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Cognitive flexibility as the shifting of brain network flows by flexible neural representations

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Our ability to overcome habitual responses in favor of goal-driven novel responses depends on frontoparietal cognitive control networks (CCNs). Recent and ongoing work is revealing the brain network and information processes that allow CCNs to generate cognitive flexibility. First, working memory processes necessary for flexible maintenance and manipulation of goal-relevant representations were recently found to depend on short-term network plasticity (in contrast to persistent activity) within CCN regions. Second, compositional (i.e. abstract and reusable) rule representations maintained within CCNs have been found to reroute network activity flows from stimulus to response, enabling flexible behavior. Together, these findings suggest cognitive flexibility is enhanced by CCN-coordinated network mechanisms, utilizing compositional reuse of neural representations and network flows to flexibly accomplish task goals.

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Introduction

Here, I define cognitive flexibility broadly, as the ability to effectively pursue a wide variety of possible task goals, especially when overcoming habitual/automatic responses to do so [1]. As an example of highly flexible cognition, I will frequently return to rapid instructed task learning (also termed zero-shot learning), which is the ability to learn and perform novel tasks immediately upon instruction [2,3]. This article will end with the conclusion that cognitive flexibility is likely generated by shifts in brain network activity flows, driven by flexible goal-relevant neurocognitive representations. How will I get us to this conclusion? The story begins with a recent shift in perspective toward a network view of cognitive control and the role of distributed networks in generating cognitive flexibility.

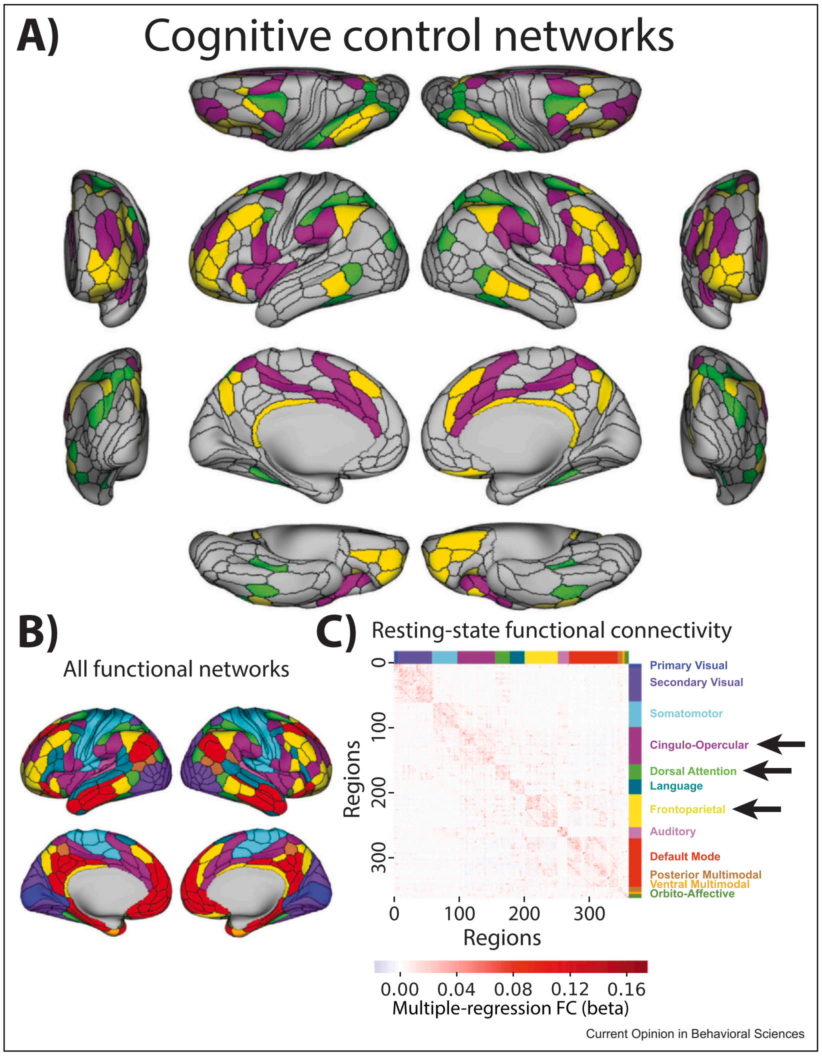
A brief history of cognitive control networks and their role in cognitive flexibility

