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Systematic network lesioning reveals the core white matter scaffold of the human brain

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Brain connectivity loss due to traumatic brain injury, stroke or multiple sclerosis can have serious consequences on life quality and a measurable impact upon neural and cognitive function. Though brain network properties are known to be affected disproportionately by injuries to certain gray matter regions, the manner in which white matter (WM) insults affect such properties remains poorly understood. Here, network-theoretic analysis allows us to identify the existence of a macroscopic neural connectivity core in the adult human brain which is particularly sensitive to network lesioning. The systematic lesion analysis of brain connectivity matrices from diffusion neuroimaging over a large sample ($N = 110$) reveals that the global vulnerability of brain networks can be predicated upon the extent to which injuries disrupt this connectivity core, which is found to be quite distinct from the set of connections between rich club nodes in the brain. Thus, in addition to connectivity within the rich club, the brain as a network also contains a distinct core scaffold of network edges consisting of WM connections whose damage dramatically lowers the integrative properties of brain networks. This pattern of core WM fasciculi whose injury results in major alterations to overall network integrity presents new avenues for clinical outcome prediction following brain injury by relating lesion locations to connectivity core disruption and implications for recovery. The findings of this study contribute substantially to current understanding of the human WM connectome, its sensitivity to injury, and clarify a long-standing debate regarding the relative prominence of gray vs. WM regions in the context of brain structure and connectomic architecture.

Keywords: connectomics, traumatic brain injury, brain network, neurotrauma, neuroimaging, MRI, DTI

INTRODUCTION

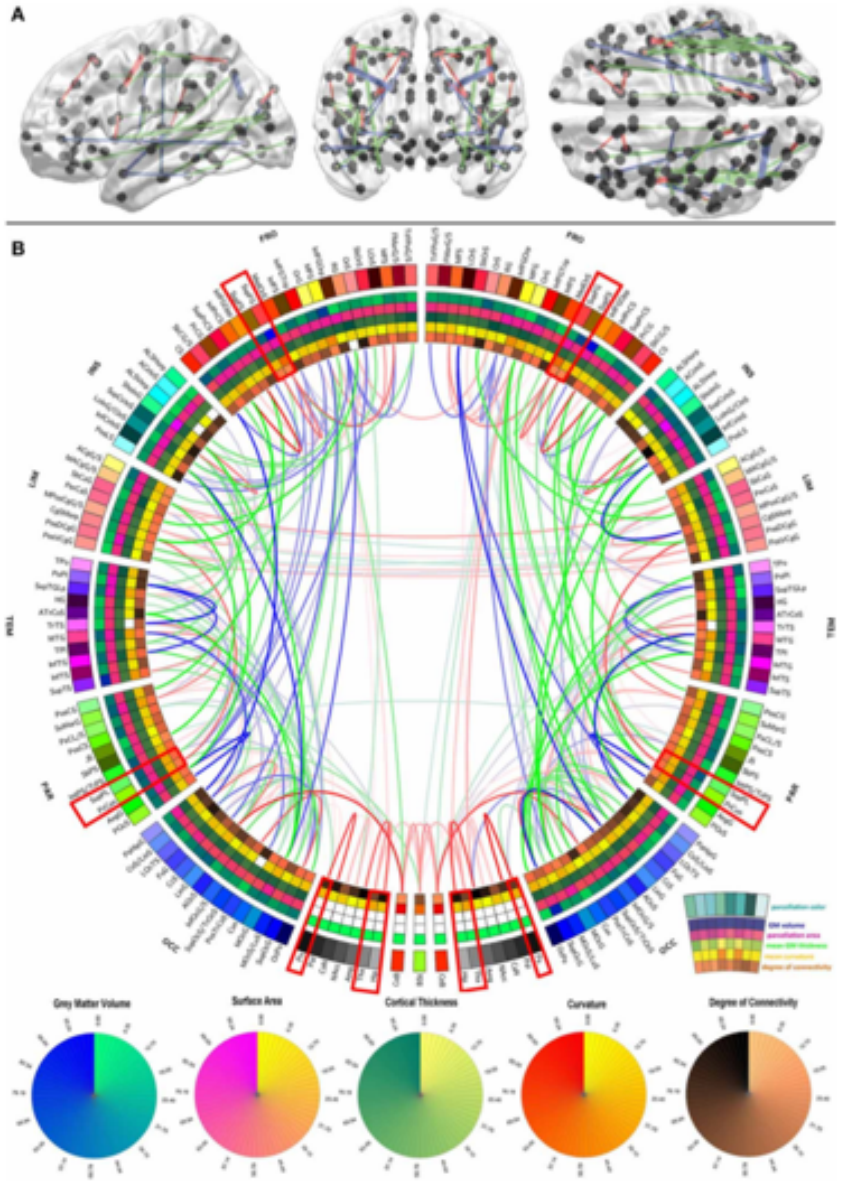

FIGURE 1 | Graphical representation of the human brain connectivity scaffold. Standard 3D graphs **(A)** and a connectogram **(B)** are used to visualize WM connections whose removal leads to significant changes in network integration and segregation. Only connections with this property are represented, and the strength of the link associated with each of them is indicated by the *F* statistic of the test. Link transparency varies such that most transparent links are those associated with the smallest *F*-values, and the most opaque ones are associated with the largest *F*-values (see section Statistical significance of edge removals for details). To facilitate visibility of the most prominent core connections, the significance threshold used for 3D graphs ($\alpha/m = 7.4 \times 10^{-9}$ where $\alpha = 0.0001$ is the statistical significance level, $m = G \times (G - 1)/2$ is the number of comparisons, and $G = 165$ is the number of parcels) is more stringent than for the connectogram ($\alpha/m = 3.7 \times 10^{-6}$ where $\alpha = 0.05$). The significance threshold used for 3D graphs **(A)** is more stringent than for the connectogram **(B)** in order to facilitate visibility of the most prominent core connections **(A)**, as opposed to all the connections whose removal leads to statistically significant changes in network integration and segregation **(B)**. Regions whose connectogram wedges are highlighted in red correspond to rich club nodes as identified by Van Den Heuvel and Sporns (2011); the number of core scaffold connections and the complexity of their pattern compared to rich club interlinks both suggest considerable differences between the rich club network and the core scaffold (see discussion). For a connectogram where network metrics—rather than morphometric variables—are encoded in each concentric circle, see our previous publication (Van Horn et al., 2012).

ARCHIVAL REPORT

Connectomic Disturbances in Attention-Deficit/Hyperactivity Disorder: A Whole-Brain Tractography Analysis

Soon-Beom Hong, Andrew Zalesky, Alex Fornito, Subin Park, Young-Hui Yang, Min-Hyeon Park, In-Chan Song, Chul-Ho Sohn, Min-Sup Shin, Bung-Nyun Kim, Soo-Churl Cho, Doug Hyun Han, Jae Hoon Cheong, and Jae-Won Kim

Background: Few studies have sought to identify, in a regionally unbiased way, the precise cortical and subcortical regions that are affected by white matter abnormalities in attention-deficit/hyperactivity disorder (ADHD). This study aimed to derive a comprehensive, whole-brain characterization of connectomic disturbances in ADHD.

Methods: Using diffusion tensor imaging, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in 71 children and adolescents with ADHD compared with 26 healthy control subjects. White matter differences were further delineated between patients with ($n = 40$) and without ($n = 26$) the predominantly hyperactive/impulsive subtype of ADHD.

Results: A significant network comprising 25 distinct fiber bundles linking 23 different brain regions spanning frontal, striatal, and cerebellar brain regions showed altered white matter structure in ADHD patients ($p < .05$, family-wise error-corrected). Moreover, fractional anisotropy in some of these fiber bundles correlated with attentional disturbances. Attention-deficit/hyperactivity disorder subtypes were differentiated by a right-lateralized network ($p < .05$, family-wise error-corrected) predominantly linking frontal, cingulate, and supplementary motor areas. Fractional anisotropy in this network was also correlated with continuous performance test scores.

Conclusions: Using an unbiased, whole-brain, data-driven approach, we demonstrated abnormal white matter connectivity in ADHD. The correlations observed with measures of attentional performance underscore the functional importance of these connectomic disturbances for the clinical phenotype of ADHD. A distributed pattern of white matter microstructural integrity separately involving frontal, striatal, and cerebellar brain regions, rather than direct frontostriatal connectivity, appears to be disrupted in children and adolescents with ADHD.

Key Words: ADHD, connectomics, diffusion tensor imaging, network, tractography, white matter

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent developmental disorder among school-age children and adolescents that commonly persists into adulthood and is characterized by symptoms of inattention and/or hyperactivity/impulsivity (1). The classical understanding of the neurobiological mechanisms of ADHD posits that abnormalities of prefrontal and striatal regions play a primary role in the pathophysiology of the disorder (2), though more recent literature also suggests a role for the cerebellum (3). A large number of task-based functional magnetic resonance imaging and structural brain imaging studies have supported this model (4–6). However, the high degree of interconnectivity between many of these regions (7) suggests that no single region may be the primary source of pathology; rather, ADHD may arise from altered connectivity within and between distributed, yet anatomically connected, circuits.

Diffusion tensor imaging (DTI) has emerged as a powerful technique for investigating white matter microstructure in vivo (8). However, DTI research into ADHD has yielded somewhat inconsistent findings: while some studies lend support to the frontostriatal model (9), many studies have identified relatively diffuse white matter abnormalities that point to an alteration of numerous axonal fiber tracts (10,11). Importantly, these studies have generally focused on regional mapping of changes in water diffusion signals without taking into account which regions might be interconnected by the affected tract. This severely limits the inferences that can be drawn concerning which specific brain networks are affected in ADHD. Though some studies have conducted detailed and focused analyses of frontostriatal tracts specifically (12), their a priori focus on specific pathways neglects consideration of the potential involvement that other neural systems may have in the pathophysiology of ADHD.

Detailed and comprehensive maps of interregional brain connectivity are now obtainable by combining diffusion tractography (13) and imaging connectomics techniques (14,15). These

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Review

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Special Issue: The Connectome

Developmental pathways to functional brain networks: emerging principles

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The human brain undergoes protracted developmental changes during which it constructs functional networks that engender complex cognitive abilities. Understanding brain function ultimately depends on knowledge of how dynamic interactions between distributed brain regions mature with age to produce sophisticated cognitive systems. This review summarizes recent progress in our understanding of the ontogeny of functional brain networks. Here I describe how complementary methods for probing functional connectivity are providing unique insights into the emergence and maturation of distinct functional networks from childhood to adulthood. I highlight six emerging principles governing the development of large-scale functional networks and discuss how they inform cognitive and affective function in typically developing children and in children with neurodevelopmental disorders.

Cognitive development from the perspective of functional brain networks

The emergence of complex cognitive functions, such as language, reasoning, and cognitive control, is a hallmark of human development [1]. These extraordinary and uniquely human abilities are made possible by a protracted trajectory of brain development and learning over the first two decades of life [2]. Understanding how the developing brain achieves such abilities ultimately depends on knowledge of how functional interactions between distributed brain regions mature with age to produce sophisticated cognitive systems. Brain network analyses are increasingly being used to characterize the developing brain and to understand the dynamic maturation processes that engender complex human cognitive abilities [3]. New research is beginning to demonstrate how functional brain networks emerge from childhood to adulthood, providing fundamental new insights not only into the ontogeny of complex brain function in typically developing individuals, but also into the processes that can go awry in neurodevelopmental disorders. The perspective advanced in this review is that a thorough understanding of the functional architecture of the adult brain requires critical consideration of the developmental pathways by which plasticity and learning lead to the construction of dedicated large-scale brain systems.

