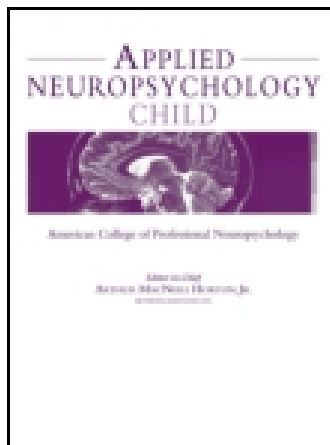


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The Small-World Organization of Large-Scale Brain Systems and Relationships With Subcortical Structures

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Brain structure and function is characterized by large-scale brain systems. However, each system has its own “small-world” organization, with sub-regions, or “hubs,” that have varying degrees of specialization for certain cognitive and behavioral processes. This article describes this small-world organization, and the concepts of functional specialization and functional integration are defined and explained through practical examples. We also describe the development of large-scale brain systems and this small-world organization as a sensitive, protracted process, vulnerable to a variety of influences that generate neurodevelopmental disorders.

Key words: brain hub specialization, functional integration, functional specialization, neurodevelopmental processes

INTRODUCTION

The first article in this series discussed the structure and function of seven basic large-scale brain systems (LSBS; Yeo et al., 2011). The interaction of these brain systems was also reviewed. Implications for modifying clinical neuropsychology’s understanding of theoretical constructs such as attention and executive functioning were also presented. This article reviews the “small-world” organization of these large-scale networks because understanding how these networks are functionally

connected to perform tasks has an impact on how we interpret any adult’s or child’s practical behavior as well as neuropsychological test data (Cole et al., 2013). The patterns of functional connectivity between and within these larger-scale systems helps explain why many neuropsychological tests have poor localization properties and why most neuropsychological test protocols are characterized by variability in test performances, even when two or more subtests seem to share the same characteristics in terms of face validity. In addition, the neo-cortex does not operate in isolation, but instead, it is dependent upon the “bottom-up” support of subcortical brain regions. Therefore, we also briefly introduce the concept of how the functions of the basal ganglia and cerebellum support the operations of LSBS. The vertical organization of the brain also warrants consideration

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in neuropsychological test interpretation (Koziol & Budding, 2009), and subcortical systems will therefore be systematically reviewed in Part III. Specifically, corticobasal ganglia and cerebro-cerebellar systems contribute to modifying and enhancing our understanding of attention, learning and memory, and executive functioning.

THE SMALL-WORLD ORGANIZATION OF LARGE-SCALE BRAIN SYSTEMS

The neocortex, the basal ganglia, and the cerebellum represent a complex network. However, does the entire brain need to be activated to perform any given task? Of course not. The brain is organized in a very economical way. While cortical and subcortical brain regions interact for the purpose of adaptation, only those brain regions that are necessary to perform the task are recruited. The biologically economical brain conserves precious resources and does not waste energy expenditure (Ito, 1997). Nature's solution to the problem of maximizing efficiency and minimizing the costs of information processing is to support segregated and specialized as well as distributed information processing (Banich & Compton, 2011). Squire (1987) presented a useful explanation in regards to the medial temporal-lobe memory system. Information is "processed" in the localized brain regions necessary for the perception of that information. Because no perception or experience has only a single characteristic, information processing is distributed by activating only those brain regions that are essential for a particular perceptual experience. For example, if we imagine an animal such as a horse, we think of the way the animal looks and thereby activate ventral brain regions that are necessary for object identification; if we more specifically imagine only a black and white horse, we additionally recruit those brain regions necessary for "color" processing; if we imagine that horse running at a race track, we recruit those brain regions necessary for the analysis of motion, etc. In terms of autobiographical memory, if we imagine last year's Thanksgiving dinner, we activate ventral brain regions necessary for "face" processing in remembering who attended; we might activate brain regions necessary for the processing of the "current events" discussion that might have taken place; we additionally activate those brain regions that were necessary for the perception of the turkey and the side dishes of the meal, as well as how they looked, smelled, and tasted. So information processing is localized for processing specific perceptions, but because no perception is unimodal, information processing is distributed in all of those brain regions that are recruited for processing the specialized aspects of the perception, which in this example

is a memory. The hippocampus acts as a "hub" region, binding these localized and distributed information-processing properties to generate an integrated perception. However, this does not require total, complete recruitment or activation of the entire cortex and medial temporal-lobe memory system. With respect to declarative and procedural memory systems, information is stored or retained in those same regions or circuits where the information was initially processed to begin with (Cisek & Kalaska, 2010). These are now well-recognized principles of brain organization.

