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**Changes in functional neural network organization during working memory task
performance: effects of age and task practice**

A Dissertation Presented

By

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Abstract of the Dissertation

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The notion that cognitive processing is not only reflected by regional changes in neural activity in the brain but also by global changes in functional connectivity pattern has greatly motivated the network approach in examining the neural substrates of cognition and their relationship with behavior. Recent human neuroimaging evidence suggests specific cognitive processes may involve distinct spatiotemporal patterns of functional connectivity across task conditions. For instance, increased cognitive demand has been shown to evoke greater network integration while changes in functional network architecture have been associated with shifting between cognitive states. However, little is known about individual differences in the functional organization of neural networks during complex tasks. Here, we examined functional connectivity during multiple cognitive tasks in late childhood/early adolescence and during multiple sessions of working memory performance in young adults. We specifically focused on studying the effects of task state and task practice as these two key factors may particularly impact the functional

architecture of large-scale neural networks. In the first experiment, the functional network architectures during resting and during three cognitive tasks were examined in children aged 9-12. Children exhibited age-dependent similarity in intrinsic network organization to that in adults and changes in network organization in response to distinct cognitive requirements. Compared to resting state, there was an increase in whole-brain functional integration during tasks. Additionally, major functional modules showed different patterns of stability and flexibility across cognitive states. In the second experiment, we investigated network organizations within and between multiple sessions in individual healthy adults during performance of a working memory task. Our results indicate while there was a broad tendency for whole-brain network integration to increase with working memory performance relative to the resting state, network configuration varied greatly across time and individuals. Furthermore, we found individual-dependent practice-related changes in connectivity patterns for different functional modules. Taken together, these findings suggest functional neural network organization varies in correspondence to changing cognitive demands. Such variability is further influenced by young age, task exposure, and individual differences.

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CHAPTER I. GENERAL INTRODUCTION

The relationship between functional network organization and cognitive processing

A major goal of cognitive neuroscience is to understand the role each brain region plays in supporting mental processes and complex behaviors. Historically, the mapping of function and structure across the cortex is largely driven by the view that responses by localized populations of neurons and individual brain regions to a variety of task conditions underlie cognition (Op De Beeck et al., 2008; Poline and Brett, 2012). Task-evoked perturbation of specific brain regions, however, can be challenging to understand as even relatively isolated and specialized cortical structures have been shown to interact and coordinate their activity putatively to support cognitive demands (Shine and Poldrack, 2017). Indeed, work in animal physiology (de Reus and van den Heuvel, 2013; Felleman and Van Essen, 1991; Scannell et al., 1995) and human anatomical (Betz et al., 2013; Hagmann et al., 2008) as well as functional neuroimaging (Meunier et al., 2009b; Power et al., 2011) has demonstrated the brain is organized into networks of highly interconnected regions. Thus, even a momentary challenge by a stimulus can bring about not only changes in discrete brain regions but also the changes in functional connectivity patterns (Mohr et al., 2016). These connectivity patterns, in turn, have been shown to potentially reflect task demands and modulate behavior (Braun et al., 2015; Yue et al., 2017). As a result, the investigation of cognition and its neural substrates may benefit from further understanding the relationship between functional network organization and the underlying cognitive processes.

One crucial question implicated in the examination of such relationship is whether neural networks flexibly adapt their connectivity configuration in response to different demands, and if so, what information changes in configuration convey about the neural basis of cognitive

processing and behavior. Attempts at this question from various studies demonstrate different cognitive states can be successfully classified using functional connectivity patterns both in the whole brain and within task-related modules (Heinzle et al., 2012; Shirer et al., 2012). More recent work examining functional brain organization in multiple tasks further supports that each task is associated with a different network architecture (Cole et al., 2014; Krienen et al., 2014). Intriguingly, such architectures are not only reflective of the specific task demands, they can also exhibit characteristics related to neuronal maturation during development including those associated with modular organization and distal connectivity strength (Baum et al., 2017; Gu et al., 2015). Other factors shown to influence neural network architecture also include aging (Gallen et al., 2016; Meunier et al., 2009a) and cognitive ability (Bassett et al., 2011; Braun et al., 2015). These findings suggest that far from being static, neural networks continually modify their organization according to both endogenous (e.g., neuronal maturation) and exogenous (e.g., environment, tasks) factors.

Characteristics of neural network connectivity patterns during cognitive demands

To support cognitive processing (e.g., working memory), neural networks may change their functional connectivity patterns to reflect the current task's requirements. A functional network refers to a set of neural elements or "nodes", which are brain regions typically co-activated during specific cognitive tasks and exhibit temporal dependency. This temporal dependency is measured by functional correlation which is an indirect measure of network connectivity. A network is also called a module, and by definition it is formed by a group of densely interconnected regions that are sparsely connected to other networks. Here, we identified functionally distinct networks associated with the frontoparietal, default mode, visual etc. and

treated them as modules. A whole-brain network architecture is defined as the specific organization or division of the whole-brain network into modules based on the connectivity patterns among the brain regions. Network configuration refers to the connectivity pattern within the network. Changes in network connectivity pattern can be evaluated with two major network measures: 1. stability and variability, and 2. integration and segregation. Specific measures to assess network architecture and configuration are described below.

Stability and variability

At the whole-brain level, the neural network architecture has been shown to stay relatively stable across multiple cognitive states (Cole et al., 2014; Deco et al., 2011). During resting, the brain can be described as a number of interconnected modules whose connections are dense within each module and sparse in between (Power et al., 2011). The identification of these modules is consistent with the functional organization of the brain as modules show distinct functional roles including executive control, attention, default mode, somatosensory, and visual (Power et al., 2011). Such resting-state (or intrinsic) network architecture remains largely unchanged during a variety of tasks such as motor, working memory, gambling, language, and emotion (Cole et al., 2014). This stability is in agreement with a previous proposal that functional network configurations are based on a stable anatomical skeleton (Deco et al., 2011). White matter pathways both enable and constrain the functional connectivity among elements of the neural network (Bullmore and Sporns, 2009; Hagmann et al., 2008). Specific evidence in functional imaging has demonstrated that functional connectivity reflects structural connectivity measured by DTI (Greicius et al., 2009) and structural connectivity in turns predicts functional connectivity (Honey et al., 2009). Thus, the functional network organizations are thought to be

built upon the physical scaffolding of the brain and are constrained as such (Bassett and Gazzaniga, 2011; Bullmore et al., 2009).

At the module level, the pattern of stability and variability is complex. During resting state, regions from task-specific modules such as those implicated in sensory processing exhibit a low degree of variability in connectivity (Zhang et al., 2016). This stability is likely related to their restricted connections to other regions belonging to the same unitary neural circuitry implicated in sensory functions (Zhang et al., 2016). Indeed, recordings in monkey visual cortex showed a low degree of fluctuation and thus supporting this proposal (Leopold and Murayama, 2003). In contrast, regions belonging to task-general modules including the prefrontal and limbic regions show a high degree of connectivity variability, putatively due to their intricate connections with other modules (Zhang et al., 2016). Such divergent patterns of connectivity have been shown during task states including working memory. For instance, sensory and somatomotor modules demonstrate no significant differences in connectivity pattern between the 0-back and 2-back conditions (Braun et al., 2015). In contrast, the frontal module undergoes changes in its architecture during the same task transition, potentially suggesting a fluid interaction and integration between the frontal regions and other brain areas (Braun et al., 2015). These findings are further corroborated by another study reporting highly variable frontoparietal network connectivity strength across multiple cognitive demands (Cole et al., 2013). Evidence of heightened variability is supported by work in human and non-human-primate (Cavada and Goldman-Rakic, 1989; Goldman-Rakic, 1988; Hagmann et al., 2008) which shows extensive anatomical connections between the frontoparietal system and other diverse brain structures. Further reports from human neuroimaging also support that neural variability in the prefrontal cortex has functional importance as it was associated with adaptively switching between

different task rules and that lack of variability in this region can hamper cognitive flexibility (Armbruster-Genc et al., 2016).

The presence of both stability and variability in brain network connectivity pattern likely has functional implications. While the precise role of neural stability is still a matter of ongoing research, it is suggested that stable global topology helps maintain efficient, orderly and accurate cognitive operations over time (Mišić et al., 2011). Instability can lead to excessive noise, redundancy, and unstable processing (Ajemian et al., 2013). However, as the external environment constantly changes, providing new information and imposing new demands on the neural system, the ability to perform complex tasks and learn novel situations is essential. The brain, as a non-linear dynamical system, must have the capability to switch across cognitive states (Deco et al., 2011) to accommodate these different demands. State switching likelihood is thought to be determined by the amount of variability present in the system: low variability prevents the system from exploring new states whereas high variability facilitates switches (Garrett et al., 2011).

Segregation and integration

Functional segregation in a neural network refers to the amount of neuronal processing that occurs among functionally related regions within modules relative to the amount of processing that occurs between them (Sporns, 2013). A segregated neural network is characterized by the high density of connectivity among members of the same module and low density of connectivity between members of different modules. Functional segregation is a fundamental feature of the dynamic and adaptable neural networks as the decomposability of the system into modules provides the necessary structure for adaptive connectivity patterns via

architectural changes (Bassett et al., 2011). Furthermore, functional segregation allows modules to perform specific functions without perturbing the remainder of the system, reduces the interdependence among modules, and potentially promotes behavioral adaptation (Félix and Wagner, 2008; Kirschner and Gerhart, 1998). Evidence for functional segregation in the human brain is abundant. At the neuronal level, strongly interconnected cells have a high degree of overlap between inputs, outputs, and response properties. Each group of neurons exhibit specific connections to a subset of other groups and to specific sensory afferents (Tononi et al., 1994). At the level of areas such as visual cortices, functional segregation stimulus attributes including color, motion, and shape has been repeatedly shown (Hubel and Livingstone, 1987; Maunsell, 1987; Zeki et al., 1991). Work using a large number of subjects confirms the presence of a stable modular organization of the functional brain networks across individuals during resting state (Cole et al., 2014; Power et al., 2011) (Fig. 1A), suggesting segregation is typical network property of the matured human brain. Abnormal loss of functional segregation has been associated with disorders including Alzheimer's disease (Supekar et al., 2008) and schizophrenia (Micheloyannis et al., 2006; Rubinov et al., 2009).

In contrast, functional integration refers to the ability of a network to integrate specialized information from distributed brain regions (Rubinov and Sporns, 2010). With integration two important aspects of network connections are achieved. First, it allows for the convergence of information from diverse sources in the brain. Such convergence is likely facilitated by the existence of highly central and interconnected regions (termed "network hubs") such as the prefrontal cortex. Second, integration enables efficient communication across networks as it reduces the shortest path between any two regions (Sporns, 2013). The notion of functional integration in human brain is supported by the observation that cortical pathways in the brain are

arranged in such a way that two neurons in any given locations are separated from each other by a small number of synaptic steps. Additionally, the existence of reciprocal connections between brain regions suggests both parallel processing and ongoing recursive signaling between neuronal groups (Finkel and Edelman, 1989; Tononi et al., 1992). Increases in functional integration have been reported primarily through the manipulation of cognitive demand (Fig. 1B-D). Braun and colleagues (2015) showed an increase in integration between frontoparietal and frontotemporal networks during the performance of working memory. Working memory-related enhancement of whole-brain integration relative to resting or cognitively less challenging tasks (e.g., motor tapping) has also been demonstrated by other groups (Alavash et al., 2016; Cohen and D'Esposito, 2016; Davison et al., 2015; Shine et al., 2016). The relationship between task complexity and the degree of functional integration may arise from the need to promote communication and interactions across regions in response to increased information processing (Shine and Poldrack, 2017). Complex tasks such as working memory which requires multiple processes including perceptual encoding, distraction inhibition, and updating likely recruit distributed regions of diverse functional roles, resulting in network-level integration. On the contrary, 'simple' tasks may rely on fewer specialist systems and thus unlikely necessitate widespread connectivity.

It should be noted that while the two measures (i.e., stability/variability and integration/segregation) concern two different aspects of functional network organization, they are not orthogonal. It has been shown that an increase in functional integration between networks tends to promote variability due to the enhanced inter-modular connections. In contrast, stability is often observed in more segregated networks (Bassett et al., 2011).

Functional network organization during working memory performance and during development

The presence of contrasting properties involving stability and variability as well as segregation and integration in functional network connectivity indicates the highly dynamic nature of neural network which may enable adaptive responses to diverse biological and environmental factors. One such biological factor is neuronal maturation in human development. Evidence from human neuroimaging studies shows functional segregation, measured by modular organization, in the human brain even during the first months of life (Fan et al., 2011) and continues to increase into early adulthood (Menon, 2013). By early adolescence, the functional organization of the child brain has largely stabilized and yet differences in functional connectivity patterns compared to young adults have been reported. For instance, children appear to have more spatially limited connections, less modular organization, and stronger subcortical-cortical but weaker cortical-cortical connections (Fair et al., 2009; Supekar et al., 2009). Such differences may affect the neural network responses to diverse cognitive processes. Yet, this possibility has not been explored.

Another factor which influences neural network configuration is task practice. Repeated exposure to motor and association tasks has been shown to alter the degree of functional integration and segregation both at the module (Bassett et al., 2015) and whole-brain levels (Mohr et al., 2016), respectively. Specifically, compared to the initial period of task performance, practice reduces the involvement of executive control modules (Mohr et al., 2016) while enhancing segregation between sensorimotor modules implicated in direct task completion (Bassett et al., 2015). It is proposed that once task performance becomes automatic, integration is less necessary as specialized modules are more capable of independent processing (Bassett et al.,

2015). However, the majority of previous investigations in practice-related neural alterations focused on simple motor tasks. Despite some preliminary evidence for increased recruitment of the prefrontal cortex and enhanced whole-brain connectivity following working memory practice, network connectivity pattern changes associated with repeated exposure to complex cognitive tasks has not been well characterized.

With these gaps in the literature, the goal of this thesis is to examine functional connectivity patterns of neural network during working memory performance as well as other cognitive tasks in young adults and early adolescent children. Findings from these investigations may help further the understanding of the relationship between cognitive processing and brain network organization.

CHAPTER II. CHANGES IN FUNCTIONAL NEURAL NETWORK PATTERNS BETWEEN COGNITIVE STATES IN LATE CHILDHOOD SHOWED AGE- AND STATE-DEPENDENT INTEGRATION AND FLEXIBILITY TY

Introduction

Late childhood or early adolescence marks a crucial period in which the emergence of complex cognitive functions is coupled with neuronal maturation processes. Cerebral development during this stage is broadly characterized by peaking in frontal and parietal grey matter volume (Giedd et al., 1999), increase in white matter density (Giedd et al., 1999), and myelination (Huttenlocher, 1979). Concurrent to the anatomical changes, neuroimaging studies have demonstrated similar development of adult-like functional network topology in preadolescent children (Menon, 2013). Relative to the young adult brain, the child brain exhibits similar global system properties including small-worldness, non-randomness, and functional organization (Supekar et al., 2009). Nevertheless, quantitatively distinct interregional connectivity patterns as well as network architecture in the child brain have also been observed. Compared to young adults, late childhood networks are characterized by more spatially limited connections (e.g., dense short-range and sparse long-range connections) (Fair et al., 2009; Kelly et al., 2009), stronger subcortical-cortical but weaker cortico-cortical connectivity (Supekar et al., 2009), and less modular organization (Baum et al., 2017). During this developmental stage, children also become increasingly capable of complex cognitive processing in domains involving working memory (Romer et al., 2009), decision making (Cauffman et al., 2010), reasoning (Solomon et al., 2011), and perception (Pivik and Dykman, 2004). However, little is known whether the

developing functional network alters its connectivity patterns to support various cognitive demands and whether such alterations age-dependent.