Most, if not all, major psychopathologies, with the exception of the dementias, have a prominent origin in childhood or adolescence [4]. The onset and diagnosis of these psychopathologies vary greatly: some, like autism, are mainly diagnosed in early childhood, others such as attention deficit hyperactivity disorder and anxiety disorders are mainly diagnosed in middle childhood, whereas bipolar disorder, depression, and schizophrenia are predominantly diagnosed in late adolescence. For the past two decades, structural brain imaging, with an emphasis on gray matter volume, was the mainstay for identifying abnormalities in children and adolescents with these disorders. An important limitation of these studies is that they provide a relatively narrow window into the distributed functional systems impacted in psychopathology. A paradigm shift is now

Glossary

Attention deficit hyperactivity disorder: one of the most common childhood disorders that can continue through adolescence and adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity.
Autism: a neurodevelopmental disorder that appears in the first 3 years of life and affects normal development of social and communication skills. Individuals with autism have difficulties with social interaction, display problems with verbal and nonverbal communication, and exhibit repetitive behaviors or narrow, obsessive interests.
Central executive network (CEN): a brain network that is responsible for high-level cognitive functions such as planning, decision making, and the control of attention and working memory.
Default mode network (DMN): a large-scale network of brain areas that form an integrated system for self-related mental activity, including autobiographical, self-monitoring, and social functions. The DMN is typically deactivated during stimulus-driven cognitive processing.
Graph-theoretical measures: a graph is a mathematical structure comprising nodes and the edges that connect them. Expressing functional brain connectivity as a graph allows quantitative association of network properties such as path length, clustering, degree, modularity, and hierarchy.
Intrinsic functional connectivity: a measure of spontaneous synchronization of brain signals between two or more areas. It is computed using the statistical relation of temporal changes in different brain areas in the absence of external stimuli i.e., ('rest').
Salience network (SN): a large-scale brain network involved in detecting and orienting to salient external stimuli and internal events.
Small-world network: a network in which most nodes are not neighbors of one another, but most nodes can be reached from every other node with a small number of links. Small-world networks optimize wiring and efficiency.

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Dynamic cooperation and competition between brain systems during cognitive control

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The human brain is characterized by a remarkable ability to adapt its information processing based on current goals. This ability, which is encompassed by the psychological construct of cognitive control, involves activity throughout large-scale, specialized brain systems that support segregated functions at rest and during active task performance. Based on recent research, we propose an account in which control functions rely on transitory changes in patterns of cooperation and competition between neural systems. This account challenges current conceptualizations of control as relying on segregated or antagonistic activity of specialized brain systems. Accordingly, we argue that the study of transitory task-based interactions between brain systems is critical to understanding the flexibility of normal cognitive control and its disruption in pathological conditions.

Overview

Cognitive control is a multifaceted construct that encompasses a diverse range of functions involved in flexibly coordinating information to achieve internal goals in a noisy and changing environment [1]. Such control processes include the ability to link multiple sources of information to solve problems, selective retrieval of information from memory, inhibition of inappropriate behavioral responses, and active selection and maintenance of behaviorally relevant information online [2]. These complex control functions are supported by anatomically distributed brain networks that share information in a dynamic manner via coordinated activity – so-called functional connectivity [3,4]. In the past decade, human neuroimaging studies have suggested a central role for frontal regions in supporting cognitive control [5], consistent with earlier evidence from patients with frontal cortex lesions (e.g., [6]). Until recently, however, it has been unclear how control-related information processing is coordinated throughout the brain. Here we review existing models of the neural architecture underlying cognitive control. Based on new evidence, we argue that current models need to be revised to account for context-specific, task-dependent interactions among hubs within widespread brain systems [7–9]. We propose that transitory changes in cross-system integration to accommodate control behavior can be summarized in the activity of two large-scale 'meta-systems'. These meta-systems are defined by their ephemeral nature and may involve integration of activity from across nodes that would otherwise be functionally segregated or antagonistic [10,11]. By virtue of these context-driven patterns of cooperation and antagonism, the two proposed meta-systems support complex control functions that transcend the segregated processes subserved by either system alone (see Glossary).

Segregated systems supporting cognitive control

Cognitive control has traditionally been associated with functioning of the frontal cortices [12]. Recent findings

Glossary

Connectome: a whole map of the anatomical or functional connections between distinct brain regions.
Effective connectivity: refers to the influence that one neuronal system exerts over another. Unlike functional connectivity, effective connectivity is based on an explicit model of the causal (directed) interactions between neuronal systems.
Functional connectivity: refers to statistical dependencies between regionally distinct neurophysiological events. Correlations and partial correlations between regional activity time series are commonly used as indices of functional connectivity.
Meta-system: transitory, task-induced changes in integration between brain regions encompassing specialized functional systems. This cross-systems interaction allows the resulting meta-systems to support functions that transcend those of specialized networks.
Node: element of a system. In this opinion article, the term 'node' is used to refer to a brain region.
Segregation: throughout this opinion article, segregation indicates that anatomically distinct cortical areas or systems are specialized for some aspects of cognitive control.
Systems (or networks): systems are defined by a set of brain regions (nodes) that are functionally interconnected (edges). Systems may be defined by measures of functional or effective connectivity.
Task set: cognitive control is thought to encompass fast-changing, context-dependent cognitive states and states that persist throughout the duration of a task [69]. The latter cognitive states are defined as task sets.

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Behavioral/Systems/Cognitive

Rich-Club Organization of the Human Connectome

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The human brain is a complex network of interlinked regions. Recent studies have demonstrated the existence of a number of highly connected and highly central neocortical hub regions, regions that play a key role in global information integration between different parts of the network. The potential functional importance of these "brain hubs" is underscored by recent studies showing that disturbances of their structural and functional connectivity profile are linked to neuropathology. This study aims to map out both the subcortical and neocortical hubs of the brain and examine their mutual relationship, particularly their structural linkages. Here, we demonstrate that brain hubs form a so-called "rich club," characterized by a tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree, providing important information on the higher-level topology of the brain network. Whole-brain structural networks of 21 subjects were reconstructed using diffusion tensor imaging data. Examining the connectivity profile of these networks revealed a group of 12 strongly interconnected bihemispheric hub regions, comprising the precuneus, superior frontal and superior parietal cortex, as well as the subcortical hippocampus, putamen, and thalamus. Importantly, these hub regions were found to be more densely interconnected than would be expected based solely on their degree, together forming a rich club. We discuss the potential functional implications of the rich-club organization of the human connectome, particularly in light of its role in information integration and in conferring robustness to its structural core.

Introduction

The human brain is a network. At the large scale, its complex wiring diagram forms a network of hundreds of brain regions and thousands of interconnecting white matter axonal pathways (Sporns, 2011). Network studies of the human brain are motivated by the idea that brain function is not solely attributable to individual regions and connections, but rather emerges from the topology of the network as a whole, the connectome of the brain (Sporns et al., 2005; Bullmore and Sporns, 2009).

Looking at the brain as an integrative complex system, one principal marker for its structural ordering is its degree distribution, expressing the probability $P(k)$ of a node to share a link with k other nodes in the network (Barabasi and Bonabeau, 2003). Studies of brain networks have shown a heavy-tailed degree distribution (Eguiluzet al., 2005; Hagmann et al., 2007; van den Heuvel et al., 2008b), indicating the existence of a number of highly connected regions (Hagmann et al., 2008). It has been noted that some of these brain regions play a central role in the overall network organization, as indexed by a high degree, low clustering, short path length, high centrality and participation in multiple communities across the network, identifying them as "brain hubs" (Sporns et al., 2007; van den Heuvel et al., 2010). Examining the function and role of these hubs is of special interest as they play a central role in establishing and maintaining efficient global brain communication, a crucial feature for healthy brain functioning (Bassett et al., 2009; van den Heuvel et al., 2009a). First studies have identified a number of key cortical hubs (Hagmann et al., 2008; Gong et al., 2009; van den Heuvel et al., 2010), but many organizational properties of brain hubs—particularly their structural linkages—have yet to be revealed.

The so-called "rich-club" phenomenon in networks is said to be present when the hubs of a network tend to be more densely connected among themselves than nodes of a lower degree (Colizza et al., 2006). The name arises from the analogy with social systems, where highly central individuals—being "rich" in connections—often form a highly interconnected club (Zhou and Mondragon, 2004; McAuley et al., 2007). The presence, or absence, of rich-club organization can provide important information on the higher-order structure of a network, particularly on the level of resilience, hierarchal ordering, and specialization (Colizza et al., 2006; McAuley et al., 2007). The strong rich-club tendency of power grids, for example, is related to the necessity of the network to easily distribute the load of one station to the other stations, reducing the possibility of critical failure, while the absence of rich-club organization in protein interaction networks has been suggested to reflect a high level of functional specialization (Colizza et al., 2006; McAuley et al., 2007). This study was aimed at examining the rich-club organization of the human connectome. Diffusion tensor imaging (DTI) was used to reconstruct the connections of the structural brain network, and rich-club organization was explored by taking into account both the density and efficacy of the white matter connections of the brain.

Materials and Methods

Subjects

A group of 21 healthy participants with no history of neurological or psychiatric disorders were included in this study [mean age (SD), 29.95 (8.3) years; 15 males, 6 females], after obtaining written informed con-

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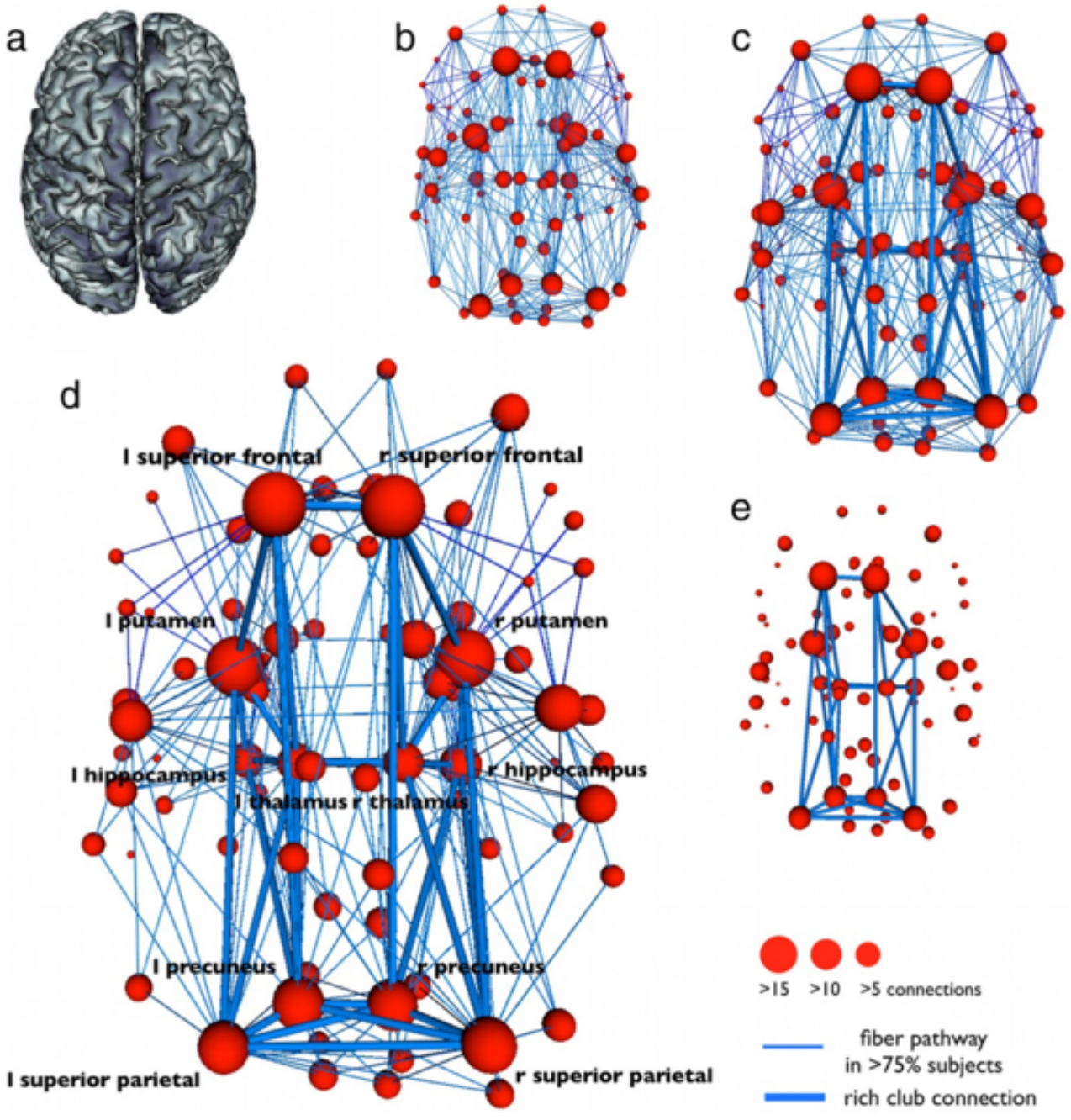

