 1097–1100. https://doi.org/10.1126/SCIENCE.1224000.

193. Berger, B., Griesmayr, B., Minarik, T., Biel, A.L., Pinal, D., Sterr, A., and Sauseng, P. (2019). Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. Nat. Commun. *10*, 4242. https://doi.org/10.1038/S41467-019-12057-0.

194. Riddle, J., Scimeca, J.M., Cellier, D., Dhanani, S., and D'Esposito, M. (2020). Causal Evidence for a Role of Theta and Alpha Oscillations in the Control of Working Memory. Curr. Biol. *30*, 1748–1754.e4. https://doi.org/10.1016/J.CUB.2020.02.065.

195. Hosseinian, T., Yavari, F., Kuo, M.F., Nitsche, M.A., and Jamil, A. (2021). Phase synchronized 6 Hz transcranial electric and magnetic stimulation boosts frontal theta activity and enhances working memory. Neuroimage *245*, 118772. https://doi.org/10.1016/J.NEUROIMAGE.2021.118772.

196. Reinhart, R.M.G., and Nguyen, J.A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat. Neurosci. *22*, 820–827. https://doi.org/10.1038/S41593-019-0371-X.

197. Shadlen, M.N., and Newsome, W.T. (1996). Motion perception: seeing and deciding. Proc. Natl. Acad. Sci. USA *93*, 628–633. https://doi.org/10.1073/PNAS.93.2.628.

198. Brunel, N., and Wang, X.J. (2001). Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. J. Comput. Neurosci. *11*, 63–85. https://doi.org/10.1023/A:1011204814320.

199. Durstewitz, D., Seamans, J.K., and Sejnowski, T.J. (2000). Neurocomputational models of working memory. Nat. Neurosci. *3*, 1184–1191. https://doi.org/10.1038/81460.

200. Wang, X.J. (1999). Synaptic basis of cortical persistent activity: the importance of NMDA receptors to working memory. J. Neurosci. *19*, 9587–9603. https://doi.org/10.1523/JNEUROSCI.19-21-09587.1999.

201. Brody, C.D., Hernández, A., Zainos, A., Lemus, L., and Romo, R. (2002). Analysing neuronal correlates of the comparison of two sequentially presented sensory stimuli. Philos. Trans. R. Soc. Lond. B Biol. Sci. *357*, 1843–1850. https://doi.org/10.1098/RSTB.2002.1167.

202. Machens, C.K., Romo, R., and Brody, C.D. (2010). Functional, but not anatomical, separation of "what" and "when" in prefrontal cortex. J. Neurosci. *30*, 350–360. https://doi.org/10.1523/JNEUROSCI.3276-09.2010.

203. Machens, C.K., Romo, R., and Brody, C.D. (2005). Flexible control of mutual inhibition: a neural model of two-interval discrimination. Science *307*, 1121–1124. https://doi.org/10.1126/SCIENCE.1104171.

204. Durstewitz, D. (2003). Self-organizing neural integrator predicts interval times through climbing activity. J. Neurosci. *23*, 5342–5353. https://doi.org/10.1523/JNEUROSCI.23-12-05342.2003.

205. Wang, J., Narain, D., Hosseini, E.A., and Jazayeri, M. (2018). Flexible timing by temporal scaling of cortical responses. Nat. Neurosci. *21*, 102–110. https://doi.org/10.1038/S41593-017-0028-6.

206. Durstewitz, D., Vittoz, N.M., Floresco, S.B., and Seamans, J.K. (2010). Abrupt transitions between prefrontal neural ensemble states accompany behavioral transitions during rule learning. Neuron *66*, 438–448. https://doi.org/10.1016/J.NEURON.2010.03.029.

207. Brenner, M., Hess, F., Mikhaeil, J.M., Bereska, L.F., Monfared, Z., Kuo, P.-C., and Durstewitz, D. (2022). Tractable Dendritic RNNs for Reconstructing Nonlinear Dynamical Systems. In Proceedings of the 39th International Conference on Machine Learning, *162*, K. Chaudhuri, S. Jegelka, L. Song, C. Szepesvari, G. Niu, and S. Sabato, eds., pp. 2292–2320.

208. Koppe, G., Toutounji, H., Kirsch, P., Lis, S., and Durstewitz, D. (2019). Identifying nonlinear dynamical systems via generative recurrent neural networks with applications to fMRI. PLoS Comput. Biol. *15*, e1007263. https://doi.org/10.1371/JOURNAL.PCBI.1007263.

209. Kramer D., Bommer P.L., Tombolini C., Koppe G., Durstewitz D. (2022). Reconstructing Nonlinear Dynamical Systems from Multi-Modal Time Series. Preprint at arXiv. p. 11613–11633. https://doi.org/10.48550/arXiv.2111.02922

210. Pandarinath, C., O'Shea, D.J., Collins, J., Jozefowicz, R., Stavisky, S.D., Kao, J.C., Trautmann, E.M., Kaufman, M.T., Ryu, S.I., Hochberg, L.R., et al. (2018). Inferring single-trial neural population dynamics using sequential auto-encoders. Nat. Methods *15*, 805–815. https://doi.org/10.1038/S41592-018-0109-9.

211. Rajan, K., Harvey, C.D., and Tank, D.W. (2016). Recurrent Network Models of Sequence Generation and Memory. Neuron *90*, 128–142. https://doi.org/10.1016/J.NEURON.2016.02.009.

212. Schmidt, D., Koppe, G., Monfared, Z., Beutelspacher, M., and Durstewitz, D. (2019). Identifying nonlinear dynamical systems with multiple time scales and long-range dependencies. Preprint at arXiv. https://doi.org/10.48550/arxiv.1910.03471.