Decades of research has established lateral prefrontal cortex as essential for cognitive control — the core set of abilities (e.g. working memory and inhibition [1]) underlying cognitive flexibility. This evidence comes primarily from human lesion studies [2] and non-human primate studies [3]. While there had been occasional reports of similar effects distal from lateral prefrontal cortex, two recent innovations increased acceptance in the field that *networks* are responsible for cognitive control abilities. These innovations were both methodological and theoretical.

First, neuroimaging matured past its focus on single regions, acknowledging distributed patterns of functional specialization throughout the brain. This broader focus resulted in evidence for a 'multiple demand' network — a set of regions involved in a wide variety of cognitive control-related functions — constituting the core of the cognitive control networks (CCNs) [4,5]. Importantly, these networks' involvement in a variety of functions has been thought to demonstrate their contribution to cognitive flexibility, especially the ability to flexibly perform a wide variety of possible tasks [6,7]. The assumption that these multiple- demand regions formed one or more network was subsequently corroborated by brain connectivity approaches, such as resting-state functional connectivity [5,8], ensuring these coactivation patterns were indeed brain networks. While the list of CCNs varies somewhat by atlas, most atlases include the frontoparietal network, the salience/cingulo-opercular network, and the dorsal attention network. Figure 1 shows a human brain atlas defined using resting-state functional connectivity [9].

A second innovation that supported a shift toward a network view of cognitive flexibility involved human lesion studies. These studies switched from single-patient reports to systematic multipatient mapping of lesion locations to cognitive abilities. This shift has revealed the causal contribution of distributed sets of

Figure 1



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CCNs. **(a)** Anatomical location of CCNs in the human cortex, parcellated into regions based on [10]. Yellow regions are part of the frontoparietal control network, purple regions are part of the cingulo-opercular network, and green regions are part of the dorsal attention network. Defined using resting-state functional connectivity by [9]. **(b)** All functional networks as defined by [9]. **(c)** A resting-state functional connectivity matrix (region by region), based on multiple-regression functional connectivity, which reduces causal confounds in functional connectivity estimation relative to the standard pairwise Pearson correlation approach [11]. The regions were ordered based on network affiliation. The CCNs are highlighted with arrows.

brain regions (rather than single regions) to cognitive control abilities [6] (but see [12]). For example, a recent study by Jiang et al. [13] used a database of lesion locations and cognitive scores to map emotion regulation ability. Emotion regulation can be considered an expression of cognitive control in the domain of emotion, and can be thought of as a form of cognitive flexibility. Jiang et al. found that a CCN, including the ventrolateral prefrontal cortex, was causally responsible for emotion regulation abilities. This CCN contrasted with a CCN connected with dorsolateral prefrontal cortex, which showed no such relationship. Thus, while CCNs overlap with a ‘multiple demand’ network [14–16], there is still some specialization among CCNs. Together, these findings support the existence of multiple CCNs that jointly support the remarkable ability of humans (and some other species) to flexibly pursue a variety of possible task goals.

Connectivity-based explanations for (activity-silent) working memory

The ability to maintain goals that differ from habitual/automatic behaviors is central to cognitive flexibility. Also important for flexibility is the ability to manipulate representations (e.g. perform mental arithmetic) in the service of goals. These abilities are made possible by working memory — the active maintenance and/or manipulation of goal-relevant information. In some sense, all cognitive control processes (and therefore cognitive flexibility) follow from the human brain's fundamental capacity for working memory [1]. Put simply, cognitive flexibility — the flexible pursuit of task goals — would not be possible without active maintenance of goal-relevant information (sometimes termed 'context') in working memory. With respect to this article's central thesis — that cognitive flexibility is generated by activity flow shifts driven by flexible representations — working memory is required to maintain these flexible goal-relevant representations so they can eventually be implemented as activity flow shifts.