Figure 4. Rich-club regions and connections. The figure shows rich-club regions and connections of the group-averaged connectome (unweighted, $k = 17$; Fig. 3*a*). Size of nodes reflect their number of connections, with bigger nodes representing more densely connected regions. ***a***, Anatomical perspective. ***b***, Group-averaged connectome. ***c***, Group connectome with rich-club connections marked in dark blue. ***d***, Connections between rich-club regions (dark blue) and connections from rich-club nodes to the other regions of the brain network (light blue). The figure shows that almost all regions of the brain have at least one link directly to the rich club. ***e***, Rich-club connections.

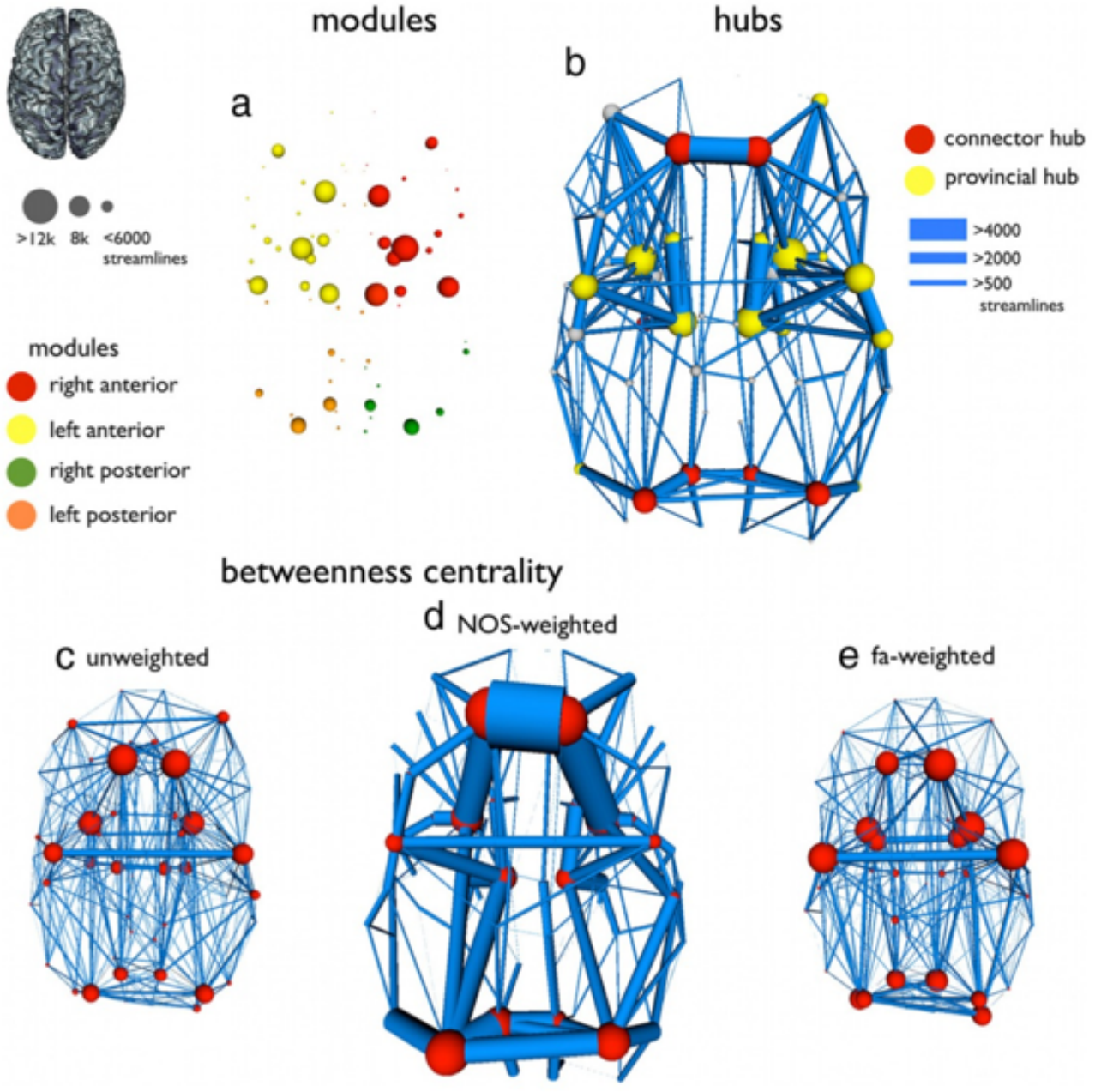

Figure 6. Module decomposition, provincial and connector hubs, centrality. ***a*** illustrates the module decomposition of the group-averaged NOS-weighted network, showing the formation of four distinct modules. ***b*** shows the backbone (*k* average of 5) of the NOS-weighted network, with provincial hubs—playing a central role in intramodule connectivity—marked in yellow, and connector hubs—nodes playing an important role in intermodule connectivity—marked in red. Note that cortical rich-club nodes are predominantly connector hubs, while subcortical rich-club nodes (putamen, thalamus) are marked as provincial hubs. ***c–e*** depict nodal and edge betweenness centrality of the unweighted, NOS-weighted, and FA-weighted group-averaged networks, respectively.

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White matter microstructure is associated with cognitive control in children☆

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ABSTRACT

Cognitive control, which involves the ability to pay attention and suppress interference, is important for learning and achievement during childhood. The white matter tracts related to control during childhood are not well known. We examined the relationship between white matter microstructure and cognitive control in 61 children aged 7–9 years using diffusion tensor imaging (DTI). This technique enables an *in vivo* characterization of microstructural properties of white matter based on properties of diffusion. Such properties include fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, measures thought to reflect specific biological properties of white matter integrity. Our results suggest that children with higher estimates of white matter integrity in the corona radiata, superior longitudinal fasciculus, posterior thalamic radiation, and cerebral peduncle were more accurate during incongruent (>><<>>, <<>><<) and neutral (-->>-, --<<--) trials of a task of cognitive control. Importantly, less interference during the task (i.e., incongruent and neutral difference scores) was associated with greater white matter microstructure in the posterior thalamic radiation and cerebral peduncle. Fiber tracts in a frontal–parietal–striatal–motor circuit seem to play a role in cognitive control in children.

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White Matter Microstructure Correlates of Mathematical Giftedness and Intelligence Quotient

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Abstract: Recent functional neuroimaging studies have shown differences in brain activation between mathematically gifted adolescents and controls. The aim of this study was to investigate the relationship between mathematical giftedness, intelligent quotient (IQ), and the microstructure of white matter tracts in a sample composed of math-gifted adolescents and aged-matched controls. Math-gifted subjects were selected through a national program based on detecting enhanced visuospatial abilities and creative thinking. We used diffusion tensor imaging to assess white matter microstructure in neuroanatomical connectivity. The processing included voxel-wise and region of interest-based analyses of the fractional anisotropy (FA), a parameter which is purportedly related to white matter microstructure. In a whole-sample analysis, IQ showed a significant positive correlation with FA, mainly in the corpus callosum, supporting the idea that efficient information transfer between hemispheres is crucial for higher intellectual capabilities. In addition, math-gifted adolescents showed increased FA (adjusted for IQ) in white matter tracts connecting frontal lobes with basal ganglia and parietal regions. The enhanced anatomical connectivity observed in the forceps minor and splenium may underlie the greater fluid reasoning, visuospatial working memory, and creative capabilities of these children. *Hum Brain Mapp 00:000–000, 2013.*

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PAPER

White matter maturation supports the development of reasoning ability through its influence on processing speed

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Abstract

The structure of the human brain changes in several ways throughout childhood and adolescence. Perhaps the most salient of these changes is the strengthening of white matter tracts that enable distal brain regions to communicate with one another more quickly and efficiently. Here, we sought to understand whether and how white matter changes contribute to improved reasoning ability over development. In particular, we sought to understand whether previously reported relationships between white matter microstructure and reasoning are mediated by processing speed. To this end, we analyzed diffusion tensor imaging data as well as data from standard psychometric tests of cognitive abilities from 103 individuals between the ages of 6 and 18. We used structural equation modeling to investigate the network of relationships between brain and behavior variables. Our analyses provide support for the hypothesis that white matter maturation (as indexed either by microstructural organization or volume) supports improved processing speed, which, in turn, supports improved reasoning ability.

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Diffusion tensor imaging correlates of reading ability in dysfluent and non-impaired readers

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ABSTRACT

Many children and adults have specific reading disabilities; insight into the brain structure underlying these difficulties is evolving from imaging. Previous research highlights the left temporal-parietal white matter as important in reading, yet the degree of involvement of other areas remains unclear. Diffusion tensor imaging (DTI) and voxel-based analysis were used to examine correlations between reading ability and tissue structure in healthy adolescents and young adults ($n = 136$) with a range of reading ability. Three complementary reading scores (word reading, decoding, and reading fluency) yielded positive correlations with fractional anisotropy (FA) that spanned bilateral brain regions, particularly in the frontal lobes, but also included the thalamus and parietal and temporal areas. An analysis of the unique effects of each reading assessment revealed that most of the variance in FA values could be attributed to sight word reading ability.