Previous fMRI studies of adult human brain networks revealed two intriguing aspects of matured network properties. On one hand, large-scale neural systems can be described by modularity and stability. Modularity is postulated to be a fundamental feature of the developed neural networks (Baum et al., 2017) as it allows for functional specialization while reducing potential interference across different circuits (Sporns and Betzel, 2016; van den Heuvel and Sporns, 2013). Stability has recently been demonstrated in an elegant study which shows the brain exhibits stable architecture across multiple cognitive states (Cole et al., 2014). On the other hand, functional integration and neural flexibility may be necessary for the completion of complex tasks. Whole-brain topology has been shown to become more efficient and integrated or less segregated with increased cognitive demand (Cohen and D'Esposito, 2016; Shine et al., 2016). Furthermore, specific cognitive demands can influence network connectivity during working memory updating (Le et al., 2017), inhibitory control (Spielberg et al., 2015), learning (Sun et al., 2007), and training (Bassett et al., 2015). These latter findings lead to the intriguing possibility that different task states may be associated with distinct spatiotemporal patterns of network connectivity. Switching between states, therefore, necessitates neural flexibility and adaptability (Bassett et al., 2015, 2011). Thus, these two characteristics suggest the complex and adaptable brain network may support a changing balance between functional integration and segregation as well as flexibility and stability in response to cognitive demand (Bassett et al., 2011; Sporns, 2013; Tononi et al., 1994). This is consistent with the proposal that while large-scale neural systems maintain a stable anatomic skeleton, they can flexibly alter their

configurations to accommodate specific task requirements (Deco et al., 2011; McIntosh et al., 2008).

Despite the emerging evidence for subtle neural network topological changes across task states in adults, it remains unclear how functional connectivity patterns vary across cognitive states during late childhood and early adolescence. It is possible that the functional network architecture in developmental stage is shaped by age-related network features in addition to task-modulated configuration. As such possibility has not been explored, we examined neural network topology in children aged between 9 and 12 in four cognitive states including resting, reward/decision, visual perception, and working memory. The intrinsic and task-evoked whole-brain network architectures were identified in the child sample and compared to an adult sample in order to identify particular effects unique to the children. We then characterized the differing degrees of functional integration during the four states. We hypothesized that the child brain would become more integrated with increase in cognitive demand, though the degree of integration would be state- and age-dependent. Flexibility at the module level was further examined for the frontoparietal (FPN), salience, default mode (DMN), visual, and somatomotor (SMN) networks. Since the executive control modules have been implicated in the transition between cognitive states (Bassett et al., 2011; Cole et al., 2013; Dosenbach et al., 2006; Duncan, 2010), we expected FPN and salience network to exhibit higher level of flexibility whereas modules associated with sensorimotor processing (e.g., visual and motor) would be relatively stable across tasks.

Materials and Methods

Data samples

Eighty children participated in 4 fMRI sessions including resting, reward task, visual perception task and spatial working memory task. Results from the working memory task were previously reported elsewhere (Huang et al., 2016). Here, we analyzed a subset of the sample due to excessive head motion in at least one of the fMRI sessions (20 participants) and failure to follow task instructions (8 participants). Thus, a total of 52 participants (age 9-12, mean 10.3 years, 27 females) with complete fMRI data for the resting and three tasks were included in the final analysis. For community detection in resting state, usable data from the 52 plus 7 more participants were used to maximize group consensus accuracy (i.e., resulting group network architecture more reflective of any given individual). The Pubertal Development Scale was used to measure puberty score at the time of fMRI. The participants had a mean puberty score of 8.37 ± 2.36 (data was missing from one male subject). Informed consent was obtained from parents of participants prior to participation in accordance to the local Institutional Review Board.

To compare network properties in our group with those in adults, we used a subsample of 60 young adults from the Cambridge Buckner 1000 Connectomes Project dataset (referred to as CB sample from here on) (Biswal et al., 2010). These subjects (age 20-23, mean 21.2 years) were selected to match the age variance in our child sample.

Tasks

Each child performed the following tasks during fMRI:

Reward task (Fig. 2A): On each trial, after a 2-s fixation, two doors were displayed on the screen for 2 s and participants were instructed to indicate their door selection by pressing the left or right button. After a brief fixation (800 ms), feedback of monetary gain (“You Win”) or loss (“You Lose”) was displayed for 1.2 s. There were a total of 60 trials (30 win, 30 loss), with

win/loss trials in a pseudorandom order. The intertrial interval (ITI) was jittered (average: 2 s, range: 0-14 s), with an average trial duration of 8 s. The total scan time was 8.5 minutes.

Perception task (Fig. 2B): There were four different block conditions: neutral faces, sad faces, happy faces, and houses. Each block was 16-s long and contained 4 trials. At the beginning of each block, a 1-s warning fixation which changed in color from black to blue to cue the starting of the block. On each trial, a 600-ms fixation cross was followed by the simultaneous 3000-ms presentation of two images, either two faces or two houses and participants made a button press to indicate whether the two images were identical or different (50/50 chance). There were 3 blocks per condition, in a pseudorandom order. These task blocks were interleaved with 14 s of fixation. The run lasted 6 minutes.

Working memory task (Fig. 2C): We used a 1-back spatial working memory paradigm with two load conditions (Load 1 and Load 3), during which 1 and 3 rabbits were presented in different locations, respectively. The two load conditions were presented in blocks of 5 trials. On each trial except the first trial of each block, participants pressed a button to indicate whether any rabbit was in a different location from the previous trial. In the Load 3 condition, only one of the rabbits ever changed location on a change trial. The rabbits were located randomly around an invisible circle with a radius of 5° visual angle. The rabbits were presented for 200 ms. There were 8 possible locations shifted between 5° to 10° from regular clock orientation. Locations were masked with 8 rabbit holes (average 1° visual angle) presented during a variable ITI of 2.3, 3.3 or 4.8 s (average 3.2 s). Each task block lasted 17 s and 13-s fixation period was inserted between blocks. There were two runs of 4 min 12 s each (8 blocks/run).

Resting: Resting state fMRI data were acquired in two sessions (6 minutes each), during which participants were instructed to relax and look at the fixation point in the middle of the screen.

Resting-state sessions were performed prior to all task-state sessions.

To ensure compliance, subjects practiced all tasks prior to scanning. During fMRI sessions we monitored the participants' eye position with an Eyelink 1000 eye-tracking system (SR Research Ltd., Mississauga, ON, Canada). Due to computer software malfunctions, behavioral data were only recorded during the working memory and perception task for 35 and 39 participants, respectively. Thus, while fMRI data were available and analyzed for 52 individuals, behavioral analyses were only performed on the subset of those participants.

Data acquisition and Analysis

Imaging Parameters

Data were collected on a 3 T Siemens Tim Trio whole-body MRI system (Erlangen, Germany) with a 12-channel head coil. Whole-brain structural anatomical images were acquired in the sagittal plane with a T1 weighted MPRAGE scanning sequence (TR = 2400 ms; TE = 3.16 ms; slices = 176; flip angle = 8°; FOV = 256 × 256; matrix = 256 × 256; resolution = 1 × 1 × 1 mm³). T2-weighted structural images were collected in the axial oblique plane parallel to the AC-PC (TR = 6450; TE = 88; slices = 37, 3.5 mm with 0 mm gap; flip angle = 120°; FOV = 256 × 256; matrix = 256 × 256; resolution = 1 × 1 × 3.5 mm³). Two runs of the reward task (130 volumes each), one run of the perception task (183 volumes), and two runs of the working memory task (126 volumes each) were acquired in the axial oblique plane parallel to the AC-PC with a T2*- weighted single-shot echo-planar pulse sequence (TR = 2000 ms; TE = 30 ms; slices

= 37; flip angle = 90°; FOV = 224 × 224; matrix = 64 × 64; resolution = 3.5 × 3.5 × 3.5 mm³).

Each session began with 3 dummy scans which were discarded prior to data analysis.

The adult data sample used the following parameters. Structural images were collected using the MPRAGE sequence: slices = 192, matrix size = 144 x 192, resolution = 1.20 x 1.00 x 1.33 mm³. Resting state T2*-weighted axial images were acquired using the EPI sequence: 47 interleaved axial slices, TR = 3000 ms, resolution = 3.0 x 3.0 x 3.0 mm³ (119 volumes).

Image preprocessing

Images were preprocessed with SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Images were first screened by visual inspection for obvious artifacts and motion. Standard preprocessing steps were applied to each dataset including slice timing correction, volume alignment for motion correction, and co-registration of anatomical to the mean EPI image. A unified segmentation algorithm was applied to the high-resolution structural images to separate the gray matter, white matter, and CSF. The functional and anatomical images were then spatially normalized and transformed into the MNI space, using affine nonlinear transformation, and then spatially smoothed with a 4-mm full-width at half-maximum Gaussian kernel.

To assess the functional connectivity between different areas of the brain, additional preprocessing steps were performed. A nuisance regression was constructed to control for the following confounding variables: 6 motion parameters up to their second derivatives, scans with excessive motion, modeled physiological signal generated through aCompCor (Behzadi et al., 2007) of the white matter and CSF voxels, and the linear drift. For resting state data, the residuals of this regression were then filtered utilizing a bandpass between the frequencies of 0.008 and 0.09 Hz and despiked using CONN toolbox (<https://www.nitrc.org/projects/conn>). For

the task state data, similar to a previous study (Cole et al., 2014), no low pass filter was applied (i.e., bandpass = .008 Hz - Inf) to preserve the possible presence of task signals at higher frequencies than the relatively slow resting-state fluctuations. We chose not to regress out the global signal in order to retain the interpretability of negative correlations (Murphy et al., 2009). In addition, to reduce potential influence of transient task-related effects, all task events were treated as events of no interest in a standard general linear model regression. The residuals from these regression models were used to estimate functional connectivity during the tasks.

Functional connectivity

We first conducted Pearson correlations between time series in all pairs of brain regions from the commonly used 264 cortical and subcortical regions-of-interest (ROIs) atlas from Power et al. (2011). ROIs were spheres of 5-mm radius centered at the coordinates. Correlation coefficients were Fisher's Z transformed and used for all subsequent computations. As there is no clear consensus on the treatment of task events, we conducted another set of analyses without the removal of task events and produced similar results. Here, we chose to report the findings with task events removed. Only relevant task blocks were included in the time series (i.e., no fixation blocks), with 6 s of hemodynamic delay accounted for, and concatenated prior to correlation calculation.

Community Detection

To partition the 264 ROIs into functional modules in the resting-state data, we used the Louvain community detection algorithm with two free parameters. The density parameter determines the threshold of connection strength. Connections with strength below this threshold were removed prior to community detection. The structural resolution parameter was used to restrict the number of communities identified in the functional connectivity matrix. To be

consistent with previous work by Cole et al., (2014), we applied the same range for density threshold (40% to 2% in steps of 2.5) and resolution (0 to 3 in steps of 0.2). Parameter optimization was based on two criteria 1) a peak of partition similarity with Power et al. (2011), and 2) distinct functional communities as previously found in the adult population. (While we are not aware of an existing partition for this youth population, previous research indicated similar neural network topology in children aged 7-9 to young adults (Supekar et al., 2009)). The combination of these criteria yielded optimal density threshold of 0.045 and resolution of 2.2 which produced a twelve-community partition similar to Power et al. (2011).

The optimal parameters obtained from resting-state community detection were subsequently applied to the task data to identify communities in the three task states. As the Louvain algorithm is stochastic, we ran this algorithm 150 times to obtain 150 partitions. These partitions were then used to create an agreement matrix which was subjected to consensus clustering (Lancichinetti et al., 2009) to yield a final partition for each subject at each task state. To examine changes in community structure within each module across the four cognitive states, community detection was applied to key neurocognitive modules including frontoparietal, salience, default mode, visual, and somatomotor using data from each of the four states. Changes in community structure across states, both at global and module levels, were quantified by adjusted Rand index (Hubert and Arabie, 1985), which measures the similarity between two partitions while accounting for chance of similarity due to randomness. Partition similarity between the child and the CB samples was calculated to examine potential age effects. Brain network graphs were visualized with BrainNet Viewer (Xia et al., 2013, <https://www.nitrc.org/projects/bnv/>).

Graph theoretical metrics

At the global level, we examined changes in functional segregation and integration in brain connectivity across the cognitive states. Functional integration refers to the transferring of specialized information among distributed brain regions. The higher the degree of functional integration, the more efficiently different brain regions communicate with each other (Rubinov and Sporns, 2010). Functional segregation refers to the tendency for stronger coupling within densely interconnected groups of brain regions relative to coupling with other regions. The higher the degree of functional segregation, the more modular the neural processing in a network (Rubinov and Sporns, 2010). Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>, Rubinov & Sporns, 2010) and custom Matlab scripts were used to calculate these measures. Connectivity matrices were thresholded with the density of 0.045 (as determined by community detection optimization) prior to obtaining the graph metrics.

For the measures of integration/segregation, we used global efficiency, participation coefficient, connector hub, modularity, and transitivity (Fig. 3). Global efficiency refers to the measure of average inverse shortest path length between nodes within a network (Latora and Marchiori, 2001). Higher global efficiency is indicative of stronger connections between modules and thus higher degree of integration. Global efficiency is defined as follows:

$$E_{\text{global}} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{i,j}}$$

where L is the minimum path length, N is the number of nodes in graph.

Participation coefficient refers to the measure of diversity of inter-modular connections of individual nodes. A network with high participation coefficient contains nodes that have dense connections with other networks. Participation coefficient is defined as follows:

$$PC_i = 1 - \sum_{s=1}^{N_M} \left(\frac{k_{is}}{k_i} \right)^2$$

where k_{is} is the degree (number of connections) of node i to other nodes in its own network (s), and k_i is the degree of node i regardless of network membership. By subtracting that ratio from 1, participation coefficient is normalized and thus the measure does not involve connections that are within a node's own network, or that are across networks.

A connector hub is a high-degree node that displays a diverse inter-modular connectivity profile (van den Heuvel and Sporns, 2013). Here, connector hubs are defined as nodes with high participation coefficient (>0.8) and low within-module degree (<1.5) (Guimera and Amaral, 2005; Guimerà and Amaral, 2005).

Modularity is the degree to which the network may be subdivided into non-overlapping groups of nodes such that the number of within-group edges is maximized while the number of between-group edges is minimized. Modularity is defined as follows:

$$Q = \sum_{n=1}^m (e_{ii} - x_i^2)$$

where e_{ii} is the fraction of all edges connecting two nodes within module n , x_i is the fraction of edges connecting a node in module i to any other node, and m represents the total number of modules.

Transitivity is the amount of clustering in the network, quantified by the ratio of triangles to triplet which nodes form locally. High transitivity reflects tightly clustered groupings of regions and thus high degree of segregation. Transitivity is defined as follows:

$$\text{Transitivity index} = \frac{\# \text{Transitive triads}}{\# \text{Possible transitive triads}}$$

At the module level, we assessed the stability and variability of connectivity pattern for the key functional modules across the four cognitive states. Specifically, we used connectivity

variability, node flexibility, and module partition similarity. Connectivity variability refers to the variability in connectivity strength measured by standard deviation across the four cognitive states (see global variability coefficient in Cole et al., (2013)). Nodal flexibility is the probability of a node switching module membership when transition from one state to another, calculated by the number of time a node changes membership normalized by the total possible number of changes (Bassett et al., 2011) (Fig. 1B). In the current study, nodal flexibility was averaged across the three resting-to-task switches (i.e., rest to reward, rest to perception, and rest to working memory). Module partition similarity is the similarity between resting partition and a task partition for a given module. The same community detection procedure used for whole-brain architecture was performed for each state at the module level.

To determine potential age effects in the children sample, we correlated the participants' age (in months) with the graph measures to explore any potential relationship.

Results

We first identified the whole-brain network architectures in each of the four cognitive states (i.e., resting, reward, perception, and working memory) then examined their properties and relationship in the children sample. Measures of cross-state network flexibility and stability at both global and module level were utilized to determine the degree of network adaptability associated with each task and each functional module.

