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Abstract

Although brain plasticity is greatest in the first few years of life, the brain continues to be shaped by experience throughout adulthood. Advances in fMRI have enabled us to examine the plasticity of large-scale networks using blood oxygen level-dependent (BOLD) correlations measured at rest. Resting-state functional connectivity analysis makes it possible to measure task-independent changes in brain function and therefore could provide unique insights into experience-dependent brain plasticity in humans. Here, we evaluate the hypothesis that resting-state functional connectivity reflects the repeated history of co-activation between brain regions. To this end, we review resting-state fMRI studies in the sensory, motor, and cognitive learning literature. This body of research provides evidence that the brain's resting-state functional architecture displays dynamic properties in young adulthood.

Keywords

brain plasticity, experience, resting-state fMRI, functional connectivity, training, practice, cognitive, sensory, motor, adult

Although the brain undergoes remarkable changes during early childhood, it retains the capacity to adapt to experience throughout life. Several decades ago, the late William T. Greenough proposed that brain plasticity is induced both by expected experiences shared among members of a species, or experience-expectant plasticity, and experiences that are specific to individuals, or experience-dependent plasticity (Greenough and others 1987). Although these mechanisms likely fall along a continuum (Galván 2010), the concept of experience-dependent brain plasticity provides the impetus for studying the brain changes that occur in adulthood as a result of the repeated engagement of specific neural systems through practice or training.

In the 65 years since Hebb (1949) first proposed the idea that patterns of coincident neuronal firing lead to structural changes that strengthen a synapse, research in laboratory animals has led to remarkable progress in our understanding of brain plasticity at the cellular and systems levels (Blundon and Zakharenko 2013; Hensch 2005; Lisman and others 2002). More recently, advances in structural MRI and fMRI data analysis have enabled us to measure experience-dependent brain plasticity in humans at the level of large-scale brain networks. In particular, Raichle and others' (2001) discovery of temporally correlated, low-frequency spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals across brain regions, known as resting-state functional

connectivity (rs-FC), provides an excellent opportunity to study brain plasticity in humans. Indeed, it has been hypothesized that these temporal correlations reflect the prior history of co-activation between brain regions (Buckner and Vincent 2007; Dosenbach and others 2007; Miall and Robertson 2006). In this review, we evaluate the strength of the evidence for this claim.

Resting-state BOLD correlations are observed when subjects are instructed to relax inside the MRI scanner without engaging in a specific task. Temporal correlations do not appear to be random because patterns of connectivity have been reliably identified across studies and subjects (Damoiseaux 2006; Smith and others 2009). Further, patterns of correlation at rest follow along anatomic networks within primary sensory and motor cortices, as is the case of the somatomotor network (SMN) and visual network (Fig. 1). Resting-state networks (RSNs) within association cortices include the dorsal

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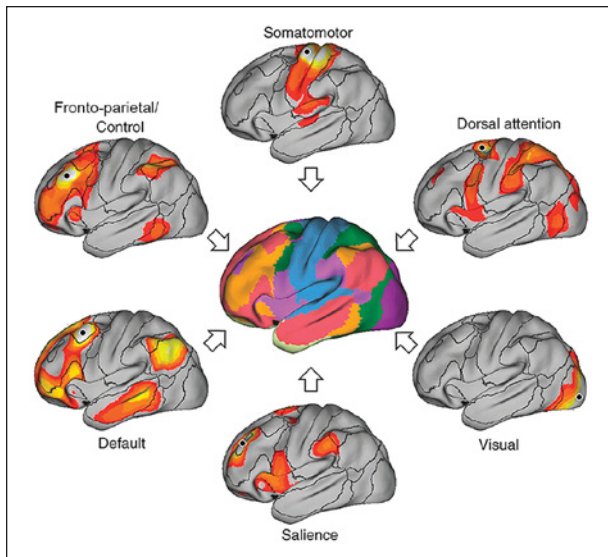


Figure 1. Resting-state functional connectivity maps illustrate the organization of the human cortex into major large-scale networks. The outer maps show, in red-yellow color scale, the regions that are functionally connected to the seed regions (dark circle). The visual and somatomotor networks show predominantly local connectivity. The default network, frontoparietal/control network, and salience network present more distributed connectivity and lack strong coupling to sensory and motor areas. The map in the center displays a composite of the surrounding networks. We review findings from the motor, sensory, and cognitive learning literature showing changes in the connectivity strength of these networks or between two independent regions. Adapted with permission from Buckner and others (2013).

attention, control/frontoparietal, salience, auditory, and default mode networks (DMNs) (Buckner and others 2013). The RSNs include but are not limited to areas that are monosynaptically connected. For example, the right prefrontal cortex (PFC) and left parietal cortex show tightly correlated time courses at rest, but these regions are separated by at least two synapses.

