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Strengthening connections: functional connectivity and brain plasticity

Clare Kelly[1] and **F. Xavier Castellanos**[1,2]

[1]Center for Neurodevelopmental Disorders, New York University Child Study Center, New York, NY

[2]Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY

Abstract

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

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

What is intrinsic functional connectivity?

In 1995, in a paper entitled “Functional connectivity in the motor cortex of resting human brain using echo-planar MRI,” Biswal and colleagues provided the first description of a phenomenon now known as “resting state” or intrinsic functional connectivity (iFC) (Biswal et al., 1995). In that paper, Biswal et al. documented low frequency (<0.1Hz) fluctuations in the resting state functional MRI (R-fMRI) blood-oxygen-level dependent (BOLD) signal (i.e., functional imaging, but with no explicit task) that were correlated across primary and supplementary motor cortex, mapping out a network that overlapped substantially with that activated by the performance of a finger-tapping task. The authors concluded that these hitherto ignored low frequency BOLD fluctuations provided an index of neurophysiological activity that was coordinated among functionally related regions, thus providing a task-independent counterpart to Friston’s (1993) description of task-related functional connectivity. Although Biswal et al. were by no means the first to note that the brain exhibits spontaneous activity, in contrast to activity evoked by a particular stimulus or task (for a review, see Raichle, 2011), they were the first to demonstrate that such activity, recorded using BOLD fMRI, could be used to infer the brain’s organization into large-scale functional networks.

Although first met with skepticism (Mitra et al., 1997, Turner et al., 1998), the field gained momentum following the publication of several seminal papers demonstrating that iFC mapping could be extended *beyond* primary sensory and motor systems to circuits supporting higher order cognitive and social function (Greicius et al., 2003, Beckmann et al., 2005, Fox et al., 2005, Fransson, 2005). A decade later, R-fMRI has become established as a mainstream approach to mapping brain functional circuitry in health and disease, across the lifespan (He et al., 2007a, Greicius, 2008, Uddin et al.,2010, Zhang and Raichle, 2010, Kelly et al., 2012, Whitfield-Gabrieli and Ford, 2012, Ferreira and Busatto, 2013). We now know that the brain expends a considerable proportion of its energy budget consistently maintaining organized systems of synchronized spontaneous fluctuations (Raichle and Mintun, 2006, Raichle, 2010), that this intrinsic functional architecture provides the functional scaffold upon which evoked functional responses are built (Fox et al., 2006, Fox et al., 2007, Mennes et al., 2013), that these functional relationships are maintained across a variety of states including rest, task performance, sleep, and sedation, and that this phenomenon is not unique to humans, but is observed across species (Vincent et al., 2007, Greicius et al., 2008, Horovitz et al., 2008, Kelly et al., 2008). Importantly, while the spontaneous activity underlying iFC is modulated by factors such as the content of resting cognitions (Shirer et al., 2012), mood (Harrison et al., 2008), drowsiness (Samann et al., 2011) and whether a participant’s eyes are open or closed (Yan et al., 2009), intrinsic activity is a distinct phenomenon with a neurophysiological basis unrelated to any specific cognitive process or brain system (Buckner, 2011). What remains unclear is the return the brain receives on this substantial investment – why is so much energy dedicated to maintaining iFC?

A clue is provided by the correspondence between the brain’s intrinsic and extrinsic (i.e., task-evoked) architectures. Although there is regional variation in the degree of correspondence (Mennes et al., 2013; see Figure 1), in general, patterns of iFC recapitulate

patterns of task-evoked coactivation (Smith et al., 2009). This correspondence suggests that correlated intrinsic activity serves to maintain the integrity of neuronal networks supporting cognition and action, even in the absence of processing demands. Patterns of iFC are understood to constitute a trace of task-evoked coactivation among regions within an individual. By consequence, the complete set of iFC networks (termed intrinsic connectivity networks, ICNs) within an individual, termed the *functional connectome*, can be seen to comprise both universal and unique aspects (Biswal et al., 2010). The human brain comprises a set of phylogenetically determined functional networks that, in the absence of gross developmental aberration, emerge in all individuals (Buckner and Krienen, 2013). These functional networks constitute the universal aspects of the functional connectome, and are evident in observations of precursory ICNs in infants and young children (Gao et al., 2009, Dinstein et al., 2011, Fransson et al., 2011), of homologous ICNs in other species (Vincent et al., 2007, Margulies et al., 2009, Hutchison et al., 2012, Lu et al., 2012), in the reproducibility of ICNs across hundreds of studies and samples (e.g., Biswal et al., 2010), and in the moderate-to-high test-retest reliability of ICNs over both short and long intervals (Shehzad et al., 2009, Thomason et al., 2011). The unique aspects of the functional connectome, on the other hand, appear to reflect the individual history of interaction each person has with the world, which sculpts patterns of evoked coactivation and thus fine-tunes the intrinsic brain architecture (Harmelech and Malach, 2013). This aspect is captured by studies linking differences in iFC to genetic variation (Glahn et al., 2010, Liu et al., 2010, Wiggins et al., 2012, Tunbridge et al., 2013), environmental influences (e.g., early life stress; Burghy et al., 2012, Herringa et al., 2013), and interindividual differences in a variety of phenotypic characteristics including task performance, social competence, and personality (e.g., Hampson et al., 2006, Di Martino et al., 2009, Tambini et al., 2010, Adelstein et al., 2011). Together, these traces or echoes of previous patterns of coactivation provide a predictive neural context, a preparatory state that anticipates future patterns of evoked coactivation (Fox and Raichle, 2007, Deco and Corbetta, 2011, Raichle, 2011, Engel et al., 2013). That is, spontaneous fluctuations within ICNs capitalize on the individual's history of interactions with the world to optimize the brain's readiness to respond to similar inputs in the future. In this context, it is worth noting that while the gross topography of ICNs is relatively stable, functional interactions among regions (i.e., the strength of specific connections) exhibit a significant degree of temporal variability that is not captured when standard average correlation approaches are adopted (Allen et al., 2012, Smith et al., 2012). Engel et al. propose that this variability enhances the power of synchronized spontaneous fluctuations to prepare functional networks for participation in upcoming tasks (Engel et al., 2013).

It is this dependence on experience that makes R-fMRI and iFC mapping of particular interest to neuropsychology. First, by examining changes in iFC that occur in response to insult or injury, we hope to better understand the pattern of phenotypic deficits observed, as well as the brain's attempts to compensate for the injury (Carter et al., 2012, Gillebert and Mantini, 2013). Second, since iFC is largely experience-dependent, it should be possible to alter iFC as a result of practice and training. By understanding the effects of experience-dependent change at the macro level of large-scale functional networks, we may be able to better devise training and remediation interventions to best facilitate recovery of function.

Further, iFC measures may serve to index the efficacy of treatment interventions. With these long-term goals in mind, we will review studies dealing with this second aspect of iFC plasticity – plasticity occurring as a result of practice and training. We note the pleomorphic nature of the concept of plasticity within the functional connectome, and acknowledge several important areas of research which extend beyond the scope of the current review – for example, developmental plasticity (Power et al., 2010, Uddin et al., 2010), changes in iFC occurring as a result of pharmacological manipulations (Kelly et al., 2009, Cole et al., 2013) and plasticity induced by neural stimulation techniques (e.g., transcranial magnetic stimulation – TMS; transcranial direct current stimulation – tDCS) (Fox et al., 2012a). Further, we focus our review on the effects of *direct* manipulations (i.e., training, practice), rather than the correlates of expertise, and we restrict our focus to review studies that examined practice and training-related change in iFC during *resting state* (identified using seed-based or independent components analysis (ICA), for example). Thus, in this limited overview, we will not consider alternative measures of intrinsic brain function or changes in task-based functional connectivity.