Maturation of White Matter is Associated with the Development of Cognitive Functions during Childhood

Zoltan Nagy, Helena Westerberg, and Torkel Klingberg

Abstract

■ In the human brain, myelination of axons continues until early adulthood and is thought to be important for the development of cognitive functions during childhood. We used diffusion tensor MR imaging and calculated fractional anisotropy, an indicator of myelination and axonal thickness, in children aged between 8 and 18 years. Development of working memory capacity was positively correlated with fractional anisotropy in two regions in the left frontal lobe, including a region between the superior frontal and parietal cortices. Reading ability, on the other hand, was only correlated with fractional anisotropy in the left temporal lobe, in the same white matter region where adults with reading disability are known to have lower fractional anisotropy. Both the temporal and the frontal regions were also correlated with age. These results show that maturation of white matter is an important part of brain maturation during childhood, and that maturation of relatively restricted regions of white matter is correlated with development of specific cognitive functions. ■

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Microstructure of Temporo-Parietal White Matter as a Basis for Reading Ability: Evidence from Diffusion Tensor Magnetic Resonance Imaging

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Summary

Diffusion tensor magnetic resonance imaging (MRI) was used to study the microstructural integrity of white matter in adults with poor or normal reading ability. Subjects with reading difficulty exhibited decreased diffusion anisotropy bilaterally in temporo-parietal white matter. Axons in these regions were predominantly anterior–posterior in direction. No differences in T1-weighted MRI signal were found between poor readers and control subjects, demonstrating specificity of the group difference to the microstructural characteristics measured by diffusion tensor imaging (DTI). White matter diffusion anisotropy in the temporo-parietal region of the left hemisphere was significantly correlated with reading scores within the reading-impaired adults and within the control group. The anisotropy reflects microstructure of white matter tracts, which may contribute to reading ability by determining the strength of communication between cortical areas involved in visual, auditory, and language processing.

A growing body of evidence suggests that dyslexia is a neurological disorder. A genetic basis for dyslexia has also been suggested (e.g., Pennington et al., 1991). Postmortem studies of dyslexic brains have discovered a consistent pattern of pathological changes (cortical microlesions and glial scars) throughout the left perisylvian cortices, along with reduced left–right asymmetry of the planum temporale (Galaburda et al., 1985; Humphreys et al., 1990). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have found atypical activation patterns in the temporo-parietal cortex of adult dyslexics during reading tasks, particularly on tasks involving the recoding of written symbols into their phonological counterparts (Rumsey et al., 1992, 1997; Paulesu et al., 1996; Shaywitz et al., 1998). Studies using magnetoencephalography (MEG) have also found differences in the time course of cortical processing in poor readers compared to normal readers (Salmelin et al., 1996; Nagarajan et al., 1999). Each of these findings is consistent with a neural basis for dyslexia, but the underlying cause of these differences in neural processing is not currently known.

Two studies have suggested that developmental dyslexia may represent a disconnection syndrome in which communication is impaired between cortical areas involved in reading. In particular, dyslexic individuals have exhibited decreased correlations of cortical activity between the angular gyrus and inferior frontal, extrastriate occipital, and temporal areas (Horwitz et al., 1998). Another study has suggested such an impairment based on the basis of abnormal patterns of activation in the temporo-parietal, frontal, and insular cortices in dyslexic adults (Paulesu et al., 1996). This proposal is consistent with behavioral evidence that dyslexic individuals are

PNAS PLUS

Development of white matter and reading skills

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White matter tissue properties are highly correlated with reading proficiency; we would like to have a model that relates the dynamics of an individual's white matter development to their acquisition of skilled reading. The development of cerebral white matter involves multiple biological processes, and the balance between these processes differs between individuals. Cross-sectional measures of white matter mask the interplay between these processes and their connection to an individual's cognitive development. Hence, we performed a longitudinal study to measure white-matter development (diffusion-weighted imaging) and reading development (behavioral testing) in individual children (age 7–15 y). The pattern of white-matter development differed significantly among children. In the left arcuate and left inferior longitudinal fasciculus, children with above-average reading skills initially had low fractional anisotropy (FA) that increased over the 3-y period, whereas children with below-average reading skills had higher initial FA that declined over time. We describe a dual-process model of white matter development comprising biological processes with opposing effects on FA, such as axonal myelination and pruning, to explain the pattern of results.

plasticity | neuroprognosis | education | dti | tensor

ages of 7 and 12 y, longitudinally for 3 y to disambiguate the relationship between white-matter development and the maturation of reading skills. From the initial cohort, 39 children were measured at least three times with diffusion-weighted imaging; cognitive, language, and reading skills were assessed each year with norm-referenced standardized tests.

Results

Identification of Key White-Matter Fascicles. The act of reading can be separated into phonological (auditory) and orthographic (visual) processing that use different neural pathways (20–23). We identified two major white-matter fascicles (Fig. 1) that project to (*a*) regions of cortex involved in phonological manipulations, and (*b*) regions involved in seeing words. The arcuate fasciculus (blue in Fig. 1*C*) is a fiber tract that connects the posterior inferior frontal cortex, including Broca's area, and the lateral temporal cortex, including Wernicke's area. This pathway is important for phonological awareness, an essential skill in reading development (6, 24, 25). The ILF (orange in Fig. 1*C*) is a principal pathway carrying signals between the occipital lobe and the anterior, medial, and inferior temporal lobe. A portion of the ILF projects to the visual word form area (VWFA) in the occipital temporal sulcus (7). The

Mechanisms of white matter changes induced by meditation

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Contributed by Michael I. Posner, May 9, 2012 (sent for review April 6, 2012)

Using diffusion tensor imaging, several recent studies have shown that training results in changes in white matter efficiency as measured by fractional anisotropy (FA). In our work, we found that a form of mindfulness meditation, integrative body–mind training (IBMT), improved FA in areas surrounding the anterior cingulate cortex after 4-wk training more than controls given relaxation training. Reductions in radial diffusivity (RD) have been interpreted as improved myelin but reductions in axial diffusivity (AD) involve other mechanisms, such as axonal density. We now report that after 4-wk training with IBMT, both RD and AD decrease accompanied by increased FA, indicating improved efficiency of white matter involves increased myelin as well as other axonal changes. However, 2-wk IBMT reduced AD, but not RD or FA, and improved moods. Our results demonstrate the time-course of white matter neuroplasticity in short-term meditation. This dynamic pattern of white matter change involving the anterior cingulate cortex, a part of the brain network related to self-regulation, could provide a means for intervention to improve or prevent mental disorders.

alteration. Depending upon the brain region examined, these studies found either only RD increase, or both RD and AD increase, or RD increase and AD decrease (6–8). These results showed considerable diversity in the way in which brain regions respond to aging or neurodegenerative diseases. In contrast to aging, training in reading, use of the abacus, and working memory have resulted in FA increase by decreasing RD without changing AD. This pattern supports the notion that myelination is the predominant process of the increased FA following training in specific tasks (2–4). Keller and Just (3) proposed that skill learning would increase neural firing and thus increase myelination (decrease in RD and increase in FA). The increased myelination would enhance communication among cortical areas, resulting in better performance.

Our previous study showed that 4 wk of integrative body–mind training (IBMT) (11 h in total) enhanced FA in several brain areas involved in communication to and from the anterior cingulate cortex (ACC), including the corpus callosum and anterior and superior corona radiata (5). However, whether the FA increase is a result of changes in AD or RD in our study is unknown. We

Molecular Psychiatry (2012), 1 – 5

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ORIGINAL ARTICLE

Brain white matter tract integrity as a neural foundation for general intelligence

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General intelligence is a robust predictor of important life outcomes, including educational and occupational attainment, successfully managing everyday life situations, good health and longevity. Some neuronal correlates of intelligence have been discovered, mainly indicating that larger cortices in widespread parieto-frontal brain networks and efficient neuronal information processing support higher intelligence. However, there is a lack of established associations between general intelligence and any basic structural brain parameters that have a clear functional meaning. Here, we provide evidence that lower brain-wide white matter tract integrity exerts a substantial negative effect on general intelligence through reduced information-processing speed. Structural brain magnetic resonance imaging scans were acquired from 420 older adults in their early 70s. Using quantitative tractography, we measured fractional anisotropy and two white matter integrity biomarkers that are novel to the study of intelligence: longitudinal relaxation time (T1) and magnetisation transfer ratio. Substantial correlations among 12 major white matter tracts studied allowed the extraction of three general factors of biomarker-specific brain-wide white matter tract integrity. Each was independently associated with general intelligence, together explaining 10% of the variance, and their effect was completely mediated by information-processing speed. Unlike most previously established neurostructural correlates of intelligence, these findings suggest a functionally plausible model of intelligence, where structurally intact axonal fibres across the brain provide the neuroanatomical infrastructure for fast information processing within widespread brain networks, supporting general intelligence.

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Keywords: diffusion tensor imaging; information-processing speed; intelligence; magnetisation transfer imaging; tractography; white matter

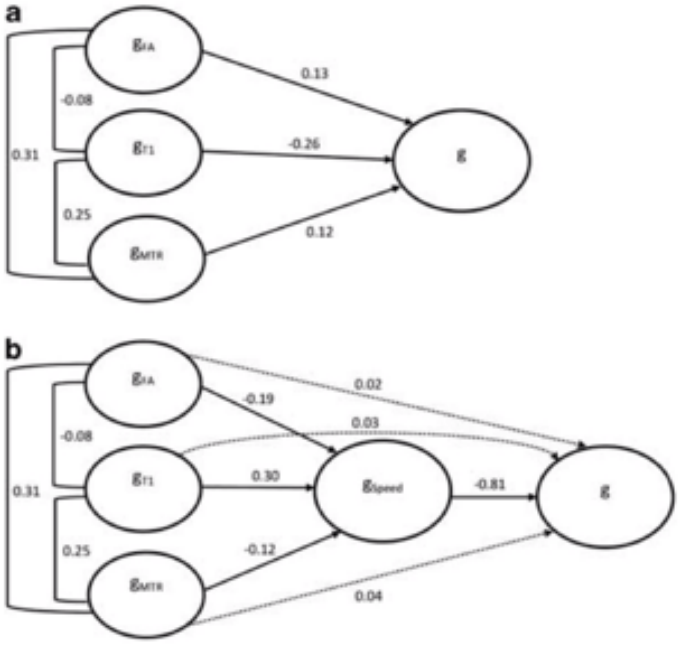

Figure 2. Results of SEM of the three white matter integrity factors, general intelligence, and information-processing speed. Only the latent variables are depicted. For full measurement models see Supporting Online Materials. All path estimates are standardised. (**a**) g_{FA}, g_{T1} and g_{MTR} (common latent factors each defined by their respective tractography estimate for all 12 tracts) are independently associated with general intelligence (*g*) ($\chi^2(755) = 1721.27$, CFI = 0.945, NNFI = 0.938, RMSEA = 0.055, SRMR = 0.054), explaining 10.0% of the variance. (**b**) Cognitive information-processing speed (g_{Speed}) mediates the association between the three latent white matter tract integrity factors and general intelligence. Note that higher values of g_{Speed} indicate slower (less favourable) information-processing speed. The model with solid lines fits the data well ($\chi^2(880) = 1900.894$, CFI = 0.943, NNFI = 0.936, RMSEA = 0.053, SRMR = 0.053, AIC = 36524.9, BIC = 37151.1). Additional direct paths from g_{FA}, g_{T1} and g_{MTR} to *g* (dotted lines) have negligible, non-significant path estimates and decrease model fit (AIC = 36530.1, BIC = 37168.5), indicating full mediation of the effect of the three white matter tract integrity indices on general intelligence by cognitive information-processing speed.