The strength of correlations within and between networks has behavioral relevance. For example, visual connectivity is related to perceptual discrimination ability (Baldassarre and others 2012), and frontoparietal connectivity is related to fluid intelligence and working memory (Cole and others 2012). These findings support the hypothesis that training-related changes in rs-FC support performance improvements; they are not only an epiphenomenon of repeated co-activation. The association to behavior also speaks to the relevance of examining changes in rs-FC in the context of plasticity and learning.

This review begins with methodological considerations and then presents evidence supporting that rs-FC reflects experience-dependent plasticity by summarizing

findings from resting-state fMRI studies involving healthy young adults. It will also present studies that have used neuroscientific methods to induce plasticity, such as transcranial direct current stimulation (tDCS). This review will not cover the effect of medication on resting-state BOLD correlations nor review findings from developmental samples or clinical populations (for a recent review covering studies on brain injury, see Gillebert and Mantini [2013]).

Methodological Considerations

To evaluate the evidence in support of dynamic changes in rs-FC, we will first briefly address important methodological considerations that could bias the signal and interpretation of rs-FC. We will also consider physiological factors that impact connectivity patterns measured at rest.

Experimental Design

The instruction that a participant receives prior to scanning could influence resting-state connectivity patterns. For example, Benjamin and others (2010) compared connectivity in the DMN after subjects received instructions to attend to the scanner background noise, not to attend to that noise, or simply relax and remain still. When subjects were asked to attend or ignore the noise compared with asked to relax, there was greater activation in the dorso-medial PFC. The studies included in this review have taken precautions with respect to the instructions provided to participants. In some studies, however, participants received instructions to either keep their eyes open, closed, or fixated on a simple visual stimulus (e.g., a crosshair). Even though these factors modulate the strength of the connectivity of RSNs (Patriat and others 2013), researchers minimized these confounders by giving participants the same instructions in the baseline and posttraining scanning sessions.

In addition to the instructions that a participant receives for the resting-state fMRI scan itself, activities performed immediately preceding the resting scan could also impact the rs-FC signal. For instance, slow fluctuations occurring during cognitively demanding tasks have been found to have a greater delayed recovery period, indicating that traces of BOLD response to the cognitively demanding tasks do not subside, even after task completion (Barnes and others 2009). Tung and others (2013) showed that even a task as simple as pressing a button for a fixed duration could significantly affect rs-FC correlations and fluctuations between regions and that these changes return to baseline only after several minutes. The slow recovery period from a task could impact BOLD correlations observed during resting scans that are acquired directly after the task. Although the

influence of prior cognitive tasks could bias rs-FC, there are pragmatic reasons that an experimenter would choose to acquire resting scans at the end of an experimental session or in addition to other tasks, such as the considerable cost for running a longitudinal imaging study. Of the studies included in this review, researchers conducting rs-FC at the end of the sessions minimized potential confounding effects by keeping the sequence of the tasks fixed across participants and experimental conditions (Mackey and others 2013; Powers and others 2012; Uner and others 2013). Nonetheless, we encourage researchers to attempt to control as much as possible the level of cognitive demand required by participants before or during the scanning session.

Scan duration could also influence the reliability of rs-FC. Birn and others (2013) investigated rs-FC in time series lengths varying from 3 to 27 minutes in 3-minute increments. The length of the scan significantly increased the consistency of rs-FC measured within a session, as measured by an increase of the intraclass correlation coefficient; this increase slowed down after 9 minutes and plateaued at 13 minutes. However, Van Dijk and others (2010) acquired scans varying in length between 2 to 12 minutes and found that approximately 5 minutes of data were sufficient to obtain moderate to high reliability.

Data Analysis

In addition to design confounders, data processing steps could also influence the strength or directionality of the correlations between regions. For example, the use of global signal removal has been subject to debate because this preprocessing step could bias the rs-FC signal by introducing anticorrelations. These negative correlations arise due to the mathematical properties of global signal regression, which leads to a negative mean correlation value in seeded connectivity analyses (Murphy and others 2009). Some researchers argue that global signal regression is a useful step because it removes high correlations driven by physiological noise. These researchers have opted to perform separate correlation analyses using only positive, only negative, and only absolute values (Cole and others 2012). Others have proposed that anatomically and temporally constrained methods of physiological noise reduction make it possible to observe real, not artifactual, anticorrelations between networks (Chai and others 2014). These anticorrelations are believed to reflect behaviorally relevant network segregation (Behzadi and others 2008).

Physiological Confounders

In addition to factors related to experimental design and data analysis, the physiological state of the participants

can also influence the connectivity patterns observed (Duncan and Northoff 2013). Stress and sleep patterns in the days leading up to the resting-state scan could affect the architecture of the RSNs and the strength of rs-FC. Such effects have not been widely reported, but these factors are of prime concern given their well-documented influence in plasticity (McEwen and Morrison 2013; Walker and Stickgold 2006). In a recent study (Vaisvaser and others 2013), a nonclinical sample of young males were subjected to the Trier Social Stress Test, and rs-FC changes were analyzed from a scan acquired before the stressor, one scan recorded shortly after the stress induction, and one acquired after a 90-minute intermission. Although most transient changes in rs-FC were not significantly different from baseline by the third scan, the strength of the correlation between the posterior cingulate cortex and hippocampal regions of interest (ROIs) remained significantly stronger. The change in rs-FC between these regions was also correlated with changes in the subjective perception of stress.

