Dynamic reconfiguration of frontal brain networks during executive cognition in humans

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The brain is an inherently dynamic system, and executive cognition requires dynamically reconfiguring, highly evolving networks of brain regions that interact in complex and transient communication patterns. However, a precise characterization of these reconfiguration processes during cognitive function in humans remains elusive. Here, we use a series of techniques developed in the field of “dynamic network neuroscience” to investigate the dynamics of functional brain networks in 344 healthy subjects during a working-memory challenge (the “*n*-back” task). In contrast to a control condition, in which dynamic changes in cortical networks were spread evenly across systems, the effortful working-memory condition was characterized by a reconfiguration of frontoparietal and frontotemporal networks. This reconfiguration, which characterizes “network flexibility,” employs transient and heterogeneous connectivity between frontal systems, which we refer to as “integration.” Frontal integration predicted neuropsychological measures requiring working memory and executive cognition, suggesting that dynamic network reconfiguration between frontal systems supports those functions. Our results characterize dynamic reconfiguration of large-scale distributed neural circuits during executive cognition in humans and have implications for understanding impaired cognitive function in disorders affecting connectivity, such as schizophrenia or dementia.

dynamic network | working memory | graph theory | frontal cortex | flexibility

The era of human brain mapping has demonstrated the power of associating brain regions to specific cognitive functions. However, emerging evidence indicates that many so-called “domain-general” areas engage in multiple functions, differing from “domain-specific” areas such as primary visual cortex that perform a very specific function (1, 2). Such broad engagement is enabled by two fundamental features of brain function: time and interconnectivity. Brain areas and associated circuits or networks may be engaged in tasks differently over time: some transiently and some consistently (2, 3). A fundamental understanding of cognition in general and executive cognition in particular should therefore address the dynamic, interconnected nature of brain function.

Here, we use and extend emerging tools from “dynamic network neuroscience,” a field of neuroscientific inquiry that embraces the inherently evolving, interconnected nature of neurophysiological phenomena underlying human cognition (3, 4). Building on the formalism of network science (5), this approach treats the patterns of communication between brain regions as evolving networks and links this evolution to behavioral outcomes. Conceptually, this approach is particularly useful in examining the consistent or transient engagement of neural (or cognitive) circuits or putative functional modules (Fig. 1). We define a network module to be a set of brain regions that are strongly connected to each other and weakly connected to the rest of the network. Using dynamic network-based clustering techniques (6), we seek to observe the

flexible recruitment and integration of neural circuits underlying executive function in the form of working memory.

Working memory lies at the interface of perception and action (7) and requires the integration of large-scale neural circuits (8–11). Theoretical frameworks for working memory call on the interplay of distinct components (12) and their integration in broader cognitive circuits (1). The empirical neuroimaging literature has bolstered these conceptualizations by identifying several distinct sets of brain areas underlying working-memory performance (13–17). Nevertheless, a fundamental understanding of the flexible integration and recruitment of these circuits remains incomplete.

In the present study, we characterize the time-dependent interactions between putative neural circuits [network modules (3)] underlying working-memory performance in humans as elicited by an *n*-back task performed during the acquisition of functional MRI (fMRI) data (Fig. 1*A* and *B*). By deploying a sliding time window analysis (18, 19), we capture brain network dynamics during working-memory function (2-back), during a baseline condition

Significance

Cognitive flexibility is hypothesized to require dynamic integration between brain areas. However, the time-dependent nature and distributed complexity of this integration remains poorly understood. Using recent advances in network science, we examine the functional integration between brain areas during a quintessential task that requires executive function. By linking brain regions (nodes) by their interactions (time-dependent edges), we uncover nontrivial modular structure: groups of brain regions cluster together into densely interconnected structures whose interactions change during task execution. Individuals with greater network reconfiguration in frontal cortices show enhanced memory performance, and score higher on neuropsychological tests challenging cognitive flexibility, suggesting that dynamic network reconfiguration forms a fundamental neurophysiological mechanism for executive function.