213. Hanson, J., Raginsky, M., Bayen, A., Jadbabaie, A., Pappas, G.J., Parrilo, P., Recht, B., Tomlin, C., and Zellinger, M. (2020). Universal Simulation of Stable Dynamical Systems by Recurrent Neural Nets. Proc. Mach. Learn. Res. *120*, 384–392.

214. Kimura, M., and Nakano, R. (1998). Learning dynamical systems by recurrent neural networks from orbits. Neural Netw. *11*, 1589–1599. https://doi.org/10.1016/S0893-6080(98)00098-7.

215. Schmidt D., Koppe G., Monfared Z., Beutelspacher M., Durstewitz D. (2021). Identifying Nonlinear Dynamical Systems with Multiple Time Scales and Long-Range Dependencies. ICLR 2021 Conference. https://openreview.net/forum?id=_XYzwxPlQu6

216. Paninski, L., Ahmadian, Y., Ferreira, D.G., Koyama, S., Rahnama Rad, K., Vidne, M., Vogelstein, J., and Wu, W. (2010). A new look at state-space models for neural data. J. Comput. Neurosci. *29*, 107–126. https://doi.org/10.1007/S10827-009-0179-X/FIGURES/6.

217. Yu, B.M., Cunningham, J.P., Santhanam, G., Ryu, S.I., Shenoy, K.V., and Sahani, M. (2009). Gaussian-process factor analysis for low-dimensional single-trial analysis of neural population activity. J. Neurophysiol. *102*, 614–635. https://doi.org/10.1152/JN.90941.2008.

218. Mante, V., Sussillo, D., Shenoy, K.V., and Newsome, W.T. (2013). Context-dependent computation by recurrent dynamics in prefrontal cortex. Nature *503*, 78–84. https://doi.org/10.1038/NATURE12742.

219. Yang, G.R., Joglekar, M.R., Song, H.F., Newsome, W.T., and Wang, X.J. (2019). Task representations in neural networks trained to perform many cognitive tasks. Nat. Neurosci. *22*, 297–306. https://doi.org/10.1038/S41593-018-0310-2.

220. Schrader, S., Grün, S., Diesmann, M., and Gerstein, G.L. (2008). Detecting Synfire Chain Activity Using Massively Parallel Spike Train Recording. J. Neurophysiol. *100*, 2165–2176. https://doi.org/10.1152/JN.01245.2007.

221. Harris, K.D., Csicsvari, J., Hirase, H., Dragoi, G., and Buzsáki, G. (2003). Organization of cell assemblies in the hippocampus. Nature *424*, 552–556. https://doi.org/10.1038/NATURE01834.

222. Foster, D.J., and Wilson, M.A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature *440*, 680–683. https://doi.org/10.1038/NATURE04587.

223. Russo, E., and Durstewitz, D. (2017). Cell assemblies at multiple time scales with arbitrary lag constellations. Elife *6*, e19428. https://doi.org/10.7554/ELIFE.19428.

224. Ikegaya, Y., Aaron, G., Cossart, R., Aronov, D., Lampl, I., Ferster, D., and Yuste, R. (2004). Synfire chains and cortical songs: temporal modules of cortical activity. Science *304*, 559–564. https://doi.org/10.1126/SCIENCE.1093173.

225. Russo, E., Ma, T., Spanagel, R., Durstewitz, D., Toutounji, H., and Köhr, G. (2021). Coordinated Prefrontal State Transition Leads Extinction of Reward-Seeking Behaviors. J. Neurosci. *41*, 2406–2419. https://doi.org/10.1523/JNEUROSCI.2588-20.2021.

226. Aljadeff, J., Gillett, M., Pereira Obilinovic, U., and Brunel, N. (2021). From synapse to network: models of information storage and retrieval in neural

circuits. Curr. Opin. Neurobiol. *70*, 24–33. https://doi.org/10.1016/J.CONB.2021.05.005.

227. Brockmann, M.D., Pöschel, B., Cichon, N., and Hanganu-Opatz, I.L. (2011). Coupled oscillations mediate directed interactions between prefrontal cortex and hippocampus of the neonatal rat. Neuron *71*, 332–347. https://doi.org/10.1016/J.NEURON.2011.05.041.

228. Meijer, E.J., Hermans, K.H.M., Zwanenburg, A., Jennekens, W., Niemarkt, H.J., Cluitmans, P.J.M., Van Pul, C., Wijn, P.F.F., and Andriessen, P. (2014). Functional connectivity in preterm infants derived from EEG coherence analysis. Eur. J. Paediatr. Neurol. *18*, 780–789. https://doi.org/10.1016/J.EJPN.2014.08.003.

229. Alyahyay, M., Kalweit, G., Kalweit, M., Karvat, G., Ammer, J., Schneider, A., Adzemovic, A., Vlachos, A., Boedecker, J., and Diester, I. (2023). Mechanisms of premotor-motor cortex interactions during goal directed behavior. Preprint at bioRxiv. https://doi.org/10.1101/2023.01.20.524944.

230. Adesnik, H., and Abdeladim, L. (2021). Probing neural codes with two-photon holographic optogenetics. Nat. Neurosci. *24*, 1356–1366. https://doi.org/10.1038/s41593-021-00902-9.

231. Akam, T., and Kullmann, D.M. (2014). Oscillatory multiplexing of population codes for selective communication in the mammalian brain. Nat. Rev. Neurosci. *15*, 111–122. https://doi.org/10.1038/nrn3668.