The effects of stress have also been observed over more prolonged periods of exposure to stressors. For example, Soares and others (2013) measured the effects of stress on DMN functional connectivity in medical interns over a three-month preparation period for the residency examination. Compared with the changes observed in medical interns who were not preparing for the examination, the stressed group showed stronger connectivity within RSNs, such as the SMN and DMN. These participants also showed increased cortisol response and self-reported feelings of stress after this period of preparation. In this study, the effects of studying for the examination remain elusive because they were not reported or correlated with the functional data. Although the effects of chronic and acute stress produce different physiological effects, it would be of interest to use a similar analytic approach to compare the results of Soares and others (2013) and Vaisvaser and others (2013) and to gain a better understanding of the different effects of acute and chronic stress on rs-FC.

Partial sleep deprivation has also been reported to affect the properties of rs-FC. Following a night of no sleep, young adults with otherwise normal sleep routines showed decreased coupling within the DMN compared with controls whose sleep was undisturbed (De Havas and others 2012). Similar results were observed in a study that measured functional connectivity from resting periods of a memory task in participants who experienced a night of sleep deprivation (Gujar and others 2010). The connectivity patterns showed significantly less deactivation of the dorsal anterior cingulate cortex (ACC) with the DMN.

Summary

The studies reviewed above indicate that experiment design decisions that could impact the cognitive demand required by subjects, subject-level physiological characteristics, and data analysis steps are important factors to consider in evaluating resting-state fMRI studies of brain plasticity, as they could confound the effects of training at the individual and group levels. At the end of this review, we provide recommendations for future investigations.

Experience-Dependent Changes in rs-FC

We begin by presenting findings from sensory and motor training studies, given their prominence in the study of plasticity. We will then review findings from the cognitive training literature, which has been traditionally more focused on human studies. In studies from these three domains, we expect to see changes in rs-FC between regions and within networks that are implicated in the trained domain. A summary of the results from the studies covered in this section is presented in Table 1.

Plasticity in the Sensory Domain

Sensory plasticity can take place relatively fast, and rs-FC could be a valuable index of the functional changes taking place between regions that support sensory processing. This idea is supported by research conducted by Powers and others (2012), who trained participants in multisensory temporal integration by providing accuracy feedback to the participant's judgment of whether an auditory stimulus was played synchronously with a visual stimulus that was displayed 150 milliseconds before or after the onset of the sound in 50-millisecond intervals. Performance on this task improved significantly after one training session, and the resting-state fMRI scans revealed increased coupling between the posterior superior temporal sulcus, secondary auditory cortex, superior colliculus, and superior cerebellum, among other regions (Fig. 2). These areas support the audiovisual perception and integration capacity as well as the timing of the integration.

Sensory plasticity has also been observed during motion perception task training. In this study, Uner and others (2013) investigated the lasting effects of visual learning by acquiring resting scans immediately after the training session and 24 hours later and used stochastic dynamic causal modeling to test for changes in connectivity at these two time points. The day after training, the best-fitting model showed a lasting increase in bidirectional connectivity between the hippocampus and striatum, which was interpreted as an index of consolidation. These findings suggest that even after a training

period is over, changes in rs-FC can be observed. It is unknown whether these functional connections remain present for longer periods after learning.

The plasticity of other sensory modalities, mainly somatosensory input, has been examined through the use of acupuncture (Dhond and others 2008) and electrical nerve stimulation (Klingner and others 2013). These studies have shown changes in rs-FC after a single session, either in canonical RSNs or the connectivity between regions of the secondary somatosensory cortex, thalamus, and association areas.

These studies provide evidence that repeated training can induce plasticity in the specific networks and brain regions involved in sensory processing. The regions that exhibited change in rs-FC were consistent with the sensory experience manipulated in the training paradigm. Interestingly, these changes could be observed even after a single training session, which may suggest rapid plasticity of the regions supporting sensory processing; however, it would be important to examine whether the changes resulting from repeated experience are sustained for longer periods of time or are only transient adaptations that result from the short length of training. A distinction between these two effects was tested by Uner and others (2013) but only after a 24-hour delay.

Plasticity in the Motor Domain

The use of rs-FC has provided opportunities to study the effects of motor learning in areas that are not classically defined as motor regions (i.e., support limb movement) but contribute to developing a complex motor skill. For example, changes in coupling between motor regions and visual areas were observed after participants learned to reach for a target, guiding their movements with indirect visual feedback and readjusting against resistance (Vahdat and others 2011). Vahdat and colleagues (2011) were able to dissociate rs-FC changes related to training that were mutual or exclusive to perceptual and motor learning. As shown in Figure 3, the changes in rs-FC between the primary motor cortex and cerebellum were exclusive to the motor index of learning. These findings illustrate the benefit of using rs-FC measures to dissociate changes that occur in different systems that are not contingent on a specific task.