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Fig. 1. Network reconfiguration during executive function. (A) We use a numerical n -back task consisting of 0-back and 2-back conditions. (B) We define 270 cortical and subcortical regions of interest (36), and (C) extract the mean time course from each region. (D) A sliding window comprising 15 volumes with no gap was applied to regional mean time courses, and for each window we estimated the functional connectivity between pairs of regions using coherence. This procedure resulted in a sequence of 114 time-ordered adjacency matrices. (E) Using a dynamic community detection algorithm (part 1 in panel), we identified network modules in each time window and tracked their evolution over time. (F) By estimating the probability that a brain region changes its allegiance to modules between any two consecutive time windows (part 2 in panel), we observed that whole-brain flexibility oscillated between unitask (2-back or 0-back only) and dual-task (2-back and 0-back in same time window) conditions.

(0-back), and in transitions between baseline and task (Fig. 1 C and D). We identify putative functional modules in each time window and track how brain regions change their engagement in these modules over time (Fig. 1 E and F). We quantify those changes over time by flexibility, which measures how often a particular brain region changes its modular allegiance. Based on the cognitive load of the 2-back condition (20–22), we hypothesize that the brain transiently reorganizes functional modules during task performance in comparison with baseline. Furthermore, we hypothesize that this reconfiguration is driven by higher order cognitive control systems, particularly in frontal cortex (2), which are known to play a role in task switching. Finally, based on prior evidence linking network reconfiguration to behavioral adaptation (3), we hypothesize that individuals who display more flexible network structures will perform better than individuals with more rigid network structures.

Results

Dynamics of Flexibility. How do cognitive systems interact as individuals perform a working-memory task? To answer this question, we must understand how network modules form and evolve during task execution. These processes can be revealed using a network-based clustering technique (6) applied to fMRI data acquired during task execution (3, 23–25). We first extracted

functional networks from overlapping time windows of fMRI data (Methods), and linked networks in consecutive time windows to form a multilayer network (e.g., a network of many time layers), providing important statistical benefits for the estimation of network modules (3, 6). Next, we performed a network-based clustering technique referred to as “dynamic community detection” to extract network modules: each network module corresponded to a set of brain areas that are coherently active in a single time window, forming a putative cognitive system. In essence, a region was assigned to a module composed of regions to which it was most densely connected, and not assigned to a module composed of regions to which it was sparsely connected. The set of fixed assignments of nodes to modules is referred to as a hard partition, and the goodness of this partition is statistically quantified by a modularity quality function (3, 6). Following module extraction, we quantified module evolution throughout the experiment by computing a time-dependent network flexibility: the time-dependent flexibility of a region was defined as the probability that a brain region changed its allegiance to putative functional modules between any two consecutive time windows, and the time-dependent flexibility of a person was defined as the average regional flexibility over all brain areas included in the network. Intuitively, flexibility can be thought of as a statistic to quantify the amount of reconfiguration in functional connectivity patterns that a brain region displays over time.

We observed that the time-dependent network flexibility oscillates across task execution, reaching clear maxima in time windows dominated by either the 2-back or 0-back (baseline) conditions [Fig. 1F; repeated-measures ANOVA with condition as factor: $F_{(2,343)} = 20.75$, $P < 0.001$]. This increase in brain-wide flexibility was not modulated by cognitive load: whole-brain flexibility was not significantly different between the 2-back and 0-back conditions [post hoc paired t test: $t_{(343)} = 1.31$, $P = 0.19$].

Dynamic Network Reconfiguration. Although the changes in flexibility indicate network reconfiguration dynamics, they do not address the cognitive systems engaged. To uncover these systems and isolate their reconfiguration properties, we next identified the modules of the multilayer networks by distilling a consensus partition of brain regions into network modules that was most representative of all subjects and all times for each level of cognitive load separately (Fig. 2 A and B). Several modules were consistently identified in both the 0-back and 2-back conditions: somatomotor, visual, subcortical, and hippocampal modules. However, the two conditions differed markedly in frontal-mediated modules (Fig. 2C). First, the frontoparietal module was composed of more medial structures in the 0-back condition, and more lateral structures in the 2-back condition; in the 2-back condition, this module also prominently included several regions in the left dorsolateral prefrontal cortex that were missing in the control condition. Second, in the 2-back condition a module consisting of nodes in the right prefrontal cortex dissociated from the bilateral frontotemporal module detected during the 0-back condition. To quantify these results, we compared the consensus partitions for both conditions and each subject separately for frontal and nonfrontal regions using a z score of the Rand coefficient (25, 26), which quantifies the similarity between two partitions. A paired t test on the z score for frontal vs. nonfrontal regions showed a significantly higher similarity for nonfrontal regions [$t_{(343)} = -10.32$, $P < 0.001$], supporting the visually marked differences between frontal and nonfrontal modules.