Global network architectures across cognitive states

Using Louvain community detection algorithm, we identified 12 communities in the resting-state data. These communities were consistent with the 12 functional modules previously defined in adults (Power et al., 2011), including hand-related somatomotor, mouth-related

somatomotor, cingulo-opercular, auditory, default-mode, visual, frontoparietal, salience, subcortical, ventral attention, dorsal attention, and cerebellum. The optimal resting-state community detection parameters were then applied to the three task states, yielding the same 12 communities for each of the reward, perception, and working memory tasks. Group consensus algorithm showed similar community structures across the four states (Fig. 4A). Adjusted Rand index (ARI) was used to quantify partition similarity between resting and tasks. ARI was higher among the three task states than between resting and task states (p 's < 0.01) (Fig. 4B). Reward-resting partition similarity (M[SD] = .25[.06]) was significantly greater than perception-resting partition similarity (M[SD] = .23[.07]) ($t(51) = 2.43, p < .05$) but only marginally greater than working memory-resting partition similarity (M[SD] = .24[.07]) ($p = .17$).

To determine whether the child sample had comparable network partition to the adults, we measured partition similarity between our sample and a subset of the CB resting-state dataset relative to a published adult network structure Power et al., (2011). As expected, while the child partition showed high similarity to the Power partition (M [SD] = .25 [.06]), the similarity was significantly higher between the CB and Power partitions (M [SD] = .29 [.05]) ($t(117) = 3.8, p < .001$). Indeed, an age effect within our child sample was found, represented by a positive correlation between age (in months) and the degree of similarity between the CB and child intrinsic network architecture ($r = .33, p = .01$) (Fig. 4C). To determine whether head motion in the children sample may have impacted the architectural similarity between the two groups, we accounted for the rate of change of BOLD signal across the entire brain at each frame of data (DVRS) (Power et al., 2012) in the correlation which subsequently remained significant ($r = .34, p = .016$).

We further examined whether the degree of similarity in child-CB network structure during resting varied with different functional modules including the frontoparietal, salience, default mode, visual, and somatomotor modules. The salience (M [SD] = .14 [.11]) and frontoparietal (M [SD] = .15 [.1]) modules in our child sample were significantly less similar to the CB group than the other modules (all p 's < .001), whereas the default mode (M [SD] = .19 [.06]) visual (M [SD] = .2 [.08]) and somatomotor (M [SD] = .23 [.1]) modules were more similar.

Thus, consistent with previous reports in young adults, the children showed stable whole-brain network structures across different cognitive states, with small but detectable differences between resting and task states. The degree of similarity to the adult network organization was age-dependent.

Functional integration and segregation in different cognitive states

Next, we examined network measures associated with functional integration and segregation in the child and the CB samples for comparison. Across all measures of network integration, task states had significantly higher integration than resting state. Specifically, compared to resting, there was a significant task-related increase in global efficiency (all corrected p 's < .001) (Fig. 5A), number of connector hubs (all corrected p 's < .001) (Fig. 5B), and participation coefficient (all corrected p 's < .002) (Fig. 5C). Furthermore, there were small but significant differences among the tasks such that the visual perception task had higher global efficiency than the other two tasks (p 's < 0.05) and had higher participation coefficient and connector hubs than reward (p 's < .004).

For functional segregation, there was a significant decrease in transitivity from rest to tasks (all corrected p 's < .001) (Fig. 5D). However, modularity did not significantly differ across

the four states (all p 's > .28) (Fig. 5E). As reduced modularity was associated with cognitive processing in adults (Cohen and D'Esposito, 2016), we examined the effect of age on modularity and found that the older the participants, the lower the task modularity index (averaged across the three task states) ($r = -.35, p < .01$). Compared with the CB group, the child sample did not significantly differ on most measures (p 's > .14) with the exception of participation coefficient which was lower in the young adult group ($t(110) = 4.13, p < .001$).

To rule out the possibility that the children's sample head motion may have impacted the measures of integration and segregation, we correlated DVARS with each graph measure. No significant correlations were obtained (p 's > .21).

Differentiable patterns of stability and variability in functional modules

While global architecture reveals useful information about the broad changes in network properties due to cognitive demands, it may overlook nuanced patterns of network adaptability at the module level. We defined DMN, FPN, Salience, Visual, and SMN using resting data (Fig. 6A) then evaluated their connectivity variability, nodal flexibility, partition similarity, and partition coefficient across the cognitive states.

Among all, FPN showed the highest connectivity variability (i.e., standard deviation of connectivity strength across task states) (all corrected p 's < .05) (Fig. 6B) whereas visual module had the lowest (all corrected p 's < .05). A similar pattern was observed for nodal flexibility (i.e., the probability of nodes switching membership during resting state from one module to another module during the three task states). Sensory modules showed the lowest nodal flexibility (all corrected p 's < .05) with nodes in Visual and SMN having .08 and .14 switching probability, respectively. In contrast, FPN demonstrated the highest nodal flexibility (all corrected p 's < .005) at .24 switching probability. DMN and Salience modules exhibited moderate degrees of nodal

flexibility (Fig. 6C-D). As high nodal flexibility is associated with an integrative system which allows regions to switch community membership (Braun et al., 2015), we next assessed the degree of inter-modular integration for each functional network. FP and Salience modules showed a significant increase in participation coefficient from resting to task states (all corrected p 's < .001) while changes in DMN, Visual, and SMN were minimal (all p 's > 0.14 with the exception of Visual module between resting and perception, $t(51) = 3.9$, corrected $p < .01$).

In terms of the architecture of these modules, the average ARI (rest vs. reward, rest vs. perception, and rest vs. working memory) revealed that FPN had significantly lower partition similarity than all other modules (p 's < .05, corrected) except Salience ($p = .45$). This result further demonstrates the highly variable nature of the executive control modules. In sum, FPN (and to a lesser degree, Salience) showed greatest flexibility in connectivity pattern, modules associated with visual and motor processing indicated a relatively more stable architecture whereas DMN was somewhere in between.

Relationship between connectivity profiles and task performance

We conducted exploratory analysis to examine whether integration and flexibility in network properties are associated with individual differences in behavioral performance on the visual perception and working memory tasks. (We did not examine the reward task due to the lack of interpretable behavioral measures.)

For working memory, load effect on performance accuracy (i.e., Load 3 accuracy minus Load 1 accuracy, abbreviated L3-L1Acc) was negatively associated with the number of connector hubs ($r = -.49$, $p < .005$) (Fig. 7A), indicating a higher degree of inter-modular connectivity predicted poorer working memory. In conjunction, there was a positive relationship between rest-WM partition similarity and L3-L1Acc ($r = .41$, $p < .05$) (Fig. 7B), suggesting a

lower degree of changes in community architecture may have benefited performance. Further analyses at the module level confirmed this advantage of network stability during working memory, with L3-L1Acc negatively correlated with nodal flexibility in DMN ($r = -.4, p < .05$) (Fig. 7C) and SMN ($r = -.38, p < .05$) (Fig. 7D) while response time positively correlated with that of the Salience module ($r = .5, p < .005$) (Fig. 7E).

For the perception task, global efficiency during visual perception positively correlated with performance accuracy ($r = .39, p < .005$) (Fig. 8A). Additionally, there was a positive relationship between transitivity and response time variability ($r = .47, p < .005$) (Fig. 8B), indicating low transitivity was coupled with more stable behavior. At the module level, average FPN, Salience, DMN, Visual, and SMN partition similarity between resting and perception state negatively correlated with performance accuracy ($r = -.41, p < .01$) (Fig. 8C), suggesting a flexible connectivity pattern was preferred to stability for better performance on visual perception.

Taken together, these results suggest that greater functional integration and flexibility enhanced perceptual processing while some degree of stability may have benefited working memory performance in this age group.

Discussion

By examining the functional neural network across cognitive states in children during late childhood/early adolescence, we showed state-related functional network connectivity pattern changes which were both adult-like and age-dependent. As in adults (e.g., Cohen and D'Esposito, 2016; Cole et al., 2014; Shine et al., 2016), while the basic community architecture remained relatively stable from resting to task state, there was a global increase in functional

integration putatively to support complex cognitive demand. Furthermore, across cognitive states, the FPN and Salience modules demonstrated greater variability and flexibility in connectivity patterns while the sensorimotor modules were less variable and flexible. Network configurations were also age-dependent as the older children showed higher similarity in their network topology relative to adults during resting and lower degree of modularity organization during tasks.

Intrinsic and task-evoked network structure in late childhood

We first examined whether the developing brain possesses adult-like intrinsic network architecture and remains stable throughout various cognitive states. Previous literature examining global neural architecture in children has shown that even at the first month of life, the infant brain already exhibits non-random modular organization (Fan et al., 2011). From these early stages, the brain quickly develops core functional modules associated with cognitive functioning including frontoparietal, dorsal attention, and default mode (Doria et al., 2010; Fransson et al., 2011, 2007) and shows broadly defined network topology around 2 years of age (Gao et al., 2013). By age 7, major measures of network topology reach stability (Supekar et al., 2009; Uddin et al., 2011). In the current study, examining the brain during late adulthood and early adolescence (i.e., age 9-12), we confirmed the presence all of intrinsic functional networks previously defined in young adults (Power et al., 2011).

Our partition similarity findings further demonstrated that the intrinsic network architecture remained preserved during various cognitive states. Connectivity patterns displayed similar community structure when subjects performed reward, perception, and working memory tasks. In adults, it has been reported that whole-brain network architecture varies minimally

across a large number of cognitive tasks and highly resembles that during resting state (Cole et al., 2014). Our findings confirm stable intrinsic network topology is also present during cognitive states during late childhood, thus representing the primary functional network architecture underlying complex cognitive processing. Despite the child network structure's resemblance to that of young adults, we observed an important relationship between the children's age and the degree of similarity to the adult network topology. This similarity was also module-dependent such that frontoparietal was the least similar to that in adults and visual and motor modules were the most similar. This evidence is in agreement with the developmental literature which suggests protracted maturation of the frontal lobe (Lenroot and Giedd, 2006; Shaw et al., 2008). Thus, despite the identification of distinct neural systems associated with executive functions, default mode, attention, and sensory processing at rest, brain organization likely continues to be refined during late childhood.

Shift toward global functional integration during cognitive processing

In previous literature, while the broad network architecture across multiple cognitive states has been shown to be stable, small but functionally relevant changes in neural network properties are also observed during tasks to support complex cognitive, emotional, and motor functions (Cohen and D'Esposito, 2016; Cole et al., 2013; Shine et al., 2016). One such important change is the balance of functional segregation and integration. On one hand, segregation is fundamental to brain organization (Friston, 2009; Sporns, 2013) as it allows for functional specialization and lowers interference between neural systems (Baum et al., 2017). Furthermore, the segregation of the neural system into modules provides the necessary structure for adaptive reorganization (Bassett et al., 2011). On the other hand, there may be a need for the

coordination of specialized information from diverse neural elements to support complex behaviors, necessitating integration across the community structure (Sporns, 2013). Thus, there is likely a constantly shifting balance between segregation and integration, modulated by the underlying cognitive processing.

A number of studies have reported such effects of cognitive processing on network topology, particularly network integration, in young healthy adults. Cohen and D'Esposito (2016) showed higher global efficiency, lower modularity, and a greater number of connector hubs during n-back task performance in comparison to resting. This pattern was corroborated by other findings that enhanced coupling across distributed networks involving frontal and parietal association regions was observed during task performance (Krienen et al., 2014). In preadolescent children, there is preliminary evidence for widespread activations in a number of tasks including working memory (Güler and Thomas, 2013; O'Hare et al., 2008), tracking stop (Rubia et al., 2007), go/no-go (Suskauer et al., 2007), and flanker (Vaidya et al., 2005). The current study further showed that similar to young adults, task state in preadolescence was characterized by a significant gain in global efficiency, participation coefficient, and the number of connector hubs during reward, perception, and working memory processing. Such changes indicated a shift of balance toward more extensive and efficient interactions across topologically distant brain regions, potentially facilitating information transfer to accommodate complex cognitive processes.

Our findings of functional segregation in the children cohort showed mixed patterns compared with previous reports in young adults. Consistent with previous investigations which demonstrated less transitive networks during n-back (Cao et al., 2014; Cohen and D'Esposito, 2016) and face matching (Cao et al., 2014) tasks relative to resting in adults, the degree of

transitivity significantly diminished in response to cognitive processing in our child sample. Reduced transitivity likely reflects the weakening of connections at the local level, which, coupled with our evidence of heightened integration, suggests a shift from local to network connectivity configuration. Nevertheless, our child sample did not show lowered modularity during tasks as previously reported in adults (Cao et al., 2014; Cohen and D'Esposito, 2016). Modularity is a crucial feature of complex neural systems (Sporns and Betzel, 2016), observed early in development (Fan et al., 2011; Gao et al., 2013) but subject to changes over the age between 8 and 25 years (Fair et al., 2009). Our participants demonstrated a negative relationship between participants' age and task-related modularity, indicating an age-related bias for within-module connectivity during tasks. This finding is in line with past research suggesting that at the preadolescence stage, long-range connections are sparser while short-range connections are denser than young adults (Fair et al., 2009; Kelly et al., 2009).

It should be noted that while transitivity and modularity both assess local specialization, different results from the two measures likely reflect distinct aspects of segregation. In graph theory, transitivity refers to the tendency for neighboring nodes to form triangles, hence measuring the density of triangles relative to density of clusters containing two paths. Modularity, on the other hand, measures the edge density within cluster in relation to edge density between clusters. Thus, the combination of low transitivity and high modularity suggests a locally sparse configuration but potentially without strong long-range connections to reduce modularity. Taken together, there was a shift toward functional integration to accommodate cognitive processing in late childhood. Yet, the relatively high age-related modularity during tasks in comparison to adults indicates the ongoing fine-tuning process during neural circuitry maturation in children.

Executive control, visual, and motor networks show differentiated patterns of flexibility

One characteristic of the complex neural system is its flexibility in reorganizing the functional connectivity patterns in response to changing cognitive demands (Bassett et al., 2015, 2011). The current study revealed the developing brain during late childhood exhibited a high degree of variability and flexibility in modules associated with executive control including frontoparietal and salience modules. In contrast, modules implicated in visual and motor processing showed stable community structure, minimal module switches, and low participation coefficient. Our evidence of different flexibility patterns across distinct functional modules has a number of implications. First, we confirm previous findings in both adult humans (Laskaris et al., 2003; Neumann et al., 2003) and animals (Arieli et al., 1996) that the brain's natural state is variable and such variability may be functional. It has been suggested that variability can help the brain switch between different network configurations in support of specific cognitive operations (Deco et al., 2009; McIntosh et al., 2008). Indeed, recent research (Braun et al., 2015) as well as the current study have shown differentiable network topological structures for different tasks. Second, as most studies investigated trial-to-trial signal variability during task performance (Armbruster-Genc et al., 2016; Dinstein et al., 2012; Fox et al., 2007), their findings primarily focused on the contribution of stochastic brain dynamics to cognitive processing at the individual trial level. A few studies assessed flexibility as a function of network connectivity pattern changes at a longer temporal scale but limited their investigation to the learning of single tasks including motor (Bassett et al., 2015, 2011) and working memory (Braun et al., 2015). Finally, the current study's findings of adaptive network integration at the whole-brain level and

flexibility at the module level further established the dynamic nature of the cognitive control modules during the late childhood stage in flexibly switching from one state to another.