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The neuropsychological profile of vascular cognitive impairment not demented: A meta-analysis

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The most common cause of vascular cognitive impairment not demented (VCIND) is cerebral small vessel disease leading to diffuse subcortical white matter lesions. While many studies indicate that the core cognitive features of VCIND are executive dysfunction and impaired processing speed, this finding is not always consistent, and may be partially dependent on the comparison group applied. Hence, we undertook two systematic meta-analytic reviews on neuropsychological test performance across eight cognitive domains: between VCIND and healthy controls (data from 27 studies), and between VCIND and non-vascular mild cognitive impairment (nv-MCI; data from 20 studies). Our quantitative synthesis of the research literature demonstrates that individuals with VCIND show weaknesses across all cognitive domains relative to healthy controls, with the greatest impairment in the domain of processing speed ($Md = -1.36$), and the least affected being working memory ($Md = -.48$) and visuospatial construction ($Md = -.63$). When compared directly with nv-MCI, individuals with VCIND had significantly greater deficits in processing speed ($Md = -.55$) and executive functioning ($Md = -.40$), while those with nv-MCI exhibited a greater relative deficit in delayed memory ($Md = .41$). Our analyses indicate that disruption to subcortical white matter tracts impairs more cognitive processes than is typically thought to be directly related to the fronto-subcortical network. The data also suggest that differing brain aetiologies can be responsible for similar cognitive profiles. Although the findings do not evince diagnostic value, they allude to the interconnectivity of disparate cognitive processes and call for further research on the behavioural outcome of network disruption.

Table 6. Neuropsychological performance by cognitive domain: VCIND versus nv-MC

Cognitive domain	*nd*	*Md*	*SEd*	*p*-value	95% CI	OL%
General functioning	29	−.007	0.054	.892	−.11 to .10	100.0
Language	27	−.224	0.060	<.001	−.34 to −.11	85.3
Attention						
Working memory	24	−.144	0.058	.013	−.26 to −.03	88.8
Processing speed	19	−.550	0.105	<.001	−.76 to −.34	64.2
Executive functioning	39	−.396	0.099	<.001	−.59 to −.20	72.6
Immediate memory	29	.160	0.078	.040	.01 to .31	88.8
Delayed memory	46	.408	0.083	<.001	.25 to .57	72.6
Visuospatial construction	20	−.325	0.099	.001	−.52 to −.13	78.7

Note. Positive effect size values indicate a magnitude difference in favour of VCIND (i.e. worse performance for nv-MCI relative to VCIND), whereas negative values indicate worse performance in VCIND relative to nv-MCI.

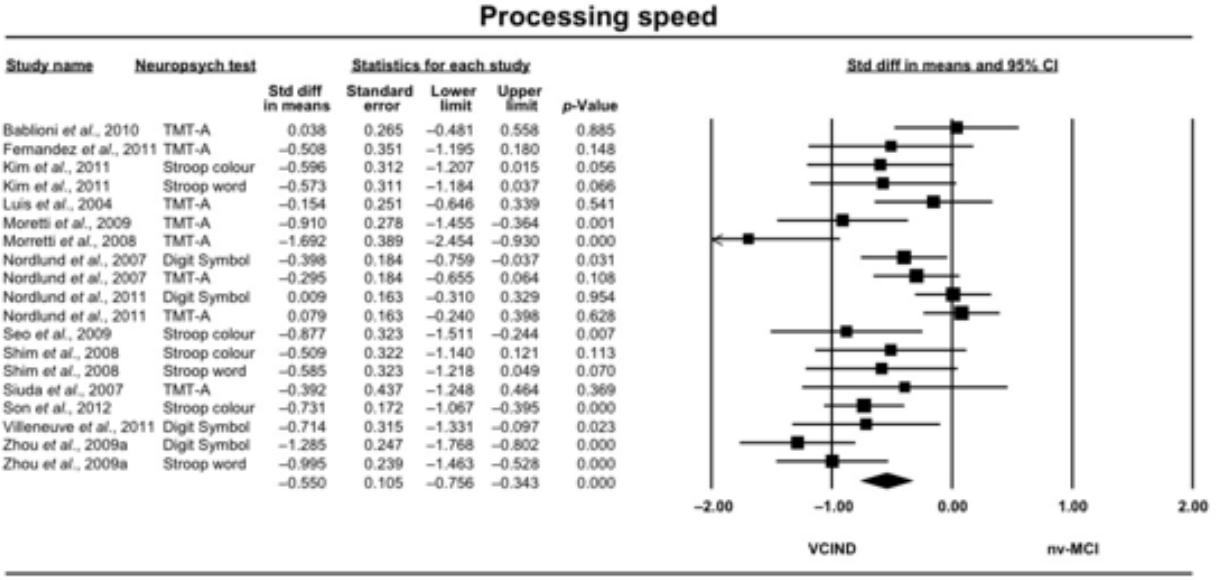

Figure 2. Processing speed forest plot: VCIND versus nv-MCI.

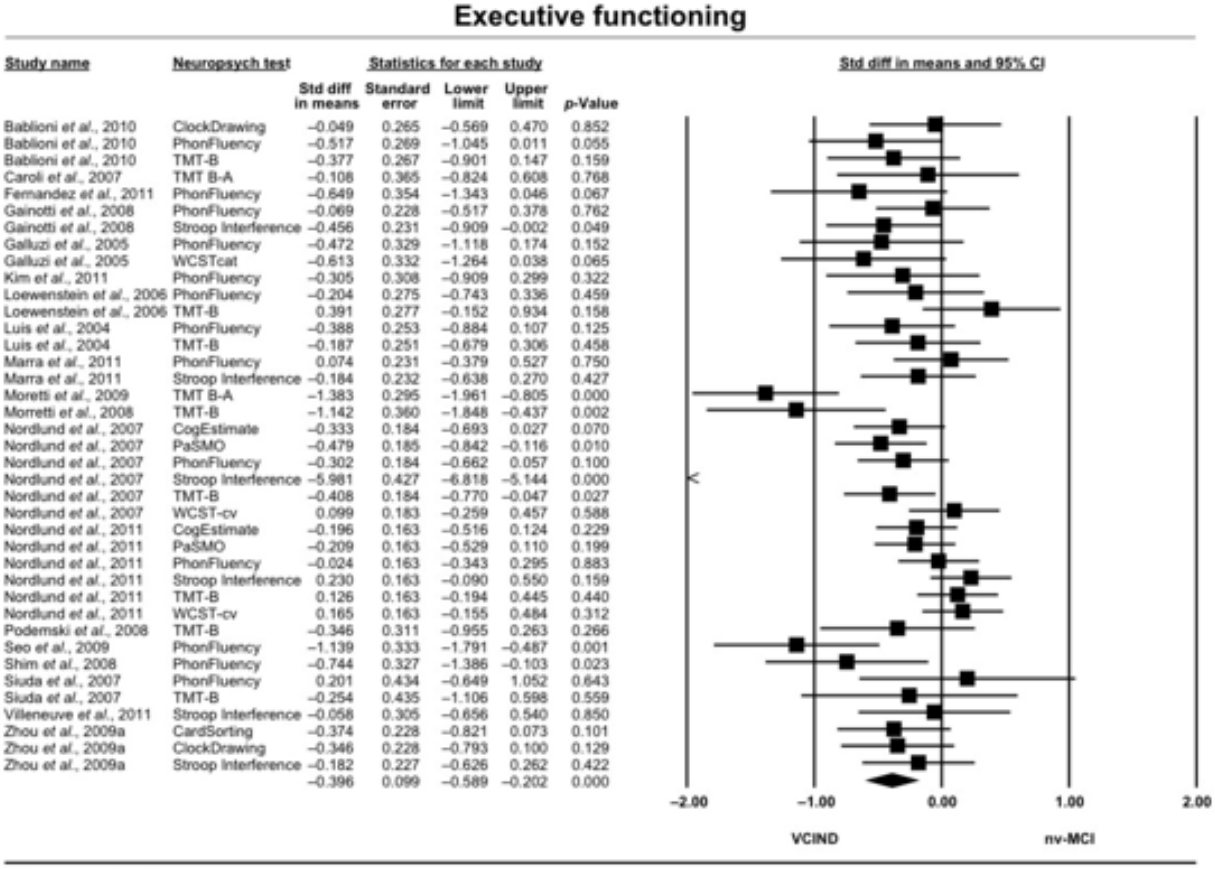

Figure 3. Executive functioning forest plot: VCIND versus nv-MCI.

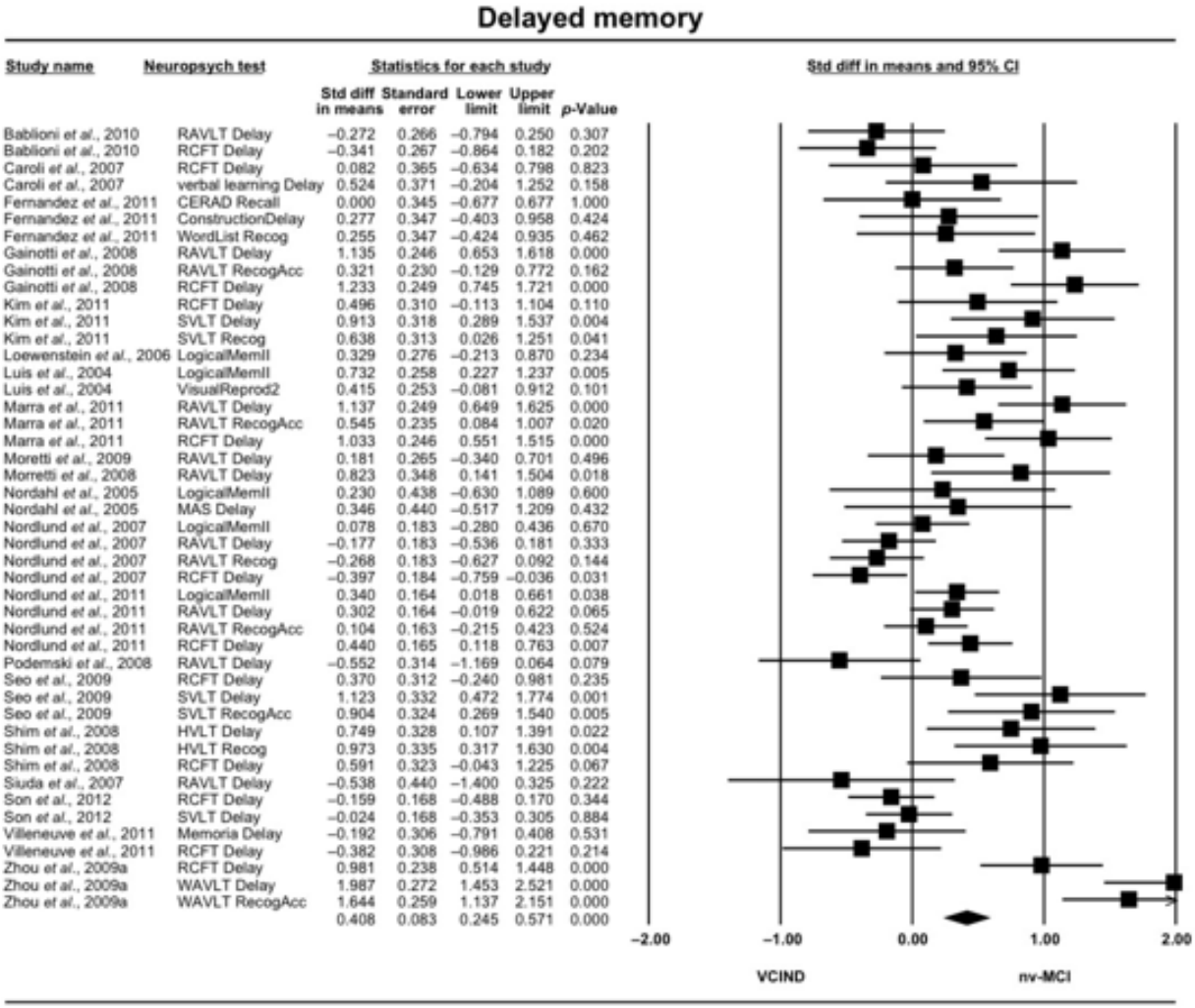

Figure 4. Delayed memory forest plot: VCIND versus nv-MCI.

