
CRITICAL REVIEW

Neuroimaging of working memory dysfunction and the dilemma with brain reorganization hypotheses

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Abstract

There is a growing literature examining working memory deficits using functional imaging and there has been great convergence in the findings, to date, but interpretations have varied. Investigators consistently observed recruitment of neural resources in clinical samples, with some examiners attributing these findings to neural inefficiency and others attributing differences to neural compensation and/or brain reorganization. It is the goal of this paper to address the current interpretation of altered brain activation in clinical imaging studies of working memory dysfunction with specific emphasis on findings in prefrontal cortex (PFC). Throughout this review, the methods used to examine brain reorganization associated with working memory dysfunction are critiqued with the goal of understanding how study design has influenced data interpretation. It is proposed that much of what has been considered “aberrant” neural activity is not indicative of neural compensation, as it has been typically defined, and does not represent brain reorganization. Instead, recruitment of neural resources in PFC can be explained by a natural, and largely overlooked, role of cognitive control in accommodating neural dysfunction secondary to brain injury and disease. This paper provides predictions based on this proposition and a critique of the current methods available for testing these predictions. (*JINS*, 2008, *14*, 526–534.)

Keywords: Plasticity, Traumatic brain injury, MS, Working memory, Reorganization, Cognitive control, Prefrontal, Functional magnetic resonance imaging

An Alternative to Brain Reorganization Hypotheses

Functional imaging techniques afford the unique opportunity to examine the relationships between basic brain changes and the behavioral deficits associated with brain injury and disease. There is a growing functional imaging literature examining the effects of neurological insult on working memory (WM), or the ability to maintain and/or manipulate small amounts of information for brief periods of time. In the functional imaging literature examining WM dysfunction, there has been increasing reference to “neural compensation” and “brain reorganization” to describe the altered (and almost universally increased) neural activation observed when comparing clinical samples

to healthy adults. Specifically, the term “compensation” has been used to describe either transient or permanent alterations in neural activity, which operates to facilitate performance. Therefore, in this paper, the term “compensation” will be used to indicate a positive relationship between task performance and brain activation. The term “brain reorganization” has typically been used to indicate that the neural networks associated with WM have been permanently altered because of neurological insult, so that insult induces a “rewiring” of WM networks. Therefore, the primary distinction between “compensation” and “brain reorganization” is that the former may be transient whereas the latter represents permanent changes in the neural networks involved in WM. Both of these terms, however, are used to describe increased neural activity that facilitates performance in clinical samples. Investigators have thus concluded that altered neural activity on tasks of WM in clinical samples is explicitly caused by the injury and represents: (1) recruitment of neural resources to bolster WM

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performance, and/or (2) permanent brain changes in the neural networks responsible for WM. These interpretations are challenged in this paper by first addressing the argument that clinical and control groups have been equated for task performance and, second, by proposing that a native support mechanism, cognitive control, may account for the findings to date.

In brief, cognitive control has been used to describe the neural resources that provide a framework for assisting in task processing by maintaining superordinate goals and the means to achieve those goals (Miller & Cohen, 2001). The neural substrate of cognitive control processes has been hypothesized to include anterior cingulate cortex (ACC) and prefrontal cortex (PFC), with ACC being dedicated to conflict monitoring (Botvinick et al., 1999; van Veen et al., 2001), including semantic and retrieval conflict (Maril et al., 2001; van Veen & Carter, 2005) and PFC operating to process task demands and response preparation (see Cohen et al., 2000). Cognitive control is theorized to provide “top-down” supervisory control during the development of sub-routines, which operate to facilitate task performance and has been conceptualized as an emergent property of WM (for review see Baddeley & Dela Sala, 1996; Courtney, 2004; Gruber & Goschke, 2004). Imaging studies of WM in humans have been particularly important in demonstrating the role of PFC in providing control resources for the maintenance, selection, and manipulation of information in working toward a goal state (D’Esposito et al., 1998; Smith & Jonides, 1999; Wagner, 1999; Wagner et al., 2001).

In the clinical imaging studies investigating WM, an interpretation that has been proposed elsewhere (Hillary et al., 2006) and is extended here, is that the increased PFC involvement on tasks of WM represents neither “compensation” operating to bolster task performance nor “brain reorganization.” Instead, it is proposed that the increased neural activity in PFC commonly observed in clinical studies of WM is associated with poorer performance and largely represents transient fluctuations in the recruitment and reassignment of attentional resources, or cognitive control (Hillary et al., 2006).