While the exact nature of neural flexibility is still a matter of ongoing research, our finding of frontoparietal flexibility across cognitive states is consistent with both recent human functional (Cole et al., 2013; Power et al., 2011; van den Heuvel and Hulshoff, 2010) and animal electrophysiological (Cavada and Goldman-Rakic, 1989; Goldman-Rakic, 1988; Hagmann et al., 2008) reports. These studies show dense frontal and parietal connections to various regions, putatively to integrate information across different neural circuitries. Other work also suggests frontal regions can adapt functional connectivity according to task state (Bassett et al., 2006; Sakai, 2008). Furthermore, increased activation in the frontal areas has been observed during implementation of novel tasks (Cole et al., 2013b; Dosenbach et al., 2006; Duncan, 2010) which likely require the adaptation of brain-wide functional connectivity patterns to accommodate new cognitive control processes. Thus, an important property of the FPN may be the ability to flexibly modify connectivity patterns in response to task demand.

Relationship between behavioral performance and functional network connectivity patterns

We found evidence for a relationship between behavioral performance and changes in the balance involving functional integration and neural flexibility in two tasks. For the perception task, better performance was related to increased integration and decreased segregation at the global level. Such results indicate a connectivity profile characterized by enhancement in interaction across multiple modules and in flexible network connectivity patterns. This is consistent with the idea that face (Haxby et al., 2002; Ishai et al., 2005) and scene perception

(Epstein, 2005) recruits distributed cortical regions including both visual and higher-order cortices. Previous work in young adults from our laboratory indeed showed widespread activation (Oh and Leung, 2009) and connectivity (Le et al., 2017) involving temporo-occipital and frontoparietal systems during the processing of face and scene information. In children, while fine-tuning changes in neural selectivity continue to occur into adolescence (Cohen Kadosh and Johnson, 2007), similar activation patterns during face and scene perception (Scherf et al., 2007) have been observed. Thus, it stands to reason that integration across multiple cortical structures may facilitate visual perception and ultimately result in behavioral benefits.

For the working memory task, the connectivity profile suggests some degree of functional segregation and stability may have helped behavioral performance. This intriguing finding appears to differ previous reports showing a relationship between enhanced working memory performance and increased functional integration in healthy adults (Cohen and D'Esposito, 2016). However, as we discovered, there was a lack of modularity organization during cognitive processing, coupled with high participation coefficient at rest in our children sample relative to adults. This age-specific characteristic may have resulted in a different network topological response to working memory processing compared to adults. Furthermore, past research suggests stable activation during working memory may be beneficial (Hampson et al., 2006; Otten and Rugg, 2001) while abnormal amount of variability during working memory can be detrimental to performance as shown in the case of individuals with schizophrenia (Manoach, 2003; Meyer-Lindenberg et al., 2001). Neural stability can promote stronger information representation while helping to suppress distractor (Armbruster-Genc et al., 2016). During working memory, relevant information may benefit from protection against interference (Jonides and Nee, 2006; Kane and Engle, 2000; Le et al., 2017; Lustig et al., 2001). Thus, it is

plausible that too much flexibility and variability can induce spurious communication from different neural structures, resulting in degradation of working memory representation.

Conclusions

The current study shows that late childhood and early adolescence is characterized by the intrinsic neural network architecture which is highly similar to that in young adults. We also show the potential fine-tuning of the network architecture by age even in this narrow age range. During various cognitive states, although the network architecture retains the basic configuration as previously shown in adults, whole-brain network connectivity pattern alterations were observed. In particular, increased in functional integration was associated with the task states relative to the resting state. At the module level, the FPN and SN were more flexible and variable whereas sensory modules remained relatively stable across the cognitive states. These findings add to the understanding of the spatiotemporal patterns of cortical network organization in the youth brain during various cognitive states and how they may contribute to explaining brain, cognitive, and behavioral development.

CHAPTER III. RELATIONSHIP BETWEEN FUNCTIONAL NEURAL NETWORK CONNECTIVITY PATTERNS AND WORKING MEMORY UPDATING AND MAINTENANCE

Introduction

Recent human neuroimaging evidence suggests while the whole-brain functional network architecture remains stable across different cognitive states (Cole et al., 2014), the connectivity pattern within this architecture is capable of changes in response to changing cognitive demand (Deco et al., 2011). One consistent finding for such changes has been the enhanced integration of connectivity within and between neural ensembles following an increase in cognitive processing such as working memory (Cohen and D'Esposito, 2016; Davison et al., 2015; Shine et al., 2016). Emerging findings, however, indicate the relationship between cognitive processing and functional network connectivity patterns is more complex. Repeated task exposure including training on a motor task is associated with reduced integration and greater segregation among functional modules (Bassett et al., 2015). Furthermore, individual differences have also been linked to changes in network configuration. Specifically, the degree of segregation predicts an individual's learning speed of motor sequences in a motor task (Bassett et al., 2015) while the density of inter-modular connections in whole-brain topology has been related to higher working memory performance (Langer et al., 2013). Thus, further understanding of functional network connectivity in correspondence to cognitive processing requires consideration of multiple factors including task difficulty, task practice, learning, and individual differences in performance. As these effects factors can greatly vary across individuals, the common method of reporting results

based on group averaging may potentially obscure distinct network patterns at the individual subject level.

Past research demonstrates that the functional properties of neurons, as well as the neural circuitry within various brain areas, retain a significant degree of plasticity during adulthood (Buonomano and Merzenich, 1998). One factor associated with this plasticity is neuronal changes due to task practice. Findings of practice effects, particularly in motor tasks, in human neuroimaging studies show decreased activity in brain regions implicated in control and attention (e.g., prefrontal cortex) (Dahlin et al., 2008; Petersen et al., 1998; Poldrack and Gabrieli, 2001) and increased activity in those directly involved in task performance (e.g., sensorimotor areas) (Lacourse et al., 2005; Olsson et al., 2008; Petersen et al., 1998). This evidence suggests potential redistribution and/or reorganization of functional activations, reflecting changes in the neural efficiency and/or functional roles (e.g., degree of involvement) of the distributed task networks (Kelly and Garavan, 2005). Such changes in neural network organization likely involve adjustments in the interactions within and between different neural circuitries (Bassett et al., 2015). Another factor which can play a contributory role in network connectivity pattern changes is task complexity. Practice on simple tasks increases within-network connectivity in task-specific modules whereas practice on complex tasks enhances connectivity in a more distributed manner (Buchel et al., 1999; Kelly and Garavan, 2005; McIntosh, 1999). These few studies indicated that the effects of task practice are unlikely to be limited to single brain regions or a single pattern of functional connectivity. Yet, despite this rich body of literature, little is known about network connectivity patterns following practice of complex cognitive tasks such as working memory. As working memory processing recruits and putatively maintains the involvement of higher-order structures (e.g., prefrontal cortex) even during working memory

delay without the presence of stimuli (Courtney et al., 1997; Curtis and D'Esposito, 2006; Goldman-Rakic, 1995), functional reorganization involving such structures may be fundamentally different to those implicated in motor learning.

A recent study of a single subject involving the longitudinal assessment of various biological measures including neural functional connectivity patterns, gene expression, and metabolomic dynamics (Poldrack et al., 2015) provides important implications for the investigation of network connectivity pattern changes over time. First, it was shown that the brain is highly dynamic in its connectivity which shows alterations in the course of days to months. Second, such alterations are related to a number of factors that represent an interaction between biological constraints and environmental influence (e.g., gene expression, diet, task requirements). Third, there is a distinct degree of within-subject neural variability in various neural measures including network functional connectivity organization. Crucially, the pattern of this variability is not observed at the between-subject level. Thus, these findings call for the individual-subject approach in examining functional network changes over time. Specifically, this approach involves the consideration of individual differences that may be obscured in group analyses.

To characterize large-scale functional connectivity patterns in response to different cognitive demands and task practice, we examined network architecture and properties during a working memory updating task. Our task design has two important features. First, unlike previous studies using block designs involving the n-back task (Cohen and D'Esposito, 2016; Shine et al., 2016), we used an event-related design which included a substantially long working memory delay. This delay served two purposes. It allowed for the construction and evaluation of network connectivity patterns at the individual trial basis. Additionally, it enabled the specific

examination of the working memory maintenance and updating without the potential influence of factors including stimulus presentation or motor responses. Second, the majority of the participants completed two scan sessions which were separated by a week, thus providing the opportunity to investigate the practice effect. Finally, to reveal nuanced network connectivity patterns associated with individual differences, we adopted the individual subject analysis approach. Graph theory measures of network properties were used to calculate the degree of functional integration and segregation of each network in each subject. We hypothesized that neural network configuration would show a broad trend of increased integration during working memory processing relative to resting, reflecting the heightened cognitive efforts. We further hypothesized that while the whole-brain neural network architecture may remain largely stable across cognitive demands and practice sessions, there would be architectural changes that are subject-specific. Finally, we examined practice-related architectural changes in major modules including the frontoparietal, default-mode, visual, and somatomotor during the working memory updating and maintenance.

Materials and Methods

Participants

8 young adults (4 females, age $M[SD] = 23.4[5.6]$ years) participated in the study in exchange for course credit or money or a combination of both. All participants were without history of psychiatric or neurological illnesses and gave written consent prior to participation. The study was approved by the local Institutional Review Board.

General experiment procedure

Prior to the first fMRI session, participants completed the prescreen questionnaire for fMRI safety, practiced two runs of the behavior tasks, and were acclimated to the imaging procedures in a mock scanner. For each fMRI session, resting-state scan was performed first, followed by 4 runs of working memory task, a structural scan which also served as a break for participants, and another 4 runs of working memory task. Of the 8 participants, 1 completed 4 sessions, 3 completed 3 sessions, 6 completed 2 sessions, and 2 completed 1 session. See Table 1 for demographic characteristics and number of sessions for all subjects included in the final analysis. Subsequent sessions were scheduled 7-8 days after the preceding session. During the fMRI session, we monitored the participants' pupil diameter and saccade locations with an Eyelink 1000 eye-tracking system (SR Research Ltd., Mississauga, ON, Canada).

Visual stimuli

Eight pictures of faces (half were females) with neutral expressions were used as stimuli (Minear and Park, 2004) and 8 pictures of scenes (urban houses and buildings) collected from the internet were used as stimuli in the working memory task. All images were scaled to the same size (154x186 pixels), converted to black and white, and equalized for overall brightness. A different set of images with the same graphic constraints was used for each subsequent scan session.

Behavioral task

We used a delayed recognition task with a cue inserted during the delay period similar to our previous studies in young adults (Le et al., 2017; Oh and Leung, 2009). The task included an updating condition (Remember Face Update, Remember Scene Update) and a non-updating

condition (Remember Face Non-update, Remember Scene Non-update) (Fig. 9). At the beginning of each trial, a fixation cross was presented for 1980 ms, which turned green for 200 ms as a warning, 270 ms before stimulus presentation. For the updating trials, two images (a face and a scene) were then presented sequentially, each for 990 ms with a 247-ms inter-stimulus interval, followed by a checkerboard mask displayed for 496 ms. For the non-updating trial, a scrambled image and a face or scene image were presented. After a delay of either 2970 ms or 4950 ms, a cue word (“Face” or “Scene”) appeared at the center of the screen for 990 ms indicating the stimulus category to be remembered for the recognition test. For the updating trials, Face and Scene cue appeared at the same frequency. For the non-updating trials, the cue always indicated the category of the non-scrambled image. After a 31680-ms postcue delay, either the target or a new image of the cued category was presented as a probe for recognition. To discourage participants from selective encoding of isolated stimulus features (e.g., eyes, nose, door, window etc.), half of the probe image was randomly greyed out, leaving the other half visible. Four random possibilities were used for the probe visibility: top, bottom, left, or right. A face probe would be presented on trials with the “Face” cue and a scene probe for the “Scene” cue. Thus, all cues were fully informative. Chance of a matching and nonmatching probe was equal (50/50) for each condition. The order of stimulus presentation and the stimulus types were counterbalanced. Participants responded with a button press to indicate whether the probe was the remembered item. Intertrial interval (ITI) varied between 12870 ms and 14850 ms with an average of 13860 ms. There were 3 trials per condition per run for 8 runs, giving a total of 24 trials per condition per session, and a total of 96 trials per session. There were two task design versions, differing in the trial order within each run and the run order. These two versions were alternated from session to session for each subject.

Imaging protocol and preprocessing of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3T system (Siemens Prisma; 64-channel head and neck coil). A single high-resolution T1-weighted gradient-echo scan was obtained. One hundred and seventy-six sagittal slices covering the whole brain were acquired with TR=2400ms, TE=2.24ms, flip angle = 8°, field of view = 256x256 mm, matrix = 320x320, 0.8mm³ isotropic voxels. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a gradient-echo echo-planar imaging (EPI) sequence. Fifty-six axial slices parallel to the AC-PC line covering the whole brain were acquired with multi-slice acceleration factor (“multiband”) = 4, TR=990 ms, TE=30 ms, flip angle=52°, field of view=207×207 mm, matrix=90x90, 2.3mm³ isotropic voxels with no gap between slices. There were seven hundred image volumes in each task session for a total of 8 sessions. A single resting-state scan was placed before the task scan and contained seven hundred and forty six image volumes. During all BOLD sessions, physiological signals were recorded via the built-in Siemens Prisma hardware and the “Online” software setting. Respiration was recorded with a breathing band, and heart rate was recorded with a pulse oximeter.

Image preprocessing

Images were preprocessed with SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) in an identical procedure to the first study in Chapter 2 with one exception. As physiological data were collected during scanning, extra steps were taken to minimize the influence of these sources of noise, including regressing out

respiration and heart rate using a model-based Bayesian method with the DRIFTER toolbox in SPM12 (Särkkä et al., 2012; <http://becs.aalto.fi/en/research/bayes/drifter/>). Briefly, the interacting multiple models filter algorithm estimated the frequency trajectories of the physiological signals. A Kalman filter and Rauch-Tung-Striebel smoother separated the BOLD time courses into a cleaned activation-related signal, physiological noise, and white noise, and we used the cleaned activation-related signal for all analyses.

To assess the functional connectivity between different areas of the brain, additional preprocessing steps were performed. A nuisance regression was constructed to control for the following confounding variables: 6 motion parameters up to their second derivatives, scans with excessive motion, modeled physiological signal generated through aCompCor of the white matter and CSF voxels, and the linear drift. For resting state data, the residuals of this regression were then filtered utilizing a bandpass between the frequencies of 0.008 and 0.09 Hz and despiked. For the task state data, similar to a previous study (Cole et al., 2010), no low pass filter was applied (i.e., bandpass = .008 Hz - Inf) to preserve the possible presence of task signals at higher frequencies than the relatively slow resting-state fluctuations. We chose not to regress out the global signal in order to retain the interpretability of negative correlations (Murphy et al., 2009).

Regions-of-interest

Similar to our previous study, we used the 264 cortical and subcortical ROIs from Power et al. (2011). As our previous studies (Le et al., 2017; Oh and Leung, 2009), which used a similar task design, showed preferential activation and connectivity in visual association cortices (VAC) to faces and scenes, we also included these regions in our analyses. Specifically, face- and scene-

processing regions were defined from the group-level analysis of the working memory task data. Briefly, we built the first-level analysis using General Linear Model to estimate activation in the stimulus presentation, cue, postcue delay, and probe events. The events were convolved with a canonical hemodynamic response function. For the localization of the VAC, we used the contrast between the two non-updating conditions (i.e., Remember Face non-updating vs. Remember Scene non-updating) during the stimulus presentation period. This resulted in the identification of the typical face- (bilateral fusiform face area, occipital face area, and superior temporal sulcus) and scene- (bilateral parahippocampal place area, retrosplenial cortex, and transverse occipital cortex) networks (coordinates in Table 2). All ROIs were spheres of 5-mm radius centered at the coordinates.