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The Role of Fronto-Parietal and Fronto-Striatal Networks in the Development of Working Memory: A Longitudinal Study

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The increase in working memory (WM) capacity is an important part of cognitive development during childhood and adolescence. Cross-sectional analyses have associated this development with higher activity, thinner cortex, and white matter maturation in fronto-parietal networks. However, there is still a lack of longitudinal data showing the dynamics of this development and the role of subcortical structures. We included 89 individuals, aged 6–25 years, who were scanned 1–3 times at 2-year intervals. Functional magnetic resonance imaging (fMRI) was used to identify activated areas in superior frontal, intraparietal cortices, and caudate nucleus during performance on a visuo-spatial WM task. Probabilistic tractography determined the anatomical pathways between these regions. In the cross-sectional analysis, WM capacity correlated with activity in frontal and parietal regions, cortical thickness in parietal cortex, and white matter structure [both fractional anisotropy (FA) and white matter volume] of fronto-parietal and fronto-striatal tracts. However, in the longitudinal analysis, FA in white matter tracts and activity in caudate predicted future WM capacity. The results show a dynamic of neural networks underlying WM development in which cortical activity and structure relate to current capacity, while white matter tracts and caudate activity predict future WM capacity.

Keywords: caudate nucleus, cortical thickness, development, DTI, fMRI, working memory

during childhood and adolescence (Olesen, Nagy, et al. 2003; Nagy et al. 2004; Østby et al. 2011; Vestergaard et al. 2011).

These studies thus suggest that improvements in WM capacity are associated with a gradual maturation of white and gray matter in a fronto-parietal network. It is not clear, however, how these changes are related to each other, and if certain changes cause the later changes in WM performance. The role of the striatum for development is also unclear. The caudate nucleus is activated during performance of WM tasks in nonhuman primates (Levy et al. 1997), children (Klingberg et al. 2002; Ziermans et al. 2012), and adults (Postle et al. 2000), but its role in development is unclear.

One reason why the dynamics of WM development has not been clarified is that most of these studies have been cross-sectional, correlating the current cognitive ability with current structure or activity. An exception here is the study by Ullman et al. (2014), who used a longitudinal design and a multivariate analysis to show that there were differences between multivariate models correlating with current cognitive capacity and the models predicting the change of capacity over the next 2 years. Since this study was multivariate, it was not designed to specify the role of anatomically defined regions or networks.

In the current study, we first identified the regions of interest (ROIs) based on the main effect of WM during development (Dumontheil et al. 2011; Ziermans et al. 2012) for a group of 89 individuals, aged 6–25 years, who were scanned 1–3 times

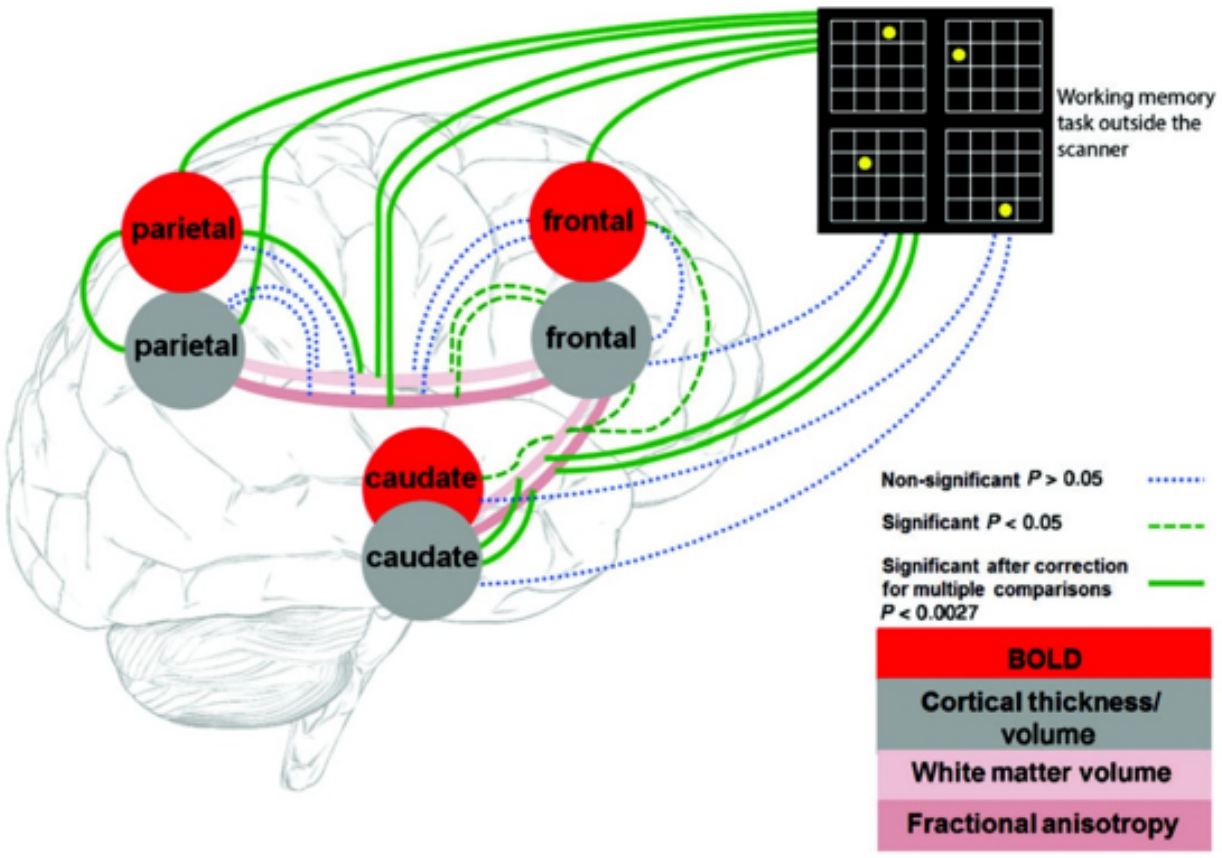

Figure 4. Cross-sectional analysis of correlations between brain–brain and brain–WM. The correlations include all 3 rounds of repeated measures for all variables. The dashed green and dotted blue lines show the significant and nonsignificant correlations, respectively, based on Tables 1 and 2. The thick green lines are those that survived the multiple comparisons correction.

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Fronto-Parietal Anatomical Connections Influence the Modulation of Conscious Visual Perception by High-Beta Frontal Oscillatory Activity

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May white matter connectivity influence rhythmic brain activity underlying visual cognition? We here employed diffusion imaging to reconstruct the fronto-parietal white matter pathways in a group of healthy participants who displayed frequency-specific ameliorations of visual sensitivity during the entrainment of high-beta oscillatory activity by rhythmic transcranial magnetic stimulation over their right frontal eye field. Our analyses reveal a strong tract-specific association between the volume of the first branch of the superior longitudinal fasciculus and improvements of conscious visual detection driven by frontal beta oscillation patterns. These data indicate that the architecture of specific white matter pathways has the ability to influence the distributed effects of rhythmic spatio-temporal activity, and suggest a potentially relevant role for long-range connectivity in the synchronization of oscillatory patterns across fronto-parietal networks subtending the modulation of conscious visual perception.

(Romei et al. 2010; Thut et al. 2011) and entrain synchronization throughout a fronto-parietal dorsal network, considered key for spatial attentional orienting and the top-down modulation of visual perception (Chanes et al. 2012).

Stimulation site and frequency were matched to those of a nonhuman primate study reporting the engagement of high-beta (22–34 Hz) activity across frontal and parietal dorsal regions during a visual search task involving endogenous attentional orienting (Buschman and Miller 2007). In our population, short episodes of 30-Hz spatio-temporal activity delivered to the right FEF prior to target onset induced statistically significant improvements of perceptual sensitivity in a visual detection task, which were absent when control nonfrequency-specific stimulation patterns were employed (Chanes et al. 2013). Interestingly, despite robust statistically significant group effects, across-subject performance differ-

Archival Report

Connectomic Disturbances in Attention-Deficit/Hyperactivity Disorder: A Whole-Brain Tractography Analysis

Soon-Beom Hong, Andrew Zalesky, Alex Fornito, Subin Park, Young-Hui Yang, Min-Hyeon Park, In-Chan Song, Chul-Ho Sohn, Min-Sup Shin, Bung-Nyun Kim, Soo-Churl Cho, Doug Hyun Han, Jae Hoon Cheong, and Jae-Won Kim

Background: Few studies have sought to identify, in a regionally unbiased way, the precise cortical and subcortical regions that are affected by white matter abnormalities in attention-deficit/hyperactivity disorder (ADHD). This study aimed to derive a comprehensive, whole-brain characterization of connectomic disturbances in ADHD.

Methods: Using diffusion tensor imaging, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in 71 children and adolescents with ADHD compared with 26 healthy control subjects. White matter differences were further delineated between patients with ($n = 40$) and without ($n = 26$) the predominantly hyperactive/impulsive subtype of ADHD.

Results: A significant network comprising 25 distinct fiber bundles linking 23 different brain regions spanning frontal, striatal, and cerebellar brain regions showed altered white matter structure in ADHD patients ($p < .05$, family-wise error-corrected). Moreover, fractional anisotropy in some of these fiber bundles correlated with attentional disturbances. Attention-deficit/hyperactivity disorder subtypes were differentiated by a right-lateralized network ($p < .05$, family-wise error-corrected) predominantly linking frontal, cingulate, and supplementary motor areas. Fractional anisotropy in this network was also correlated with continuous performance test scores.

Conclusions: Using an unbiased, whole-brain, data-driven approach, we demonstrated abnormal white matter connectivity in ADHD. The correlations observed with measures of attentional performance underscore the functional importance of these connectomic disturbances for the clinical phenotype of ADHD. A distributed pattern of white matter microstructural integrity separately involving frontal, striatal, and cerebellar brain regions, rather than direct frontostriatal connectivity, appears to be disrupted in children and adolescents with ADHD.

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Intelligence and the brain: A model-based approach

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Various biological correlates of general intelligence (*g*) have been reported. Despite this, however, the relationship between neurological measurements and *g* is not fully clear. We use structural equation modeling to model the relationship between behavioral Wechsler Adult Intelligence Scale (WAIS) estimates of *g* and neurological measurements (voxel-based morphometry and diffusion tensor imaging of eight regions of interest). We discuss psychometric models that explicate the relationship between *g* and the brain in a manner in line with the scientific study of *g*. Fitting the proposed models to the data, we find that a MIMIC model (for multiple indicators, multiple causes), where the contributions of different brain regions to a unidimensional *g* are estimated separately, provides the best fit against the data.

Keywords: Intelligence; Cognitive neuroscience; *g*; Structural equation modeling; Neuro *g*; Psychometrics.

Review

Cell PRESS

The connectome

Neural correlates of establishing, maintaining, and switching brain states

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Although the study of brain states is an old one in neuroscience, there has been growing interest in brain state specification owing to MRI studies tracing brain connectivity at rest. In this review, we summarize recent research on three relatively well-described brain states: the resting, alert, and meditation states. We explore the neural correlates of maintaining a state or switching between states, and argue that the anterior cingulate cortex and striatum play a critical role in state maintenance, whereas the insula has a major role in switching between states. Brain state may serve as a predictor of performance in a variety of perceptual, memory, and problem solving tasks. Thus, understanding brain states is critical for understanding human performance.

medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC), often called the Default Mode Network (DMN), along with a number of other areas that are active and correlated at rest [7–10].