Classically, sustained activity in the lateral prefrontal cortex has been considered the primary neural mechanism underlying working memory [17]. Yet, just like other cognitive control abilities, this view is giving way to considering distributed CCNs as the basis for working memory [18]. As this shift was beginning, however, it was also revealed that working memory can be maintained in some situations without sustained activity, based on multiunit lateral prefrontal cortical activity in non-human primates [19] and whole-brain electroencephalography (EEG) activity in humans [20,21]. Specifically, engaging in a secondary task (i.e. experiencing robust distractors) during a working memory delay can make the activity coding for working memory content drop to baseline levels.

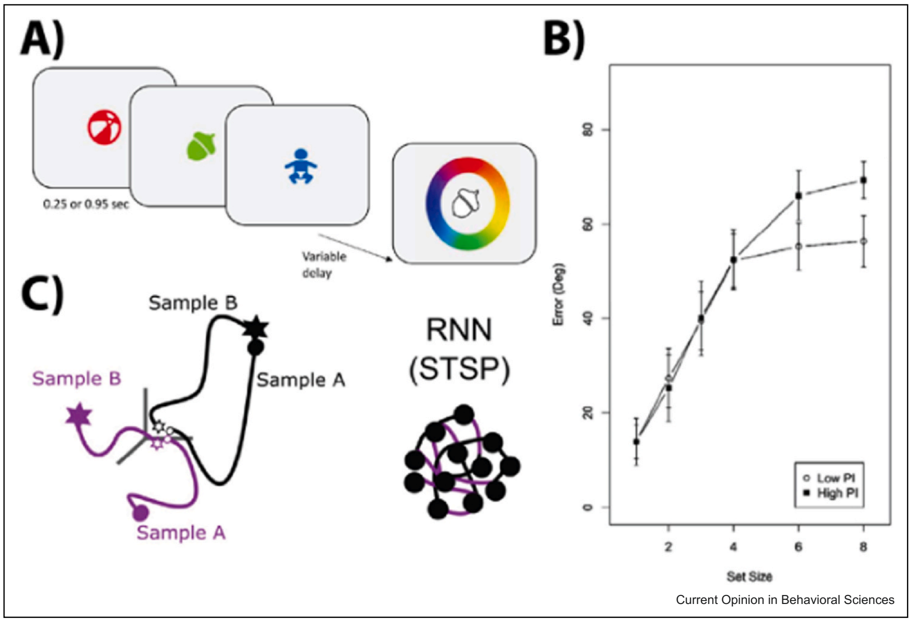
A recent theoretical account suggested that long-term memory encoding fills this gap [22], and therefore may be the true basis of cognitive flexibility rather than working memory. After all, the hippocampus is capable of rapidly encoding complex information in synaptic weights (i.e. long-term connectivity changes) that can easily span working memory delays in an activity-silent manner. This compelling theoretical account led to a clever behavioral study to test this hypothesis [23] (Figure 2a). The core insight driving this study was that a key advantage of working memory is reduced proactive interference (PI) relative to long-term memory. This prediction was leveraged into a group manipulation, in which one group of participants had stimuli reused across trials (to cause PI), whereas the other group saw new stimuli on each trial.

Briefly, across four experiments, Oberauer and Awh [23] found that PI had no effect on working memory performance (Figure 2b). This was the case across multiple stimulus types and even with a secondary task manipulation known to induce activity-silent working memory. This suggested that long-term memory encoding, which is more prone to PI, is unlikely to explain activity-silent working memory. Importantly, however, when the working memory set size exceeded working memory capacity (four items), PI did have an effect. Thus, long-term memory plays a role in working memory, but only when working memory capacity has been exceeded. This suggests cognitive flexibility is likely enhanced by long-range network interactions with the hippocampus, utilizing long-term memory mechanisms when working memory capacity is exceeded.