BOLD signal amplitude

Work from our own laboratory (Le et al., 2017; Oh and Leung, 2009) and others (Gazzaley et al., 2005; Peters et al., 2012) has shown enhanced activity in visual association areas during the processing of relevant visual information and attenuated activity when the information is irrelevant. To replicate these previous findings, we compared activity level in the face and scene modules during the postcue delay in the two trial types involving Face and Scene cue. We chose the first 8 seconds of the postcue delay for this analysis as visual association cortical activity diminishes during a long postcue delay (Oh and Leung, 2009; Riggall and Postle, 2012). Furthermore, to take advantage of the large number of trials across sessions, we grouped the first and second sessions together. Separating the two sessions yielded a similar pattern, albeit slightly less robust, results.

Functional connectivity

We first conducted Pearson correlations between time series in all pairs of brain regions from the 264 cortical and subcortical ROIs from Power et al. (2011) as well as the 12 visual association areas. Correlation coefficients were Fisher's Z transformed and used for all subsequent computations. Only data from the postcue delay period were included in the time series, with 6 s of hemodynamic delay accounted for. A separate network was constructed for each trial. The length of the postcue delay (32 TR's or ~32 s) was appropriate for network construction as indicated by a previous study investigating the detection of functional brain networks using different window sizes (Telesford et al., 2016). Since the postcue delay was sufficiently long to minimize the stimulus effects from the stimulus presentation, we opted to not remove task events from the time series. Nevertheless, we conducted another set of analyses with task events removed and produced similar results. Here, we reported findings without the task events removed.

Community Detection

Community detection was performed using an identical procedure described in our study in Chapter II. To maximize precision of the algorithm, we used resting data from the first two sessions of all subjects. Parameter optimization yielded optimal density threshold of 0.115 and resolution of 2.5 which produced a twelve-community partition similar to Power et al. (2011).

The optimal parameters obtained from resting-state community detection were subsequently applied to the working memory task data to identify community structure in each trial. As the Louvain algorithm is stochastic, we ran this algorithm 150 times to obtain 150 partitions for each trial. These partitions were then used to create an agreement matrix which was subjected to consensus clustering (Lancichinetti et al., 2009) to yield the trial's partition.

To examine changes in community architecture within each module during working memory, community detection was applied to key neurocognitive modules including frontoparietal (FP), default mode (DMN), visual, and somatomotor (SMN) using data from each trial. Community detection was not applied to the face and scene modules as the low number of regions (6 each) would have resulted in unstable structure estimation. Changes in community architecture across states, both at global and modular levels, were quantified by normalized mutual information (NMI) (Danon et al., 2005), which measures the similarity between two partitions. We also calculated module partition similarity to compare resting partition and working memory task partition for a given module. The same community detection procedure used for whole-brain architecture was performed for each state at the module level.

Graph theoretical metrics

At the global level, we examined changes in functional segregation and integration in brain connectivity across task conditions and across sessions. Connectivity matrices were thresholded with the density of 0.115 (as determined by community detection optimization) prior to obtaining the graph metrics.

For the measures of integration/segregation, we used global efficiency, local efficiency, and transitivity (see methods section of Chapter 2 for detailed definitions of these measures). For the working memory task, these measures were calculated for each trial. For the resting state, we separated the resting time courses into 48 overlapping bins with each bin's length equal that of the postcue delay (32 TR's). Graph measures were calculated for each bin.

Results

Behavioral performance

We examined performance accuracy and response time of the six subjects with two sessions of data (Table 3). With the exception of one subject during session 1, no subject showed a significant performance difference between the two working memory conditions (updating vs. non-updating) (p 's > .29). Across the two sessions, only one subject demonstrated improvement in accuracy following practice ($p < .01$) while the remaining five subjects showed no significant differences in either task condition (p 's > .1) (Fig. 10A). With response time, four subjects showed faster responses with practice (p 's < .05) whereas the other two did not show significant changes (p 's > .15) (Fig. 10B). Overall, there was only limited practice-related improvement in response time.

fMRI result

BOLD signal amplitude in modules associated with visual working memory

Face module showed higher percent signal change (relative to the baseline of the average of second and third scans of each trial) in the face conditions (i.e., Remember Face updating and Remember Face non-updating) relative to the scene conditions (i.e., Remember Scene updating and Remember Scene non-updating) in two subjects (p 's < .01) and no significant changes in the remaining four subjects (p 's > .4). The weak cue effect in the face module was expected as previously reported (Gazzaley et al., 2005). The scene module showed higher percent signal change in the scene condition relative to the face condition in all (p 's < .05) but one subject ($p = .8$). The inclusion of the two subjects with one single session as well as the third and fourth sessions from two other subjects did not change the pattern of relatively weak cue effect in the face module and relatively robust cue effect in the scene module.

Since FPN and DMN have been implicated in visual working memory maintenance of relevant and inhibition of irrelevant information (Chadick and Gazzaley, 2011), we compared activity in these modules during the updating and non-updating conditions. FPN showed significantly higher activity for the updating relative to the non-updating condition in one subject ($p < .05$) and numerically higher activity in two others (p 's $\leq .14$), whereas three subjects did not exhibit significant differences (p 's $> .35$). No significant differences activity were found in the DMN between the two working memory conditions (p 's $> .07$), except for one subject ($p < .05$). As a control, we compared SMN activity across cue types and task conditions and found no significant differences in any of the subjects (p 's $> .07$). In sum, we observed a relatively weak cue effect in the face module and a relatively robust cue effect in the scene module, while the FPN and DMN did not show strong differences across the updating and non-updating conditions.

Effect of working memory demand on whole-brain network integration

To investigate whether working memory demand affects the degree of integration and segregation at the subject level, we compared global efficiency, local efficiency, and transitivity between resting and working memory in each session and each subject individually. (The two conditions were combined because few differences were observed between updating and non-updating conditions). Significant increases in global efficiency during working memory relative to resting were found in three subjects in session 1 (p 's $< .05$) and five subjects in session 2 (p 's $< .01$) (Fig. 11A). Significant decreases in local efficiency during working memory compared to resting were found in all subjects in session 1 (p 's $< .01$) as well as session 2 (p 's $< .01$) (Fig. 11B). Finally, significant decreases in transitivity during working memory relative to resting were found in all subjects in session 1 (p 's $< .01$) and in five subjects in session 2 (p 's $< .05$) (Fig. 11C). Overall, compared to resting all subjects showed a significant reduction in local

processing and all but one subject showed significant enhancement in functional integration during working memory.

We further examined whether the degree of integration and segregation changed with task practice. Global efficiency, local efficiency, and transitivity measures for the task state in each session were corrected by subtracting the measures obtained from resting state of the same session. Global efficiency showed a practice-related increase in four subjects (p 's $\leq .001$) and a decrease in the remaining two subjects (p 's $< .01$). The reversed pattern is true of transitivity in the same subjects. Local efficiency was less consistent, with one subject showing a significant increase ($p < .05$), another showing a significant decrease ($p < .001$) and four showing no significant session differences (p 's $> .13$).

Next, we measured the fluctuation of integration and segregation over time for each subject. To avoid the potentially distinct effects due to different cognitive demands, updating and non-updating conditions were analyzed separately. The degree of integration and segregation varied greatly across trials and across runs within a session. To characterize such variability across runs, we calculated the intra-subject covariation of variance (iCV) for global efficiency, local efficiency, transitivity, and response time for each task condition and each subject. iCV is measured by the standard deviation divided by the mean of each measure across trials within a session. Treating the six subjects as a group, iCV did not significantly differ between the two sessions for any of the integration measures (p 's $> .07$) or response time (p 's $> .06$). Furthermore, across subjects there were no differences in iCV between the updating and non-updating conditions in either session (p 's $> .14$) or between resting and task (p 's $> .32$). To determine any potential relationships between variability in integration and response time/performance accuracy, we correlated the run average of these measures within each

subjects. Except for two significant correlations between performance accuracy and transitivity ($r = .83, p = .01$) as well as global efficiency ($r = -.85, p = .008$) in the non-updating condition for one subject during session 1, no other significant correlations were found (p 's $> .07, -.57 < r < .67$) (Fig. 12).

Overall, most subjects demonstrated an increase in functional integration and a decrease in segregation during working memory relative to resting. This relationship was observed in both session 1 and session 2. The degree of functional integration appeared to change with task practice though the direction of change varied vastly across runs and sessions from subject to subject. Furthermore, integration as well as response time varied across time within subjects and yet no clear associations were observed between the two.

Effect of task practice on whole-brain and module network architecture

To determine whether network architecture remained stable or changed with task practice, we measured the partition similarity of the network architecture in resting state and in task state for each session then compared the two sessions.

Whole-brain network architecture. Relative to session 1, one subject showed a decrease and two subjects showed an increase in similarity with resting in session 2 in the updating condition (p 's $< .01$), while the other three subjects exhibited no significant changes (p 's $> .08$) (Fig. 13A). For the non-updating condition, similarity to the intrinsic architecture significantly increased in two subjects (p 's $< .05$), significant decreased in two subjects (p 's $< .01$), and showed no significant difference (p 's $> .05$) following task practice. To show that group averaging can obscure individual changes in architectural similarity which may range from increases to decreases across individuals, we calculated the difference in similarity value

between the two sessions for each subject (Fig. 13 B). Indeed, the average of these values across the six subject was close to zero ($\sim .005$), incorrectly suggesting that as a group, the subjects did not alter task-evoked network architecture due to practice. In sum, our results suggest a mixed pattern of whole-brain task-evoked network architectural changes across subjects: some became more similar to resting state, some became more dissimilar and some remained relatively unchanged.

Module network architecture. As different functional modules may express different patterns of architectural changes related to practice, we compared the resting-task partition similarity across the two sessions for FPN, DMN, Visual, and SMN. Since there were no differences in this analysis for the updating and non-updating conditions, we combined these two conditions for simplicity. Relative to session 1, in session 2 task-evoked FPN showed significantly less similarity to its intrinsic architecture in three subjects (p 's $< .001$), significantly more similarity in one subject ($p < .001$), and no significant changes in two subjects (p 's $> .09$) (Fig. 14A). With practice, task-evoked DMN showed increased similarity to its intrinsic architecture in two subjects (p 's $< .001$), decreased similarity in one subject ($p < .001$), and no significant changes in three subjects (p 's $> .07$) (Fig. 14B). Similarly, task-evoked Visual network demonstrated a mixed pattern of similarity change: three subjects showed significantly more similarity (p 's $< .001$), two showed significantly less similarity (p 's $< .001$), and one did not show a significant difference ($p = .17$) (Fig. 14C). For SMN, all but one subject showed higher similarity in session 2 (p 's $< .001$) while the remaining subject only showed a numerical increase ($p = .15$) (Fig. 14D). In sum, we demonstrated that different modules exhibited different patterns of architectural change relative to their intrinsic state following task practice. FPN exhibited decreased similarity or no change compared to resting after practice while the reverse

pattern was true for SMN. DMN and Visual both showed a mixture of decreasing and increasing similarity to resting, depending on the subject.

Discussion

We investigated neural network structure and properties during two sessions of working memory task in six individuals. Consistent with previous literature, we found whole-brain network connectivity showed greater integration during working memory relative to resting, and this relationship was largely preserved at the individual subject level for both sessions. Whole-brain network architecture showed changes with practice. Different subjects exhibited different patterns of changes such that whether the task-evoked architecture became more or less similar to the intrinsic architecture at “resting” was subject-dependent. Similarly, at the module level, with the exception of SMN, variable architectural alterations were found for distinct modules across different subjects, suggesting nuanced functional alterations that may not have been captured at the whole-brain or group level in previous studies.

Functional integration increase with working memory maintenance

By examining global functional integration during working memory maintenance and processing, we found evidence for a shift toward a more integrative state in comparison to resting. This shift was characterized by enhanced global efficiency, attenuated local efficiency and transitivity. Changes in functional integration and segregation in relation to specific cognitive demands have been reported in recent literature. The performance of a cognitive challenging task such as working memory or cognitive reasoning consistently leads to enhanced global integration and diminished segregation relative to rest (Braun et al., 2015; Cohen and D’Esposito, 2016; Hearne et al., 2017; Shine et al., 2016). It is thought that such integrative state

reflects the increased coordination of specialized and distributed regions for more efficient information processing in support of complex behaviors. Such interpretation agrees with past reports of widespread activation in cortical and subcortical areas during working memory (Owen et al., 2005; Rypma et al., 1999; Smith and Jonides, 1997). Evidence of increases in connectivity across multiple brain regions including frontal, parietal, visual association, and striatum in working memory (Brooks and Pavese, 2011; Chadick and Gazzaley, 2011; Haeger et al., 2015) has provided further corroboration. In contrast, reduced functional connectivity during cognitive tasks has been associated with task performance deficits in attention-deficit hyperactivity disorder (Cubillo et al., 2010), autism (Villalobos et al., 2005), and schizophrenia (Fornito et al., 2011). Thus, findings from the current study add to the accumulating evidence that our ability to effectively switch cognitive states and engage in complex cognitive processing may arise from the brain's capacity to flexibly reorganize interactions among spatially distributed systems.

Using a working memory design with an extended delay enabled the current study to characterize the relationship between functional integration and working memory demand specifically in the context of information maintenance and updating. Recent work investigating network configuration in relation to working memory processing has typically utilized the n-back task (Braun et al., 2015; Cohen and D'Esposito, 2016; Shine et al., 2016). While the n-back serves well as an effortful cognitive task compared to rest, it simultaneously engages multiple complex processes including encoding, maintenance, updating, and motor response/decision making. Due to such complexity, it is not possible to attribute changes in integration and segregation to a particular aspect of working memory. Previous research has demonstrated that despite the overlapping in neural substrates, different processes in working memory recruit distinct neural circuitries such as the frontoparietal, striatal, and sensory systems (D'Esposito et

al., 1999; Mayer et al., 2010; Rypma et al., 1999). Among these processes, working memory maintenance receives a significant amount of attention as its neural mechanism remains inadequately understood. Various studies have suggested the contribution of different regions and networks involving the prefrontal (Goldman-Rakic, 1995; Miller et al., 1996), posterior parietal (Bettencourt and Xu, 2015; Todd and Marois, 2004), and visual (Harrison and Tong, 2009; Riggall and Postle, 2012) cortices. By restricting our analysis to the postcue delay, we extended previous research by showing increased global integration during both working memory maintenance and updating.

Despite the consistent relationship between cognitive effort and functional integration, we observed a significant degree of integration variability across trials and across runs. This finding complements recent reports that whole-brain network fluctuates between an integrated and segregated state during resting (Mišić et al., 2011; Shine et al., 2016). Other studies have also indicated changes in strength and spatial distribution of functional connectivity patterns in an ongoing temporal manner during auditory detection (Sadaghiani et al., 2015) and working memory (Shine et al., 2016) tasks. While the neural mechanism of such variability is currently not well defined, neural variability is thought to be a fundamental characteristic of the brain network (Deco et al., 2009; Dinstein et al., 2015; McIntosh et al., 2008). Variability may facilitate switching between network configurations to aid the transition across different cognitive states (Armbruster-Genc et al., 2016; Bassett et al., 2011; Cole et al., 2013). In our task, such switching may have been related to the constant trial-to-trial shifts between the updating and non-updating conditions.

Individual differences in network measures and performance

It is worth noting that neither trial-to-trial nor run-to-run variability in network integration or architecture exhibited a clear relationship with task performance. This lack of an association between neural and behavioral measures may have been related to a number of factors. First, while task performance accuracy and response time are informative behavioral indicators, they may not accurately reflect working memory processing due to the potential influence of decision making and speed of motor response. Second, the long postcue delay may have introduced unintended mindwandering and thus functional networks constructed from this window potentially included other mental processes in addition to working memory. Third, thermal noise and physiological artifacts may have affected the variability in neural activity. Previous research (Bodurka et al., 2007; Triantafyllou et al., 2011, 2005) has indicated that such noise could result in reduced sensitivity to task-induced activation changes. While the current study adopted a stringent procedure of scanning protocol and post-scan artifact correction, the complete removal of noise is presently not feasible. Finally, due to the extended scan time, it is plausible that fluctuations in motivation, attention, and fatigue played a role in the absence of a clear relationship between neural network characteristics and task performance. In the future, measures of more restricted time windows and/or more task-driven localization including those associated with multivariate pattern analysis and region-specific connectivity will be utilized to explore evidence for such relationship.