Structure-function relationships and the brain's response to injury

Intrinsic functional connectivity constitutes an index of the *functional connectome* – the complete set of functional interactions among brain areas, within an individual. Structural connectivity (either monosynaptic or polysynaptic; direct or indirect) is a prerequisite for functional connectivity. However, the functional and structural connectomes are not equivalent – they do not exhibit a 1:1 relationship – and iFC cannot be considered merely a physiological index of anatomical connectivity. For example, strong interhemispheric iFC is observed between regions known to lack direct (monosynaptic) interhemispheric axonal connections (e.g., primary visual cortex; basal ganglia). At the macro scale, structural connectivity is typically measured in terms of indices of white matter ultrastructure using diffusion weighted imaging (DWI). Although studies have revealed positive associations between DWI indices (e.g., fractional anisotropy; connection density) and iFC indices, those relationships are remarkably variable (ranging from as low as $r^2 = 0.04$, to as high as $r^2 = 0.62$) (Hagmann et al., 2008, Honey et al., 2009, Hagmann et al., 2010), and have been shown to be subject to change over time, for example, in association with development (Hagmann et al., 2010).

A recent experimental study in macaques illustrates how functional and structural connectivity can appear uncoupled. O'Reilly et al. (2013) collected R-fMRI data from 3 macaque monkeys before and 8 months after commissurotomy. In two monkeys, they removed all commissural (i.e., interhemispheric) connections, while in a third, they spared the anterior commissure. The monkeys who received a complete section exhibited a significant (but not complete) loss of interhemispheric iFC. In these two monkeys, intrahemispheric iFC increased, though its overall organization was maintained. Surprisingly, in the third monkey, interhemispheric connectivity throughout the brain remained within the normal range, despite depending on a highly reduced number of direct interhemispheric structural connections (those via the anterior commissure). O'Reilly et al. conclude that while their data support the conclusion that corticocortical white matter projections are a causal basis for iFC, they also emphasize the role of network-level rather

than direct, pairwise connections in the maintenance of iFC (e.g., temporally coordinated interactions between C and A, and between C and B can account for measured iFC between A and B, as shown by Adachi et al., 2012). One reasonable hypothesis is that subcortical areas (e.g., thalamus) play a role in the orchestration of network-level interactions across the brain, particularly when interhemispheric connections are either absent or impaired (Uddin et al., 2008).

While this apparent dissociation might at first seem unhelpful in the task of understanding the consequences of brain injury, it may be informative with regard to the mechanisms underlying the sequelae of brain insult, whether positive (functional recovery) or negative (loss of function). For example, as O'Reilly et al., point out, their findings offer an explanation for why apparently paradoxical increases in iFC are often seen in conditions characterized by impaired structural connectivity. Further, the uncoupling of iFC from direct anatomical connectivity and maintenance of normal patterns of iFC in the absence of direct anatomical connections suggests that there is considerable redundancy in the functional connectome. A potential function of iFC may therefore be to provide resilience to focal brain injury or disruption. Under typical conditions, ICNs represent "preferential channels through which neuronal populations in different areas can communicate" (Lewis et al., 2009), but if an underlying primary structure is damaged or fails, alternative routes for maintaining affected functional interactions can be used. This hypothesis may also explain some of the more confusing observations in the iFC literature, including lack of deficits in iFC despite known structural deficits, and dearth of differences between clinical groups. Together, these observations underscore the plasticity of iFC and the potential utility of iFC analyses to reveal the functional, network-level implications of brain insult and injury, which may not be captured by structural imaging methods.

The growing literature of studies examining iFC following brain injury (e.g., as a result of stroke) has been authoritatively reviewed elsewhere (Grefkes and Fink, 2011, Carter et al., 2012, Gillebert and Mantini, 2013). R-fMRI approaches are proving particularly advantageous in this neuropsychological setting, since the absence of task demands renders the approach suitable for patients who are severely cognitively or behaviorally impaired by their injury. Briefly, studies have demonstrated that changes in iFC following injury (e.g., stroke) predominantly occur within networks functionally connected to the injured site, although decrements in other circuits are also observed. Most promising with respect to the potential of iFC to serve as a metric of clinical severity, as well as a measure of functional recovery, several papers have shown that decrements in iFC are correlated with severity of behavioral deficits, and that behavioral recovery is associated with restitution of iFC (e.g., He et al., 2007b, Carter et al., 2010). One notable advantage of iFC over conventional task-based MRI in this context stems from the ability to map out multiple functional networks using data collected in a single R-fMRI scan, which permits clinicians to identify both direct (in the affected network) and indirect (in networks not containing the lesioned area) effects of focal brain insult or dysfunction. In contrast, with conventional task-based MRI, researchers are limited by the requirement to select the appropriate behavioral assay. In a recent study illustrating this benefit, Ovadia-Caro et al. (2013) sought to evaluate whether iFC within networks that included the injured area following stroke were more affected and for longer durations than iFC in networks that did not include the injured area. R-fMRI data

were collected from 31 stroke patients with heterogeneous lesions. Using an eight-ICN template (Beckmann et al., 2005), Ovadia-Caro et al. then classified networks according to whether they contained or did not contain the injured region, and used spatial concordance (Lohmann et al., 2012) to quantify change over time for each network. As expected, spatial concordance was lower in affected than unaffected networks, reflecting greater change in iFC over time in affected networks. Further, a measure of the average difference in concordance between affected and unaffected networks was positively correlated with change over time in the National Institute of Health Stroke Scale. Although this method does not provide information about the direction of change in either iFC or behavior over time (it could be positive or negative), these data demonstrate that changes in iFC post-injury are linked with behavior. This raises the question of how might the robustness of iFC be harnessed to best facilitate recovery from injury? To attempt to answer this question, we must first understand the effects of direct manipulations of iFC plasticity.

Effects of practice and training on iFC

To date, few studies have examined the effects of training interventions on iFC in the context of recovery from brain injury. Nonetheless, studies involving healthy control participants can provide initial insights into experience-driven plasticity of iFC. In a 2005 review of the literature on the effects of practice on *task-evoked* functional activity, Kelly and Garavan (2005) proposed an organizing framework to guide understanding and interpretation of findings that may also have relevance for interpreting the effects of practice on iFC. Specifically, the pattern of practice-induced change in task-evoked activation – increase, decrease, redistribution or reorganization - was proposed to depend on several factors. Three primary factors are: (1) The effect of practice on the cognitive processes supporting task performance. A *reorganization* of task-evoked activity suggests a change in cognitive processes (e.g., a shift in task strategy). In contrast, a *redistribution* of task-evoked activity occurs when practice brings about decreased reliance of frontoparietal control and attentional processes and increased involvement of task- or domain-specific processes in task-dependent regions. (2) Task domain. Different representational modes and mechanisms of plasticity in sensory/motor cortex, relative to association cortex, mean that practice has divergent effects on functional activations, typically increasing activation in sensory/motor tasks and decreasing activation in tasks that place demands on higher cognitive function. (3) The time-window of imaging. The point in practice/training at which participants are imaged is a strong determinant of the levels of activation observed. To make strong conclusions regarding the effects of practice in any study, researchers must be sure they have imaged the entire window of practice-related effects, that is, beyond the point where practice-related changes in behavior have leveled off. Several other factors that can influence findings include: the level of previous experience with the task, individual differences in performance, and confounding factors related to changes in behavioral output, task difficulty or load, and task-independent cognition.

As detailed below, the framework used for interpreting the plasticity of task-evoked functional activations is easily adapted to provide a framework for the interpretation of the effects of practice on iFC. For example, consistent with observations from the task literature, training on sensorimotor tasks tends to bring about a *redistribution* of iFC. Early in practice,

increased iFC between task-dependent regions (regions whose activity is necessary to support task performance regardless of practice level) and higher-level cognitive and associative cortex (typically medial and lateral prefrontal, premotor and parietal cortex) is observed. With extended training, as performance asymptotes, connectivity with these scaffolding regions returns to baseline, while persistent changes between nodes of task-specific regions is altered (increased).

Practice on perceptual and motor tasks

Of particular relevance to neuropsychological applications are studies examining the effect of training on networks supporting motor function. In one of the earliest studies to examine training-related plasticity in iFC, Albert et al. (2009) had participants perform a short (11 minutes) task in which they had to adapt their visuomotor movements to an altered cursor-joystick relationship that required progressively increasing compensation. A control group performed a task with a veridical cursor-joystick relationship. Comparing iFC before and after the adaptation task between groups revealed increased iFC within frontoparietal and cerebellar networks in the adaptation group only, demonstrating that short-term motor learning (but not simple motor performance in the absence of learning) modulated iFC in task-relevant networks. The authors suggested that this change in iFC may reflect ongoing offline processing (i.e., consolidation) of information acquired during learning. With regard to our framework, this study captures the very earliest phase of visuomotor learning (i.e., while performance is still changing in response to practice), and thus the earliest phase of redistribution, whereby increases are observed both in frontoparietal areas supporting effortful control and attentional processes and in regions supporting task-specific processes.