For the purposes of this paper, the current review will be limited to studies examining traumatic brain injury (TBI) and certain brain diseases such as multiple sclerosis (MS) and human immunodeficiency virus (HIV). The primary reason for focusing on a subset of neurological disorders is that, in cases of injury and disease, there is typically an identifiable time period, prior to which the neural system was considered “normal” in its functioning. This approach allows one to examine how a previously healthy neural system adapts to neurological insult. Such a goal is significantly more challenging in disorders such as schizophrenia, for example, where there exist neurodevelopmental and even chronic pharmacologic influences on the neural environment making interpretations about the “normal” role of PFC and cognitive control tenuous. Moreover, in other clinical samples including cerebrovascular accident and cortical and subcortical degenerative processes, the confluence

of normal aging and pathophysiology simultaneously influence the expression of neural plasticity. Therefore, the literature discussed here is gathered from studies of TBI, HIV, MS, chronic fatigue syndrome (CFS), and alcohol abuse.

Goals of this Paper

This paper will focus on a subset of functional imaging studies in order to achieve two goals, both organized around the study of brain reorganization hypotheses. The first goal of this review is to summarize the findings and interpretations in the current clinical WM literature. It is a primary aim in this first part to offer an alternative explanation to the prevailing view that changes in neural activity in clinical samples represent neural compensation and/or brain reorganization. Secondly, it is a goal to develop testable predictions for examining the nature of PFC recruitment in WM dysfunction and to outline the methodological difficulties encountered when using functional imaging to test these predictions.

Integrating the Current Findings: Determining the Meaning of PFC Recruitment

Accuracy, reaction time, and activation

In order to understand how data in the clinical WM literature have been interpreted, a brief background on performance measurement is required.

Two of the most consistent methodological constraints in functional imaging work are to keep the study participant “busy” during data acquisition and guarantee that participants maintain high rates of task accuracy (the latter being critically important if response scenarios are dichotomous). Failure to comply with these mandates results in: (1) data that misrepresent the cognitive function examined because “activation” includes excessive off-task averaging, and (2) data that are difficult to interpret because of chance performance; the examiner cannot guarantee that the subject was occupied with the task during the experiment. In doing so, task accuracy is artificially restricted and reaction time (RT) better characterizes the variance in task performance; yet in clinical imaging studies, to date, RT has been under-examined.

Imaging data have little meaning without a behavioral reference point, and what requires emphasis is the very long history dedicated to understanding the relationship between accuracy, RT, and task load manipulations (see Donders, 1969; Sternberg, 1969; Treisman & Souter, 1985). There are important differences in the types of information provided by measures of accuracy and RT and by examining accuracy in isolation, there is critical variability in behavioral performance that has been under-examined in clinical functional imaging studies of WM. For example, RT has been shown to be more sensitive than response accuracy in predicting PFC involvement during

tasks of speeded processing and WM; RT has been shown repeatedly in healthy adults to maintain a positive relationship with the extent of neural activation in PFC (Bergerbest et al., 2004; Durston et al., 2003; Rypma et al., 2002; Rypma & D'Esposito, 2000).

At least one clinical imaging study of WM has incorporated information about RT noting a relationship between RT and neural recruitment, even when the rate of accuracy was comparable between groups (Chang et al., 2001). Chang et al. (2001), examined individuals with HIV demonstrating that, compared to accuracy, RT maintained a greater correlation with neural recruitment (e.g., % signal change, extent of activation) in PFC. These findings are important for the current review primarily because of the assumption often presented by examiners of WM dysfunction: if there are no between-group differences in task accuracy, the differences in task-related brain activation indicate permanent changes in the representative neural network. This method for equating behavioral performance between groups is problematic, because it may be insensitive to very fundamental between-group differences in information processing speed/efficiency.

Current Findings in Clinical Imaging of WM

Nearly all imaging studies of WM dysfunction have noted some difference in the brain "activation" between clinical samples and healthy adults. When the results of these studies are considered together, the primary findings are remarkably consistent (see Table 1 for a summary). With few exceptions, WM is associated with increased neural activity, or more elaborate neural networks (i.e., "dispersion"), in clinical samples, and a primary site of additional neural recruitment has been ventrolateral and dorsolateral prefrontal cortex (VLPFC and DLPFC).