Task practice and individual differences affect functional network configuration

Recently, reports of alterations in large-scale functional networks due to practice, particularly in motor tasks, have begun to emerge. A number of studies have demonstrated that the learning of motor sequences decreases the task-evoked activation in the dorsolateral

prefrontal cortex and presupplementary motor area (Floyer-Lea, 2005; Sakai et al., 1999) while increasing activation in the primary motor cortex (Honda et al., 1998), primary somatosensory cortex, and cerebellum (Floyer-Lea, 2005). Findings of changes in functional connectivity show heightened interactions among cortico–striatal, cortico–cerebellar and limbic structures at the early phase of learning, which may contribute to developing specific motor programs (Doyon et al., 2003; Doyon and Benali, 2005). Once the motor skills have become automatic, increased dissociation between these systems is observed (Doyon et al., 2003; Wu et al., 2004). More recently, it was shown that extensive training on simple motor sequences over the course of six weeks led to segregation between the visual and motor modules (Bassett et al., 2015). The authors interpreted the transition of motor and visual areas from functioning as a cohesive unit to two relatively independent systems as evidence for neural automaticity following skill acquisition. Collectively, these studies demonstrated practice-related changes in brain activity and connectivity in agreement with previous proposal (Petersen et al., 1998) that practice reduces the recruitment of higher-order cortical regions (e.g., prefrontal cortex) and facilitates the involvement of task-related areas (e.g., sensorimotor).

Literature on practice effects of complex cognitive tasks including working memory so far has suggested a different pattern of neural alterations. Practice on a visuo-spatial n-back task was associated with increased task-evoked activity in the dorsolateral prefrontal cortex and parietal (Hempel et al., 2004). Similarly, repeated exposure to object (Moore et al., 2006) and verbal (Wexler et al., 2000) working memory tasks led to higher frontal and parietal activity. Nevertheless, these changes in the frontal cortex was not associated with improvement on task performance. Furthermore, unlike motor learning, integration across distant brain regions has been associated with higher performance during working memory practice across subjects

(Langer et al., 2013). Simple motor tasks (Biswal et al., 1995; Weinstein et al., 1997) have been shown to recruit fewer brain regions than working memory (Desimone, 1996). Additionally, working memory requires the updating of information constantly, necessitating the need to process and spread such new information to different neural systems (Christophel et al., 2017), making network communication less likely to be reduced with task exposure. Our own findings support this possibility. We found a greater degree in functional network integration after practice, lending weight to the suggestion that the neural alterations involved in working memory task training are likely to be substantially differentiable from those underlying the learning of motor processing. It is also worth noting that two of our subjects did exhibit diminishing integration in the second session. Thus, individual differences may further contribute to the altered connectivity patterns though further research is needed to shed light on this possibility.

Another finding from the current study is the architectural changes at the whole-brain and module levels due to working memory practice but vary in different directions from individual to individual. Such evidence for adaptive and flexible functional network configuration agrees with previous research which shows organizational changes in functional modules following task training (Bassett et al., 2011). In this particular study, the authors reported increased switching of nodal membership (i.e., when a node becomes a member of a different module to the one it previously belonged to) in subjects with faster learning rates (Bassett et al., 2011). As such nodal flexibility is related to the stability of network architecture, these results suggest learning capacity and behavioral adaptation may have implications in neural network connectivity pattern changes. This is in line with the idea that architectural flexibility is beneficial as it promotes probabilistic decision making, signal detection, or creative thought (Deco et al., 2009). In

contrast, pathologically low flexibility is associated with tissues damage due to seizures (Protzner et al., 2010) as well as autism spectrum disorder (Bosl et al., 2011).

It should be pointed out that a recent study (Cole et al., 2014) has reported a high degree of network architectural stability across multiple cognitive states including working memory, reasoning, decision making, language, and motor. However, that study did not investigate changes due to task practice. Furthermore, as our results indicated, individual subjects exhibited different patterns of alterations relative to resting. Group averaging can mask these individual differences, leading to a potentially incorrect conclusion of minimal changes across tasks. We also provided evidence for different degrees and trajectories (i.e., similarity vs. dissimilarity) of architectural change in FPN, DMN, Visual, and SMN. These module differences are unlikely to be detectable at the whole-brain level. As it is beyond the scope of the current study to delineate the neural mechanism underlying such differences, our findings call for a closer examination of module architecture in future work to further understand the contribution of these modules to the global patterns in support of cognitive processing.

Limitations

A limitation with the current study is the small sample size. Across six subjects, we found different patterns of network connectivity pattern alterations during working memory processing. While individual differences were predicted, the small number of subjects prevented better characterization of these patterns according to individuals' task performance levels and learning ability. Another potential limitation is the long experiment time. The significant time in the scanner can lead to change in motivation and fatigue, affecting task performance and increasing motion-related artifact. For future continuation of the study, shorter sessions may be considered.

CHAPTER IV. GENERAL DISCUSSION

Our two studies demonstrated that the functional brain network can adaptively and flexibly vary its connectivity patterns to support cognitive processing. Such changes likely reflective of both biological constraints and demand from external environment. In the first study, we specifically examined the neural network in late childhood/early adolescent children during the performance of three cognitive tasks. Our findings suggest an interaction between neuronal maturation, which have been shown to affect the development of functional network organization (Menon, 2013, Fair et al., 2009), and the ability to switch between different cognitive states in response to changing task demands. Our study replicated and extend previous literature by showing that network configuration may be a useful measure for both cognitive ability and neuronal maturation during development. Such measure can potentially be utilized to track healthy as well as atypical trajectories of neural and cognitive progress in children. Several recent studies have provided preliminary evidence for abnormalities in functional brain network in a number of neurodevelopmental and neurological disorders including autism (Di Martino et al., 2014; Rudie et al., 2013), epilepsy (Bonilha et al., 2014; Kellermann et al., 2015), and attention deficit hyperactivity disorder (Alonso et al., 2014; Xia et al., 2014). Findings from these studies suggest these disorders can be described in terms of altered functional connectivity in the large-scale neural systems. Network alterations may further be investigated in relation to specific information processing patterns associated with each disorder.

In the second study, we focused our investigation on the association between cognitive demand and neural network organization in healthy adults during working memory processing. Our findings add to the expanding body of literature showing that functional network connectivity patterns can be measured during the extended working memory postcue delay and

this patterns showed clear changes from the resting state. Importantly, these changes are subject to temporal variability and individual differences which likely include learning rate and cognitive capacity. The impacts of individual differences should be addressed in future studies with a larger sample. Understanding the complex relationship between task practice and neural network reorganization can further the efforts to derive global markers for training efficacy. Recently, there has been increasing attention given to the effectiveness of cognitive training, particularly in the working memory domain (Melby-Lervåg and Hulme, 2013; Shipstead and Engle, 2012). Current evidence is inconclusive, particularly regarding the long-term impact of such training on the neural substrates that underlie cognition. Disentangling any potential training effects is further complicated by the variability in functional connectivity patterns over time and across individuals. Nevertheless, these challenges also represent an opportunity to further improve our methodology to better characterize the relationship between the dynamic brain and the constantly changing environment.

While the two studies investigated two distinct populations, they converge in showing the use of the network approach is well suited for the investigation of the neural substrates of cognition and complex behavior. Far from a unitary function, cognitive processing, particularly working memory processing, is supported by multiple neural systems with different anatomical and functional characteristics. The patterns of interaction among these systems can be reliably identified and measured. More importantly, such patterns have been shown here and in other work (e.g., Cole et al., 2014; Heinzle et al., 2012; Shier et al., 2012) to reflect the underlying cognitive processing. The two studies also revealed complex patterns of connectivity at the module level. First, it calls for careful considering whole brain measures and individual measures, which can produce mixed results if not considered together and also separately.

Second, it also demonstrates the importance of the examination of individuals as group averages may produce false null effects. Finally, our results highlight the significance of a balance in using network measures to evaluate the neural substrates of cognition. While examining the large-scale neural configuration can be meaningful, such configuration represents the collective connectivity and activity of multiple circuitries with distinct functions and properties.

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Table 1. Participant demographics and number of task sessions completed for study 2.

Subject	Age	Sex	No. of sessions
1	34	M	4
2	19	M	2
3	28	M	3
4	20	F	2
5	23	F	3
6	26	F	3
7	18	F	1
8	19	M	1

Table 2. MNI coordinates of face and scene regions.

	Face module			Scene module			
	x	y	z	x	y	z	
lFFA	-41	-43	-26	lPPA	-25	-36	-17
rFFA	46	-50	-24	rPPA	28	-34	-15
lOFA	-43	-85	-15	lTOS	-36	-82	11
rOFA	46	-80	-12	rTOS	37	-85	18
lSTS	-50	-59	9	lRSC	-16	-59	11
rSTS	56	-64	13	rRSC	14	-52	6

Table 3. Behavioral results. Mean (standard deviation) of performance accuracy (in percentage) and response time (in millisecond) for the updating and non-updating condition in each session. Abbreviations: ACC: accuracy; RT: response time; NUD: non-updating; UD: updating.

Subject	Session 1				Session 2		
	ACC - NUD	RT - NUD	ACC - UD	RT - UD	ACC - NUD	RT - NUD	ACC - UD
1	85.41 (35.7)	1250.2 (267.8)	91.66 (27.9)	1237.3 (234.6)	89.95 (30.9)	1211.2 (256.6)	89.95 (30.9)
2	52.08 (50.5)	1777.2 (396.9)	50 (50.5)	1837.9 (598.6)	79.16 (41.0)	1288.0 (340.2)	85.41 (35.7)
3	91.6 (27.9)	1952.7 (365.6)	91.6 (27.93)	1872.4 (449.0)	87.5 (33.42)	1896.9 (377.8)	89.95 (30.9)
4	77.0 (42.4)	1321.6 (486.7)	79.16 (41.04)	1387.3 (457.9)	87.5 (33.42)	1182.7 (333.2)	85.41 (35.7)
5	93.7 (24.4)	1276.7 (293.4)	75 (43.75)	1281.9 (391.2)	79.16 (41.04)	1040.3 (255.2)	75 (43.75)
6	93.7 (24.4)	1063.4 (268.8)	93.75 (24.46)	1125.6 (292.8)	87.5 (33.42)	993.0 (176.9)	83.33 (33.33)

Figure 1. Functional segregation and integration. (A) Intrinsic functional neural network (i.e., during resting state) shows a high degree of segregation. (B-C) Distinct cognitive processes enhance integration between specific modules. During cognitive processing, nodes belonging to a module may switch membership to another module, as illustrated by change of node color compared to resting state. (D) Task-evoked functional network shows a high degree of integration.

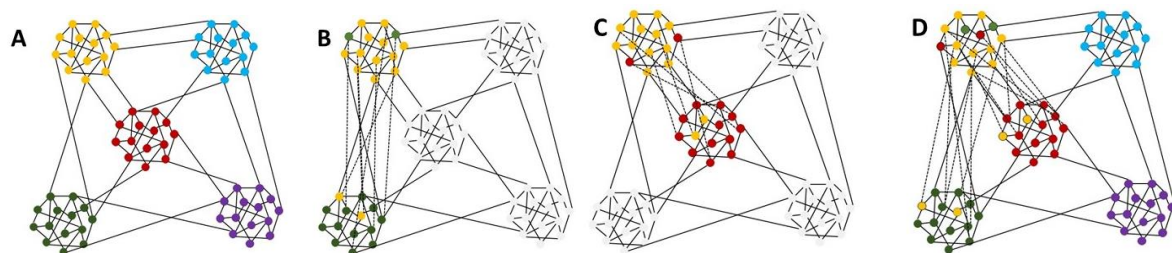


Figure 2. Task schematics for study 1. **(A)** Reward/decision task: participants were instructed to choose one of the two doors which resulted in either a win or a loss. **(B)** Visual perception task: visual discrimination was required to determine either two faces or the houses were identical. **(C)** Working memory task: 1-back task with two load conditions required participants to indicate whether the current location(s) of the stimulus differed from that in the previous trial.

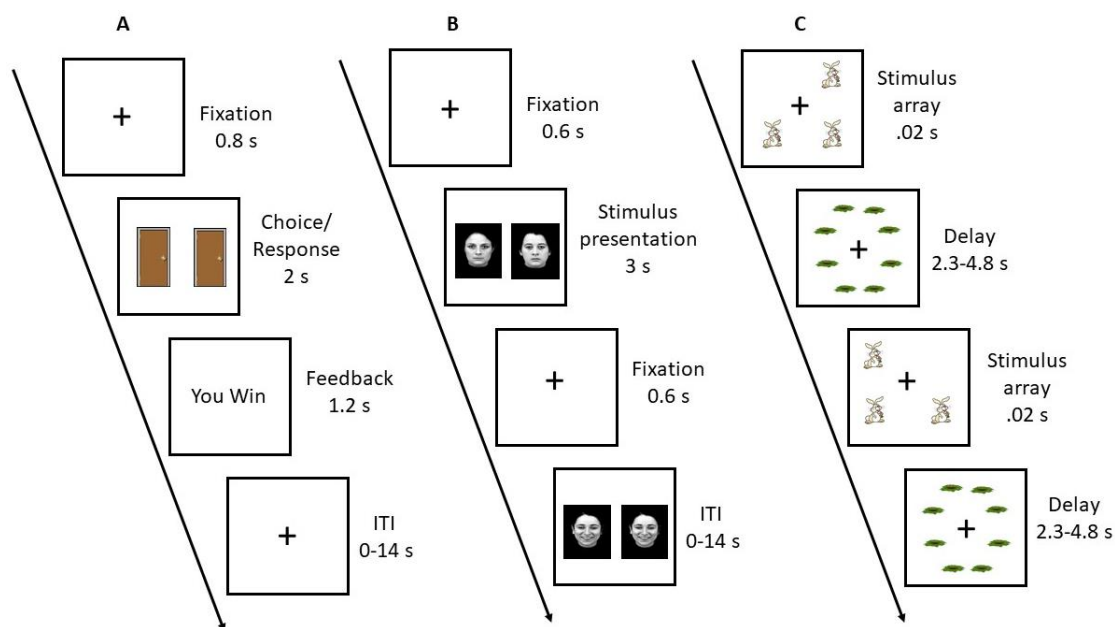


Figure 3. Visual illustration of graph theory measures. **(A) Global efficiency:** a network with high global efficiency (left) is more densely connected and thus having shorter paths between any two given nodes than a network with low global efficiency (right). **(B) Participation coefficient:** a network with a high participation coefficient (left) has more inter-modular connections than a network with a low participation coefficient (right). **(C) Transitivity:** a network is highly transitive when it has more nodes that form a complete triangle (far right) and fewer nodes that do not (far left). **(D) Connector hubs:** nodes (in red) that have more connections between different modules than within a module.