A crucial determinant of the pattern of practice effects obtained is the duration of practice/training; Albert et al. examined a brief practice period – only 11 minutes. To best understand their findings, researchers should attempt to capture the full window of practice effects. In some cases, this means having participants practice for extended periods of time (weeks or months). However, practice over these kinds of intervals bears the greatest relevance to rehabilitative situations, where training interventions take place over similarly extended periods. By training participants on a difficult perceptual target detection task for several days, Lewis et al. (2009) were able to capture processes related to both early and late learning. Participants' behavior on the task improved significantly. Comparing R-fMRI data acquired pre- and post-training revealed that after training, negative iFC between the trained portion of visual cortex and regions of the dorsal attention network (DAN), including the frontal eye fields, was strengthened, while negative correlations with the default network were weakened. The former change was also associated with behavioral evidence of learning. The authors interpret the redistribution of iFC observed to reflect the active decoupling of DAN and visual areas that occurs with the development of expertise on and automation of the trained task.

In a study that examined more prolonged training, Taubert et al. (2011) had participants train on a dynamic balance task (keeping an unstable stabilometer platform in a horizontal position for as long as possible) once per week for six weeks. Participants were imaged at baseline and every 2 weeks thereafter for a total of 4 scans along with a control group who

did not practice the balancing task. From the first to second sessions, the trained group exhibited increased "global connectedness" (quantified via eigenvector centrality - EC; Lohmann et al., 2010) in bilateral supplementary motor area (SMA) and preSMA and ventral premotor cortex that was absent in the control group. When seed-based iFC of these nodes was interrogated, increased iFC with parietal and frontal areas was observed. While the EC of ventral premotor cortex returned to baseline by the final fMRI session (7 weeks after initiation of practice), EC of preSMA/SMA remained unchanged and EC of medial parietal cortex increased in relation to performance improvements over time. This pattern of changes suggests that the authors captured the early stage of learning (and scaffolding of motor performance by frontoparietal attention areas) as well as later stages associated with improved, albeit not asymptotic, performance.

Taken together, these studies highlight the tendency to observe "scaffolding connectivity" in frontoparietal areas supporting effortful control and task-dependent motor regions during early learning in healthy participants. We suggest that this pattern may also be observed in rehabilitative training situations, as part of the acute response to insult. That is, attentional and control processes may be recruited during the acute stages of recovery in order to "scaffold" impaired functioning. As recovery proceeds, these compensatory patterns of iFC may diminish as reliance on effortful control processes is relinquished, although such diminishment may be contingent on behavioral recovery. Three further motor learning studies also illustrate this type of functional scaffolding. During 4 weeks of practice on a finger-to-thumb motor sequence (15 minutes per day), Ma et al. (2011) detected non-linear changes in iFC, such that iFC between right postcentral gyrus and right supramarginal gyrus increased between weeks 0 and 2, but decreased from weeks 2 to 4. Further illustrating the role of effortful attention processes, Sami et al. (2013) compared two groups of participants who practiced either an explicit (aware) or implicit (unaware) version of the serial reaction time task (for ~10 minutes each). Those who practiced the explicit learning version of the task exhibited increases in frontoparietal, visual and motor areas for a variety of connectivity metrics. In contrast, in the implicit learning group, increases were restricted to sensorimotor and supplementary motor regions. Finally, Yoo et al. (2013) scanned participants before and after 8 weeks of practicing chopsticks use with their non-dominant hand (they were already expert users with their dominant hand). iFC decreased between parietal cortex and primary and secondary motor areas and the cerebellum. Interestingly, this decrease in iFC occurred in the absence of any changes in evoked activation during a simple chopsticks-handling task performed in the magnet, demonstrating the additional information yielded by R-fMRI data.

Practice on cognitive tasks

Investigations of iFC plasticity following practice on higher levels cognitive tasks are also beginning to emerge. Jolles et al. (2013) scanned a group of adults before and after practicing a difficult object-verbal working memory task for 6 weeks and examined changes in iFC within a frontoparietal network and the default network. Within the frontoparietal network associated with a right middle frontal gyrus (MFG) seed, iFC increased from pre- to post-training, particularly in "border zone" areas such as posterior dorsolateral and medial frontal/anterior cingulate cortex, which exhibited weakly positive or even negative iFC with MFG pre-training. Within the default network, decreased iFC was observed between medial

PFC and posterior middle temporal cortex. When the pre-post change in performance was added as a covariate, those showing the greatest increase in anterior-posterior default network connectivity between medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)/precuneus showed the greatest behavioral improvements. In contrast, no such changes were observed in a group of 9 children who also practiced the task. In interpreting these findings, it is worth noting that practice was not extensive – participants practiced 90 trials an average of only 16 times during the 6-week period (2-3 times per week). After practice, the adults' performance had still not reached a theoretical ceiling (accuracy improved from ~78%to ~90%, and RT decreased from almost 1500ms to ~1200ms), while the children's performance had only reached the level of the adults pre-training. The increased spatial spread of iFC (i.e., recruitment of additional areas into the network) likely reflects the continued reliance of effortful processes for performing the task. Our prediction is that in the context of sufficient training, whereby performance asymptotes, iFC increases would be more focal, observable only between nodes that continue to be necessary to task performance, while connectivity with "scaffolding" regions would decrease. The failure to observe any training-related changes in iFC in the group of children is difficult to interpret, but likely reflects the fact that in such a small developmental sample, interindividual variability in the neuronal response to training would obscure any consistent pattern.

In another study of working memory training, Takeuchi et al. (2013) scanned 41 adults before and after 4 weeks (27 days, 20-60 minutes per day) of working memory training. A control group (n = 20) did not perform any training. Visuospatial and auditory working memory training increased iFC between nodes of the default network (mPFC and precuneus) and increased the negative correlation between mPFC and nodes of the fronto-parietal executive control network. Both patterns of connectivity have been linked with interindividual variations in behavioral performance (Hampson et al., 2006, Kelly et al., 2008), although no relationship with performance improvements was observed by Takeuchi et al.

In an innovative study, Mackey et al. (2013) scanned 25 aspiring lawyers who were enrolled in a preparatory course for the Law School Admissions Test (LSAT), a standardized test that taxes relational reasoning abilities. Participants were scanned before initiating the course, which involved 70 hours of instruction, and 90 days later. A comparison group of 24 pre-law students who did not enroll in the course were also scanned. Course participants exhibited significant performance gains on the reasoning components of the LSAT (corresponding to a mean improvement from the 44th to the73rd percentile). In the trained group, increased frontoparietal, parietostriatal and frontostriatal iFC was observed, with increases in frontoparietal and parietostriatal iFC being associated with improvements in LSAT performance (though it should be noted that the brain-behavior correlations were uncorrected for multiple comparisons). Another study (Martinez et al., 2013) also observed increased iFC within frontoparietal and lateral and medial temporal networks (also at uncorrected thresholds) following 4 weeks of practice on a puzzle-solving game. As in the study by Jolles et al. (2013), it is possible that the increased iFC within higher-level cognitive networks observed in these two studies reflects the fact that even after practice performance was not asymptotic, and required the continued scaffolding support of widespread increases in iFC.

Toward rehabilitation: training the elderly brain

The studies described in the preceding section demonstrate the utility of iFC analyses for tracking the effects of training in healthy individuals. Currently, we lack studies directly examining the effects of a training intervention on iFC in patient groups. There is, however, a growing literature investigating the impact of cognitive and aerobic training regimes in elderly individuals. In an exemplary study, Voss et al. (2010) scanned two groups of older adults assigned to one of two year-long physical activity interventions involving either aerobic (n = 30; walking) or non-aerobic (n = 35; flexibility, toning and balance) fitness training. They identified regions that showed age-related decreases and increases in iFC, contrasted to 32 young adults which allowed them to differentiate between exercise related changes in compensatory circuits (circuits that differed from young adults before training) or exercise-related remediation of connectivity (i.e., restoration of connectivity in circuits that show reduced iFC relative to younger adults). Older adults showed decreased iFC in default, cingulo-opercular and fronto-parietal networks (including visual cortex) and reduced differentiation (reduced negative connectivity) between the default network and cingulo-opercular and fronto-parietal networks. Both types of exercise led to increased iFC in the regions exhibiting age decrements and increased differentiation between executive and default networks. Changes in functional connectivity in the default network were correlated with improvements in executive function (on measures of task switching, spatial working memory, and perseveration). Two other studies (Pieramico et al., 2012, Strenziok et al., 2013) adopted similar approaches, albeit with more limited implications due to the failure of pre-post differences to survive correction for multiple comparisons, or a restricted between-groups design that did not reveal general training-related changes in iFC.

