Network Modularity as a Foundation for Neural Reuse

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The neural reuse framework developed primarily by Michael Anderson proposes that brain regions are involved in multiple and diverse cognitive tasks and that brain regions flexibly and dynamically interact in different combinations to carry out cognitive functioning. We argue that the evidence cited by Anderson and others falls short of supporting the fundamental principles of neural reuse. We map out this problem and provide solutions by drawing on recent advances in network neuroscience, and we argue that methods employed in network neuroscience provide the means to fully engage in a research program operating under the principles of neural reuse.

1. Introduction. The *neural reuse* framework developed primarily by Michael Anderson offers a valuable and potentially revolutionary way to understand the neural underpinnings of cognitive functioning (Anderson 2007, 2010, 2015, 2016; Anderson, Kinnison, and Pessoa 2013; Anderson and Penner-Wilger 2013). Neural reuse maintains that brain regions are involved in multiple and diverse cognitive tasks and that brain regions flexibly and dynamically interact in different combinations to achieve a variety of cognitive functions (Anderson 2010, 2015). Accordingly, most cognitive functions are possible only because different brain regions are dynamically and functionally assembled, disassembled, and then redeployed in different combinations.

A research program operating under the principles of neural reuse departs from the aims of more traditional neuropsychology and cognitive neuroscience research. Much of the research from these disciplines has progressed by characterizing the functions of specific, localized brain regions using psychological manipulations. Anderson (2015) refers to this as the "what" strategy. For example, using functional magnetic resonance imaging (fMRI), a researcher

Received May 2017; revised March 2018.

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Philosophy of Science, 86 (January 2019) pp. 23–46. 0031-8248/2019/8601-0002$10.00
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https://doi.org/10.1086/701037 Published online by Cambridge University Press

might design a study in which participants engage in one task, A, that involves certain cognitive processes, $X_1 \ldots X_n$. Participants would then engage in another task, B, that is assumed to involve all the processes engaged in A plus another process of interest, Y. By subtracting the brain activity during A from B, the resultant neural activation is thought to be subserving process Y. This strategy—often referred to as the "subtraction method"—allows researchers to find either single or double dissociations in order to identify particular localized brain regions thought to subserve specific cognitive functions (Klein 2010, 2012; Bergeron 2016). Functional neuroimaging research employing these methods in healthy individuals is purportedly complemented by single and double dissociations identified in lesion studies; selective cognitive impairments have been documented in patients with fairly localized brain lesions (Bergeron 2007, 2016). Cognitive functions are ascribed to localized neural structures on the basis of the behavioral deficits accompanying such lesions.

Proponents of neural reuse instead argue that the brain typically achieves such diverse and varied cognitive functions by redeploying the same regions in a variety of circumstances, and the ways in which different regions functionally cooperate, or interact, bring about different cognitive functions (Anderson 2015). Each brain region operates as a member of many different interacting coalitions at multiple spatial scales for different purposes. Anderson (2010, 2015) seems to suggest that, when multiple brain regions are involved in carrying out a function in service of some task, relatively stable structure-function mappings can be obtained but that mapping includes the specification of functional interactions between brain regions. That is, whenever participant A engages in task X, the same set of functionally cooperating brain regions should subserve the task. However, those regions are likely redeployed to subserve other functions during other tasks in different combinations.

Neural reuse is an attractive general framework for understanding how the brain supports diverse cognitive functioning. But despite its promise, Anderson's evidence in support of the central tenets of neural reuse is, at best, incomplete. Moreover, the meta-analytic methods used by Anderson and colleagues to purportedly provide support for neural reuse do not allow researchers to engage in the research program moving forward, and to date no comprehensive set of methods has been offered to engage in new empirical research operating under the assumptions of neural reuse. We argue that by conceptualizing the brain as a large-scale, complex network and by drawing on recent advances in multivariate complex network analyses of task-evoked functional brain data, we can provide strong support for the fundamental principles of neural reuse. We can also offer a means to fully engage in empirical research operating under the assumptions of neural reuse to make new discoveries about the neural underpinnings of cognitive functioning. More specifically, we argue that conceptualizations of modularity in network science ($\text{modularity}_{\text{net}}$) along with recently developed data-driven $\text{modularity}_{\text{net}}$ algorithms provide the conceptual

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and methodological means to support the fundamental principles of neural reuse and to engage in a research program operating under these principles. Furthermore, modularity$_{net}$ offers a unique way to understand and investigate the neural underpinnings of cognitive functioning that is completely distinct from the varieties of modularity that Anderson (2015) criticizes.

To these ends, in section 2, we identify two fundamental guiding principles of neural reuse. In section 3, we provide a brief primer on complex brain networks, focusing primarily on how they are constructed from the underlying brain data. Then, in section 4, we show that the underlying assumptions made when employing modularity$_{net}$ algorithms in network neuroscience are consistent with the fundamental guiding principles of neural reuse. We also show that existing empirical research employing modularity$_{net}$ has provided support for the fundamental principles of neural reuse and that modularity$_{net}$ and related algorithms offer tools for further testing their validity. In section 5, we argue that the extant evidence allegedly supporting neural reuse only partially informs the fundamental principles of the framework and that the meta-analytic methods typically employed to provide support for neural reuse do not allow researchers to fully engage in the research program. We further argue that existing research using modularity$_{net}$ provides better evidence for the two fundamental principles of neural reuse and that using modularity$_{net}$ allows researchers to more fully develop the research program moving forward. Modularity$_{net}$ and complementary algorithms allow researchers to investigate how and to what extent functionally cooperating sets of brain regions assemble and disassemble across specific tasks and conditions and in different populations. Finally, in section 6, we conclude by briefly outlining how progress can be made by cognitive neuroscientists operating within the neural reuse research program.

2. Neural Reuse. In this section, we briefly contrast the underlying assumptions of neural reuse with those of other research programs in the cognitive neurosciences, and we identify the two fundamental guiding principles of neural reuse. Research in the cognitive neurosciences has traditionally operated under the assumption that cognitive functions can be straightforwardly mapped onto specialized, localized brain regions (Anderson 2015; Burnston 2016). For example, some have argued that a specific, localized neural structure on the ventral surface of the temporal lobe—the fusiform face area—is responsible for carrying out face perception (Kanwisher et al. 1997). By localizing functions to specific brain regions, researchers would, in theory, be able to decompose the entire system (i.e., the brain) into parts, characterize those parts in functional terms, and then explain the behavior of the system by appealing to the functions of the parts (Burnston 2016). Traditionally, the statistical methods used to arrive at these interpretations preclude researchers from making any claims whatsoever about functional interactions between brain regions.