Within the topographical organization of larger-scale brain systems, there is always some degree of functional specialization so that the entire brain system need not be activated for any given task. The "small-world" organization of LSBS is quite complex and requires an understanding of the emerging, contemporary neuroscientific terms, such as "hubs," "functional specialization," and "functional connectivity and integration." This system might appear daunting to understand, but it is critically important because we believe this underlies aspects of variability in neuropsychological test (general task) performances and functional adaptation in real-world settings. To illustrate the small-world organization of LSBS, we will consider an example involving implementation of a plan that involves multiple components.

Imagine working on a project, such as developing a new neuropsychological testing "package" for computerized administration. Imagine this "project" being managed by a core group of individuals. In aggregate, there is a "cliquishness" about the group; they work together. They are a "hub." However, they each have their own area of functional specialization. One member of this "clique" might have special expertise in functional neuroanatomy; another member might have expertise in test construction; another member might have expertise in statistics; and another member has expertise in research. Together, as a group, they have solved the specialized problem of developing a test battery. However, both individually and as a group, they have limited knowledge in computer science and programming; one or two of them has adequate "business knowledge" for marketing purposes. As it turns out, one person in the "clique" knows an individual in another city who has expertise in computer programming, and that person has access to a small specialized team of experts who are willing to take on the job of programming the new test battery; this establishes a "functional connection" with another "hub." The statistician in the "hub" knows others in a relatively nearby city with expertise in Web site design for business and marketing purposes; this establishes yet another "functionally connected hub." Information is shared, they decide to meet to work out all the details, and in

this process, they have established a “functionally integrated” network. As each hub interacts with another, changes and adjustments are made in the test battery, a business plan is established and implemented, and this process resembles the rapid updating of “functional connectivity” according to the demands of the original task. Therefore, the core group started out as a cliquish hub, functioning as a closely, densely packed network composed of each individual’s separate but related skills, and then established a few distal or longer-range connections with other “hubs” as was necessary dependent upon the demands of our task. This example illustrates the “small-world” organization that characterizes the relationships within and between LSBS. If all “hubs” function efficiently, the demands of the task are successfully met; if one of the “hubs” functions less efficiently, slowly, or fails to promptly communicate with another “hub,” we are now mimicking variability in test performances. After the global task is completed, the “functional connectivity” initially recruited is no longer necessary; the computer programmers and marketing teams or “hubs” go their separate ways and take on other contractual tasks; this aspect of the project illustrates the transient, dynamic, context-specific interactions that were required for this specific project. However, in the future, the original core group might decide to expand their initial test battery as new principles and ideas emerge. After the test package is up and running for a period of time, perhaps they discover a few “bugs” in the system that they would like to update. The core group can now again contact the same “hubs” and recruit them for this updating and expansion, and perhaps even contact a new group of people or another “hub” to develop a computer printout to assist in analyzing and interpreting the clinical data. This demonstrates the ability to reorganize the project efficiently, through ‘reuse’ of hubs that were useful in the past while simultaneously recruiting new ones for project expansion.