If rapid connectivity changes in the hippocampus are unlikely to explain activity-silent working memory, what plausible mechanisms are left? Kozachkov et al. [24] used computational modeling combined with empirical multiunit recording to test the hypothesis that short-term synaptic plasticity — brief connectivity changes within a CCN region (lateral prefrontal cortex) — could explain activity-silent working memory (Figure 2c). A series of computational models were tested, with direct comparison to non-human primate lateral prefrontal cortex multiunit activity during working memory task performance. They found that the models including a calcium-dependent short-term plasticity mechanism best matched the multiunit activity data. This contrasted with the more traditional working memory models that represented working memory content using persistent activity patterns within a recurrent neural network. Notably, both types of networks could perform working memory tasks in the presence of distractors, but only the short-term plasticity network did so with activity-silent delay periods. Further, they found that the short-term plasticity models were more robust to network degradation, suggesting some advantages of short-term plasticity that were potentially selected for by evolution.

Adding additional nuance to the role of network processes in working memory, two recent studies demonstrate that the hippocampus supports working memory even at small memory loads [25,26]. The first study used lesions to find that dorsal hippocampus supports spatial working memory in rats [25]. The second study found that human hippocampal lesion patients had impaired working memory [26]. This study went further, however, using location–color pairings (similar to Figure 2a but using spatial locations rather than objects) to show that the working memory impairment was a deficit in the *precision* or *fidelity* of the working memory content (e.g. forgetting the exact color associated with a location). An additional functional magnetic resonance imaging (fMRI) experiment with healthy humans showed hippocampal activity was associated with working memory precision. In combination with the Figure 2b results, these studies suggest that the hippocampus is able to somehow support working memory without increasing

Figure 2



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Evidence for short-term synaptic plasticity (a network mechanism within CCN regions) underlying activity-silent working memory. **(a)** The working memory paradigm used by [23], in which the color of the previously encoded item indicated on the last screen needed to be selected from a continuous color wheel. Set size varied from 1 to 8 across trials, with most prior evidence suggesting visual working memory capacity is approximately 4 items. PI between trials was higher in one group (high PI) than the other group (low PI), since items were reused with distinct colors across trials in the high-PI group. Long-term memory was expected to involve more PI, given that long-term memory content is (by definition) maintained longer and therefore more likely to interfere with future trials. **(b)** Working memory performance errors increased with set size, but differentiated between high- and low- PI groups only at the higher set sizes. This is consistent with long-term memory only being used for set sizes beyond working memory capacity (4 items). This suggests standard working memory does not utilize long-term memory, as previously hypothesized by others [22]. **(c)** A recent computational modeling study that directly compared model mechanisms to non-human primate prefrontal cortex activity [24] found evidence that activity-silent working memory involves short-term synaptic plasticity (i.e. transient within-prefrontal cortex connectivity changes). The working memory encoding neural activity trajectory (black lines) does not contain information after encoding (the endpoints do not differ by condition), whereas the connectivity patterns (purple lines) do contain information (the endpoints differ by condition).

PI, at least at low working memory loads. It will be important for future studies to investigate what this mechanism could be (e.g. short-term network plasticity within the hippocampus).

Together, these results suggest a nuanced account of the role of network processes in supporting cognitive flexibility: short-term synaptic plasticity within CCNs typically maintains goal-relevant representations. However, this is supplemented by long-range network interactions with the hippocampus, enhancing working memory precision and capacity. Further, it appears that this strategy at high working memory loads has the side effect of increasing information interference/conflict, likely reducing cognitive flexibility at higher working memory loads (relative to lower working memory loads).

Flexible network activity flows as the basis for cognitive flexibility

Once a goal representation has been loaded into working memory, how does it get implemented as behavior? As a matter of logic, the information maintained within CCNs (e.g. lateral prefrontal cortex) must directly or indirectly influence neural activity in primary motor cortex, such that the goal can be achieved via action. For example, when someone driving a car (with the goal of getting safely to a destination) approaches an intersection, the color red should trigger one foot-related motor response, whereas a green light should trigger another. These neural episodes, as with many situations in everyday life, involve the flexible/context-dependent flow of activity from the sensory cortex to motor cortex. Thus, network activity flow shifts between brain regions are central to the story of cognitive control and cognitive flexibility.