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Instead, these methods are designed only to identify transient increases and decreases in activity within specific, circumscribed, localized regions.

More recently, however, Anderson (2015) and others have argued that specific neural structures are very rarely specialized to achieve specific cognitive functions. For example, Anderson (2015) argues that while Broca's area has traditionally been associated with language production, it is also involved in movement preparation, action sequencing, action recognition, imitation, and other functions. Similarly, insula activation has been associated with diverse functions, including gustation, empathy, disgust, pain, and attention (Menon and Uddin 2010; McCaffrey 2015).

As we discuss at length in what follows (esp. sec. 5), the evidence provided by Anderson and colleagues purportedly showing that brain structures are rarely specialized for specific functions mostly comes from large-scale meta-analyses of existing univariate activation results from hundreds of studies across diverse task domains (e.g., vision, attention, inhibition; Anderson and Pessoa 2011; Anderson et al. 2013). Generally speaking, univariate activation analyses are implemented to isolate the function(s) of individual brain regions, but they provide no information indicating whether or to what extent those regions are functionally connected with other brain regions. In addition to these activation-based meta-analyses, Anderson and Penner-Wilger (2013) performed a meta-analysis of functional connections between brain regions on the basis of results from hundreds of different studies broadly falling into 10 different task domains (e.g., attention, emotion, memory). This analysis allowed them to identify which brain regions were most often functionally connected within each task domain. Their results suggest that brain regions rarely share the same direct functional partners across these different task domains. Ultimately, Anderson (2015) suggests that the vast majority of brain regions are involved in many diverse cognitive functions and that the different interactions between rapidly and transiently assembled, functionally cooperating subsets of brain regions are actually responsible for carrying out cognitive functions. So, the functional interactions between brain regions are what really differentiate the ways in which cognitive functions are neurally instantiated.

Anderson (2015) offers two fundamental principles of neural reuse. The first fundamental principle of neural reuse (*Principle 1*, or the *Multifunction Principle*) is that brain regions are used and reused for diverse purposes in various task domains (Anderson 2015). Especially for higher-order cognitive functions, there is no one-to-one mapping of neural structure to cognitive function. The second fundamental principle (*Principle 2*, or the *Interaction Principle*) is that functional differences between task domains are critically reflected in the different patterns of interactions between many of the same elements forming the right neural team for a job (Anderson 2015). Sets of functionally cooperating brain regions are responsible for carrying out cognitive functions. These sets of functionally cooperating brain regions are thought to be consistently employed when a given person engages in the same task at different

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times. These two principles are not necessarily at work for the neural instantiation of every possible cognitive function; however, functional localization to specific, circumscribed brain regions is thought to be the exception rather than the rule (Anderson 2016). In sum, a given brain region will be involved in many different cognitive functions, and it will be involved in carrying out each function by uniquely interacting with certain other brain regions. These two principles form the foundation of neural reuse.

3. A Brief Primer on Complex Brain Networks. This section provides a brief overview of the concepts and methods for complex brain network analyses in contemporary cognitive neuroscience research. Modularity$_{net}$, like other graph metrics, describes the topological properties of networks using the formalisms of graph theory (Newman 2006). Graph-theoretic representations are used to model and characterize real-world networks (Rathkopf 2018). All graphs that model real-world networks are composed of differentiable elements of the system (nodes) and pairwise relationships between those elements (edges). In the context of human functional brain networks, each node represents a discrete parcellation (i.e., circumscribed, defined piece) of brain tissue, and edges represent measured functional interactions (connections) between pairs of nodes (for reviews, see Bullmore and Sporns 2009; Rubinov and Sporns 2010; Pessoa 2014).[1] More specifically, functional connections have traditionally been defined as temporal correlations, or statistical dependencies, between spatially remote neurophysiological events (Friston 2011). If there is a functional connection between two nodes, then those nodes are thought to be communicating or sharing information with each other in order to carry out some function. As a point of contrast, in human structural brain networks, nodes also represent discrete parcellations of brain tissue, but edges represent the number of white matter tracts, the average fractional anisotropy of tracts connecting nodes, or similarities in other structural neural properties (Bullmore and Sporns 2009; Sporns 2011; Hermundstad et al. 2013).

Adjacency matrices, or matrices in which both rows and columns are labeled by an ordered list of elements (nodes), represent the full set of nodes and connections for functional or structural networks (Pessoa 2014). If a connection, however it is defined in application, exists between two nodes, their

1. It is critical to make a distinction between functional activations and functional connections. Other multivariate techniques (e.g., representational similarity analysis or partial least squares analysis) are typically used to assess similarities or differences in functional activations. Statistically, this is traditionally done without reference to how that brain region is connected—directly or indirectly—to other brain regions. Modularity$_{net}$ and other graph metrics are computed by taking into account the set of connections between brain regions in the network. (We thank an anonymous reviewer for inviting us to clarify this point.)

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intersection in the matrix receives a value corresponding to whether there is a connection between the nodes (for a binary, unweighted network), the extent to which the nodes are connected (for a weighted network), or causal directionality between the nodes (for a directed network; Bullmore and Sporns 2009; Friston 2011). Figure 1 depicts an example of a binary adjacency matrix and the corresponding graph representation (adapted from Rathkopf 2018). The adjacency matrix A has six nodes (a–f); an edge (connection) exists between nodes if the intersection in the matrix is a 1, and an edge does not exist between nodes if the intersection in the matrix is a 0.

Figure 2 depicts an example of a weighted adjacency matrix and the corresponding graph representation. In figure 2, the adjacency matrix A also has six nodes (a–f); however, the strength of the connections between nodes, computed using a Pearson's correlation, can take different values between 0 and 1, with 0 indicating no relationship and 1 indicating the strongest possible relationship. The width of the edges in the graph represents the strength of the connections. To assess how $\text{modular}_{\text{net}}$ architectures change between cognitive tasks or conditions, $\text{modularity}_{\text{net}}$ algorithms have been implemented on both binary and weighted functional brain networks. (See Bullmore and Sporns [2009] for a detailed depiction of the steps implemented to create and analyze brain networks in practice.)