This simple yet practical example allows us to easily understand the small network organization of the brain and to define the appropriate terminology. *Functional specialization* is defined as “the degree of processing specificity of a given brain region for a particular cognitive ability or facet of cognitive operations” (Stevens, 2009, p. 2). However, this local cognitive processing that occurs in relatively isolated regions of the brain, within LSBS, must somehow communicate with other brain regions, in other brain systems, to effectively implement adaptive behavior. This “communication” defines the “functional integration” of distal brain regions. This refers to “transient, dynamically changing, ongoing, and context-specific regional interactions that convey information through subsets of anatomical connections among a limited handful of brain regions engaged by

a particular cognitive process” (Koziol & Stevens, 2012, p. 4). Therefore, the “small-world” organization of LSBS is characterized by both regional functional segregation and specialization, as well as functional integration within and between these larger-scale systems. We can think of these small areas of specialization as “hubs.” These hubs are dense, locally clustered areas that manage highly specific aspects of the information processing necessary for the completion of a highly specific task; they are brain areas of “cliquish” connections that have “spokes” or dynamic “functional connectivity” to other more distal brain regions that are necessary to perform aspects of other tasks (Bassett & Bullmore, 2006). There is an inherent flexibility in this system so that brain regions can very rapidly update their pattern of global functional connectivity according to task demands (Cole et al., 2013).

As described in Part I of this series, we are continually interacting within a changing environment. Extensive evidence implies the brain has the ability to adaptively implement and execute an extremely wide variety of tasks and to quickly learn new ones. This ability, which can operate explicitly when learning new tasks or implicitly when preferentially engaging in routine tasks, presumably reflects the operations of the frontoparietal network (FPN). Cole and colleagues (2013) applied the principles of “small-world” organization to LSBS in a seminal study that characterized brain network organization and dynamics. By adapting functional magnetic resonance imaging (fMRI) methodologies used to identify functional connectivity in resting states and in identifying patterns of functional connectivity during task performance, they concluded that “flexible hubs” were recruited for adaptive task control. They used 64 tasks across three distinct domains that required logical decision making, sensory and semantic information processing, and motor responses to demonstrate patterns of functional connectivity and integration during task performance. They found that the FPN was characterized by a brain-wide functional connectivity pattern; the FPN was capable of recruiting a wide variety of brain systems. When different tasks were performed, the FPN’s functional connectivity pattern “shifted” significantly more during the changing patterns of connectivity than those of any other large-scale brain network. While different tasks recruited different “hubs” of the small-world organization of large-scale brain networks, Cole and colleagues further demonstrated very impressively that simply observing the changing connectivity of functional brain systems as manifest by fMRI actually predicted or identified the specific task that was being performed. In addition, this investigation revealed that these connectivity patterns were similar or consistent across “practiced” or routine tasks and the learning of novel tasks. They concluded

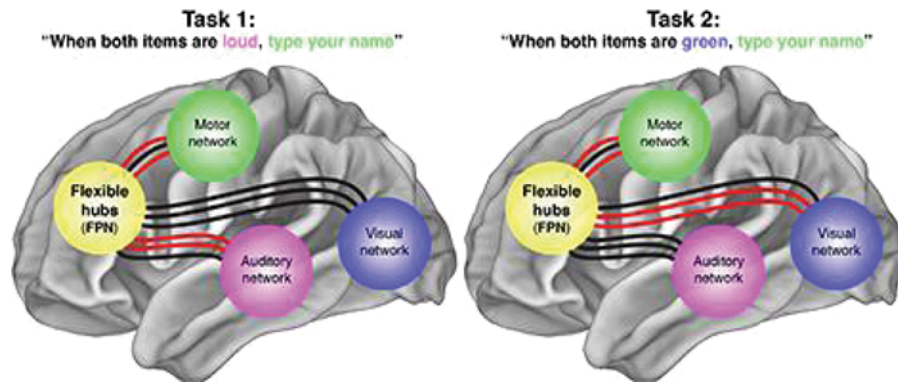


FIGURE 1 The brain's frontoparietal network region is shown to play a central role in routing the processing of cognitive tasks among a range of specialized cognitive-processing hub networks, such as the linkages shown here among the visual, auditory, and motor network hubs. *Source:* Cole et al. (2013).

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that the brain “reuses” flexible hub connectivity patterns to facilitate the performance of novel tasks. In aggregate, the findings supported a central and critical role for “flexible hubs” organized within a dynamically changing cognitive control system for adaptation to task demands. The organization and functional activity of “small-world” flexibility interacting with the FPN is illustrated in Figure 1.