What neural mechanisms might account for the network activity flow shifts necessary to flexibly implement goals maintained in working memory? It may appear that rapidly flexible network changes are necessary for such context-dependent activity flow shifts. However, previous learning could have gradually set connectivity patterns such that distinct activity patterns from different stimulus inputs (e.g. a red vs. a green light) could lead to differential activity flows to distinct portions of motor cortex. Thus, static connectivity pathways have the potential to support highly flexible activity flows.

Consistent with this, a series of studies has shown that simulating the flow of activity using a static connectivity graph — structural connectivity or resting-state functional connectivity — is sufficient to predict task-condition-specific activations across a wide variety of brain regions [27–30]. Notably, these studies included multiple cognitive control tasks involving extensive cognitive flexibility. Further, a recent study using a single static network architecture (estimated using resting-state functional connectivity) showed that complex context-dependent behavior requiring extensive cognitive flexibility could be generated based on interactions between CCN activity flows and sensory input activity flows [31] (Figure 3).

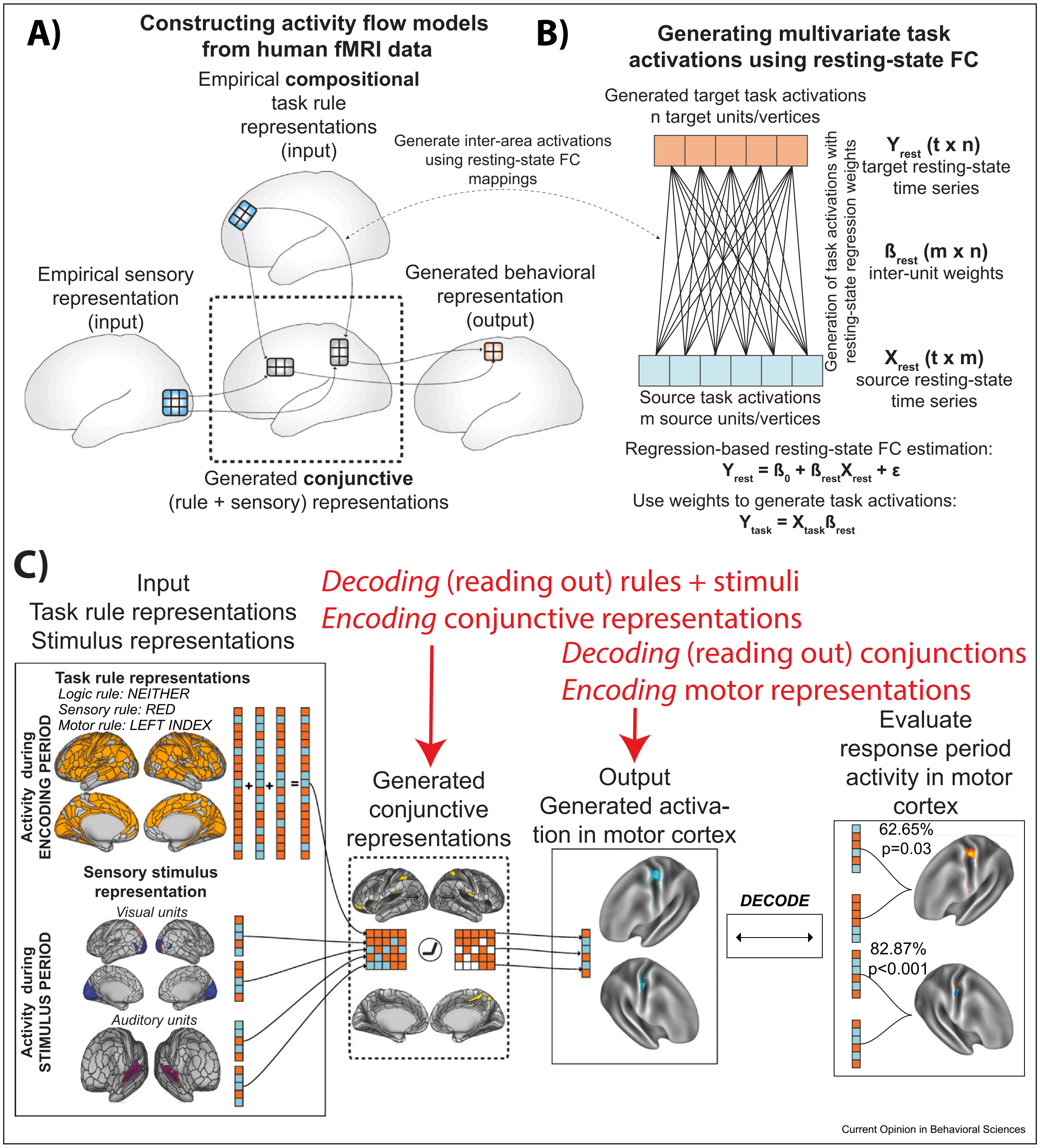
Briefly, this fMRI study began by localizing brain regions representing all task-relevant information, including sensory stimulus and flexible task rule representations, their interaction (conjunctions), and motor response representations (Figure 3a). Resting-state functional connectivity was then fit (using multiple regression) between these brain regions (Figure 3b), estimating what can be thought of as the brain's equivalent of artificial neural networks' connectivity weights. Finally, these pieces were put together, with flexible task rule representations and sensory inputs flowing into conjunction regions, which in turn flowed into motor response regions. The motor response activity patterns were then decoded, demonstrating that the model performed a variety of complex tasks above chance. Thus, the network flow dynamics generated by differential activity pattern inputs were sufficient to drive flexible cognitive behavior, with no need for flexible network changes. Notably, however, the model's behavior was not perfect, suggesting additional mechanisms (such as flexible network changes) may be necessary to achieve full human-level cognitive flexibility.