In animal and human studies sleep states have been shown to be important for learning, memory consolidation, and brain plasticity [11–14]. Although brain states such as sleep have been widely studied in both animals and humans, it has been less common to investigate brain states when awake and usually researchers focus on only one waking state [9,15]. As a consequence, the neural mechanisms of effectively achieving and maintaining appropriate brain states or switching between brain states during task performance have received little attention.

In this article, we discuss the resting state, the alert

High-cost, high-capacity backbone for global brain communication

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Network studies of human brain structural connectivity have identified a specific set of brain regions that are both highly connected and highly central. Recent analyses have shown that these putative hub regions are mutually and densely interconnected, forming a "rich club" within the human brain. Here we show that the set of pathways linking rich club regions forms a central high-cost, high-capacity backbone for global brain communication. Diffusion tensor imaging (DTI) data of two sets of 40 healthy subjects were used to map structural brain networks. The contributions to network cost and communication capacity of global cortico-cortical connections were assessed through measures of their topology and spatial embedding. Rich club connections were found to be more costly than predicted by their density alone and accounted for 40% of the total communication cost. Furthermore, 69% of all minimally short paths between node pairs were found to travel through the rich club and a large proportion of these communication paths consisted of ordered sequences of edges ("path motifs") that first fed into, then traversed, and finally exited the rich club, while passing through nodes of increasing and then decreasing degree. The prevalence of short paths that follow such ordered degree sequences suggests that neural communication might take advantage of strategies for dynamic routing of information between brain regions, with an important role for a highly central rich club. Taken together, our results show that rich club connections make an important contribution to interregional signal traffic, forming a central high-cost, high-capacity backbone for global brain communication.

implicated in efficient integration of information between remote parts of the brain (14–16). Their aggregation into a connected rich club suggests the hypothesis that rich club regions do not act as separate entities but instead operate as a single coherent collective, a focal and centrally embedded network, with rich club connections forming a connectivity backbone linking diverse sets of regions across the brain.

In this report we investigate aspects of network cost and communication capacity for rich club connections based on in vivo diffusion magnetic resonance imaging (MRI) measurements, in relation to their topology and spatial embedding in the human brain network. Large-scale rich club connections are shown to be relatively high cost, with a tendency to link regions across long physical distances. At the same time, rich club connections participate in a large number of short communication paths, thus carrying a high proportion of the brain's signal traffic. Closer examination of the structure of these paths across the brain reveals a sequential organization suggestive of some efficient strategies for dynamic routing of interregional signals, with a central role for rich club connections.

Results

Rich Club Organization. Diffusion tensor imaging (DTI) data of 40 healthy subjects were used to map the large-scale connectivity structure of the brain network, parcellating the cortical sheet into 1,170 distinct evenly sized parcels and determining a group-averaged level of connectivity as the number of reconstructed streamlines between all parcels. A second set of 40 healthy sub-

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REVIEW

Attention-Deficit/Hyperactivity Disorder and Attention Networks

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Research attempting to elucidate the neuropathophysiology of attention-deficit/hyperactivity disorder (ADHD) has not only shed light on the disorder itself, it has simultaneously provided new insights into the mechanisms of normal cognition and attention. This review will highlight and integrate this bidirectional flow of information. Following a brief overview of ADHD clinical phenomenology, ADHD studies will be placed into a wider historical perspective by providing illustrative examples of how major models of attention have influenced the development of neurocircuitry models of ADHD. The review will then identify major components of neural systems potentially relevant to ADHD, including attention networks, reward/feedback-based processing systems, as well as a 'default mode' resting state network. Further, it will suggest ways in which these systems may interact and be influenced by neuromodulatory factors. Recent ADHD imaging data will be selectively provided to both illustrate the field's current level of knowledge and to show how such data can inform our understanding of normal brain functions. The review will conclude by suggesting possible avenues for future research.
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Keywords: attention; ADHD; imaging; reward; cingulate; prefrontal

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REVIEW

Strengthening Connections: Functional Connectivity and Brain Plasticity

Clare Kelly · F. Xavier Castellanos

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Abstract The ascendancy of functional neuroimaging has facilitated the addition of network-based approaches to the neuropsychologist's toolbox for evaluating the sequelae of brain insult. In particular, intrinsic functional connectivity (iFC) mapping of resting state fMRI (R-fMRI) data constitutes an ideal approach to measuring macro-scale networks in the human brain. Beyond the value of iFC mapping for charting how the functional topography of the brain is altered by insult and injury, iFC analyses can provide insights into experience-dependent plasticity at the macro level of large-scale functional networks. Such insights are foundational to the design of training and remediation interventions that will best facilitate recovery of function. In this review, we consider what is currently known about the origin and function of iFC in the brain, and how this knowledge is informative in neuropsychological settings. We then summarize studies that have examined experience-driven plasticity of iFC in healthy control participants, and frame these findings in terms of a schema that may aid in the interpretation of results and the generation of hypotheses for rehabilitative studies. Finally, we outline some caveats to the R-fMRI approach, as well as some current developments that are likely to bolster the utility of the iFC paradigm for neuropsychology.

Linking localized brain injury or dysfunction to phenotypic deficits is the sine qua non of neuropsychology. Yet, neuropsychologists are often confounded by the observation that diverse injuries can produce similar clinical presentations. This phenomenon can become less puzzling when a network-based approach to understanding brain function is adopted, and patients are grouped according to affected *networks*, rather than affected regions (Carter et al. 2012). Intrinsic functional connectivity (iFC) mapping of resting state fMRI (R-fMRI) data constitutes an ideal approach to measuring macro-scale networks in the human brain. The value of this approach to neuropsychology goes beyond its utility in charting how the functional topography of the brain is altered by insult and injury, however. By examining plastic changes in iFC—how iFC is altered by training and practice, we may uncover the mechanisms underlying the sequelae of brain insult—in terms of both loss *and* recovery of function. Here, we review the literature on iFC plasticity, with a focus on the effects of training and practice. In doing so, we hope to highlight the ways in which R-fMRI approaches may illuminate our understanding of the brain's vulnerability to dysfunction following injury, and its often remarkable propensity to recover from a range of insults.

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REVIEW

Brain Networks in Schizophrenia

Martijn P. van den Heuvel · Alex Fornito

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Abstract Schizophrenia—a severe psychiatric condition characterized by hallucinations, delusions, loss of initiative and cognitive function—is hypothesized to result from abnormal anatomical neural connectivity and a consequent decoupling of the brain's integrative thought processes. The rise of in vivo neuroimaging techniques has refueled the formulation of dysconnectivity hypotheses, linking schizophrenia to abnormal structural and functional connectivity in the brain at both microscopic and macroscopic levels. Over the past few years, advances in high-field structural and functional neuroimaging techniques have made it increasingly feasible to reconstruct comprehensive maps of the macroscopic neural wiring system of the human brain, know as the connectome. In parallel, advances in network science and graph theory have improved our ability to study the spatial and topological organizational layout of such neural connectivity maps in detail. Combined, the field of neural connectomics has created a novel platform that provides a deeper understanding of the overall organization of brain wiring, its relation to healthy brain function and human cognition, and conversely, how brain disorders such as schizophrenia arise from abnormal brain network wiring and dynamics. In this review we discuss recent findings of connectomic studies in schizophrenia that examine how the disorder relates to disruptions of brain connectivity.

Keywords Schizophrenia · Brain networks · Connectome · Connectomics · Structural connectivity · Functional connectivity

Schizophrenia—A Disorder of Brain Connectivity

Schizophrenia is a severe psychiatric disease characterized by hallucinations, delusions, loss of initiative and cognitive dysfunction. The notion that schizophrenia may be related to disrupted brain connectivity dates back to work of pioneering anatomists and psychiatrists in the 19th and 20th century. Early thinkers like Theodor Meynert (1833–1892), Carl Wernicke (1848–1905) and Emil Kraepelin (1856–1926) were among the first to notice that brain function and higher-order cognitive processes are the result of functional integration between multiple, spatially distributed brain regions (Wernicke 1885), and that conversely neural dysfunction need not necessarily be the product of focal lesions in specific brain regions, but could also equivalently be related to damage of their interconnecting axonal pathways. Emil Kraepelin gained notoriety as the father of modern descriptive psychiatry by providing one of the first systematic clinical descriptions of dementia praecox – a degenerative neuropsychiatric condition with early onset (Kraepelin 1919) which is widely recognized as a foundation for current diagnostic formu-

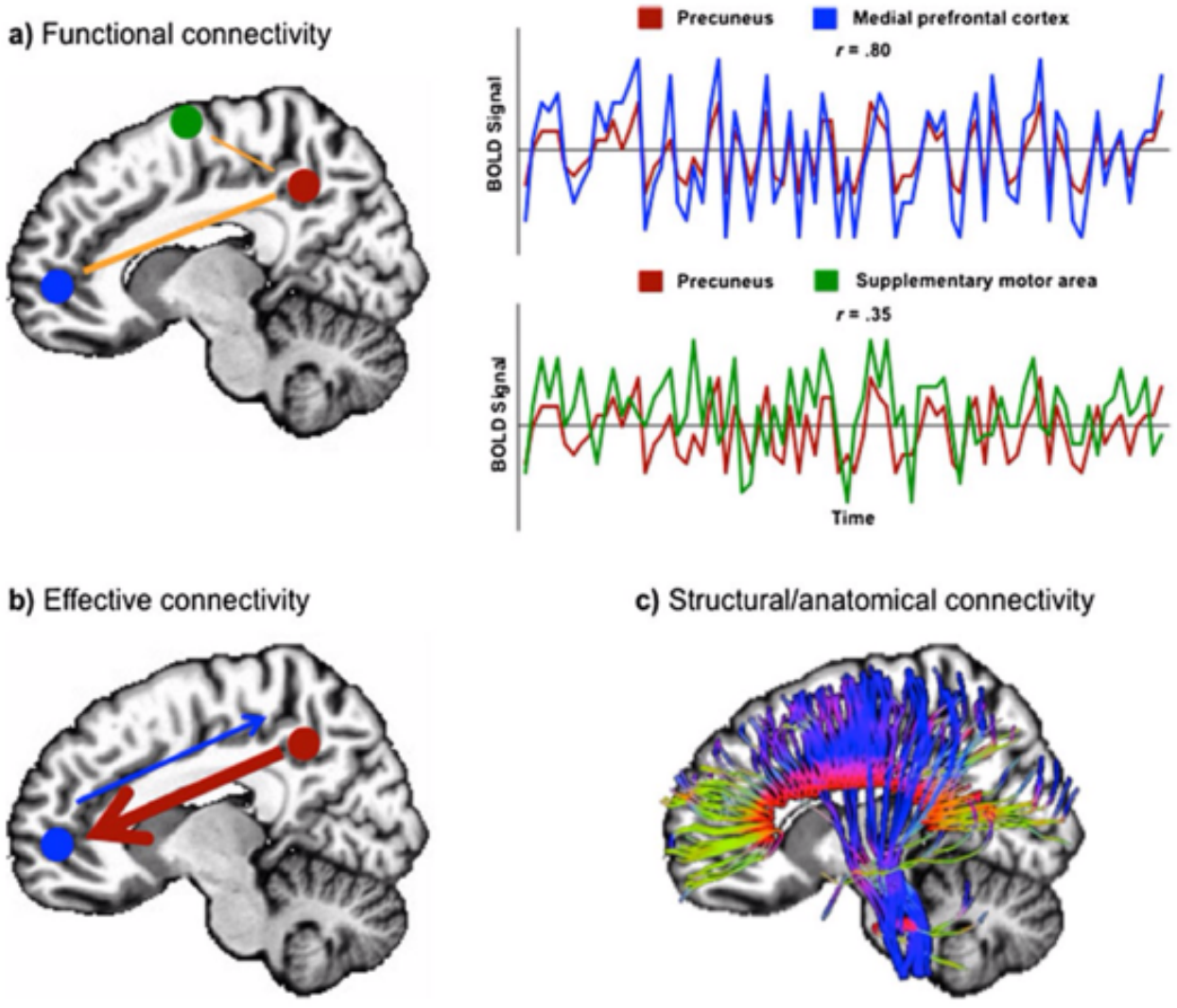

Fig. 1 Models of brain connectivity. Sketches illustrate: **a** functional connectivity between two sets of brain areas. *Top panel graph*: high correlation between precuneus and medial prefrontal cortex; and *bottom panel graph*: weaker correlation between precuneus and supplementary motor area; **b** effective connectivity (information flow) between two regions; and **c** structural/anatomical connectivity depicted by white matter fiber tracts