THE DEVELOPMENT OF LARGE-SCALE BRAIN SYSTEMS

The development of LSBS and functional connectivity across the life span is perhaps the most rapidly emerging area of neuroscience. Therefore, this review must necessarily be highly selective and restricted to the most pertinent and clinically relevant issues. That said, the human develops from having a brain that is equipped with basic, seemingly primitive functional capacities to an efficient network that facilitates complex cognitive processes and behaviors. The protracted period of neurodevelopment begins during gestation and continues at least into young adulthood. The functional connectivity of LSBS can be observed from the gestational age of 20 weeks onward through the application of noninvasive resting-state fMRI investigations (Hoff, Van den Heuvel, Benders, Kersbergen, & De Vries, 2013). This early observed functional connectivity is quite remarkable and generates the foundation for each large-scale brain network to be established. Not at all unexpectedly, visual and sensorimotor systems develop first; for example, because we were born, we must move! To guide movement, we must see! Through this visually guided movement process, we discover objects and their meaning, or relevance. As we indicated in Part I of this series, it is no accident that the dorsal and ventral

systems are integrated by the age of 9 months (Kaldy & Leslie, 2003; Njiokiktjien, 2010). Other networks develop next, at different rates (Khundrakpam et al., 2013). This is characterized by an increase in the connectivity of each system or network over time, as well as a corresponding increase in network size. As a general rule, notable “fine-tuning” and specialization occurs in regions necessary for the support of higher-order cognitive functions by childhood (Tau & Peterson, 2010).

As described, functional “hubs” are brain regions that play a critical role in facilitating communication, or information sharing, among distributed brain networks within all sensory and motor systems. It has been known for quite some time that all sensory and motor systems are organized in parallel (Kolb & Whishaw, 2009; Mishkin & Appenzeller, 1987). Our understanding of functional hubs remains in its infancy, although a few general principles have emerged. Hwang and colleagues (2013) evaluated 99 participants ranging in age from 10 to 20 years. They observed that the small-world organization of *hub architecture* was evident in late childhood and remained stable through adolescence to early adulthood. From childhood to adolescence, connections between cerebellar hubs (to be reviewed in the next article in this series) and cortical regions increased. The conclusion was offered that stable functional hub architecture is foundational for information flow in the brain. In addition, the increased connections between cerebellar hubs and the cortex highlight the role of the cerebellum in the “bottom-up” support for the development of mature cognition. Two general summary conclusions can also be made from these and other data (Grayson et al., 2014). First, both children and adults demonstrate a robust, *structurally* rich hub organization. These hubs become highly integrated within the brain's major networks. Second, *functional* connectivity increases over time but with a high level of segregation between LSBS.

Menon (2013) and Rubia (2013) have provided comprehensive, integrated reviews concerning the developmental pathways that result in the development of functional brain networks. From these seminal reviews of numerous studies, which relied upon a variety of neuroscientific technologies and computational models, six emerging principles of *functional* brain network development emerged. These principles are relevant for both the “typically developing” brain and are important for understanding neurodevelopmental disorders as well. There is an inherent vulnerability in brain development because numerous “events” can generate anomalies in both *structural and functional* brain organization. Put very bluntly, the developing brain is not nearly as “plastic” as perhaps was once believed.