Further evidence that only static connectivity is sufficient to generate (at least basic) cognitive flexibility comes from a recent study suggesting each CCN region's functionality is defined by its unique connectivity pattern [32]. This study specifically showed that each CCN region's unique set of flexible task rule representations could be predicted based on that region's unique brain-wide static connectivity pattern. Together with the study illustrated in Figure 3, this study supports the notion that most task-evoked neural dynamics — even those involved in cognitive flexibility — originate from activity flowing over static network connections.

Is static connectivity all there is? A long literature has established that — despite overall similarity across states — functional connectivity can change depending on the task state [33,34]. A recent study went further, showing that using task-state functional connectivity from a given task (rather than resting-state functional connectivity) significantly improved activity flow predictions of task-evoked activations throughout the brain [27]. Thus, activity flows can shift either due to differential input activity patterns (as in Figure 3) or due to task-state functional connectivity changes. With regard to cognitive flexibility, it has been shown that these task-state functional connectivity changes likely play an important role during complex tasks requiring cognitive flexibility, with CCNs systematically shifting their global connectivity patterns depending on which task set is currently being utilized [35,36]. These results suggest that, despite contributing the minority of connectivity variance in most cases, task-state functional connectivity changes likely play an important role in the activity flow changes necessary for flexible cognition.