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Mapping White Matter Integrity in Elderly People with HIV

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Abstract: People with HIV are living longer as combination antiretroviral therapy (cART) becomes more widely available. However, even when plasma viral load is reduced to untraceable levels, chronic HIV infection is associated with neurological deficits and brain atrophy beyond that of normal aging. HIV is often marked by cortical and subcortical atrophy, but the integrity of the brain's white matter (WM) pathways also progressively declines. Few studies focus on older cohorts where normal aging may be compounded with HIV infection to influence deficit patterns. In this relatively large diffusion tensor imaging (DTI) study, we investigated abnormalities in WM fiber integrity in 56 HIV+ adults with access to cART (mean age: 63.9 ± 3.7 years), compared to 31 matched healthy controls (65.4 ± 2.2 years). Statistical 3D maps revealed the independent effects of HIV diagnosis and age on fractional anisotropy (FA) and diffusivity, but we did not find any evidence for an age by diagnosis interaction in our current sample. Compared to healthy controls, HIV patients showed pervasive FA decreases and diffusivity increases throughout WM. We also assessed neuropsychological (NP) summary *z*-score associations. In both patients and controls, fiber integrity measures were associated with NP summary scores. The greatest differences were detected in the corpus callosum and in the projection fibers of the *corona radiata*. These deficits are consistent with published NP deficits and cortical atrophy patterns in elderly people with HIV. *Hum Brain Mapp 35:975–992, 2014.*

Key words: brain integrity; white matter; diffusion tensor imaging; cognition; HIV; cART

◆ Human Brain Mapping 00:00–00 (2014) ◆

White Matter Development and Early Cognition in Babies and Toddlers

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Abstract: The normal myelination of neuronal axons is essential to neurodevelopment, allowing fast inter-neuronal communication. The most dynamic period of myelination occurs in the first few years of life, in concert with a dramatic increase in cognitive abilities. How these processes relate, however, is still unclear. Here we aimed to use a data-driven technique to parcellate developing white matter into regions with consistent white matter growth trajectories and investigate how these regions related to cognitive development. In a large sample of 183 children aged 3 months to 4 years, we calculated whole brain myelin volume fraction (VF_M) maps using quantitative multicomponent relaxometry. We used spatial independent component analysis (ICA) to blindly segment these quantitative VF_M images into anatomically meaningful parcels with distinct developmental trajectories. We further investigated the relationship of these trajectories with standardized cognitive scores in the same children. The resulting components represented a mix of unilateral and bilateral white matter regions (e.g., cortico-spinal tract, genu and splenium of the corpus callosum, white matter underlying the inferior frontal gyrus) as well as structured noise (misregistration, image artifact). The trajectories of these regions were associated with individual differences in cognitive abilities. Specifically, components in white matter underlying frontal and temporal cortices showed significant relationships to expressive and receptive language abilities. Many of these relationships had a significant interaction with age, with VF_M becoming more strongly associated with language skills with age. These data provide evidence for a changing coupling between developing myelin and cognitive development. *Hum Brain Mapp 00:000–000, 2014.* © 2014 Wiley Periodicals, Inc.

Key words: white matter; myelin volume fraction; cognitive development; multicomponent relaxometry; language; neurodevelopment

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Abnormalities of Cortical Thickness, Subcortical Shapes, and White Matter Integrity in Subcortical Vascular Cognitive Impairment

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Abstract: Subcortical vascular cognitive impairment (sVCI) is caused by lacunar infarcts or extensive and/or diffuse lesions in the white matter that may disrupt the white matter circuitry connecting cortical and subcortical regions and result in the degeneration of neurons in these regions. This study used structural magnetic resonance imaging (MRI) and high angular resolution diffusion imaging (HARDI) techniques to examine cortical thickness, subcortical shapes, and white matter integrity in mild vascular cognitive impairment no dementia (VCIND Mild) and moderate-to-severe VCI (MSVCI). Our study found that compared to controls (n = 25), VCIND Mild (n = 25), and MSVCI (n = 30) showed thinner cortex predominantly in the frontal cortex. The cortex in MSVCI was thinner in the parietal and lateral temporal cortices than that in VCIND Mild. Moreover, compared to controls, VCIND Mild and MSVCI showed smaller shapes (i.e., volume reduction) in the thalamus, putamen, and globus pallidus and ventricular enlargement. Finally, compared to controls, VCIND Mild, and MSVCI showed an increased mean diffusivity in the white matter, while decreased generalized fractional anisotropy was only found in the MSVCI subjects. The major axonal bundles involved in the white matter abnormalities were mainly toward the frontal regions, including the internal capsule/corona radiata, uncinate fasciculus, and anterior section of the inferior fronto-occipital fasciculus, and were anatomically connected to the affected cortical and subcortical structures. Our findings suggest that abnormalities in cortical, subcortical, and white matter morphology in sVCI occur in anatomically connected structures, and that abnormalities progress along a similar trajectory from the mild to moderate and severe conditions. *Hum Brain Mapp 35:2320–2332, 2014.*

◆ Human Brain Mapping 35:2448–2458 (2014) ◆

Age-Related Increases in Stroop Interference: Delineation of General Slowing Based on Behavioral and White Matter Analyses

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Abstract: The Stroop interference task is a widely used paradigm to examine cognitive inhibition, which is a key component of goal-directed behavior. With increasing age, reaction times in the Stroop interference task are usually slowed. However, to date it is still under debate if age-related increases in reaction times are merely an artifact of general slowing. The current study was conducted to investigate the role of general slowing, as measured by Trail-Making-Test-A, in age-related alterations of Stroop interference. We applied Diffusion Tensor Imaging (DTI) to determine the topography of neuronal networks underlying Stroop interference under control of general slowing. On the behavioral level, linear regression analysis demonstrated that age accounted for significant variance on Stroop interference, whereas TMT-A performance did not. Controlling for TMT-A, DTI based white matter analyses demonstrated a strong association of Stroop interference with integrity measures of genu of corpus callosum, bilateral anterior corona radiata, and bilateral anterior limb of capsula interna. These pathways are associated with frontal brain regions by either connecting the bilateral dorsolateral prefrontal cortex or the anterior cingulate cortex with frontal and subcortical regions or by containing fibers which are part of cortico-thalamic circuits that cross prefrontal regions. Importantly, results expand our knowledge of the neural basis of Stroop interference and emphasize the importance of white matter integrity of frontal pathways in the modulation of Stroop interference. Combining behavioral and DTI findings our results further suggest that cognitive inhibition, as measured by Stroop task, is a qualitatively distinct cognitive process that declines with age. *Hum Brain Mapp 35:2448–2458, 2014.*

Key words: stroop interference; normal aging; general slowing; white matter integrity; DTI

Additional Supporting Information may be found in the online version of this article

INTRODUCTION

◆ Human Brain Mapping 35:2073–2098 (2014) ◆

Concordance of White Matter and Gray Matter Abnormalities in Autism Spectrum Disorders: A Voxel-Based Meta-Analysis Study

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Abstract: There are at least two fundamental unanswered questions in the literature on autism spectrum disorders (ASD): Are abnormalities in white (WM) and gray matter (GM) consistent with one another? Are WM morphometric alterations consistent with alterations in the GM of regions connected by these abnormal WM bundles and vice versa? The aim of this work is to bridge this gap. After selecting voxel-based morphometry and diffusion tensor imaging studies comparing autistic and normally developing groups of subjects, we conducted an activation likelihood estimation (ALE) meta-analysis to estimate consistent brain alterations in ASD. Multidimensional scaling was used to test the similarity of the results. The ALE results were then analyzed to identify the regions of concordance between GM and WM areas. We found statistically significant topological relationships between GM and WM abnormalities in ASD. The most numerous were negative concordances, found bilaterally but with a higher prevalence in the right hemisphere. Positive concordances were found in the left hemisphere. Discordances reflected the spatial distribution of negative concordances. Thus, a different hemispheric contribution emerged, possibly related to pathogenetic factors affecting the right hemisphere during early developmental stages. Besides, WM fiber tracts linking the brain structures involved in social cognition showed abnormalities, and most of them had a negative concordance with the connected GM regions. We interpreted the results in terms of altered brain networks and their role in the pervasive symptoms dramatically impairing communication and social skills in ASD patients. *Hum Brain Mapp 35:2073–2098, 2014.*

Key words: autism spectrum disorder; white matter changes; gray matter changes; VBM; DTI; ALE meta-analysis

◆ Human Brain Mapping 35:2561–2572 (2014) ◆

Gray and White Matter Correlates of Navigational Ability in Humans

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Abstract: Humans differ widely in their navigational abilities. Studies have shown that self-reports on navigational abilities are good predictors of performance on navigation tasks in real and virtual environments. The caudate nucleus and medial temporal lobe regions have been suggested to subserve different navigational strategies. The ability to use different strategies might underlie navigational ability differences. This study examines the anatomical correlates of self-reported navigational ability in both gray and white matter. Local gray matter volume was compared between a group (N = 134) of good and bad navigators using voxel-based morphometry (VBM), as well as regional volumes. To compare between good and bad navigators, we also measured white matter anatomy using diffusion tensor imaging (DTI) and looked at fractional anisotropy (FA) values. We observed a trend toward higher local GM volume in right anterior parahippocampal/rhinal cortex for good versus bad navigators. Good male navigators showed significantly higher local GM volume in right hippocampus than bad male navigators. Conversely, bad navigators showed increased FA values in the internal capsule, the white matter bundle closest to the caudate nucleus and a trend toward higher local GM volume in the caudate nucleus. Furthermore, caudate nucleus regional volume correlated negatively with navigational ability. These convergent findings across imaging modalities are in line with findings showing that the caudate nucleus and the medial temporal lobes are involved in different wayfinding strategies. Our study is the first to show a link between self-reported large-scale navigational abilities and different measures of brain anatomy. *Hum Brain Mapp 35:2561–2572, 2014.*

Key words: navigational abilities; diffusion tensor imaging; voxel-based morphometry; caudate nucleus; parahippocampal gyrus; hippocampus; sense of direction; volumetry; magnetic resonance imaging