These findings are conceptually consistent with previous results on the structure of working-memory networks (7, 27) involving frontotemporal and frontoparietal systems, and indicate that a reconfiguration between conditions is most prominent in frontal and frontal-related systems.

We next asked how individual modules differentially reconfigure within both conditions. Each identified cognitive system contributed differently to the observed brain-wide flexibility that dominated

Fig. 2. Evolving network organization. (A) To determine whether cognitive systems are transiently or consistently recruited during task execution, we construct a modular allegiance matrix T by computing the contingency matrix N for each window: the element N_{ij} is equal to 1 if nodes i and j are in the same module and is equal to zero otherwise. We sum all contingency matrices for each condition to obtain the modular allegiance matrix T , whose elements T_{ij} indicate the fraction of time windows in which nodes i and j have been assigned to the same module. We then apply a community detection algorithm to T to obtain a “consensus partition” (25), which represents the common modular structure across all time windows. (B) The modular allegiance matrices for the 0-back condition (Left) and 2-back condition (Right). The letter beneath the block diagonal elements indicates the network module identified in the consensus partition: F, frontal; FP, fronto-parietal; FT, frontotemporal; H, hippocampal; O, occipital; P, parietal; PF, right prefrontal; S, subcortical; SM, somatomotor. (C) A mapping of the frontal modules obtained in B to their brain coordinates for the 0-back (Left) and 2-back condition (Right); labels are as in C. (D) Frontal systems show high integration during 2-back, whereas during 0-back occipital and parietal systems show an equally strong interaction. Error bars indicated SEs of mean over partitions belonging to either to 0-back or 2-back conditions.

0-back and 2-back condition time windows. We calculated the flexibility of each network module in the consensus partition. During the 2-back condition, flexibility was highest in fronto-related systems [repeated-measures ANOVA with modules as categorical factor: $F_{(8,343)} = 29.95$, $P < 0.001$; post hoc paired t test between frontal-related and nonfrontal modules: $t_{(343)} = 9.42$, $P < 0.001$]. This pattern was conserved during the 0-back condition [$F_{(7,343)} = 11.75$, $P < 0.001$; post hoc paired t test between fronto-related and nonfrontal modules: $t_{(343)} = 4.98$, $P < 0.001$]. However, flexibility was more evenly distributed in the 0-back condition between systems as evidenced by a significant main effect of task and significant interaction in a two-way repeated-measures ANOVA with task and

frontal vs. nonfrontal as categorical factors [main effect of task: $F_{(1,343)} = 6.25$, $P < 0.013$; effect of interaction: $F_{(1,343)} = 16.5$, $P < 0.001$]. These findings were robust to variations in the connectivity method (correlation instead of coherence), parameter selection in the community detection algorithm, and changes in the window size (SI Results, Robustness of Results).

Flexibility can be driven by transient interactions between modules: the more transient module–module interactions, the more likely regions are to flexibly alter their allegiance to cognitive systems. We estimated the transience of module–module interaction by averaging all elements of the module allegiance matrix T that link nodes in two different modules; we refer to this quantity as “integration” (24). Consistent with our earlier results, we observed higher integration in frontal systems than non-frontal systems in the 2-back condition, whereas in the 0-back condition we observed similar integration in both frontal and occipital-parietal systems (Fig. 2D). These results suggest that dynamic network reorganization is taking place predominately in frontal systems and is driven by a constant readaptation and interaction of frontal systems with each other.