Despite their importance, the mechanisms underlying these task-state functional connectivities remain unclear. One possibility emphasized by Cole et al. [27] and Ito et al. [37] is that nonlinearities within each neural population (e.g. a sigmoid transfer function, as used in many neural network simulations) can account for much of the state-dependent connectivity changes. These results were based on fMRI-based and multiunit spiking-based functional connectivity. Another form of task-state functional connectivity involves neural oscillations. These functional connections are calculated using high-temporal-resolution data (e.g. local field potential or EEG recordings), based on phase-dependent coupling. In a recent study involving non-human primates, Lundqvist and colleagues showed evidence that working memory content is controlled by a 'push–pull' relationship between gamma- and beta-frequency coupling [38]. Briefly, it was observed that during working memory, encoding gamma and content-carrying spiking activity suppressed beta activity, whereas when working memory content was no longer needed, increased beta activity suppressed gamma activity and the corresponding content-carrying spiking activity. Further, it was shown that this basic mechanism controlled the spatial flows of activity between portions of lateral prefrontal cortex. Thus, a given neural population could be controlled by task-state functional connectivity changes specific to each frequency, with any of a variety of possible working memory contents flexibly stored in that neural population. The authors suggested that this flexible neural mechanism could facilitate flexible cognitive processes, such as generalization and rapid instructed task learning (also termed zero-shot learning).

Figure 3



(caption on next page)

Generating conjunctive control representations from compositional activity flows over static (resting-state) functional connections. **(a)** Flexible cognitive behavior requires the interaction (conjunction) between compositional rule and sensory representations. Ito et al. [31] constructed an empirical neural network (ENN) model to test whether resting-state functional connectivity patterns can account for how task-evoked activity patterns (neural representations) interact to produce conjunctive representations and subsequent behavior (motor representations). **(b)** Resting-state functional connectivity was computed using multiple regression on fMRI time series as subjects rested in the scanner. Fine-grained activity patterns between vertex patterns (fMRI voxels projected to the cortical surface) were estimated. Activity flow was then computed by multiplying the source activity patterns with the connectivity mappings to generate target activity in downstream brain regions. **(c)** The full ENN model, taking sensory and compositional rule representations as inputs (based on empirically observed task-evoked activations). Those inputs were then multiplied by the connectivity patterns to conjunction regions to generate conjunctive representations. A nonlinearity (rectified linear function) was necessary to produce the conjunctive representations. These generated activity patterns were then multiplied by connectivity with the primary motor cortex to generate motor activations. These motor activations were then decoded to determine what motor response was made, with high task performance accuracy (see far right of figure) resulting.

Notably, a recent study used intracranial EEG in humans to find similar effects of low-frequency (theta) functional connectivity changes in the control of working memory content [39].

The importance of control representations (compositions and conjunctions) in the rerouting of network activity flows underlying flexible behavior

A series of recent studies have emphasized the importance of *control representations* — localized activity patterns in the brain that represent cognitive control-relevant information — for cognitive flexibility [40–42]. These representations can be thought of as the working memory content described in previous sections, but with an emphasis on maintenance and implementation of the rules necessary for flexible task performance (rather than arbitrary stimuli). This could be something as simple as the rule 'A→left' (if you see the letter A, press the left button), or something as complex as one of the 64 tasks used in the study shown in Figure 3, such as "if both stimuli are vertical press your left index finger." Regardless of the complexity of the rule that the CCN activity pattern represents, that CCN activity pattern must somehow reroute network activity flows to flexibly implement task-appropriate actions [31].

One set of studies has emphasized the importance of conjunctive representations stored in CCNs for flexible cognition. For example, Kikumoto, Mayr, and Badre [42] showed how the nonlinear interaction of task rules, stimuli, and responses was important for action selection during a context-dependent cognitive control task. Similarly, Ito et al. [31] demonstrated that a nonlinear interaction between task rule representations and multiple incoming stimuli was instrumental in selecting the correct motor responses during complex content-dependent tasks (Figure 3c). This study was unique, however, in demonstrating not just that such conjunctive representations were present but also 1) how they were generated and 2) how they shifted activity flows to implement flexible task behavior. This involved simulating the flow of stimulus representations and task rule representations to what Ito et al. [31] termed 'conjunction hubs' — regions where stimulus and task rule representations interacted nonlinearly. These activity flows were simulated based on empirical task-evoked activations in the stimulus and task rule representing brain regions and their resting-state functional connections to conjunction hubs. Notably, simply adding the incoming stimulus and rule-related flows was not sufficient for the generation of conjunctive representations. Instead, a nonlinearity (a rectified linearity, or threshold) needed to be applied. After these nonlinear interactions, the resulting activity patterns then flowed to primary motor cortex, where they generated motor responses consistent with accurate task performance. Thus, the model not only demonstrated how the conjunctive representations were generated, but also how they implemented cognitive flexibility via cognitive interactions and eventual motor output (i.e. behavior).