Graph theory provides a rigorous set of tools to quantitatively describe topological properties of complex systems such as the brain (Rubinov and Sporns 2010; Rathkopf 2018). The same graph metrics can be computed on any kind of network no matter how nodes and edges are defined in practice, and networks composed of entirely different kinds of nodes and edges can possess the same topological properties. We see this with functional brain networks, as they have been constructed using diverse methods and technologies, such as fMRI (e.g., Eguíluz et al. 2005; Achard and Bullmore 2007; Heitger et al. 2012), electroencephalography (EEG; e.g., Boersma et al. 2011), and

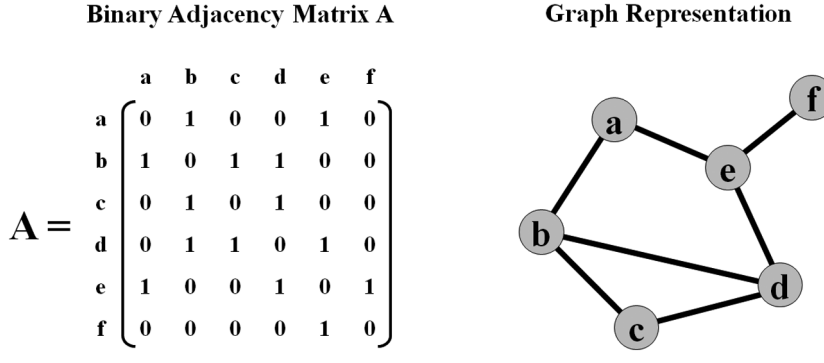


Figure 1.

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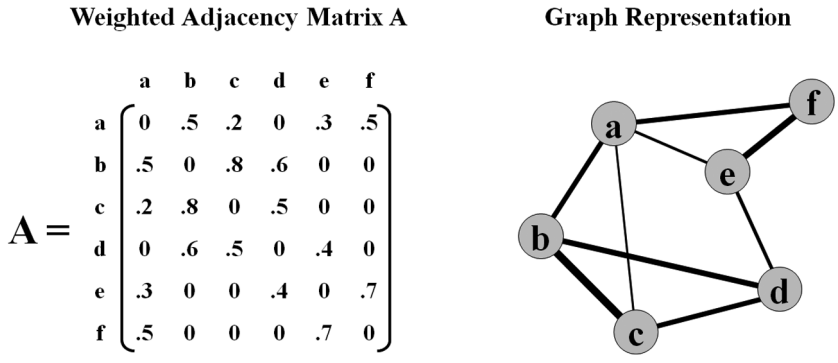


Figure 2.

magnetoencephalography (MEG) data (e.g., Stam et al. 2009). Additionally, structural brain networks have been constructed from both diffusion tensor imaging (DTI; e.g., Hagmann et al. 2008; Gong et al. 2009) and conventional MRI data (e.g., He, Chen, and Evans 2007).

Comparing different kinds of functional brain networks constructed using different technologies (e.g., fMRI, MEG, or EEG) at different spatial and temporal scales may allow for a more comprehensive analytic strategy for investigating the neural substrates of cognition (Sporns 2011). Once a brain network has been constructed from the underlying data—regardless of how nodes and edges were explicitly defined or the technology used to collect the data (e.g., fMRI, EEG, DTI)—the same set of graph metrics can be used to elucidate many different topological properties, both local and global, of the interactions between brain areas.

This allows researchers to compare topological properties of different networks that have been constructed using different technologies. For example, brain networks derived from fMRI, DTI, and MEG data all tend to possess a small subset of network hubs (van den Heuvel and Sporns 2013; Maldjian, Davenport, and Whitlow 2014). These hubs tend to have many widespread connections in the brain, and they are critical for efficient neuronal signaling and communication across a broad range of cognitive tasks (Cole et al. 2013). Assuming adequate computational power, graph metrics like modularity$_{net}$ can be computed on networks at any spatial or temporal scale, and different kinds of information can be extracted from the topology observed at different scales.

4. Modularity$_{net}$ and the Fundamental Principles of Neural Reuse. In this section, we show that the conceptual underpinnings of modularity$_{net}$ in network neuroscience are consistent with the fundamental principles of neural reuse. We also show that existing empirical research employing modularity$_{net}$ has

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provided support for them and that modularity$_{net}$ and related algorithms offer tools for further testing their validity (Stanley and De Brigard 2016).

Modularity$_{net}$ is perfectly compatible with both fundamental principles of neural reuse. Several different modularity$_{net}$ algorithms have been developed, but all modularity$_{net}$ algorithms are used to identify subsets of network nodes that are more densely interconnected among themselves than they are with other nodes in the network (Newman 2006; Sporns and Betzel 2016). For instance, using the modularity$_{net}$ algorithm developed by Blondel and colleagues (2008) for binary, unweighted networks, the extent to which a functional brain network can be partially decomposed into nonoverlapping modules$_{net}$ is quantified by the modularity$_{net}$ Q statistic. Mathematically, the value of Q assigned to a given network is ascertained as follows:

$$Q = \sum_{i=1}^{k} \left[\frac{e_{ij}}{M} - \left(\frac{a_i}{M} \right)^2 \right],$$

where e_{ij} is a measure of within-module$_{net}$ connections for module$_{net}$ i, a_i is the total number of connections in module$_{net}$ i, and M is the total number of connections in the entire network. Modularity algorithms are designed to maximize the value of Q (Blondel et al. 2008). Typically, the modularity$_{net}$ algorithm is run many times on a given network, and the run that produces the largest Q value is taken as the best partition. For the partition that produces the highest Q value, each node is assigned to a given module$_{net}$ in the network, and those assignments can be used to ascertain which nodes (if any) change module$_{net}$ allegiance (i.e., the module to which the node is assigned) during some new task or condition. Even though each node is assigned to a particular module$_{net}$, all information can still be shared between modules$_{net}$ via intermodule$_{net}$ connections (Telesford et al. 2011; Sporns and Betzel 2016).

Densely interconnected subsets of interacting brain regions (i.e., modules$_{net}$) that can be detected using modularity$_{net}$ algorithms are thought to be functionally cooperating to carry out certain cognitive functions (Sporns and Betzel 2016; Stanley and De Brigard 2016). Accordingly, modules$_{net}$ just are functionally cooperating groups of brain regions that dynamically assemble to carry out a cognitive function. The most commonly used modularity$_{net}$ algorithms in functional brain network analyses provide useful information about (1) the extent to which the entire system organizes itself into specific modules$_{net}$, (2) the spatial locations of nodes in each module$_{net}$, (3) the extent to which the nodes within each module$_{net}$ preferentially cooperate with nodes within their own module$_{net}$ versus nodes in other modules$_{net}$ in the system, and (4) the different functional roles of specific nodes within each module$_{net}$ in the system (Valencia et al. 2009; Telesford et al. 2011; Stanley et al. 2014; Sporns and Betzel 2016).