Role of Frontal Systems in Executive Functioning. Based on our finding that whole-brain flexibility is driven by reconfiguration of and between fronto-related systems, we explored the relationship between frontal flexibility and cognitive performance. We used an α -level of 0.05 for all statistical tests and report both false-discovery rate (FDR) and Bonferroni-corrected P values. We interpret results that do not pass Bonferroni correction as exploratory. During the 2-back working-memory condition, frontal flexibility was positively correlated with task accuracy (Fig. 3A; Spearman’s rank correlation coefficient $r = 0.12$, $P_{\text{FDR-corrected}} = 0.04$, $P_{\text{Bonferroni}} = 0.2$), supporting the conclusion that higher frontal flexibility is cognitively beneficial for working-memory performance.

As noted in the previous section, an important driver of flexibility is the strength of module–module integration, which can be used to

Fig. 3. Role of frontal systems in executive functioning. (A) The flexibility in the frontal cortex during 2-back is positively correlated with 2-back task accuracy, measured in percentage of right answers. (B) Integration, as the contribution to flexibility that is due to between-module reconfiguration, shows an even stronger association with task accuracy. (C and D) Furthermore, frontal integration is related to other cognitive measures as shown by correlation with the performance in the digit span test (backward, measured in number of correctly remembered items) and the performance in the trail-making test B (TMT-B, measured in seconds to task completion).

Integration Between Cognitive Modules. The simultaneous existence of flexible reconfiguration and a conserved modular structure is made possible by time-dependent integration between cognitive modules. As modules become more integrated, regions can change their allegiance to modules more quickly, potentially forming bridges of communication. Critically, we observe that network modules differ in their degree of integration with other network modules: stable core-like modules including visual and somatomotor systems show relatively weak integration with other modules, whereas frontal and frontal-mediated modules show relatively strong integration with other modules (Fig. 2D). This finding is consistent with prior work from Fornito et al. (33), showing that the frontal network displays extensive cooperation during task execution, and further complements a recent study from Cole et al. (31) demonstrating that the frontoparietal network displays a high variance in connectivity over different tasks (*Supporting Information*).

The large variation in integration across these modules suggests that cognitive systems play different roles in executive function predicated on the degree of interconnectivity with other systems. It is intuitively plausible that the strong integration of frontal systems with other network modules forms a physiological basis for cognitive flexibility (15, 41), enabling task switching and cognitive control during demanding tasks (21, 42).

Behavioral Relevance of Flexibility and Integration. Using FDR correction methods for multiple-comparisons testing, we observed that frontal flexibility and integration were correlated with working-memory accuracy during the 2-back condition. As exploratory findings, some of which did not pass Bonferroni correction, these dynamic network correlates of behavior complement and extend prior observations from static network analyses (43–45). The specificity of these correlations to the frontal systems suggests that network reconfiguration may form a putative neurophysiological mechanism of cognitive flexibility and executive function more generally (16). Indeed, this hypothesis is supported by the fact that frontal integration was associated with both the backward digit span scores (measuring active information manipulation) and TMT-B scores (measuring executive flexibility), further highlighting the critical importance of intersystem connectivity in the successful execution of more cognitively demanding tasks.

Methodological Limitations. Our findings are subject to several methodological considerations. First, we use a dynamic community detection algorithm to cluster brain regions into coherently activated communities. However, due to heuristics in the algorithm and challenges inherent to fMRI data, the assignment of nodes to communities on the individual subject level remains a statistical process, accompanied by some degree of uncertainty. Second, although we aim at a description of dynamic reconfiguration, we remain limited by the temporal resolution of fMRI data, making it likely that the modular changes and behavioral associations we observed might be further resolved in time if electrophysiological data were used. Third, we use a measure of functional connectivity that does not reflect causal interaction. Future studies might benefit from using model-based methods for effective connectivity such as dynamic causal modeling or structural equation modeling to estimate causal interactions between a smaller subsets of brain regions. Fourth, we study a hard partition of nodes into communities, which has the advantage of providing a parsimonious estimate of the module allegiance matrix that is robust to noisy measurements of functional connectivity between brain regions. Should soft partitioning methods be extended to temporal networks, they might provide complementary insights into the nature of changing community assignments. Fifth, although the n -back task is a well-studied manipulation of working-memory capacity, the structure of the task makes it difficult to distinguish the cognitive