Critically, Ito et al. [31] also demonstrated the importance of the opposite of conjunctive representations: compositional representations (Figure 3). Specifically, the rule representations used in the model were compositional, in the sense that the rules were reused across many combinations, composing a wide variety of context-dependent tasks (64 task sets). Notably, it was the nonlinear interaction of these compositional representations with stimulus representations that made them functional in the sense of generating task-implementing cognitive and motor representations. This demonstrates the potential for both compositional and conjunctive representations to increase cognitive flexibility. Indeed, it suggests that the network-based interaction of compositional and conjunctive representations may be key to allowing the generalization of knowledge/skill from previous experience (encoded in compositional representations) to be situated within a specific novel context via conjunctive representations.

The importance of compositional representations has been emphasized in the artificial intelligence and artificial neural network literatures as well. For example, Russin et al. [43] demonstrated the well-established 'catastrophic forgetting' effect in artificial neural networks, wherein learning new tasks leads to forgetting of previously learned tasks. However, Russin et al. [43] went on to show that adding a working memory layer to the artificial neural network, which maintained the current task context and modulated ‘hidden unit’ activity within the network, substantially reduced catastrophic forgetting. This suggests that the CCN-implemented working memory mechanisms discussed earlier may be sufficient to avoid catastrophic forgetting, which is the first step toward the kind of compositional learning and transfer of compositional representations to novel task scenarios emphasized above.

A more recent study found that standard artificial neural networks, which have long been thought to be incapable of extreme cognitive flexibility (e.g. rapid instructed task learning), are able to learn and systematically implement compositional representations (enabling rapid instructed task learning) after all [44]. This was achieved through a form of curriculum learning, wherein a variety of simple tasks built out of components (e.g. ‘skip’ and ‘jump twice’ combined as ‘skip twice’) were learned and linked to arbitrary instruction-like character strings. This was conceptualized as meta-learning (‘learning to learn’), an approach to training networks via systematically exposing the network to multiple tasks to facilitate learning additional new tasks [45]. These results suggest that compositional representations — and supposedly the conjunctive representations needed to implement them — are learnable within artificial neural networks given an appropriately compositional set of training tasks. It will be important to determine whether human development provides such training, or if some other inductive biases within the human brain facilitate the generation of compositional representations beyond training/experience.

Conclusions

Cognitive control processes and the flexible thoughts and behaviors they enable are fundamentally brain network processes. This has been shown by the existence of highly distributed CCNs that increase their activity with cognitive control demands [7] and represent a wide variety of control-related information [32]. Additional evidence comes from models suggesting a central role for within-CCN short-term synaptic plasticity in working memory maintenance [24], as well as data-driven models revealing a prominent role for network activity flows in generating conjunctive representations that implement context-dependent behavior [31]. While these studies demonstrate how fundamental brain network processes are to cognitive control, they reveal a vast space of exciting future studies to answer the many questions left regarding the network basis of flexible cognition. For example, despite some evidence that nonlinear interactions play a role [31], it remains unclear exactly how activity flow routing (e.g. from stimulus to response) is flexibly and rapidly updated according to task demands. More generally, the fundamental nature of task-state functional connectivity remains to be discovered — are such connectivity changes due to nonlinearities, oscillations, or short-term synaptic plasticity? — with major implications for understanding the dynamic routing of activity flows underlying flexible cognitive processes.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

No conflicts of interest to report.

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This important study is part of a series of studies by Kikumoto et al. that emphasizes the importance of conjunctive representations in cognitive control. Together, these studies establish the importance of interactions between representations in generating flexible cognition. These representational interactions likely occur via connectivity-based mechanisms, but more work is needed to establish the role of connectivity in these interactions and discover the exact mechanisms by which connectivity supports these interactions.

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