While we await studies prospectively assessing the effects of remediation treatments, a preliminary, retrospective study by Koyama et al. (2013) illustrates how iFC analyses can distinguish normalization (or recovery) of function from compensation. Koyama et al. contrasted children with dyslexia who had received reading interventions and who exhibited varying degrees of remediation, with children with dyslexia who had received no interventions and with healthy comparison children. They observed differences in iFC between children with dyslexia who exhibited remediation of function and children who had received no treatment. Specifically, they observed increased positive iFC between the fusiform gyrus and middle occipital gyrus, part of the dorsal visual stream, as well as stronger negative iFC between fusiform gyrus and medial prefrontal cortex (i.e., the anterior node of the default network; Figure 2). They suggested that these changes were consistent with cortical compensation, rather than normalization, as the remediated groups differed significantly from unimpaired comparisons in these relationships.

Extensions of mapping the plasticity of functional connectivity

There are other potentially important applications of neuroimaging of brain plasticity in clinical populations. For example, although plastic changes in the brain often represent an adaptive response to injury and loss of input or function, negative effects can also result from the brain’s immense capacity for plasticity and reorganization. By using iFC to track the effects of rehabilitative training, in terms of its impact on *intact* as well as impaired

functions, we can best modulate neural plasticity for optimal behavioral gain (Pascual-Leone et al., 2005). Looking forward, integrating practice-related changes in task-evoked activity with changes in iFC is desirable. While several studies have examined plasticity in *task-related* functional or effective connectivity (e.g., Sun et al., 2007, Coynel et al., 2010), such changes are presumably context-dependent, and cannot inform us about effects on the underlying intrinsic architecture.

One particularly innovative line of work is the use of real-time fMRI-based neurofeedback (see Ruiz et al., 2013, for a review). In these studies, investigators capture and analyze fMRI signals online to provide real time feedback to participants regarding their own brain activity. Participants learn to use this feedback to modulate the activity within specific brain regions. Such training has been observed to result in substantial, enduring changes in iFC detected during subsequent R-fMRI scans. For example, Harmelach et al. (Harmelech et al., 2013) found that, following a single neurofeedback session in which participants learned to modulate the activity of dorsal anterior cingulate cortex, there were widespread changes (increases and decreases) in the iFC of that region that were linearly related to the magnitude and direction of the activity co-modulation observed during neurofeedback training. Although yet to be applied to rehabilitative contexts, initial applications of neurofeedback training in psychiatric populations are promising. For example, patients with contamination anxiety who learned to modulate activity in the amygdala exhibited altered iFC in networks associated with emotion regulation that endured for several days after the completion of neurofeedback training (Scheinost et al., 2013). Finally, while real-time fMRI may ultimately prove too financially onerous to be routinely adopted, studies have demonstrated that EEG-based neurofeedback also elicits changes in R-fMRI measures of iFC (Kluetsch et al., 2013).

Another promising avenue of investigation centers on the potential for stimulation techniques to boost the effects of training and practice. Initially demonstrated in the context of motor learning (Nitsche et al., 2003, Kim et al., 2004), stimulation-linked facilitation of learning has also recently been demonstrated in the cognitive domain (Cohen Kadosh et al., 2010, de Vries et al., 2010). For example, Meinzer et al. (2013) applied either sham or anodal transcranial direct current electrical stimulation (tDCS) over the left posterior temporo-parietal junction while participants acquired a novel vocabulary (i.e., they learned new non-word names for familiar and novel objects) over the course of five days. Participants in the anodal tDCS condition exhibited steeper learning curves and significantly more recall after learning, effects that were maintained for at least one week after the end of training.

The facilitation of motor and language learning by means of tDCS raise hopes that such protocols could be applied to facilitate the rehabilitation of function in the context of brain injury or dysfunction. Indeed, tDCS has been suggested as an adjunct treatment for post-stroke language disorders (Holland and Crinion, 2012), and offers advantages over pharmacological enhancements in terms of its safety profile (Meinzer et al., 2013). Initial applications to a variety of patient groups have reported mixed results, however, with large individual differences in patient response (Floel, 2013). In a promising development, Fox et al. (2012b) recently demonstrated that iFC mapping may be helpful in selecting

individualized targets for transcranial magnetic stimulation (TMS) in treating depression. Specifically, they demonstrated large, reproducible individual differences in iFC between dorsolateral prefrontal cortex and the subgenual cingulate, such that iFC mapping could be used to identify the sites within dorsolateral prefrontal cortex where TMS is most likely to produce a therapeutic effect. Likely, similar approaches could be adopted to improve the efficacy of adjunct rehabilitative treatments using tDCS (Castellanos and Proal, 2012). In addition, following up such treatments by means of R-fMRI scanning and iFC mapping could be highly informative with regard to our knowledge of the mechanisms by which tDCS facilitates learning and recovery of function.

In summary, a growing literature is documenting iFC plasticity in response to training and practice in healthy participants, suggesting that similar approaches can be usefully applied in clinical populations. In the final section, we discuss some caveats to consider when adopting the iFC approach.

Considerations for R-fMRI studies in clinical populations

Although the R-fMRI approach has proven extremely fruitful, researchers using R-fMRI approaches currently face several challenges. In particular, recent work from multiple laboratories has raised strong methodological concerns regarding the confounding effects of motion and of preprocessing strategies (especially “denoising” strategies such as global signal regression) on the findings obtained, particularly in the context of group comparisons (e.g., patients vs. comparisons). Thankfully, efforts to address these methodological concerns are underway, supporting the assertion that R-fMRI will ultimately transcend these challenges and fulfill its promise as a translational approach that faithfully reveals macro-scale brain function in health and disease (Castellanos et al., 2013).

Motion

Participant movement has always posed a challenge for functional neuroimaging. Head motion induces signal intensity changes as a result of physical displacement and partial voluming, and causes more complex artifacts due to spin history effects and alterations to magnetic field homogeneity (e.g., Friston et al., 1996). The challenge presented by motion is greater for R-fMRI data, and is amplified in studies of developing and aging populations, as well as those characterized by motor dysfunction (e.g., neurodevelopmental disorders featuring hyperactivity). Use of correlation (i.e., iFC) as a primary analysis strategy increases susceptibility to contamination from motion, which exhibits patterns of positive and negative correlation across the brain. Accordingly, motion has been shown to alter iFC in a distance dependent manner (Power et al., 2012, Power et al., 2013b, Satterthwaite et al., 2013b). Even more troublesome, a slew of recent papers has drawn attention to the confounding effects of even “micro” (<0.5mm) movements (Power et al., 2012, Satterthwaite et al., 2012, Van Dijk et al., 2012, Power et al., 2013a, Power et al., 2013b, Satterthwaite et al., 2013a, Satterthwaite et al., 2013b, Yan et al., 2013) on R-fMRI measures, and the prolonged (>6 seconds) persistence of effects after the motion event (Power et al., 2013b, Satterthwaite et al., 2013a). In response to this considerable challenge, several retrospective analytic approaches that aim to correct for or ameliorate the effects of motion have already been developed (Power et al., 2013b, Satterthwaite et al., 2013a, Yan et

al., 2013). Potentially more promising are emerging imaging techniques that aim to address the problem of motion by means of novel image acquisition sequences and related analyses (Bright and Murphy, 2013, Kundu et al.,2013). Finally, in recognition of the insidious effects of motion, many researchers are redoubling their efforts to reduce participant motion by using mock scanner training sessions, or scanning participants during natural sleep. Future R-fMRI studies should ideally aim to utilize a combination of these approaches to mitigate the potentially confounding effects of motion on their data.