SIX PRINCIPLES OF THE DEVELOPMENT OF LARGE-SCALE BRAIN SYSTEMS

The first of Menon’s (2013) general principles describes LSBS as characterized by the inherent “small-world” formation and organization of “hubs.” These hubs, which we have illustrated by practical examples and the resultant “operational” definitions, form the neuro-anatomical “backbone” or “skeleton” of the brain. Although Hwang and colleagues (2013) studied children aged 10 years and older, hubs are constructed very early on in development and are reasonably *mature by 2 years of age*. The more global brain architecture of segregated LSBS is evident and reasonably mature by the age of 8 years. However, there is a notable restructuring of these brain systems from later childhood to adolescence. This results in refinement of functional “hubs” that integrate complex interactions between *internal* and *external* processes that integrate *internal* and *externally driven cognitions and behaviors*. For example, in Part I of this series of manuscripts, it was stated that the left-hemisphere FPN guides behavior according to current cognitive context, according to the routine behaviors that are appropriate for what an individual is thinking about for the currently appropriate context or familiar, “routine” situation. The functioning of the right-hemisphere FPN was characterized as critical for the FPN’s processing of cognitive task novelty, task orientation, and the generation of novel problem-solving strategies. An investigation by Xu, Calhoun, Pearlson, and Potenza (2014) differentiated the roles of overlapping FPNs. The left-hemisphere FPN was strongly implicated in task conditions of low attentional load—in other words, engaging in routine, familiar cognitive processes and behaviors. The right-hemisphere FPN, while recruiting the dorsal attention network, was critically involved in task situations that were unfamiliar, new, or novel—in other words, requiring high

demands on the “attentional” system required for task orientation and the generation of novel problem-solving strategies. An identical inference can be made from the findings of Dennis and colleagues (2013). They demonstrated greater “small-world” organization in the right hemisphere than within the left cerebral hemisphere, consistent with the neurobiologically situated principle that right-hemisphere versus left-hemisphere information processing is characterized by a division of labor that is dependent upon task demands. One would predict that frequently occurring routine information requires less “cognitive processing” than infrequently occurring novel information for efficient adaptation; the “newness” or lack of familiarity inherent in novelty requires more sensitivity to detect differences and places increased demands on information processing, consistent with the greater, yet compact small-world organization observed in the right cerebral hemisphere. Therefore, principles of brain development and organization clearly support the “novelty routinization” and neurobiologically situated principle of *functional* brain systems organization, in sharp contrast to the artificial construct of the “verbal versus nonverbal” dichotomy, an outmoded principle of hemispheric functional brain organization (Podell, Lovell, & Goldberg, 2001). In fact, an analogous left–right asymmetrical division of labor is also evident at the level of the brainstem, the relevance of which will be discussed in Part III.

A second general principle of LSBS development concerns the ongoing segregation of functional circuits. Development is actually characterized by increased functional segregation. However, there is a critically important shift from “short-range” connections in children to longer-range connections in adults; this allows for the recruitment of greater regions and areas of cortex, presumably supporting higher-level cognitive functions and the potential imposition of “top-down” regulation of behavior when necessary (Cao et al., 2014; Hwang, Hallquist, & Luna, 2013).

Third, Menon (2013) considers the changing landscape of the reconfiguration of subcortical–cortical connections as the major hallmark of the development of LSBS. Behavioral routines and habits, incentive-based explicit and implicit learning, reward preferences, and motivation all undergo dramatic changes from childhood to adulthood, and these are all dependent upon cortical–basal ganglia interactions and their changing patterns of connectivity. However, the changes that “code” or “map” sensory, mnemonic, attentional, emotional, and motivational experiences onto LSBS networks are heterogeneous because they are dependent upon the unique experiences of the developing brain. In addition, neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), certain anxiety disorders, autism, and certain symptoms of

depression have all been implicated as manifestations of anomalies within cortical-basal ganglia circuitry (Dubois et al., 2010; Huyser, Veltman, de Haan, & Boer, 2009; Padmanabhan, Lynn, Foran, Luna, & O'Hearn, 2013; Sonuga-Barke, 2003; Sonuga-Barke, Bitsakou, & Thompson, 2010; Yadid & Friedman, 2008). This general organizational profile also helps explain individual differences.

As a fourth principle, there is a dynamic pruning of functional circuitry. Perhaps the three most important networks to consider include the FPN cognitive control system, the salience network, and the default mode network (DMN) because most studies imply that within adult populations, these are “core” networks that play distinct roles in cognition. All of these networks support orientation of attention to what is relevant to assist with goal-directed behavior; encoding, maintaining, and updating working memory for judgment and making decisions; and the self-referential thinking necessary for planning and social cognition. Although these networks are evident during the emergent toddler years, slowly occurring changes in the distribution of the nodes of these networks and the strength of these network connections are observed between the ages of 7 and 20 years and presumably reflect an underpinning for flexible cognitive control. In this regard, there appears to be a critical, inverse relationship between the FPN and the DMN. This relationship is age-related and follows a progressive developmental trajectory. In general, a highly active DMN is related to weaker cognitive control; superior cognitive performance is related to stronger FPN activation and weaker DMN recruitment. In this way, the relationship between FPN and DMN activation patterns might represent a neurodevelopmental marker for the increase in working-memory capacity and executive function—cognitive control that emerges from childhood to young adulthood (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014).