Modules$_{net}$ are not functionally autonomous, and individual nodes need not operate as singularly dedicated neural structures that must remain in only

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one module$_{net}$ across tasks (Telesford et al. 2016). Furthermore, given that brain networks are massively nonlinear systems, modules$_{net}$ are not separately modifiable. In functional whole-brain networks, all nodes in the network usually remain interconnected, albeit indirectly, via intermodule$_{net}$ connections (Telesford et al. 2011; Sporns and Betzel 2016). Removing or adding connections in the network will likely change the entire modular$_{net}$ architecture of the system. While modules$_{net}$ are not separately modifiable, autonomous, encapsulated processing units, they do still perform particular, specialized functions during certain tasks via the interactions between brain regions within each module$_{net}$ itself. As such, specific modules$_{net}$ are thought to perform specific functions, even though each module$_{net}$ remains interconnected with all other modules$_{net}$ in the system through intermodule$_{net}$ connections. For example, relative to the modules$_{net}$ identified during resting state, a module$_{net}$ identified in visual cortex had a more consistent and densely interconnected structure across participants when those participants were engaged in a visual task (i.e., watching a movie clip; Moussa et al. 2011). This module$_{net}$, consistently identified across participants in visual cortex, was composed of many different functionally cooperating brain regions working together to allow participants to perceive incoming visual information from the environment. Similarly, in another study conducted by Stanley and colleagues (2014), as a working memory task became more demanding, a consistent and densely interconnected functional module$_{net}$ assembled, which included posterior parietal and lateral prefrontal regions. Presumably, the spatially distributed brain regions functionally cooperating in the assembled module$_{net}$ during the more demanding working memory task facilitate performance on the task. Thus, modules$_{net}$ can capture principle 2 of neural reuse, namely, that interactions between particular subsets of brain regions are responsible for carrying out different cognitive functions.

In using modularity$_{net}$ algorithms to investigate neural reuse, nodes can change in module$_{net}$ allegiance between any set of tasks, if there are real differences in the neural teams that must be dynamically assembled to carry out those different tasks. If in fact nodes change their functional interactions to carry out new tasks by assembling new interconnected, functionally cooperating groups (modules$_{net}$), it is possible to identify which nodes shifted modular$_{net}$ allegiance and how they shifted. As such, one can empirically determine the extent of overlap (if any) in brain regions comprising different functionally cooperating teams carrying out two or more cognitive tasks. Figure 3 provides a conceptual example of how nodes might shift modular$_{net}$ allegiance between two cognitive tasks. Graphical depictions of functional brain networks are presented for three participants in a study. While in the fMRI scanner, each participant engages in cognitive task 1 and cognitive task 2. Separate functional brain networks are constructed for when participants engage in the respective cognitive tasks. After running the modularity$_{net}$ algorithm on these data, it was

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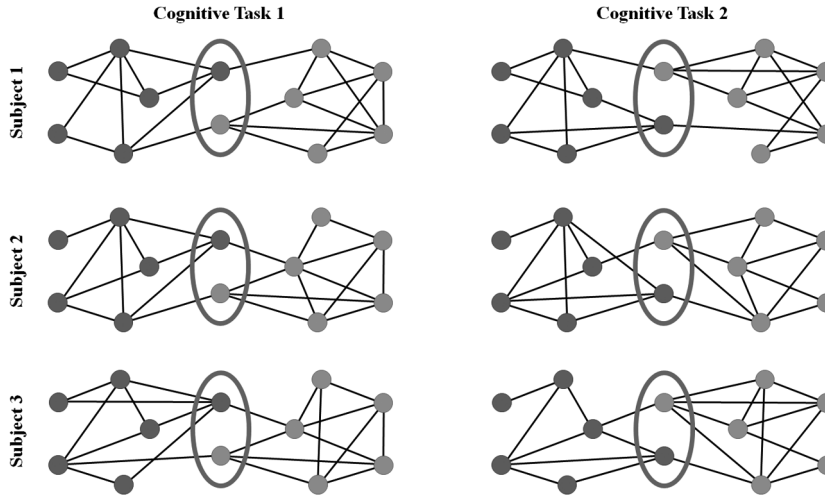


Figure 3. Color version available as an online enhancement.

determined that each participant had two different $\text{modules}_{\text{net}}$ during cognitive task 1 and cognitive task 2, respectively. Node color corresponds to $\text{module}_{\text{net}}$ assignment, which is determined by running the $\text{modularity}_{\text{net}}$ algorithm. Circled nodes (i.e., brain regions) change $\text{modular}_{\text{net}}$ allegiance between the two cognitive tasks consistently across the three participants.

Empirical research has shown that human functional brain networks exhibit a $\text{modular}_{\text{net}}$ architecture, but that architecture is neither temporally static nor anatomically fixed. Instead, nodes do indeed alter their interactions with other nodes in the network to form new $\text{modules}_{\text{net}}$ depending on the cognitive demands on the system (Moussa et al. 2011, 2014; Cao et al. 2014; Meunier et al. 2014; Stanley et al. 2014; Telesford et al. 2016). Thus, network nodes can and do change $\text{modular}_{\text{net}}$ allegiance, or reorganize themselves to form new functionally interacting groups of brain regions, between different cognitive tasks to carry out new functions. This satisfies both fundamental principles of neural reuse: the same brain regions (i.e., nodes) can be used and reused to achieve diverse cognitive functions, and the dynamically assembled, functionally cooperating groups of nodes are responsible for carrying out the cognitive function.

For more complex cognitive tasks, it is even possible that multiple different $\text{modules}_{\text{net}}$ will themselves need to interact more extensively to carry out the cognitive function. For example, during a motor skill learning task, occipital regions might consistently form one functional $\text{module}_{\text{net}}$ while sensorimotor regions form another $\text{module}_{\text{net}}$ (Bassett et al. 2015). Although nodes within these respective $\text{modules}_{\text{net}}$ may not change $\text{modular}_{\text{net}}$ allegiance over time,

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the number and strength of connections between these two modules$_{net}$ may increase or decrease over time as a function of learning (Bassett et al. 2015). Similarly, premotor regions may remain in one module$_{net}$ with other sensorimotor regions across different cognitive conditions, but these premotor regions may still interact more extensively with medial temporal lobe regions like the hippocampus, which belongs to a separate module$_{net}$, in order for individuals to make motor responses after correctly retrieving certain items from memory (Geib et al. 2017). So, even if a node does not change modular$_{net}$ allegiance between two or more tasks, entire modules$_{net}$ might become more strongly connected to each other in order to carry out the cognitive function. Just as it is possible for neural teams to functionally organize into one module$_{net}$ to carry out simple tasks, multiple modules$_{net}$ carrying out different subfunctions may need to more extensively interact to carry out more complex, cognitively demanding tasks. Accordingly, modularity$_{net}$ can be used to investigate the extent to which node assignment to modules$_{net}$ changes to subserve different cognitive functions. But modularity$_{net}$ can also be used to investigate the extent to which the strength or number of connections within or between modules$_{net}$ changes, even when node assignments to modules$_{net}$ remain the same. In other words, modularity$_{net}$ can characterize just how radical functional reorganization is across different tasks or conditions.