Global signal regression (GSR)

In addition to motion, the R-fMRI signal contains contributions from several other non-BOLD "nuisance" sources, including vasomotion, cardiac pulsations and respiration as well as scanner-related processes such as thermal noise (Murphy et al., 2013). Ideally, physiological signals should be precisely recorded and removed from fMRI data (Birn, 2012, Murphy et al., 2013). However, many researchers lack recording equipment, or experience procedural difficulties (e.g., with respiratory belt calibration). In the absence of such data, the most popular approach has been to apply GSR. This entails the removal, via regression, of a global (mean) signal (usually in addition to signals from white matter and cerebrospinal fluid voxels, as well as motion parameters). GSR vastly increases sensitivity and anatomical specificity (Fox et al., 2009), but it is controversial because it mathematically shifts the distribution of correlations so that approximately half are negative (i.e., it enhances the number and magnitude of "anticorrelations") (Murphy et al., 2009). This generates interpretational problems, because the neurophysiological origin and significance of anticorrelations is unknown. Even more problematic is recent evidence that GSR can differentially alter (distort) the distribution of iFC values between groups, thus confounding group comparisons (Gotts et al., 2013, Saad et al., 2013). Nonetheless, increasing evidence suggests that GSR (1) performs best at removing motion-related artifact from iFC analyses (Power et al., 2013b, Yan et al., 2013), (2) increases the correspondence between iFC and maps of correlated electrophysiological activity in the brain (Keller et al., 2013), and (3) provides measures of iFC that have clinical and predictive utility (Fox et al., 2012a, Fox et al., 2012b). By consequence, GSR is still commonly used. Invasive electrophysiological recordings from non-human primates (Shmuel and Leopold, 2008, Scholvinck et al., 2010), and where possible, humans (He et al., 2008, Keller et al., 2011, Keller et al., 2013), are needed to shed light on the neurophysiological origins and significance of the global signal and anticorrelated intrinsic activity, and thereby adjudicate on the appropriateness of GSR.

Test-retest reliability and sample size

A particularly important consideration for pre-post studies of iFC is the reliability of iFC measures over time. In the first paper to examine the short (<1hr) and long-term (5-16 months) test-retest reliability of iFC, Shehzad et al. (2009) demonstrated intraclass correlation coefficients (ICC; a standard index used to quantify reliability) that were in the moderate range for most ICNs. Spatial correlation between group level ICNs was even more encouraging, with $r^2 > 0.8$. Several other studies have now demonstrated similar reliabilities for a variety of R-fMRI metrics, and have shown good reliability in healthy adults as well as in developing (Thomason et al., 2011) and aging (Song et al., 2012) samples (for a brief

summary, see Castellanos et al., 2013). Yet, reproducibility of iFC measures at the level of the individual subject appears less robust (Anderson et al., 2011), and the field remains some way off from attaining sensitive and specific prediction (e.g., of clinical group, prognosis, etc.) at the level of individuals (see Castellanos et al., 2013, for a detailed discussion). Nevertheless, the field of R-fMRI is profoundly multidisciplinary, and multifaceted ongoing efforts are focused on refining methods and techniques, and on honing the measured signal, so that we may move toward the goals of individualized prediction. Finally, with regard to pre-post studies, reliability is a consideration that must be taken into account when making decisions about study design, particularly sample size. According to Diggle et al. (2013), in the context of longitudinal designs (e.g.,pre/post training), to attain a given power (e.g., 80%) to detect a given effect size, the sample size required will be directly proportional to 1 minus the correlation between observations for a given individual (i.e., the correlation across time points).

Conclusions and future directions

We have asserted that investigations of the functional connectome and the iFC paradigm have the potential to transform neuropsychology by quantifying practice and training-induced plasticity. Approaches focused on iFC are fundamentally network-based, and they consequently promise to improve our understanding of the sequelae of brain injury and how to best facilitate recovery. Although R-fMRI approaches are not without caveats, the widespread availability and applicability of R-fMRI, together with ongoing efforts to address its shortcomings, render it particularly promising for neuropsychological applications. Looking forward, we suggest that a better understanding of the neuronal *mechanisms* underlying iFC plasticity may be gained by means of translational efforts. Studies in non-human primates and rodents permit direct experimental manipulations that will provide explicit causal explanations of intrinsic brain phenomena, their vulnerability to injury, and their resilience and recovery. Importantly, longitudinal studies of long-term stability and plasticity of iFC may be most experimentally tractable with animal models. In addition, such models permit concurrent invasive electrophysiological recordings, which are likely necessary for us to grasp the neurophysiological bases of intrinsic activity variation. The pursuit of these lines of research will bolster the utility of the iFC paradigm for neuropsychology.

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References

Adachi Y, Osada T, Sporns O, Watanabe T, Matsui T, Miyamoto K, et al. Functional connectivity between anatomically unconnected areas is shaped by collective network-level effects in the macaque cortex. Cereb Cortex. 2012; 22:1586–92. [PubMed: 21893683]

Adelstein JS, Shehzad Z, Mennes M, De Young CG, Zuo X, Kelly C, et al. Personality is reflected in the brain's intrinsic functional architecture. PLoS One. 2011; 6:e27633. [PubMed: 22140453]

Albert NB, Robertson EM, Miall RC. The resting human brain and motor learning. Curr Biol. 2009; 19:1023–7. [PubMed: 19427210]

Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD. Tracking Whole-Brain Connectivity Dynamics in the Resting State. Cereb Cortex. 2012

Anderson JS, Ferguson MA, Lopez-Larson M, Yurgelun-Todd D. Reproducibility of single-subject functional connectivity measurements. AJNR Am J Neuroradiol. 2011; 32:548–55. [PubMed: 21273356]

Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci. 2005; 360:1001–13. [PubMed: 16087444]

Birn RM. The role of physiological noise in resting-state functional connectivity. Neuroimage. 2012; 62:864–70. [PubMed: 22245341]

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34:537–41. [PubMed: 8524021]

Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM. Toward discovery science of human brain function. Proc Natl Acad Sci U S A. 2010; 107:4734–9. [PubMed: 20176931]

Bright MG, Murphy K. Removing motion and physiological artifacts from intrinsic BOLD fluctuations using short echo data. Neuroimage. 2013; 64:526–37. [PubMed: 23006803]

Buckner RL. The serendipitous discovery of the brain's default network. Neuroimage. 2011 Nov 01.

Buckner RL, Krienen FM. The evolution of distributed association networks in the human brain. Trends Cogn Sci. 2013

Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, et al. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nat Neurosci. 2012; 15:1736–41. [PubMed: 23143517]

Carter AR, Astafiev SV, Lang CE, Connor LT, Rengachary J, Strube MJ, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann Neurol. 2010; 67:365–75. [PubMed: 20373348]

Carter AR, Shulman GL, Corbetta M. Why use a connectivity-based approach to study stroke and recovery of function? Neuroimage. 2012; 62:2271–80. [PubMed: 22414990]

Castellanos FX, Di Martino A, Craddock RC, Mehta AD, Milham MP. Clinical applications of the functional connectome. Neuroimage. 2013; 80:527–40. [PubMed: 23631991]

Castellanos FX, Proal E. Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. Trends Cogn Sci. 2012; 16:17–26. [PubMed: 22169776]

Cohen Kadosh R, Soskic S, Iuculano T, Kanai R, Walsh V. Modulating neuronal activity produces specific and long-lasting changes in numerical competence. Curr Biol. 2010; 20:2016–20. [PubMed: 21055945]

Cole DM, Beckmann CF, Oei NY, Both S, van Gerven JM, Rombouts SA. Differential and distributed effects of dopamine neuromodulations on resting-state network connectivity. Neuroimage. 2013; 78:59–67. [PubMed: 23603346]

Coynel D, Marrelec G, Perlbarg V, Pelegrini-Issac M, Van de Moortele PF, Ugurbil K, et al. Dynamics of motor-related functional integration during motor sequence learning. Neuroimage. 2010; 49:759–66. [PubMed: 19716894]

de Vries MH, Barth AC, Maiworm S, Knecht S, Zwitserlood P, Floel A. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J Cogn Neurosci. 2010; 22:2427–36. [PubMed: 19925194]

Deco G, Corbetta M. The dynamical balance of the brain at rest. Neuroscientist. 2011; 17:107–23. [PubMed: 21196530]

Di Martino A, Shehzad Z, Kelly C, Roy AK, Gee DG, Uddin LQ, et al. Relationship between cingulo-insular functional connectivity and autistic traits in neurotypical adults. Am J Psychiatry. 2009; 166:891–9. [PubMed: 19605539]

Diggle, PJ.; Heagerty, P.; Liang, K-Y.; Zeger, S. Analysis of Longitudinal Data. Oxford University Press; Oxford, UK: 2013.