Fifth, the amygdala, which plays a role in stimulus information relevance because of its contribution to emotion-related functions, is a “hub” for processing biologic and affectively salient cues. When compared with that of adults, the functional connectivity of the amygdala with other brain regions important for affective and motivational processing is weaker in children as a group. However, anomalous development with these brain circuitries to which the amygdala projects is likely associated with anxiety and depressive disorders. The amygdala is a complex hub that can be subdivided into different subregions, connecting with the medial prefrontal cortex (mPFC) at different stages in the developmental process. Connections with subcortical regions are established and stabilize very early, and they likely support global affect generation processes. Numerous connections between the amygdala

and other limbic regions occur between 4 and 10 years of age, during which time these connections might be particularly malleable and even vulnerable to disruption. From late childhood to adolescence, a reorganization of amygdala–mPFC changes occurs and likely underpins complex emotional processing and regulation (Gabard-Durnam et al., 2014). Ameis and colleagues (2014), in investigating the entire amygdala complex, identified key nodes in the orbitofrontal cortex (OFC; an anticipatory and inhibitory brain region), the temporal cortex (a node in the salience brain regions), and the cingulate (a node in the motivational network) that connect with the amygdala. Fewer OFC–amygdala connections and reduced OFC thickness were associated with significantly higher rates of externalizing behaviors including aggression and noncompliant, oppositional behaviors in children and adolescents. In this regard, the development of the amygdaloid hub and its connections to subcortical and cortical brain regions also contribute to the efficiency and adaptability of cognitive control.

A sixth developmental principle links hyperconnectivity and hypoconnectivity with neurodevelopmental disorders. As just one brief example, Cortese and colleagues (2012) applied the seven-LSBS parcellation to a meta-analytic review of 55 fMRI investigations of ADHD. Numerous hypoactivations and hyperactivations, associated with functional connectivity, were observed and attributed to very specific symptoms. This proved to be a useful approach, particularly with respect to understanding symptomatic expression, and explained considerable variability in functioning often observed in that overarching, heterogeneous diagnostic category of ADHD. In fact, perhaps the most important point in trying to understand ADHD is to understand the variability in symptomatic expression and the reasons for symptomatic differences (Koziol, Budding, & Chidekel, 2013). In addition, different patterns of hypoactivation–hyperactivation were observed within the DMN in an investigation of autism (Lynch et al., 2013). It therefore appears as though patterns of overactivation and underactivation within and between LSBS are responsible for symptomatic expression and variability, likely across a wide range of disorders.

SUMMARY

Part II of this series described the development of LSBS. These brain systems are characterized by an efficient “small-world” organization that possesses the capability for rapidly recruiting other brain networks as might be necessary for the completion of similar, yet different tasks. While the global system is characterized by a specific “hard-wired” architecture, the small-world

organization of the “hubs” within these larger systems can rapidly recruit and update “functional connectivity” with other brain systems in a dynamic, transient way for neurobiologically economical adaptive functioning. Although development of these systems is protracted, the general architecture is established early. Hub regions appear to stabilize relatively early in development and progressively expand, connect, and refine, which results in a reorganization from childhood to adulthood. Aspects of this reorganization are unique to the personal experiences of any given individual and account for individual differences generated by interactive experiences. This protracted period of reorganization within systems is also therefore vulnerable to a variety of influences, which contribute to symptomatic expression and variability in various disorders. Part III of this series builds upon these concepts by describing how vertical brain organization contributes to adaptation and by presenting emerging concepts concerning interactions between critically important memory systems.

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