Because modularity$_{net}$ algorithms are data driven, the quantity of nodes forming any given module$_{net}$, the spatial locations of nodes within any given module$_{net}$, the consistency of modular$_{net}$ organization across a set of persons, and the extent of interconnectedness of nodes comprising each module$_{net}$ are determined by the nature of the functional brain network and not the experimenter (Newman 2006). Furthermore, modularity$_{net}$ algorithms are designed to admit the possibility that there are no clear, distinct modules$_{net}$ in the network. Consequently, modularity$_{net}$ serves both as a validation of neural reuse between different tasks and as a way to identify those functionally cooperating subsets of brain regions carrying out any task of interest. Modularity$_{net}$ makes no a priori assumptions about the selectivity of local neural structures for specific tasks. Instead, modularity$_{net}$ algorithms are entirely data driven. If local neural structures are not selective and typically contribute to many diverse tasks, then modularity$_{net}$ will show how neural structures (nodes) change modular$_{net}$ allegiances by reorganizing their connections for any set of tasks. If local neural structures are highly selective for certain functions, however, then modularity$_{net}$ algorithms will reveal that neural structures rarely change modular$_{net}$ allegiance by reorganizing their connections across different tasks. As more empirical research is published using modularity$_{net}$ and related algorithms, we will get a fuller picture of how and the extent to which each brain region alters its functional connections to achieve different cognitive functions.

There are at least two available quantitative methods for identifying the extent to which brain regions change modular$_{net}$ allegiance across different task

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conditions. These methods allow researchers to both test the validity of the fundamental principles of neural reuse and engage in a research program operating under the principles of neural reuse. That is, these methods allow researchers to investigate how functionally cooperating sets of brain regions assemble and disassemble across specific tasks and conditions and in different populations. One is the measure of *scaled inclusivity* (SI; Steen et al. 2011), which quantifies the extent to which particular nodes and $\text{modules}_{\text{net}}$ vary across different networks (within or between subjects) using set theory. SI is capable of computing how consistently each individual network node is classified in the same $\text{module}_{\text{net}}$ across networks of interest. SI is calculated by identifying the overlap of $\text{modules}_{\text{net}}$ across multiple networks in a standardized space while penalizing for the disjunction of modules. For instance, suppose node V is part of $\text{module}_{\text{net}}$ A in participant i and $\text{module}_{\text{net}}$ B in participant j. Then, SI for node V is calculated as

$$\text{SI}_{\text{V}} = \frac{|S_{\text{A}} \cap S_{\text{B}}|}{|S_{\text{A}}|} \frac{|S_{\text{A}} \cap S_{\text{B}}|}{|S_{\text{B}}|},$$

where S_{A} and S_{B} denote sets of nodes in $\text{modules}_{\text{net}}$ A and B, and $|\cdot|$ denotes the cardinality of the set. SI images represent the similarity in location and size of functional network $\text{modules}_{\text{net}}$ across a set of participant networks (Steen et al. 2011; Moussa et al. 2012; Stanley et al. 2014). Higher values of SI for a given network node indicate that the node is more frequently located within the same $\text{module}_{\text{net}}$ across participants, while lower values of SI indicate that the node is more frequently located within different modules.

Using SI, Stanley et al. (2014) showed that the nodes within the $\text{module}_{\text{net}}$ composed primarily of default-mode brain regions maintained a highly consistent, densely interconnected, functionally cooperating $\text{module}_{\text{net}}$ during a minimally demanding working memory task (i.e., the 1-back task). Because the 1-back task is so minimally demanding, participants can still perform the task while letting their minds wander to other matters. Therefore, it is not surprising that Stanley et al. (2014) identified a highly consistent $\text{module}_{\text{net}}$ encompassing default-mode regions during the 1-back task, just as they likely would during resting state. However, when more attentional and working memory resources were required to perform the task (i.e., when the participants changed tasks to engage in the 2-back task), the previously observed default-mode $\text{module}_{\text{net}}$ disassembled. During this different, more difficult working memory task, a different set of brain regions that included lateral prefrontal and parietal regions became densely interconnected, forming a new, consistent $\text{module}_{\text{net}}$ across persons. While Stanley et al. (2014) used SI to compute the consistency of $\text{modular}_{\text{net}}$ organization across participants for these two different working memory tasks (i.e., a 1-back task and a 2-back task), SI can also be computed on a nodal level to quantify the extent to which

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each network node changes $\text{modular}_{\text{net}}$ allegiance across diverse cognitive tasks for an individual person or a group of people.

The second, compatible approach for identifying the extent to which brain regions change $\text{modular}_{\text{net}}$ allegiance across different task conditions comes from recent developments in multilayer networks (Muldoon and Bassett 2016). Mucha and colleagues (2010) originally developed a unique variant of the $\text{modularity}_{\text{net}}$ algorithm that identifies how likely a given node is to remain within a $\text{module}_{\text{net}}$ over time or across multiple realizations of the network. In this way, each layer in a multilayer network constitutes a different unique network; a given layer might be constructed, for example, of a different subject, patient group, experimental condition, cognitive task, or time point (Muldoon and Bassett 2016). A node can exist in all layers or in a subset of layers and is linked throughout the layers by an edge representing the node's identity. Using multilayer networks, Bassett et al. (2015) examined changes in the $\text{modular}_{\text{net}}$ architecture of functional brain networks during several stages of learning in a simple sequence-production task. Their results show that two distinct motor and visual $\text{modules}_{\text{net}}$ were consistently identified across naive, early, middle, and late learning. However, the nodes comprising these two respective $\text{modules}_{\text{net}}$ became more preferentially interconnected with nodes in their own $\text{modules}_{\text{net}}$ (and therefore less connected with nodes in the other $\text{module}_{\text{net}}$) with task practice. These results suggest that the motor and visual $\text{modules}_{\text{net}}$ become more autonomous as the behavior becomes more automatic. Relatedly, Braun et al. (2015) showed that nodes in the $\text{module}_{\text{net}}$ comprising prefrontal brain regions changed $\text{module}_{\text{net}}$ allegiance as cognitive load increased on a standard working memory task. However, nodes in $\text{modules}_{\text{net}}$ comprising occipital and somatomotor regions did not change $\text{module}_{\text{net}}$ allegiance in the same way.