Dinstein I, Pierce K, Eyler L, Solso S, Malach R, Behrmann M, et al. Disrupted neural synchronization in toddlers with autism. Neuron. 2011; 70:1218–25. [PubMed: 21689606]

Engel AK, Gerloff C, Hilgetag CC, Nolte G. Intrinsic coupling modes: multiscale interactions in ongoing brain activity. Neuron. 2013; 80:867–86. [PubMed: 24267648]

Ferreira LK, Busatto GF. Resting-state functional connectivity in normal brain aging. Neurosci Biobehav Rev. 2013; 37:384–400. [PubMed: 23333262]

Floel A. tDCS-enhanced motor and cognitive function in neurological diseases. Neuroimage. 2013

Fox MD, Halko MA, Eldaief MC, Pascual-Leone A. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). Neuroimage. 2012a; 62:2232–43. [PubMed: 22465297]

Fox MD, Liu H, Pascual-Leone A. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. Neuroimage. 2012b; 66C:151–60. [PubMed: 23142067]

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8:700–11. [PubMed: 17704812]

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005; 102:9673–8. [PubMed: 15976020]

Fox MD, Snyder AZ, Vincent JL, Raichle ME. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron. 2007; 56:171–84. [PubMed: 17920023]

Fox MD, Snyder AZ, Zacks JM, Raichle ME. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat Neurosci. 2006; 9:23–5. [PubMed: 16341210]

Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. J Neurophysiol. 2009; 101:3270–83. [PubMed: 19339462]

Fransson P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp. 2005; 26:15–29. [PubMed: 15852468]

Fransson P, Aden U, Blennow M, Lagercrantz H. The functional architecture of the infant brain as revealed by resting-state FMRI. Cereb Cortex. 2011; 21:145–54. [PubMed: 20421249]

Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab. 1993; 13:5–14. [PubMed: 8417010]

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med. 1996; 35:346–55. [PubMed: 8699946]

Gao W, Zhu H, Giovanello KS, Smith JK, Shen D, Gilmore JH, et al. Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. Proc Natl Acad Sci U S A. 2009; 106:6790–5. [PubMed: 19351894]

Gillebert CR, Mantini D. Functional connectivity in the normal and injured brain. Neuroscientist. 2013; 19:509–22. [PubMed: 23064084]

Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, et al. Genetic control over the resting brain. Proc Natl Acad Sci U S A. 2010; 107:1223–8. [PubMed: 20133824]

Gotts SJ, Saad ZS, Jo HJ, Wallace GL, Cox RW, Martin A. The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. Front Hum Neurosci. 2013; 7:356. [PubMed: 23874279]

Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain. 2011; 134:1264–76. [PubMed: 21414995]

Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol. 2008; 21:424–30. [PubMed: 18607202]

Greicius MD, Kiviniemi V, Tervonen O, Vainionpaa V, Alahuhta S, Reiss AL, et al. Persistent default-mode network connectivity during light sedation. Hum Brain Mapp. 2008; 29:839–47. [PubMed: 18219620]

Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003; 100:253–8. [PubMed: 12506194]

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the structural core of human cerebral cortex. PLoS Biol. 2008; 6:e159. [PubMed: 18597554]

Hagmann P, Sporns O, Madan N, Cammoun L, Pienaar R, Wedeen VJ, et al. White matter maturation reshapes structural connectivity in the late developing human brain. Proc Natl Acad Sci U S A. 2010; 107:19067–72. [PubMed: 20956328]

Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. Brain connectivity related to working memory performance. J Neurosci. 2006; 26:13338–43. [PubMed: 17182784]

Harmelech T, Malach R. Neurocognitive biases and the patterns of spontaneous correlations in the human cortex. Trends Cogn Sci. 2013

Harmelech T, Preminger S, Wertman E, Malach R. The day-after effect: long term, Hebbian-like restructuring of resting-state fMRI patterns induced by a single epoch of cortical activation. J Neurosci. 2013; 33:9488–97. [PubMed: 23719815]

Harrison BJ, Pujol J, Ortiz H, Fornito A, Pantelis C, Yucel M. Modulation of brain resting-state networks by sad mood induction. PLoS One. 2008; 3:e1794. [PubMed: 18350136]

He BJ, Shulman GL, Snyder AZ, Corbetta M. The role of impaired neuronal communication in neurological disorders. Curr Opin Neurol. 2007a; 20:655–60. [PubMed: 17992085]

He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron. 2007b; 53:905–18. [PubMed: 17359924]

He BJ, Snyder AZ, Zempel JM, Smyth MD, Raichle ME. Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. Proc Natl Acad Sci U S A. 2008; 105:16039–44. [PubMed: 18843113]

Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, et al. Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. Proc Natl Acad Sci U S A. 2013; 110:19119–24. [PubMed: 24191026]

Holland R, Crinion J. Can tDCS enhance treatment of aphasia after stroke? Aphasiology. 2012; 26:1169–91. [PubMed: 23060684]

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A. 2009; 106:2035–40. [PubMed: 19188601]

Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, et al. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. Hum Brain Mapp. 2008; 29:671–82. [PubMed: 17598166]

Hutchison RM, Gallivan JP, Culham JC, Gati JS, Menon RS, Everling S. Functional connectivity of the frontal eye fields in humans and macaque monkeys investigated with resting-state fMRI. J Neurophysiol. 2012; 107:2463–74. [PubMed: 22298826]

Jolles DD, van Buchem MA, Crone EA, Rombouts SA. Functional brain connectivity at rest changes after working memory training. Hum Brain Mapp. 2013; 34:396–406. [PubMed: 22076823]

Keller CJ, Bickel S, Entz L, Ulbert I, Milham MP, Kelly C, et al. Intrinsic functional architecture predicts electrically evoked responses in the human brain. Proc Natl Acad Sci U S A. 2011

Keller CJ, Bickel S, Honey CJ, Groppe DM, Entz L, Craddock RC, et al. Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. J Neurosci. 2013; 33:6333–42. [PubMed: 23575832]

Kelly AM, Garavan H. Human functional neuroimaging of brain changes associated with practice. Cereb Cortex. 2005; 15:1089–102. [PubMed: 15616134]

Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. Neuroimage. 2008; 39:527–37. [PubMed: 17919929]

Kelly C, Biswal BB, Craddock RC, Castellanos FX, Milham MP. Characterizing variation in the functional connectome: promise and pitfalls. Trends Cogn Sci. 2012; 16:181–8. [PubMed: 22341211]

Kelly C, de Zubicaray G, Di Martino A, Copland DA, Reiss PT, Klein DF, et al. L-dopa modulates functional connectivity in striatal cognitive and motor networks: a double-blind placebo-controlled study. J Neurosci. 2009; 29:7364–78. [PubMed: 19494158]

Kim YH, Park JW, Ko MH, Jang SH, Lee PK. Facilitative effect of high frequency subthreshold repetitive transcranial magnetic stimulation on complex sequential motor learning in humans. Neurosci Lett. 2004; 367:181–5. [PubMed: 15331148]

Kluetsch RC, Ros T, Theberge J, Frewen PA, Calhoun VD, Schmahl C, et al. Plastic modulation of PTSD resting-state networks and subjective wellbeing by EEG neurofeedback. Acta Psychiatr Scand. 2013

Koyama MS, Di Martino A, Kelly C, Jutagir DR, Sunshine J, Schwartz SJ, et al. Cortical signatures of dyslexia and remediation: an intrinsic functional connectivity approach. PLoS One. 2013; 8:e55454. [PubMed: 23408984]

Kundu P, Brenowitz ND, Voon V, Worbe Y, Vertes PE, Inati SJ, et al. Integrated strategy for improving functional connectivity mapping using multiecho fMRI. Proc Natl Acad Sci U S A. 2013; 110:16187–92. [PubMed: 24038744]

Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M. Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci U S A. 2009; 106:17558–63. [PubMed: 19805061]

Liu B, Song M, Li J, Liu Y, Li K, Yu C, et al. Prefrontal-related functional connectivities within the default network are modulated by COMT val158met in healthy young adults. J Neurosci. 2010; 30:64–9. [PubMed: 20053888]

Lohmann G, Margulies DS, Horstmann A, Pleger B, Lepsien J, Goldhahn D, et al. Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain. PLoS One. 2010; 5:e10232. [PubMed: 20436911]

Lohmann G, Ovadia-Caro S, Jungehulsing GJ, Margulies DS, Villringer A, Turner R. Connectivity concordance mapping: a new tool for model-free analysis of FMRI data of the human brain. Front Syst Neurosci. 2012; 6:13. [PubMed: 22470320]

Lu H, Zou Q, Gu H, Raichle ME, Stein EA, Yang Y. Rat brains also have a default mode network. Proc Natl Acad Sci U S A. 2012; 109:3979–84. [PubMed: 22355129]

Ma L, Narayana S, Robin DA, Fox PT, Xiong J. Changes occur in resting state network of motor system during 4 weeks of motor skill learning. Neuroimage. 2011; 58:226–33. [PubMed: 21689765]

Mackey AP, Miller Singley AT, Bunge SA. Intensive reasoning training alters patterns of brain connectivity at rest. J Neurosci. 2013; 33:4796–803. [PubMed: 23486950]

Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, et al. Precuneus shares intrinsic functional architecture in humans and monkeys. Proc Natl Acad Sci U S A. 2009; 106:20069–74. [PubMed: 19903877]

Martinez K, Solana AB, Burgaleta M, Hernandez-Tamames JA, Alvarez-Linera J, Roman FJ, et al. Changes in resting-state functionally connected parietofrontal networks after videogame practice. Hum Brain Mapp. 2013; 34:3143–57. [PubMed: 22807280]

Meinzer M, Jahnigen S, Copland DA, Darkow R, Grittner U, Avirame K, et al. Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. Cortex. 2013

Mennes M, Kelly C, Colcombe S, Castellanos FX, Milham MP. The extrinsic and intrinsic functional architectures of the human brain are not equivalent. Cereb Cortex. 2013; 23:223–9. [PubMed: 22298730]

Mitra PP, Ogawa S, Hu X, Ugurbil K. The nature of spatiotemporal changes in cerebral hemodynamics as manifested in functional magnetic resonance imaging. Magn Reson Med. 1997; 37:511–8. [PubMed: 9094072]

Murphy K, Birn RM, Bandettini PA. Resting-state fMRI confounds and cleanup. Neuroimage. 2013; 80:349–59. [PubMed: 23571418]

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage. 2009; 44:893–905. [PubMed: 18976716]

Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cogn Neurosci. 2003; 15:619–26. [PubMed: 12803972]

O'Reilly JX, Croxson PL, Jbabdi S, Sallet J, Noonan MP, Mars RB, et al. Causal effect of disconnection lesions on interhemispheric functional connectivity in rhesus monkeys. Proc Natl Acad Sci U S A. 2013; 110:13982–7. [PubMed: 23924609]

Ovadia-Caro S, Villringer K, Fiebach J, Jungehulsing GJ, van der Meer E, Margulies DS, et al. Longitudinal effects of lesions on functional networks after stroke. J Cereb Blood Flow Metab. 2013; 33:1279–85. [PubMed: 23715061]

Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci. 2005; 28:377–401. [PubMed: 16022601]

Pieramico V, Esposito R, Sensi F, Cilli F, Mantini D, Mattei PA, et al. Combination training in aging individuals modifies functional connectivity and cognition, and is potentially affected by dopamine-related genes. PLoS One. 2012; 7:e43901. [PubMed: 22937122]

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012; 59:2142–54. [PubMed: 22019881]

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. Neuroimage. 2013a; 76:439–41. [PubMed: 22440651]

Power JD, Fair DA, Schlaggar BL, Petersen SE. The development of human functional brain networks. Neuron. 2010; 67:735–48. [PubMed: 20826306]

Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage. 2013b; 84C:320–41. [PubMed: 23994314]

Raichle ME. The brain's dark energy. Sci Am. 2010; 302:44–9. [PubMed: 20184182]

Raichle ME. The restless brain. Brain Connect. 2011; 1:3–12. [PubMed: 22432951]

Raichle ME, Mintun MA. Brain work and brain imaging. Annu Rev Neurosci. 2006; 29:449–76. [PubMed: 16776593]

Ruiz S, Buyukturkoglu K, Rana M, Birbaumer N, Sitaram R. Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks. Biol Psychol. 2013

Saad ZS, Reynolds RC, Jo HJ, Gotts SJ, Chen G, Martin A, et al. Correcting brain-wide correlation differences in resting-state FMRI. Brain Connect. 2013; 3:339–52. [PubMed: 23705677]

Samann PG, Wehrle R, Hoehn D, Spoormaker VI, Peters H, Tully C, et al. Development of the brain's default mode network from wakefulness to slow wave sleep. Cereb Cortex. 2011; 21:2082–93. [PubMed: 21330468]

Sami S, Miall RC. Graph network analysis of immediate motor-learning induced changes in resting state BOLD. Front Hum Neurosci. 2013; 7:166. [PubMed: 23720616]

Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J, Calkins ME, et al. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage. 2013a; 64:240–56. [PubMed: 22926292]

Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. Neuroimage. 2012; 60:623–32. [PubMed: 22233733]

Satterthwaite TD, Wolf DH, Ruparel K, Erus G, Elliott MA, Eickhoff SB, et al. Heterogeneous impact of motion on fundamental patterns of developmental changes in functional connectivity during youth. Neuroimage. 2013b; 83C:45–57. [PubMed: 23792981]

Scheinost D, Stoica T, Saksa J, Papademetris X, Constable RT, Pittenger C, et al. Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity. Transl Psychiatry. 2013; 3:e250. [PubMed: 23632454]

Scholvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. Neural basis of global resting-state fMRI activity. Proc Natl Acad Sci U S A. 2010; 107:10238–43. [PubMed: 20439733]

Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, et al. The resting brain: unconstrained yet reliable. Cereb Cortex. 2009; 19:2209–29. [PubMed: 19221144]

Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex. 2012; 22:158–65. [PubMed: 21616982]

Shmuel A, Leopold DA. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. Hum Brain Mapp. 2008; 29:751–61. [PubMed: 18465799]

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A. 2009; 106:13040–5. [PubMed: 19620724]

Smith SM, Miller KL, Moeller S, Xu J, Auerbach EJ, Woolrich MW, et al. Temporally-independent functional modes of spontaneous brain activity. Proc Natl Acad Sci U S A. 2012; 109:3131–6. [PubMed: 22323591]

Song J, Desphande AS, Meier TB, Tudorascu DL, Vergun S, Nair VA, et al. Age-related differences in test-retest reliability in resting-state brain functional connectivity. PLoS One. 2012; 7:e49847. [PubMed: 23227153]

Strenziok M, Parasuraman R, Clarke E, Cisler DS, Thompson JC, Greenwood PM. Neurocognitive enhancement in older adults: Comparison of three cognitive training tasks to test a hypothesis of training transfer in brain connectivity. Neuroimage. 2013

Sun FT, Miller LM, Rao AA, D'Esposito M. Functional connectivity of cortical networks involved in bimanual motor sequence learning. Cereb Cortex. 2007; 17:1227–34. [PubMed: 16855008]

Takeuchi H, Taki Y, Nouchi R, Hashizume H, Sekiguchi A, Kotozaki Y, et al. Effects of working memory training on functional connectivity and cerebral blood flow during rest. Cortex. 2013; 49:2106–25. [PubMed: 23079491]

Tambini A, Ketz N, Davachi L. Enhanced brain correlations during rest are related to memory for recent experiences. Neuron. 2010; 65:280–90. [PubMed: 20152133]

Taubert M, Lohmann G, Margulies DS, Villringer A, Ragert P. Long-term effects of motor training on resting-state networks and underlying brain structure. Neuroimage. 2011; 57:1492–8. [PubMed: 21672633]

Thomason ME, Dennis EL, Joshi AA, Joshi SH, Dinov ID, Chang C, et al. Restingstate fMRI can reliably map neural networks in children. Neuroimage. 2011; 55:165–75. [PubMed: 21134471]