In addition, rs-FC can also reflect the progression of the neuroplastic changes that occur throughout a training program. Ma and others (2012), for example, trained participants to repeat a finger tapping sequence with their nondominant hand. The strength of rs-FC between the right primary somatosensory cortex and right supramarginal gyrus increased after two weeks of training and decreased from the second to the fourth week. Interestingly, behavioral learning was only observed

Table 1. Summary of Results from Studies Reporting Plasticity of Resting-State Connectivity after Motor, Sensory, and Cognitive Training.

Domain	Study	Training	Duration	Control Group	N	Analysis	Connectivity Changes		
							Increases	Decreases	No Change
Sensory	Dhond and others 2008	Acupuncture	1 day; 150 seconds	N	15	ICA	Multiple DMN and SMN		
	Klingner and others 2013	Electrical nerve stimulation	1 day; 16 minutes	N	12	SCA	Somatosensory cortices (many: motor, visual)	Somatosensory cortices-thalamus	
	Powers and others 2012	Audiovisual simultaneity	1 day; 1 hour	N	11	SCA	Posterior superior temporal sulcus-auditory cortices		
	Urner and others 2013	Motion judgment	1 day; 90 minutes	N	11	ROIs	Hippocampal-striatal		
Motor	Ventura-Campos and others 2013	Phoneme discrimination	2 weeks; 6 hours	N	19	SCA; ICA	Insula-salience network	Insula-FPN	Multiple FPN; temporal seed
	Albert and others 2009	Visuomotor adaptation	1 day; 11 minutes	A	24	ICA	FPN; cerebellar component		
	Sami and Miall 2013	Visuomotor adaptation; pressing sequence	1 day; 1.5 hours	A	24	GTA	Strength (global, visual, frontal); degree (global, frontal, cerebellum)	Path length (global, frontal, cerebellum, basal); centrality (frontal, parietal)	Global efficiency and small worldness; local modularity
	Ma and others 2012	Tapping sequence	4 weeks; 7 hours	A	10	ICA	R parietal clusters	R parietal clusters	
	Taubert and others 2011	Balancing	6 weeks; 4.5 hours	NC	28	SCA; GTA	Multiple SMN; centrality of motor cortices		
	Vahdat and others 2011	Field-force reach	2 days; 2 hours	N	13	ROIs	Multiple SMN	Cerebellar frontomotor; cerebellar-parietal	DMN
	Yoo and others 2013	Tool manipulation	1 month; 30 hours	N	8	ROIs; ICA		SMN; intraparietal; parietal-cerebellar	DMN
	Cognitive Mackey and others 2013	Reasoning	3 months; 100 hours	NC	48	ROIs	Multiple FPN; parietal-striatal		
	Takeuchi and others 2013b	Working memory	27 days; 9-27 hours	NC; A	81	SCA		Medial PFC-precuneus	
	Takeuchi and others 2013a	Multitasking	27 days; 9-27 hours	NC; A	81	SCA		R dorsolateral PFC-ventral ACC	
Xue and others 2011	Integrative body-mind	1 month; 15 hours	A	32	GTA	Nodal efficiency and degree value in LACC	Nodal efficiency and degree value in frontomotor areas	Nodal efficiency and degree value in R ACC	

A = active; ACC = anterior cingulate cortex; DMN = default mode network; FPN = frontoparietal network; GTA = graph theory; ICA = independent component; L = left; N = none; NC = no contact; PFC = prefrontal cortex; R = right; ROIs = correlations of regions of interest; SCA = seed correlations; SMN = somatomotor network. Brain regions are organized into resting-state networks when possible. All connectivity increases and decreases are statistically significant at least at $P < 0.05$.