For the purposes of investigating neural reuse, a given layer might represent the network for a single cognitive task for a single person or a group of subjects. A probability matrix would then be constructed wherein each element in the matrix quantitatively represents the probability that those two nodes are assigned to the same network $\text{module}_{\text{net}}$ across the set of networks. Although Bassett et al. (2015) and Braun et al. (2015) originally characterized $\text{modular}_{\text{net}}$ allegiances as a function of a change in behavior within a particular cognitive domain (i.e., learning and working memory, respectively), more recent work has used multilayer networks to investigate how nodes alter their $\text{modular}_{\text{net}}$ allegiances across different cognitive tasks (Telesford et al. 2016). Specifically, Telesford et al. (2016) showed that across three distinct cognitive tasks, the pericalcarine cortex, lingual gyrus, and lateral occipital cortex did not change $\text{modular}_{\text{net}}$ allegiance, while the pallidum and parahippocampal gyrus did. This approach allows for the identification of the particular neural teams engaged for each cognitive task in each domain and for the characterization of how those neural teams reorganize across different tasks within and between

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domains. In the future, this technique may also help to understand how modular$_{net}$ allegiances change as a function of development as well as healthy and pathological aging (Sporns 2011; De Brigard 2017).

In sum, modules$_{net}$ in network neuroscience are conceptualized as subsets of brain regions that tend to be more functionally interconnected among themselves than with other brain regions. Modularity$_{net}$ algorithms can be used to identify which brain regions tend to interact among each other so that we can engage in a given cognitive task, and several methods have recently been developed to characterize the ways in which nodes (i.e., brain regions) change modular$_{net}$ allegiance between different kinds of cognitive tasks. Thus, it is possible to use these algorithms to rigorously characterize the extent to which different brain regions are used and reused for diverse purposes in various task domains and ways in which functional differences between task domains are reflected in the different patterns of interactions between many of the same elements forming the right neural team to carry out some cognitive task. In this way, modularity$_{net}$ is perfectly compatible with the fundamental principles of neural reuse.

5. Evidential Concerns with Neural Reuse and Resolutions with Network Modularity. We have argued that modularity$_{net}$ is consistent with the two fundamental principles of neural reuse, and that modularity$_{net}$ (along with SI or multilayer network methods) can be used to support and to investigate neural reuse. In this section, we argue that much of the empirical evidence Anderson (2015) offers to support neural reuse only minimally informs the fundamental principles of the framework, and the meta-analytic methods he employs do not allow researchers to fully engage in the research program. We suggest that existing research using modularity$_{net}$ provides better evidence for the two fundamental principles of neural reuse and that using modularity$_{net}$ allows researchers to more fully develop the research program moving forward.

Neural reuse holds that when one is considering the neural underpinnings of cognition, greater weight is placed on the functional relations and interactions between neural structures than on the actions of individual regions (Anderson 2015, 2016). As Anderson (2015, 40) puts it, "in the brain, function depends much more on interactions between parts than on the actions of parts." The prominence of interactions in the neural reuse framework is readily apparent in the Interaction Principle (principle 2), according to which functional differences between task domains are critically reflected in the different patterns of interactions between many of the same elements forming the right neural team for a job. Patterns of interactions between particular brain regions are responsible for cognitive functioning.

Most of the evidence that Anderson and colleagues have put forth for neural reuse, however, is derived from large sets of existing work employing univar-

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iate activation analyses. These kinds of analyses are meant to isolate the function(s) of individual brain regions by statistically assessing whether there is a change in blood-oxygen-level-dependent signals (activity) between cognitive tasks or conditions of interest (Hardcastle and Stewart 2002). Importantly, univariate activation analyses do not provide explicit information about functional interactions between brain regions during a particular cognitive task. A brain region need not exhibit a difference in gross activation between conditions of interest in order for that region to play a pivotal role in the functional brain network to carry out the cognitive function (Geib et al. 2015, 2017). For example, Geib et al. (2015) showed that to facilitate the retrieval of vivid visual images from memory, the hippocampus drastically reorganized its set of functional connections to bring about greater communication efficiency with the network and to become a more convergent structure for information. This was the case even though there was no difference in univariate activation for the hippocampus between the conditions of interest. Similarly, Geib et al. (2017) showed that successfully remembering compared to forgetting concrete words was associated with significant changes in the connectivity profile of the hippocampus and in its set of intermodule$_{net}$ connections. As in Geib et al. (2015), this was the case even though there was no difference in univariate activation for the hippocampus between the conditions of interest. In these two examples, although no change was detected in gross hippocampal activation between conditions, the functional connections between the hippocampus and many other brain regions changed dramatically to facilitate remembering. Thus, univariate activation analyses can at most lend support to the Multifunction Principle (principle 1) but not the Interaction Principle (principle 2).

Turning to the meta-analyses, Anderson and Pessoa (2011) examined the selectivity of 78 standard anatomical regions of the brain by determining whether and how often each was active across 1,138 experimental tasks in 11 different categories, including action execution, action observation, action inhibition, attention, audition, vision, emotion, language semantics, reason, semantic memory, and working memory. They computed how often neural activations fell into each of the task categories using a formula called *diversity variability* (DV). DV is based on a modified standard deviation:

$$\mathrm{DV} = \sqrt{\frac{\sum_{i=1}^{k}(\mathrm{Cat}_i - \mathrm{mean})^2}{k}},$$

where Cat_i refers to the proportion of activations, "mean" is the average proportion of activations, and k is the total number of categories (i.e., 11 in this case). They found that the regions examined were active in an average of 95 tasks spread across nine different cognitive domains, suggesting that the same regions are active across many diverse tasks and cognitive domains. Similarly, using functional fingerprinting, Anderson et al. (2013) quantified the di-

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versity of tasks under which different brain regions show activations by determining how often each region was active in about 2,000 different experimental tasks. They also found that the same brain regions were active across diverse tasks and cognitive domains, which corroborated earlier work.

The problem with approaches using DV and functional fingerprinting is that the meta-analytic conclusions put forth by Anderson and colleagues are based on prior univariate activation analyses; thus, they can only provide information about which localized, discrete brain regions tend to differ in gross activation between different task conditions. That is, they do not explicitly provide information about how different brain regions interact or cooperate to carry out these different tasks. For it is possible that two or more brain regions are more active in general during task X compared with task Y while not actually being functionally connected during task X or task Y. The interactions, or connections, between regions are the key to neural reuse, but research with more traditional univariate methods is ill suited to provide direct support for the existence or properties of these patterns of interactions. Furthermore, if one were to design a new study assuming that the fundamental principles of neural reuse are true, then these meta-analytic methods would provide no information about how certain brain regions functionally cooperate during that specific task of interest to carry out the cognitive function. Consequently, the meta-analytic methods employed by Anderson and colleagues to support neural reuse provide little to no information about the way in which specific regions change and functionally reorganize across a set of specific tasks.