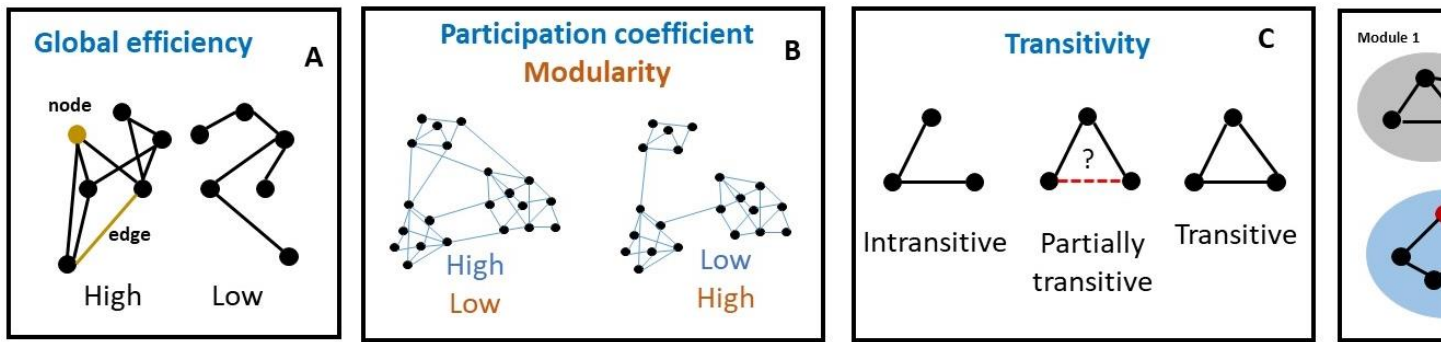


Figure 4. Community detection and neural network architecture. (A) Community partition in each of the resting and task state. (B). Partition similarity was lower between resting and each task (in blue) and higher among task states (in red). (C) Older children show higher partition similarity to young adults.

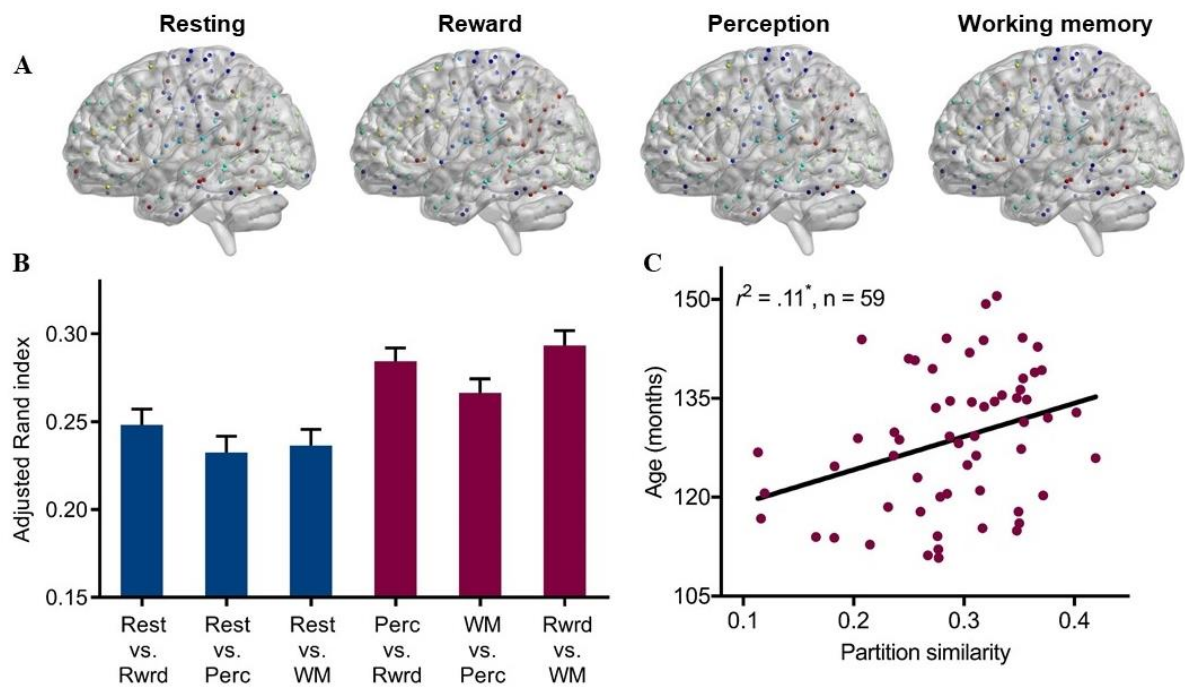


Figure 5. Changes in functional integration and segregation across tasks in children (in red). For comparison, resting state measures in young adults were also presented (in blue). Relative to resting, task states showed a significant increase in global efficiency (A), connector hubs (B), participation coefficient (C), and a significant decrease in transitivity (D). No significant differences were found for modularity (E).

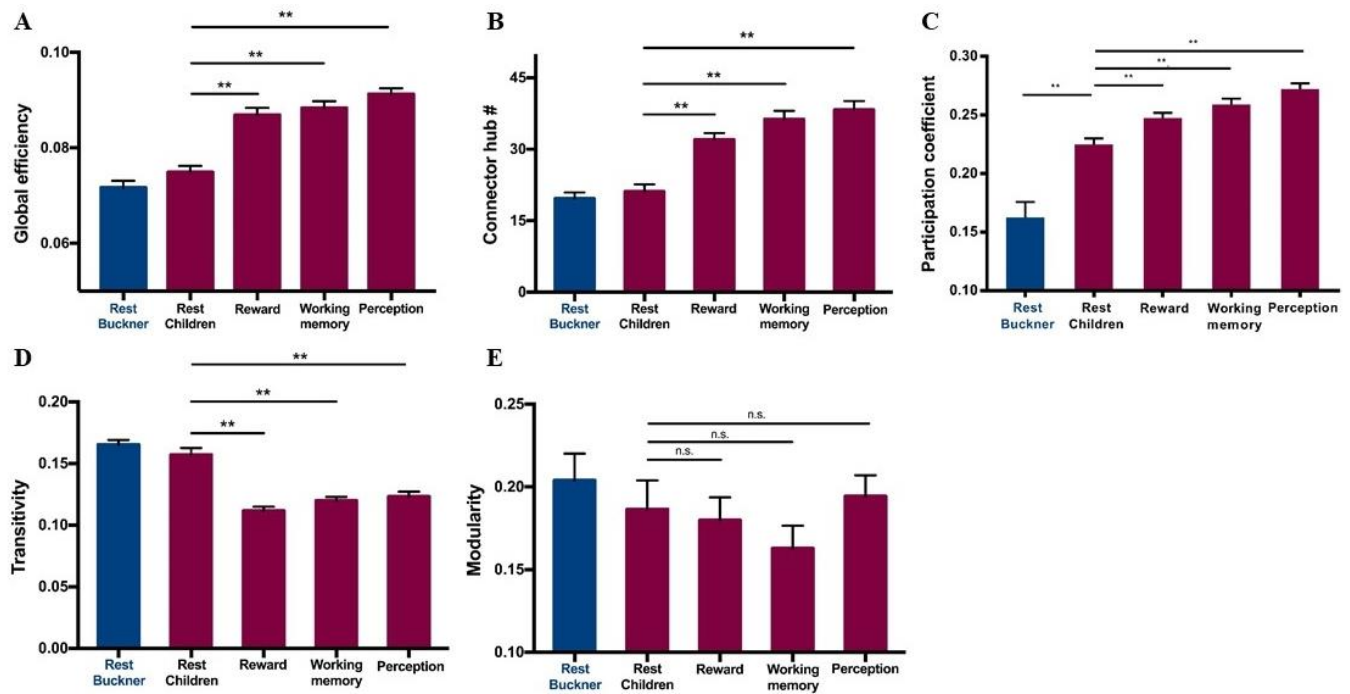


Figure 6. Stability and flexibility at the module level. (A) Functional modules (from left to right): Frontoparietal, Default mode, Salience, Visual, Somatomotor. (B) Global variability coefficient was higher in FPN relative to other modules across the four cognitive states. (C) Partition similarity between resting and task states was lower in FPN and Salience compared to other modules. (D) Nodal flexibility across resting and task states was higher in FPN than other modules.

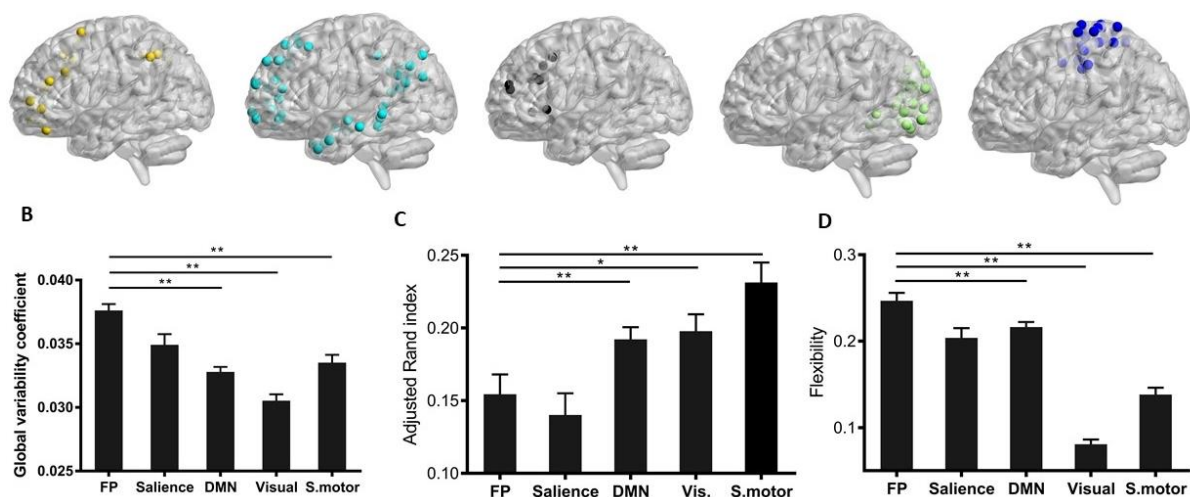


Figure 7. Relationship between neural and behavioral measures in the working memory task. **(A)** Performance accuracy (measured by load effect) negatively correlated with the number of connector hubs. **(B)** Whole-brain architecture similarity between resting and working memory state positively correlated with performance accuracy. **(C-D)** Performance accuracy negative correlated with DMN and SMN nodal flexibility. **(E)** Response time positively correlated with Salience nodal flexibility

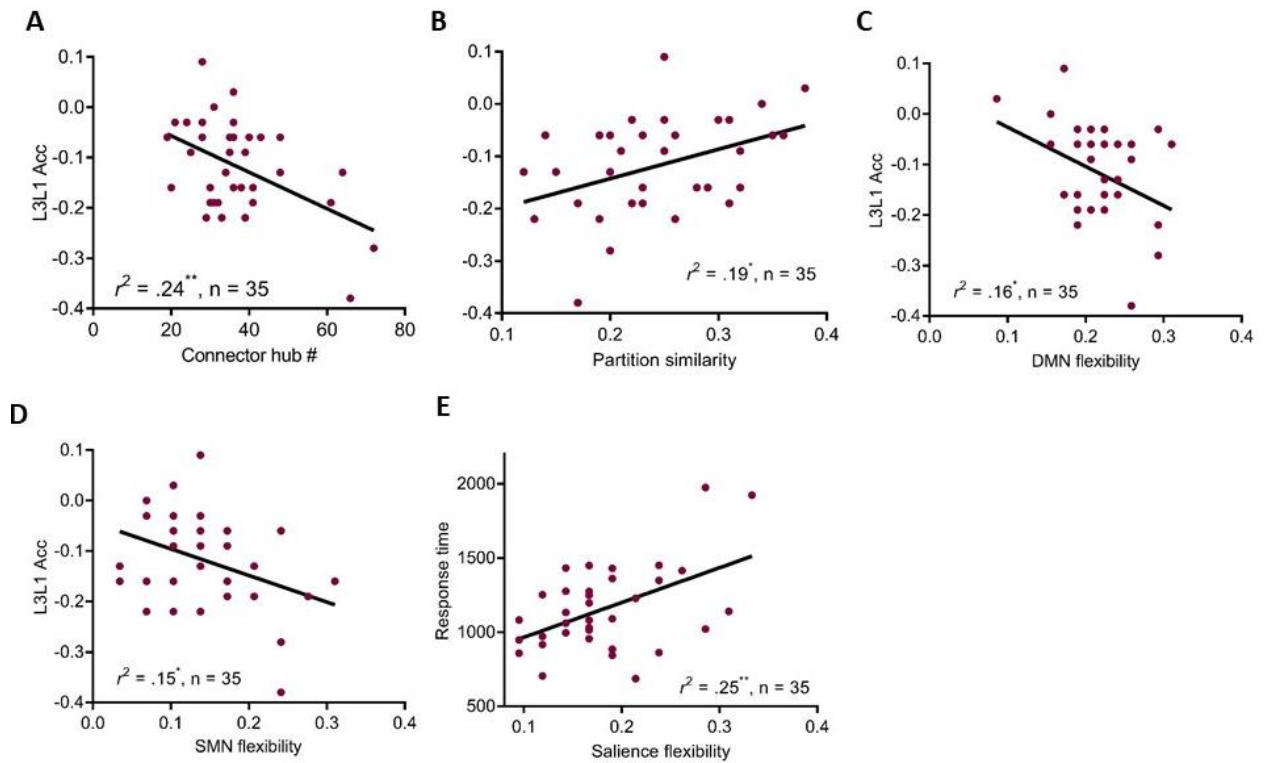


Figure 8. Relationship between neural and behavioral measures in the visual perception task. **(A)** Global efficiency positively correlated with performance accuracy. **(B)** Transitivity positive correlated with response time variability. **(C)** Partition similarity between resting and visual perception negatively correlated with performance accuracy.

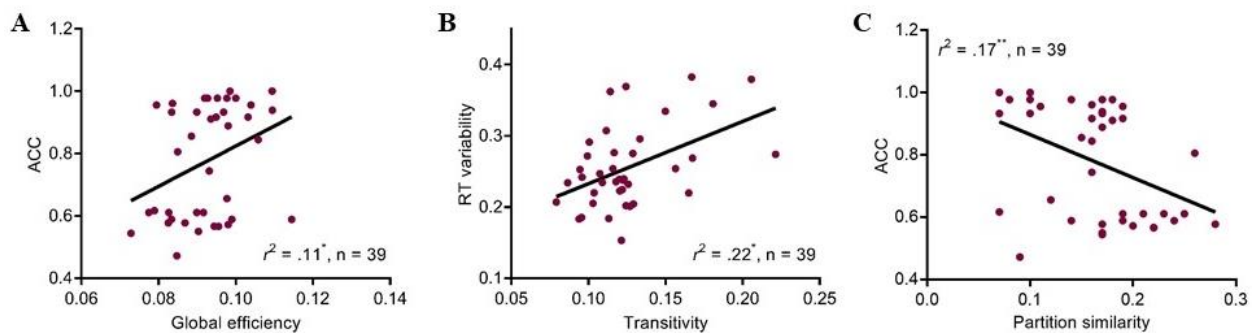


Figure 9. Working memory task design. For the update condition (first two rows), a face and a scene is presented sequentially. A following cue indicates the image to be remembered. For the non-updating conditions (last two rows), one image is a face or a scene and the other is a scrambled image. For simplicity, the visual mask and ITI (~13-15 s) were not shown in the figure.