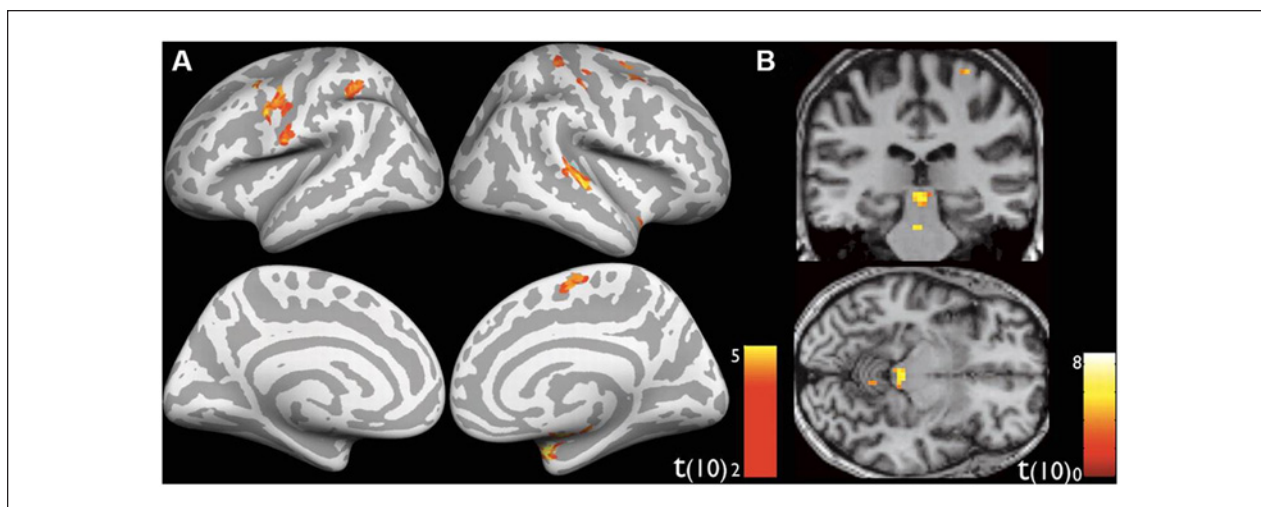


Figure 2. Data from the study of Powers and others (2012) in Table I. Resting-state functional connectivity changes after audiovisual integration training. (A) The functional map illustrates the cortical areas with a greater connectivity increase with the posterior superior temporal sulcus (pSTS). (B) This map shows a connectivity increase between the pSTS and superior colliculus. These regions support sensory integration, and the connectivity increases illustrate that changes observed at rest are seen in regions that support the trained function. Adapted with permission from Powers and others (2012).

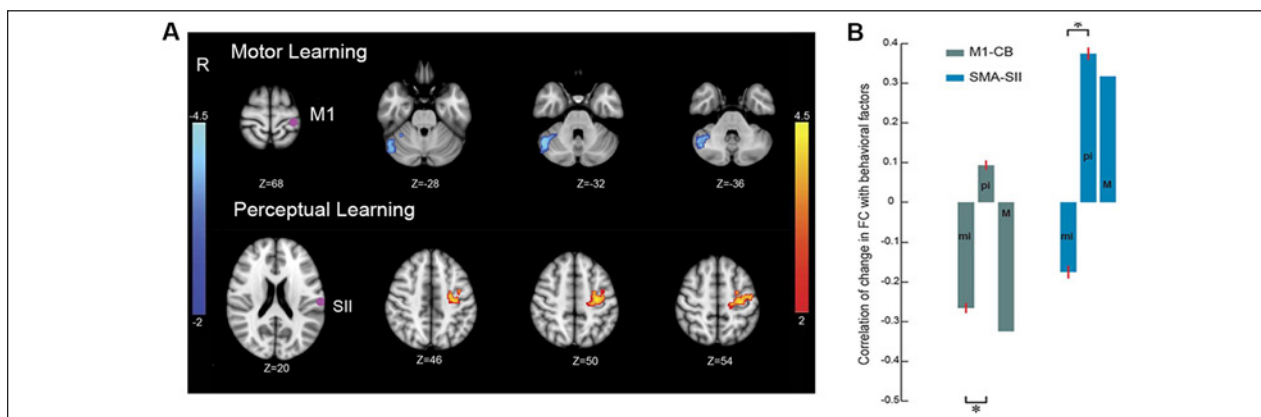


Figure 3. Data from the study of Vahdat and others (2011) in Table I. Resting-state functional connectivity changes after motor reaching specific to perceptual and motor improvements. (A) Each row represents changes in connectivity in relation to motor and perceptual learning. The left column shows the location of the seed regions of interest; other columns show clusters with significant changes in connectivity with the seed. Z-score maps show an increase in positive correlations (shown in red-yellow) and negative correlations (shown in dark-light blue) from training day (day 1) to postlearning testing (day 2) with respect to learning. (B) Mean correlations between individual changes in functional connectivity are shown in the bar graph, from left to right, for sensory (pi), motor (mi), and mutual (M) indices of learning, respectively. Green bars indicate connectivity between the primary motor cortex (M1) and cerebellum (CB). Blue bars illustrate connectivity between the supplementary motor area (SMA) and secondary somatosensory cortex (SII). Adapted with permission from Vahdat and others (2011).

after the second week and was stabilized by the fourth week. A similar decrease in connectivity was reported in a separate study in which participants learned to manipulate a tool with their nondominant hand (Yoo and others 2013). After eight weeks of practice, the correlations decreased within the sensory motor network components, specifically between the left primary motor cortex, supplementary motor area, and primary sensory

cortex. Similarly, there was a decrease in rs-FC between regions that were initially correlated with manipulation of the tool, such as between the right supramarginal gyrus and right premotor cortex. The authors suggested that this change in correlation reflects an enhanced efficiency in the functional network supporting motor control. However, the change in directionality of rs-FC is not always consistent across motor learning paradigms.