In contrast, $\text{modularity}_{\text{net}}$ is computed by detecting certain patterns in the interactions between all brain regions comprising the network. That is, $\text{modularity}_{\text{net}}$ takes into account all interactions between each and every brain region and subsequently identifies the subsets of brain regions that tend to be more densely interconnected (i.e., interacting more strongly) among themselves than the rest of the network. The functional groupings of highly interconnected brain regions observed during task A that appear consistently across subjects are thought to actually carry out the cognitive function associated with task A. While meta-analytic activation methods advocated by Anderson and colleagues do not provide explicit information about patterns of interactions between brain regions, $\text{modularity}_{\text{net}}$ is capable of identifying interacting brain regions that functionally cooperate to carry out a cognitive task. $\text{Modularity}_{\text{net}}$ can be computed on the brain networks of individual persons performing a single cognitive task or brain networks averaged across a set of participants performing a single cognitive task. Thus, $\text{modularity}_{\text{net}}$ allows researchers to investigate functional cooperation during a cognitive task in a single subject or a cognitive task across a group of subjects.

Although most of Anderson's evidence for neural reuse comes from meta-analyses of localized, isolated activations, Anderson and Penner-Wilger (2013) did perform a meta-analysis of functional connectivity data based on

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results from 1,127 experimental tasks falling into 10 different task domains. This analysis allowed them to identify which regions were most often functionally connected within each task domain. Their results do suggest that brain regions rarely share the same functional partners across different task domains. That is, functional connections do change between different task domains. While this approach is certainly a step in the right direction, it still suffers from several serious limitations.

First, the fact that anatomical networks are relatively sparse—and therefore limit the possible direct functional interactions in a brain network—underscores the importance of indirect connections in functional brain networks. In their functional connectivity meta-analysis, Anderson and Penner-Wilger (2013) only characterize the presence of bivariate, direct functional connections emanating from a brain region of interest. While direct connections indicate the immediate functional partners of brain regions, two brain regions might only be indirectly connected through a third brain region (Paolini et al. 2014). It is not possible for just any brain region to directly, functionally interact with any other brain region. There are physical limits on the possible set of direct functional connections that could exist in the network. In a seminal study, Felleman and Van Essen (1991) compiled an anatomical connectivity matrix from the prior tract-tracing literature that summarized 305 axonal connections between 32 areas of the visual cortex in the macaque monkey (Felleman and Van Essen 1991). Most connections were shown to be reciprocal, and the overall connection density was sparse. Using noninvasive imaging technologies, recent research has shown that whole-brain white-matter networks in humans are similarly sparse (Sporns 2011; Bullmore and Sporns 2012; Wang et al. 2014). Brains are efficient, economical structures organized to minimize wiring costs while supporting high dynamic complexity (Bassett and Bullmore 2006; Sporns 2011). Diverse, spatially disparate brain regions may functionally cooperate to carry out some task, but that cooperation may depend on indirect connections through other nodes in the network. Functionally cooperating brain regions carrying out some function may require information to be transferred from brain region A to brain region C but only after that information is partially processed or transformed at brain region B (Sporns 2011; Stanley et al. 2013).

For example, consider an episodic encoding task for complex visual stimuli. As an individual views a scene, information travels from (1) the retina to (2) the lateral geniculate nucleus of the thalamus to (3) early striate cortex to (4) higher-order visual regions, and eventually to (5) the medial temporal lobe structures like the hippocampus. In this example, early striate cortex and the hippocampus might end up in the same module$_{net}$, even though they are not directly connected to one another via an individual anatomical pathway. Spatially disparate brain regions like early striate cortex and the hippocampus can functionally cooperate to carry out the episodic encoding task even though they are not directly ana-

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tomically connected. To account for this, it is necessary to consider indirect connections that go through higher-order visual-processing regions in occipital, temporal, and parietal cortices. Regardless of whether the possible set of functional connections in a network is constrained by the underlying anatomical structure, $\text{modularity}_{\text{net}}$ algorithms do not require that all nodes comprising a single $\text{module}_{\text{net}}$ are directly functionally connected. $\text{Modularity}_{\text{net}}$ only requires that the set of nodes in each $\text{module}_{\text{net}}$ are generally more functionally interconnected among themselves than they are with nodes in other $\text{modules}_{\text{net}}$ in the network. Thus, $\text{modularity}_{\text{net}}$ can readily account for indirect connections in establishing functionally cooperating groups carrying out different cognitive tasks.

Additionally, brain network analyses permit researchers to constrain the set of possible functional connections by the underlying anatomy for an individual person (Honey et al. 2007; Honey, Thivierge, and Sporns 2010). A researcher might stipulate that a functional connection can only exist between any two brain regions if, say, at least one white matter tract connects those two regions. $\text{Modularity}_{\text{net}}$ can then be computed on the anatomically constrained functional networks to investigate the neural substrates of cognitive functions (Honey et al. 2010). This approach should allow for a more biologically accurate characterization of $\text{modular}_{\text{net}}$ architectures in functional brain networks. This approach also allows researchers to constrain the set of possible functional connections within individual subjects, further allowing the researcher to take into account the interindividual variability in the set of white matter connections in the brain. Notably, the functional connectivity meta-analyses performed by Anderson and colleagues do not account for whether there are underlying structural connections between regions. As such, it is possible that some of the direct functional connections identified by Anderson and colleagues are spurious, if there is no underlying structural connection between the regions. At best, those regions not connected by underlying structure might be indirectly connected in the larger network. Given current meta-analytic methods using prior functional connectivity analyses, such as those implemented by Anderson and Penner-Wilger (2013), it is not possible to constrain the identified functional connections by the underlying structure for individual persons to ensure that identified functional connections are not spurious.

The second limitation to the meta-analytic approach taken by Anderson and Penner-Wilger (2013) is that it is not possible to directly investigate whether individual differences in functional connectivity patterns are associated with behavioral performance on a given task. Anderson's meta-analyses are conducted by collapsing across large sets of localized activations or coactivations from many different studies to identify consistencies in activation or coactivation within and between task domains. Recent research has indicated that individual differences in functional connectivity patterns and in $\text{modularity}_{\text{net}}$ are closely related to behavioral performance on a

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variety of different tasks. For example, the presence of certain $modular_{net}$ architectures during tasks are related to differences in working memory performance (Stanley et al. 2014; Braun et al. 2015), episodic memory retrieval performance (Meunier et al. 2014; Geib et al. 2017), and successful decision making (Moussa et al. 2014). These studies have provided valuable information about the extent to which certain $modular_{net}$ properties allow individuals to better perform these different cognitive tasks.