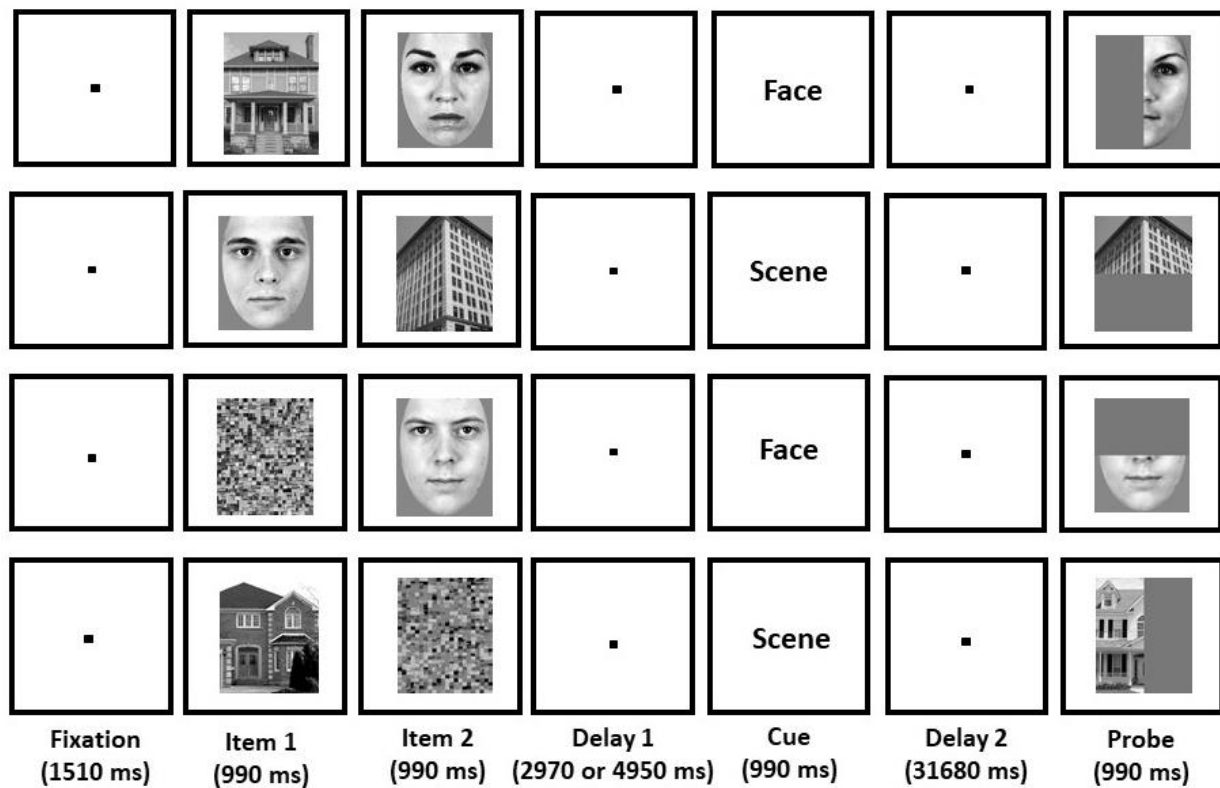


Figure 10. Behavioral results. (A) Mean accuracy in percentage for each subject in the non-updating condition for session 1 and session 2 (left 2 columns) and updating condition (right 2 columns). Lines indicate the same subject across the two conditions. (B) Mean response time in millisecond for each subject in each condition and each session. Abbreviations: UD: updating, NUD: non-updating, Sess: session.

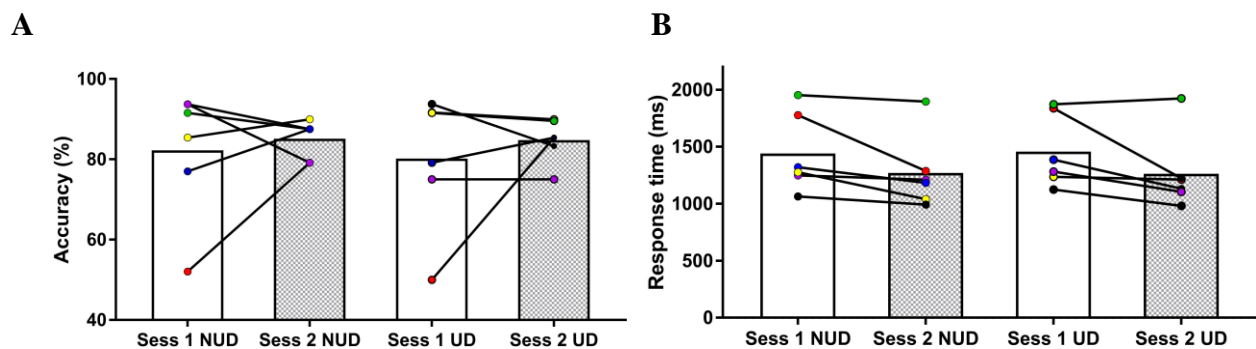
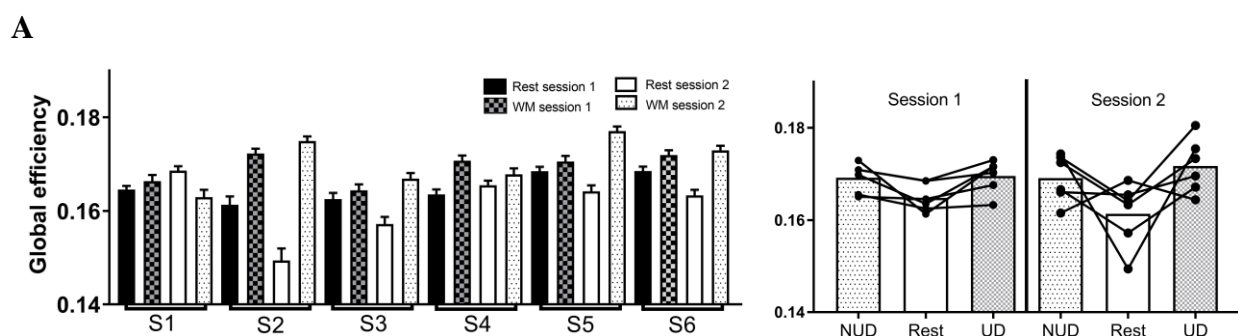


Figure 11. Functional integration and segregation during resting and during working memory task. (A) Global efficiency during resting and during both working memory conditions combined (left) and in each task condition (right), each session, and each subject. (B). Local efficiency. (C) Transitivity. Abbreviations: S: subject, wm: working memory, UD: updating, NUD: non-updating



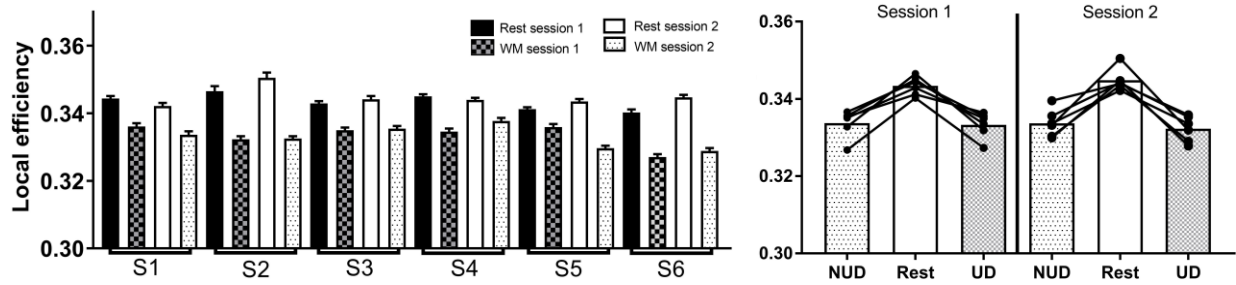
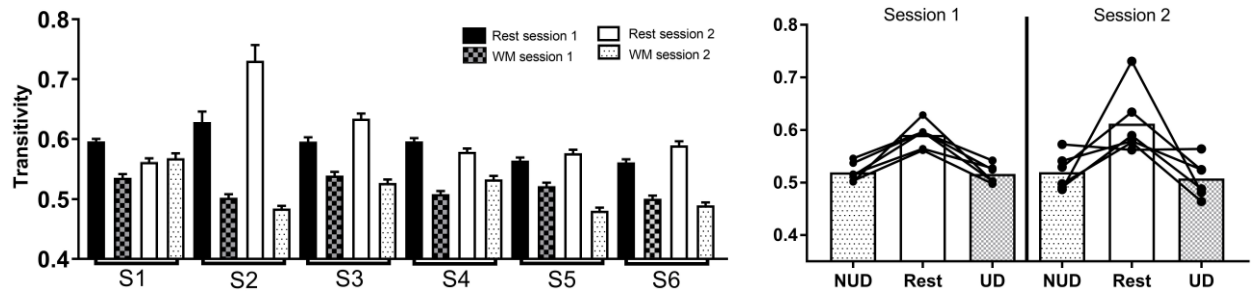
B**C**

Figure 12: Selective sample of subjects demonstrating the relationship between functional integration and task performance across both sessions. (A) Response time and global efficiency in the non-updating condition in subject 1. (B) Response time and global efficiency in the updating condition in subject 2. (C) Response time and local efficiency in the non-updating condition in subject 6. (D) Response time and local efficiency in the updating condition in subject 5. (E) Response time and transitivity in the non-updating condition in subject 4. (F) Response time and transitivity in the updating condition in subject 3.

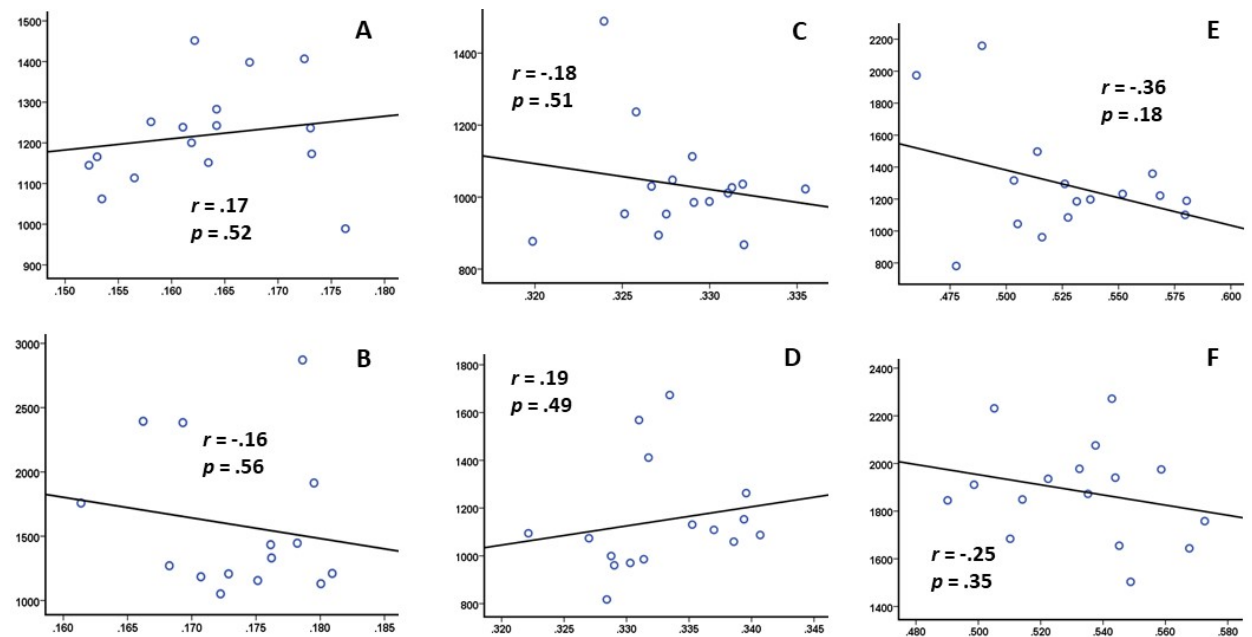


Figure 13. Whole-brain partition similarity between resting and working memory. **(A)** Partition similarity in each session and each subject (same data as in A) showing non-updating condition in session 1 (solid black) and session 2 (checkered black), updating condition in session 1 (solid white) and session 2 (dotted white) (left). Partition similarity difference in session 1 (unfilled columns) and session 2 (filled columns) (right). Each dot represents a subject. **(B)** Rest-task architectural similarity changes between session 1 and session 2 (i.e., Session 2 partition similarity – Session 1 partition similarity) in each subject. For partition similarity difference, updating and non-updating conditions were collapsed. Negative values indicate more dissimilarity to resting compared to session 1, positive values indicate more similarity to resting compared to session 1. Error bars show standard error of differences across trials. Abbreviations: NUD: non-updating; UD: updating; S: subject.

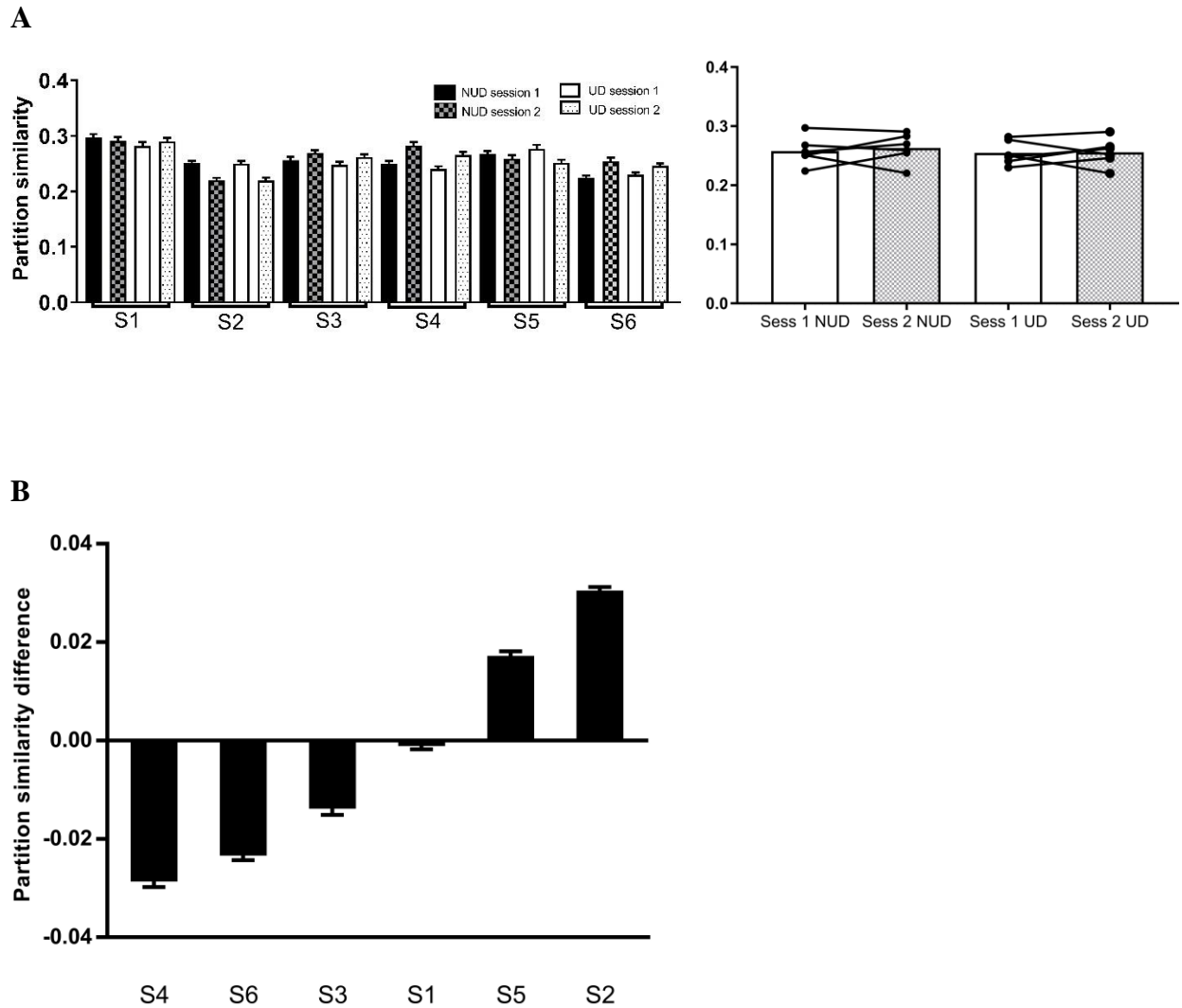


Fig 14. Rest-task partition similarity changes between session 1 and session 2 at the module level for each subject. Negative values indicate more dissimilarity to resting compared to session 1, positive values indicate more similarity to resting compared to session 1. Error bars show standard error of differences across trials. **(A)** Frontoparietal module. **(B)** Default mode module. **(C)** Visual module. **(D)** Somatomotor module. Abbreviation: S: subject.