For example, rs-FC from training involving learning to balance an unstable structure showed increased coupling between the bilateral supplementary/presupplementary motor areas and right ventral premotor cortex from baseline to the third week of training (Taubert and others 2011).

Moreover, rs-FC from motor training studies indicates that the changes associated with the development of a motor skill are not limited to the regions that support the movement initiation but rather share intrinsic correlations with regions implicated in the perceptual components of the task. It is important to note that in these studies, the networks that exhibited changes were those expected to be engaged when performing the motor skill (Vahdat and others 2011).

Plasticity in the Cognitive Domain

Behavioral and neuroimaging research examining the plasticity of higher cognition has aimed to develop and implement training regimes that could ameliorate or improve performance in a particular cognitive process, such as attention (Bavelier and others 2012; Neville and others 2013), reasoning (Bergman Nutley and others 2011; Mackey and others 2011; Mackey and others 2012; Mackey and others 2013), and working memory (Dahlin and others 2008; Klingberg 2010; Morrison and Chein 2011). As the field has progressed, emphasis has also been placed in understanding the mechanism underlying plasticity of the systems supporting these functions (McNab and others 2009). However, many findings are still subject to debate, such as individual differences determining who would benefit from an intervention showing the transfer of learning to untrained tasks (Klingberg 2010; Melby-Lervåg and Hulme 2013; Morrison and Chein 2011; Shipstead and others 2012). We argue that the analysis of rs-FC data could illuminate answers to these debates if we consider this connectivity as reflecting how networks are reconfigured as a result of repeated practice. The studies presented below demonstrate an important first step supporting the possibility that rs-FC measures could shed light on the effects of cognitive training because they show that repeated engagement of neural circuits supporting higher cognition is reflected in changes in rs-FC.

To investigate changes in rs-FC after repeated experience with reasoning problems, Mackey and others (2013) recruited two groups of age- and intelligence quotient-matched prelaw students in which only one group received preparation for the Law School Admission Test (LSAT). The preparation course consisted of 100 hours of training over a three-month period, wherein two thirds of the curriculum was devoted to solving reasoning problems. After the three months of training, the experimental

group showed an increase in frontoparietal and parietal-striatal rs-FC within and between hemispheres, as shown in Figure 4. Notably, these changes were linked to larger LSAT score improvements. Interestingly, increased connectivity between the ROIs of the striatum and PFC was associated with smaller behavioral improvements, which suggest that differences in the changes in rs-FC could also serve to reflect an individual's success in the training program.

Changes in rs-FC were also observed after four weeks of working memory training (Takeuchi and others 2013b). Participants were asked to perform a series of tasks that required them to maintain, update, or reorder verbal or visuospatial information. The group of participants that received training showed decreased coupling between the medial PFC and precuneus. Changes in the connectivity pattern were not correlated with behavioral performance on the working memory measures or reasoning tasks, which were considered transfer measures. The lack of correlation between rs-FC and behavior may be explained by the low between-subject variability in improvements after training. In a separate study by the same group (Takeuchi and others 2013a), participants were trained to multitask by performing exercises in which they had to simultaneously process and respond to different target stimuli, such as spoken numbers played to the left ear and vowels played to the other. The results showed decreased rs-FC between the dorsolateral PFC and ventral ACC, regions involved in cognitive flexibility, but these changes were not correlated with behavioral improvements in multitasking and related cognitive processes.

In these cognitive training studies, changes in rs-FC were studied in the context of experience-dependent plasticity and were also related to behavioral improvements in the trained domain (although with some mixed success, such as Takeuchi and others [2013a]). Small sample sizes may partially explain the lack of behavioral associations, and further studies should be conducted to further confirm correlations between changes in rs-FC and behavior. The relationship between the distinct patterns of rs-FC and behavioral improvements reported by Mackey and others (2013) indicates the potential of rs-FC as a measure of learning success. It remains to be tested, however, whether BOLD correlations at rest could also be used to predict performance in an untrained cognitive domain and whether these correlations can serve as an index of individual differences in the benefits obtained from training.