The third limitation is that these meta-analytic approaches cannot elucidate how functionally cooperating brain regions dynamically assemble and disassemble as individuals are repeatedly exposed to the same kinds of information or gradually learn complex behaviors. Our cognitive capacities and abilities change constantly over time. With repeated exposure or practice, we acquire the requisite expertise such that we do not need to engage in extensive searches or complex, elaborate analyses. Certainly, there are differences in the underlying functional brain activations and connections between novices and experts on diverse tasks (Patel, Spreng, and Turner 2013). Complex network analyses of neuroimaging data have provided new insights into adaptive neural processes, the attainment of knowledge, and the acquisition of new skills (Bassett and Mattar 2017). For example, Bassett et al. (2011) investigated dynamic changes in $modularity_{net}$ during a motor skill learning task. Their results indicate that as individuals learn the motor skill, changes in the allegiances of nodes to $modules_{net}$ predict the relative amount of learning in a later session. Diverse brain regions perform different roles within $modules_{net}$ during the course of motor skill acquisition, with some brain regions maintaining the same $modular_{net}$ allegiance throughout the experiment and others exhibiting shifts in $modular_{net}$ allegiance (Basset et al. 2011, 2015).

A fourth problem is that proponents of neural reuse argue that functional interactions between brain regions are responsible for carrying out cognitive functions instead of more segregated, specialized neural structures (Anderson 2015). Anderson and colleagues are right to place renewed emphasis on the importance of dynamic functional interactions in carrying out cognitive functions. Network neuroscience welcomes this renewed emphasis on the importance of functional interactions while still preserving a biologically realistic conception of functional specialization (or segregated functioning). Operating within network neuroscience, it is not necessary to build a general framework for the neural underpinnings of cognitive functioning by emphasizing the predominance of integration at the expense of segregation or vice versa. By conceptualizing the brain as a complex network and using graph metrics like $modularity_{net}$, researchers can investigate the roles of both segregated and integrative functioning within the system to carry out cognitive functions. Certain subsets of brain regions might functionally cooperate to carry out some more segregated, specialized function (i.e., $module_{net}$ 1), and other brains might functionally cooperate to carry out some other segregated, specialized function

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(i.e., module$_{net}$ 2). Through intermodule$_{net}$ interactions, it is possible to examine more global integrative properties in the network—or the ways in which brain regions carrying out more specialized functions work together—for carrying out the task. Researchers can then empirically characterize the respective roles of segregated and integrative processes, both of which are likely important (at least to some extent) for carrying out most cognitive functions (Bullmore and Sporns 2009; Sporns 2011). Specific modules$_{net}$ are thought to perform specific functions, even though each module$_{net}$ remains integrated with all other modules$_{net}$ in the system via a complex set of intermodule$_{net}$ connections. Segregated, specialized processing is achieved through strong interconnections within modules$_{net}$ for some purpose. If one grants that achieving a task is really about putting together the right "neural team" (i.e., module$_{net}$), then that module$_{net}$ is engaged in specialized processing for that specific task. With modularity$_{net}$, it is possible to retain a conception of functional specialization without assuming that it is instantiated in localized, encapsulated neural structures that carry out specific cognitive tasks. Thus understood, modularity$_{net}$ safeguards a conception of specialized, segregated functioning that has been useful and informative in cognitive neuroscience research.

In sum, we have argued that the meta-analytic methods employed by Anderson and colleagues as their primary source of evidence for neural reuse can at most support the Multifunction Principle (principle 1) but not the Interaction Principle (principle 2). Furthermore, these meta-analytic methods cannot help researchers investigate how certain brain regions change their functionally cooperating groups to carry out different cognitive functions or to facilitate improvement on one particular cognitive task. Modularity$_{net}$ can, however, provide validation and support for both principles of neural reuse, and its implementation will allow researchers to more fully engage in the neural reuse research program going forward.

6. Conclusion. Neural reuse holds tremendous promise as a framework with which to understand and investigate the neural bases of cognitive processes. We have argued that recent developments in network neuroscience offer a unique conceptualization of modularity—modularity$_{net}$—that is consistent with the fundamental principles of neural reuse. While we believe that the extant evidence offered in support of neural reuse does not support its fundamental principles, empirical research using modularity$_{net}$ clearly does. In addition, we have argued that these modularity$_{net}$ algorithms and related metrics provide the requisite tools for engaging in the research program, especially for researchers reluctant to relinquish the idea that the brain does exhibit specialized functioning to carry out cognitive functions. Specific subsets of brain regions functionally cooperate in reliable and consistent ways (i.e., form a module$_{net}$ or multiple modules$_{net}$) during a particular task in order to help carry it out. In this way, there is still a relatively stable

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neural basis for specific cognitive functions that are identified with modularity$_{net}$ algorithms.

Modularity$_{net}$ and related algorithms have the potential to revolutionize the way we think about the neural underpinnings of cognitive functions. These methods allow researchers to engage in a new research program that offers clear advantages over more traditional methods focused on localizing cognitive functions to specific neural structures. Meaningful progress will be made as researchers continue (1) to characterize how modular$_{net}$ architecture changes across a larger set of cognitive tasks and (2) to identify the unique properties of nodes and edges that influence the likelihood of a node changing modular$_{net}$ allegiance. Technological improvements in brain imaging and recording continue to provide new and more precise methods for measuring the brain's anatomical (structural) and dynamic (functional) connections (Sporns 2011; Wang et al. 2014). These improvements will help researchers to constrain functional connectivity by the underlying neuroanatomy, thereby providing a more biologically realistic picture of how modules$_{net}$ assemble and disassemble across different tasks and conditions. They will also help researchers to understand how the process of assembling and dissembling modules$_{net}$ occurs across finer temporal resolutions.

Increasingly complex data in the social, technological, and biological sciences continue to engender the development of new tools and methods for representing and analyzing networks. With this rapid growth across different fields, new methods and tools will become available to provide researchers with new insights into how neural reuse works across diverse cognitive tasks. This will, in turn, enable researchers to build new models and theories about the neural substrates of cognitive functioning. These models and theories will be consistent with the fundamental principles of neural reuse, and they will be much more likely to reflect how the brain actually subserves diverse cognitive functions.

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