subprocesses of working-memory maintenance and information manipulation (46). Finally, the behavioral correlations we observed are small and some fail to reach statistical significance under Bonferroni correction, and therefore should be interpreted with caution and validated in future studies. However, these relationships do explain additional variance in comparison with more traditional approaches, highlighting the importance of small contributions to the highly complex phenotype of brain network dynamics.

Conclusions

Here we characterize the dynamic nature of neural processes during working-memory performance, which stems from the reconfiguration of large-scale distributed neural circuits rather than from the activity of isolated brain areas. Starting from a data-driven approach to cluster brain regions into communities, we track changes in network reconfiguration to frontal-related systems and show that the adaptive nature of the frontal cortex is relevant for cognitive functioning. Our study demonstrates the power of dynamic network neuroscience approaches to the study of cognition and behavior in humans. A better characterization of how dynamic reconfiguration of networks relates to cognition should also advance our understanding of disorders in which prominent cognitive disturbance arises from developmental (e.g., autism or schizophrenia) or degenerative pathologies (e.g., dementia).

Methods

Participants, Data Acquisition, and Preprocessing. For a group of 344 healthy volunteers (180 women; mean age, 33; range, 18–51 y) as part of a multicenter study (35), blood oxygen level-dependent fMRI was acquired while subjects were performing the n -back task. All participants provided written informed consent for protocols approved by the institutional review boards of the Medical Faculty Mannheim of the University of Heidelberg, the Medical Faculty of the University of Bonn, and the Charité–University Medicine Berlin. Data were preprocessed according to standard protocols as previously described in refs. 47 and 48. After preprocessing, the mean time series in 5-mm spheres around coordinates defined by ref. 36 were extracted. For reasons of brain coverage, six additional coordinates were added based on metaanalytical studies. After applying a sliding time window with the length of 15 volumes and no gap between windows as suggested by Leonardi et al. (49), we used the Morlet wavelet transform to estimate the functional connectivity between each pair of brain regions in the frequency interval 0.08–0.15 Hz, as described previously (3). For each subject, this procedure yielded 114 weighted adjacency matrices describing the functional connectivity in each time window.

Identifying Putative Functional Modules. For each subject, the resulting matrices were partitioned into time-respecting modules using a multilayer community detection algorithm introduced in the study by Mucha et al. (6) and first applied to neuroimaging data in ref. 3. Due to heuristics in the algorithm and near degeneracy of the modularity landscape, individual runs of the algorithms could produce slightly different partitions of nodes into modules. As a common approach to dealing with this degeneracy, we repeated the modularity estimation 100 times for each subject (25). For each repetition, we calculated the flexibility change matrix F , whose binary elements F_{ij} indicate if node i changes its module between two consecutive time windows. Averaging over all repetitions, we obtain the flexibility matrix for each subject, whose elements indicate the probability that a brain region changes its allegiance to putative functional modules between any two consecutive time windows.

Consensus Partitions and Integration. To find a consensus partition that is most representative of the underlying community structure, we applied a consensus algorithm as described in detail in ref. 25. In short, to find a consensus partition S that is most representative of a number n of given partitions $C_1, C_2, \dots, C_n$, we computed for each partition $C_1, C_2, \dots, C_n$ its modular allegiance matrix T whose binary elements T_{ij} indicate if two nodes i and j have been assigned to the same module or not. Summing up all modular allegiance matrices, we obtained the consensus matrix T_{cons} , the elements of which indicate how often two nodes have been assigned to the same module. To account for noise, only elements whose assignments were higher than in an appropriate random null model were taken into account. By running a community detection algorithm on the

consensus matrix T_{consr} we obtained a consensus partition S that is most representative of the underlying structure in the initial partitions.

Further details on the methods and materials can be found in [Supporting Information](#).

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