Discussion

The studies presented in this review support the hypothesis that the dynamic nature of rs-FC reflects experience-dependent plasticity and illustrate that rs-FC patterns

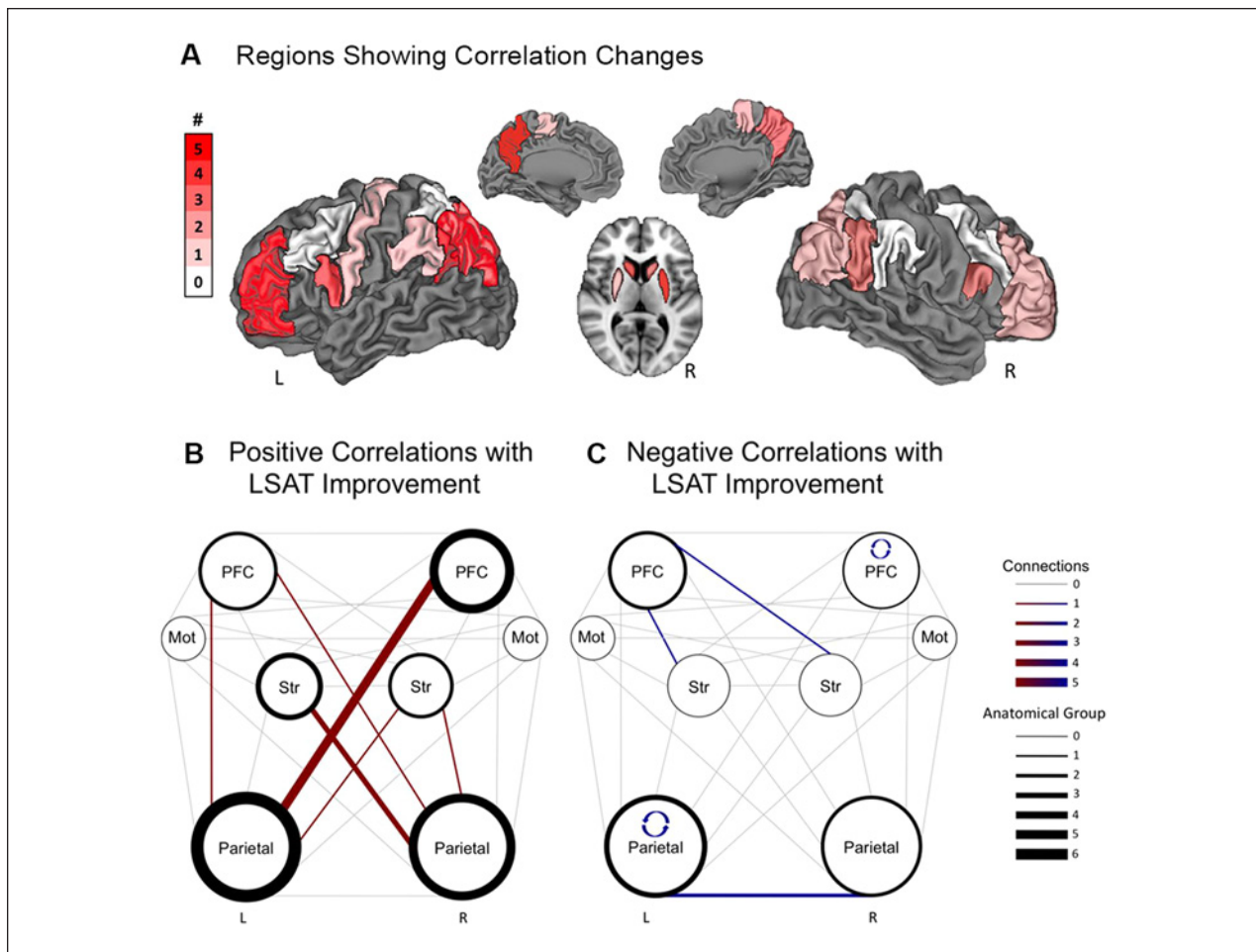


Figure 4. Data from the study of Mackey and others (2013) in Table I. Resting-state functional connectivity changes and correlation with behavioral improvements after preparation for the Law School Admission Test (LSAT), which strongly emphasizes reasoning. (A) Number of increased pairwise correlations for 11 brain regions most often recruited during reasoning performance (Prado and others 2011), including the rostralateral prefrontal cortex and angular gyrus. (B, C) These diagrams indicate the increase in pairwise functional connectivity that was positively (B) and negatively (C) correlated with improvements on the LSAT. The thickness of the lines represents the number of connections for which a significant correlation was observed. For more details, see the original study. Adapted with permission from Mackey and others (2013).

change after repeated experience with sensory, motor, or cognitive tasks. Similar changes in resting-state connectivity have also been reported from cross-sectional studies comparing the effects of expertise, such as with experienced meditators (Taylor and others 2013), trained musicians (Luo and others 2012), and expert athletes (Di and others 2012).

These findings raise questions about the nature of the resting-state architecture and the plasticity of neural systems. One important question is whether the changes observed in training studies in each domain are confined to the specific RSNs associated with training demands. In the motor training literature, changes were confined to regions believed to support motor functions but were not exclusive to the canonical motor regions. Additionally,

changes were observed in other networks that were also involved in the training (e.g., sensory cortices). However, testing for double dissociations of training effects is not widely performed. Vahdat and others (2011) tested the changes in connectivity exclusive to motor or perceptual learning. Furthermore, they tested for the changes observed at rest to be selectively present in the SMN by examining plasticity in networks that were hypothesized to be unrelated to their training task (e.g., DMN). As expected, only the strength of connectivity in the SMN changed as a result of motor practice. Similar results were observed by Yoo and others (2013), who also observed changes specific to the motor network but not the DMN. It would be of interest for future work to test for these double dissociations more regularly, as these tests

provide stronger causal evidence that the changes observed at rest reflect experience-dependent plasticity in specific circuits.