Tunbridge EM, Farrell SM, Harrison PJ, Mackay CE. Catechol-Omethyltransferase (COMT) influences the connectivity of the prefrontal cortex at rest. Neuroimage. 2013; 68:49–54. [PubMed: 23228511]

Turner R, Howseman A, Rees GE, Josephs O, Friston K. Functional magnetic resonance imaging of the human brain: data acquisition and analysis. Exp Brain Res. 1998; 123:5–12. [PubMed: 9835386]

Uddin LQ, Mooshagian E, Zaidel E, Scheres A, Margulies DS, Kelly AM, et al. Residual functional connectivity in the split-brain revealed with resting-state functional MRI. Neuroreport. 2008; 19:703–9. [PubMed: 18418243]

Uddin LQ, Supekar K, Menon V. Typical and atypical development of functional human brain networks: insights from resting-state FMRI. Front Syst Neurosci. 2010; 4:21. [PubMed: 20577585]

Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage. 2012; 59:431–8. [PubMed: 21810475]

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, et al. Intrinsic functional architecture in the anaesthetized monkey brain. Nature. 2007; 447:83–6. [PubMed: 17476267]

Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci. 2010; 2

Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol. 2012; 8:49–76. [PubMed: 22224834]

Wiggins JL, Bedoyan JK, Peltier SJ, Ashinoff S, Carrasco M, Weng SJ, et al. The impact of serotonin transporter (5-HTTLPR) genotype on the development of restingstate functional connectivity in children and adolescents: a preliminary report. Neuroimage. 2012; 59:2760–70. [PubMed: 22032950]

Yan C, Liu D, He Y, Zou Q, Zhu C, Zuo X, et al. Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. PLoS One. 2009; 4:e5743. [PubMed: 19492040]

Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage. 2013; 76:183–201. [PubMed: 23499792]

Yoo K, Sohn WS, Jeong Y. Tool-use practice induces changes in intrinsic functional connectivity of parietal areas. Front Hum Neurosci. 2013; 7:49. [PubMed: 23550165]

Zhang D, Raichle ME. Disease and the brain's dark energy. Nat Rev Neurol. 2010; 6:15–28. [PubMed: 20057496]

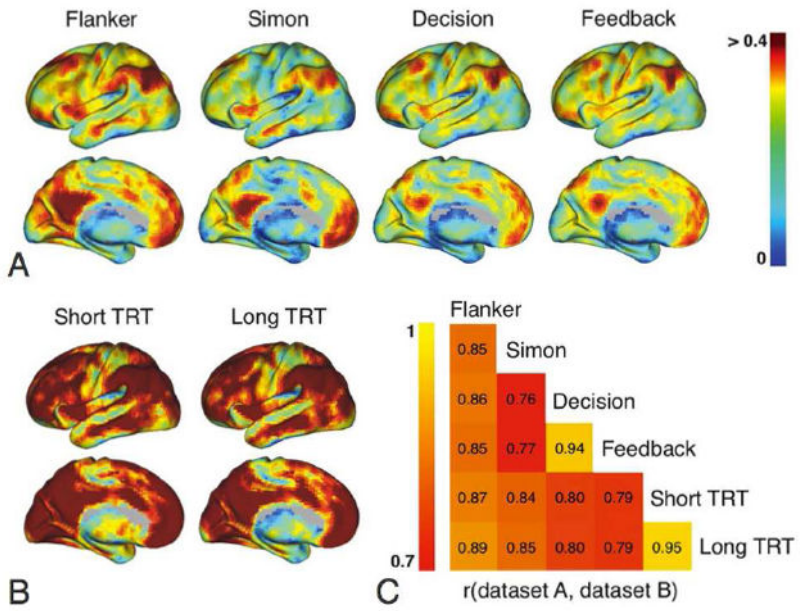

Figure 1. Correspondence between the brain's intrinsic and extrinsic (i.e., task-evoked) architectures

A. Surface maps show the mean correlation (across participants) between each voxel's pattern of intrinsic functional connectivity (iFC) and its pattern of taske-voked coactivation (i.e., extrinsic functional connectivity – eFC) obtained during an Eriksen Flanker task, a Simon stimulus-response compatibility task, and during decision and feedback phases of a risky decision-making task. The maps show that although a significant and generalizable iFC-eFC relationship is detected at virtually every brain voxel regardless of task, there is marked regional variation in the strength of the correspondence. While multimodal association areas, particularly in default and task-positive networks exhibited consistent patterns of functional interactions (connectivity or coactivation) across their intrinsic and extrinsic functional architectures, subcortical, limbic, and primary sensory and motor regions exhibited weaker correspondence. **B.** Short and long-term test-retest (TRT) reliability, assessed in terms of the mean correlation (across participants) between each voxel's pattern of iFC at time 1 and time 2 (either <1 hour (Short TRT) or 5-16 months later (Long TRT)). **C.** High between-data set correlations (ranging from 0.76 to 0.95) demonstrate that the spatial patterns of iFC-eFC correspondence and TRT reliability are largely similar across datasets.

Adapted from Mennes et al. (2013); *Cerebal Cortex* **23**, 223-9; Oxford University Press.

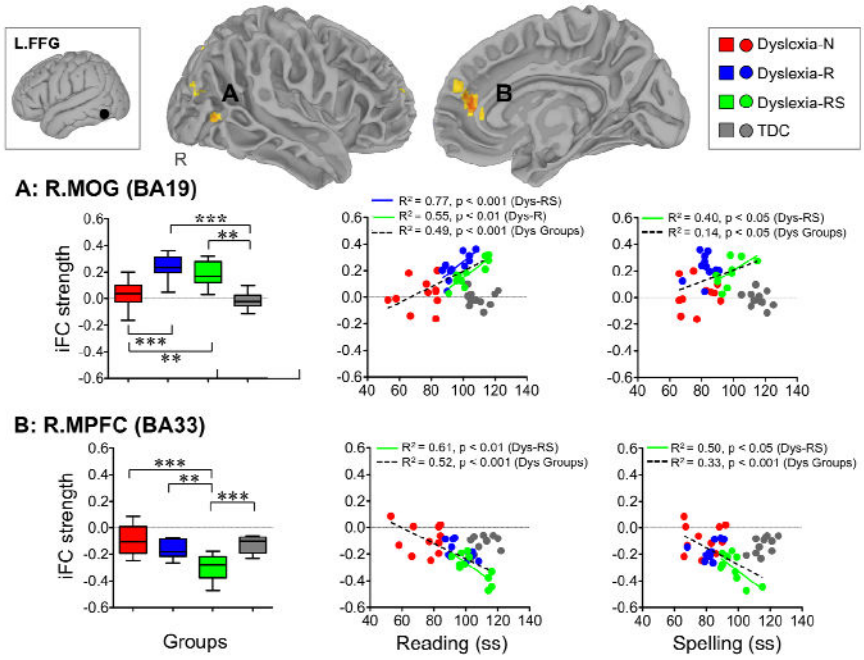

Figure 2. Evidence of compensatory changes in iFC related to reading remediation

Koyama et al. compared iFC associated with left fusiform gyrus (L.FFG) among children with dyslexia who exhibited reading remediation (Dys-R), children with dyslexia exhibited reading and spelling remediation (Dys-RS), children with dyslexia who had received no treatment (Dys-N) and typically developing controls (TDC). **A.** Children with dyslexia who exhibited remediation of function (Dys-R and Dys-RS) exhibited increased positive iFC between L.FFG and right middle occipital gyrus (R.MOG), part of the dorsal visual stream, relative to children with dyslexia who had received no treatment (Dys-N) and TDC. **B.** Dys-R and Dys-RS also exhibited more strongly negative iFC between LFFG and medial prefrontal cortex (R.MPFC; i.e., the anterior node of the default network), relative to Dys-N and TDC. The scatterplots show the brain-behavior relationships between iFC and reading and spelling scores, which indicated that children exhibited better reading and spelling performance scores also exhibited more strongly positive iFC between L.FFG and R.MOG and more strongly negative iFC between L.FFG and R.MPFC. These trends were particularly prominent in the remediation groups. ss = standard scores: ***p,0.001, **p,0.01 (corrected).

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