A second empirical question that could be addressed with rs-FC is whether distinct networks have comparable potential for malleability. The complementary use of neuroscientific tools, such as tDCS, with rs-FC will allow these comparisons. The use of this manipulation would help researchers overcome the challenge of developing a training program that would equally target different networks. For example, Polanía and others (2011) found that after 10 minutes of bipolar tDCS with anodal stimulation to the left primary motor cortex and cathode stimulation to the contralateral frontopolar cortex, there was strengthening of intrinsic coupling between motor regions (left premotor cortex, left primary motor cortex, and left parietal cortex), and this change was accompanied by an increase in the efficiency of connectivity between the region that received anodal stimulation and the rest of the brain. Such stimulation techniques could be used not only to compare the malleability potential of different networks but also the timing of these effects.

The studies reviewed from each modality (sensory, motor, and cognitive) indirectly address the belief that the rate of plasticity varies depending on which modality is being trained. This hypothesis can be inferred from the training duration necessary to induce changes in rs-FC. For example, studies examining the plasticity of higher cognition showed changes after nearly 100 hours of training (Mackey and others 2013), whereas those in the sensory domain identified plastic alterations after only 1 hour of training (Powers and others 2012). To test this hypothesis directly, multiple scanning sessions at different intervals would be necessary to capture the changes occurring as a result of training.

An important question to consider is how changes observed in rs-FC are related to changes in behavioral performance. The results from the studies included in this review indicate that changes in rs-FC were strongly correlated with changes in behavior in the trained domain (Mackey and others 2013; Taubert and others 2011). Interestingly, in the studies that acquired more resting-state data during the course of the study, certain patterns of change in rs-FC were detected prior to the actual behavioral improvement (Ma and others 2012; Taubert and others 2011). Thus, rs-FC could reflect the plasticity that can be observed prior to behavioral changes, although a link between behavioral improvements and changes in rs-FC was not observed in all studies (Takeuchi and others 2013a). In addition, correlations observed at rest have also served to predict behavioral gains from training paradigms, similar to how structural and task-based functional measures have been used in the past (Zatorre 2013). For

example, prior to training, Ventura-Campos and others (2013) were able to predict which participants would exhibit greater learning success after training that required the identification of nonnative phonemes. The participants exhibiting greater learning showed stronger rs-FC between language-specific regions at baseline compared to poorer learners. The correlations of rs-FC could serve as an additional indicator of future behavioral gains and elucidate individual differences observed in training studies.

As mentioned in the cognitive plasticity section, rs-FC could provide valuable insights to test for transfer. One can speculate that widespread changes to a network are more likely to support transfer on untrained tasks than more localized changes. Individual difference analyses could provide insights into the mechanisms that underlie transfer and predict which transfer tasks are likely to show behavioral improvements.

Functional connectivity observed at rest could be used to answer the empirical questions discussed thus far. It is important, however, for future research to also address the mechanisms underlying the changes observed in these intrinsic fluctuations. Computational and animal models are needed to formulate possible cellular underpinnings of the changes observed in rs-FC, similar to the work that has been conducted to understand the cellular basis of structural plasticity in humans (Zatorre and others 2013). These investigations could also facilitate the understanding of what increases or decreases in rs-FC after a period of training specifically indicate.

In addition to elucidating the mechanisms underlying the changes in rs-FC, it is recommended that future work follows standards to control for the possible confounding variables discussed previously. Importantly, given the documented effects of sleep and stress in plasticity and rs-FC (De Havas and others 2012; Soares and others 2013; Vaisvaser and others 2013), these physiological variables should be reported more consistently in the literature to control for potential individual and group differences. Although measuring physiological states is cost intensive when these variables are considered of no interest, it would be valuable to at least collect self-reported measures. It would also be beneficial to monitor and report as much as possible other methodological considerations that could confound within- and between-subject comparisons, such as motion during scanning and cognitive demands prior to the scanning session. Considering these factors could facilitate comparisons between studies, although when comparing data obtained from different training paradigms, the analysis approach would also need to be equated. These comparisons could help advance the understanding of the efficacy of different training programs and rs-FC plasticity.

The findings reviewed here support the concept that resting-state fMRI serves as an effective measure of

plasticity; resting-state fMRI appears to reflect a record of repeated synchronized activation between regions, as seen from correlation changes occurring in regions closely related to the trained task. The standardization of methodological approaches and better knowledge of the cellular underpinning of the changes observed in rs-FC may allow comparisons between studies and facilitate better understanding of the impact of training on connectivity observed at rest and provide greater insights into experience-dependent plasticity.

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