Despite the striking consistencies in the findings summarized in Table 1, interpretations of these findings vary, with investigators commonly arriving at one of two general conclusions. In studies of more severely impaired samples, where cognitive deficits are conspicuous, and therefore evident when measuring task accuracy alone, a negative relationship between performance and activation has been observed. These findings have been believed to represent "neural inefficiency" and increased activation in PFC and other regions has been linked to diminished performance (Chang et al., 2004; Chiaravalloti et al., 2005; Christodoulou et al., 2001; Hillary et al., 2003; Perlstein et al., 2004). In cases of mild brain dysfunction, where task accuracy alone may not differentiate the clinical and control groups, examiners have interpreted the recruitment of neural resources as "compensatory" and operating to bolster performance (Audoin et al., 2003; Lange et al., 2005; Maruishi et al., 2007; McAllister et al., 1999, 2001; Penner et al., 2003; Staffen et al., 2002) or, alternatively, as reflecting more permanent brain changes or "brain reorganization" (Audoin et al., 2005; Chang et al., 2004; Forn et al., 2006; Forn et al., 2007; Mainero et al.,

2004; Mainero et al., 2006; Pantano et al., 2006). These last two interpretations (compensation and brain reorganization) have been based on the observation that between group differences in task accuracy are negligible (e.g., between group *t*-tests were non-significant).

For example, by selecting individuals diagnosed with MS who did not exhibit obvious cognitive deficits (Forn et al., 2006, 2007), investigators have attempted to control the performance-activation confounds endemic to clinical imaging studies (see Price & Friston, 1999; Price & Friston, 2002). The investigators interpreted increased PFC activation during WM performance in this MS sample as "reflective of the existence of neural reorganizational processes" (Forn et al., 2007). However, for reasons emphasized earlier, it remains quite possible in this study and others comparing accuracy alone that subtle, but consequential, processing speed differences were present.

What is at issue here is the "dilemma" that is central to this paper: if the areas believed to represent genuine reorganization in any given neural network directly fluctuate with changes in task performance, and these areas overlap neuroanatomically with support areas observed in healthy adults, it is difficult to conclude that group differences represent brain reorganization. Support for a brain reorganization hypothesis in PFC requires that the "recruited" brain region is not a load-dependent support mechanism operating identically as it would in healthy adults. Making this determination is very difficult in the WM literature, because it requires methodological precision capable of separating "baseline" from "performance-dependent" neural functioning in PFC, one of the most highly flexible and interconnected substrates in the brain. A transient support mechanism such as cognitive control would operate to bolster attentional resources, would be evident predominantly during the creation of subroutines that later facilitate task performance and would likely diminish as performance increases. Because of this, dissociating the effects of normal plasticity from pathology-induced brain reorganization could be achieved by observing changes in the neural network as one practices a task (see Kelly & Garavan, 2005) or *via* longitudinal designs (discussed in greater detail later).

The conflicting explanations for what appears to be quite similar PFC recruitment across distinct clinical samples evokes an important question regarding how neural systems change in response to injury and disease. Is it possible that recruitment of neural resources in mild forms of neurological impairment represents compensation and/or reorganization operating to facilitate performance, yet in cases of more severe cognitive deficit, recruitment of nearly identical neural networks is associated with neural inefficiency and correlated with diminished performance? An explanation with greater parsimony for the convergent findings to date is that the regions consistently recruited across clinical samples represent a native support mechanism(s) (Hillary et al., 2006). This explanation remains at odds, however, with studies proposing that neural activity in PFC is facilitating performance and what must ultimately be

Table 1a. Studies revealing increased PFC and/or ACC activity as a primary finding

Author	Year	Sample	Method	Task	N	DLPFC	VLPFC	ACC	Other findings
Christodoulou et al.	2001	TBI	fMRI	mPASAT	9	—	x	—	Increased T, P
Maruishi et al.	2007	TBI-DAI	fMRI	PVSAT	12	x	—	—	—
McAllister et al.	1999	TBI-mild	fMRI	n-back	12	x	—	—	Increased R parietal
McAllister et al.	2001	TBI-mild	fMRI	n-back	18	x	—	—	Increased P
Perlstein et al.	2004	TBI	fMRI	n-back	7	x	—	—	Increased broca's
Scheibel et al.	2007	TBI	fMRI	Compatibility task	14	x	x	—	Decreased ACC, less PFC when correlated w/ accuracy
Audoin et al.	2003	CISSMS	fMRI	PASAT	10	x	x	—	Increased cerebellum
Audoin et al.	2005	CISSMS	fMRI	PASAT	18	—	x	—	—
Bobholz et al.	2006	MS	fMRI	Recognition*	36	x	—	x	—
Chiaravalloti et al.	2005	MS	fMRI	mPASAT	13	x	—	—	Increased P
Forn et al.	2006	MS	fMRI	PASAT	15	x	x	—	—
Forn et al.	2007	MS	fMRI	n-back	17	—	x	—	Increased insula
Hillary et al.	2003	MS	fMRI	DMS	8	x	—	—	Increased T
Mainero et al.	2004	MS	fMRI	PASAT, word recall	22	—	x	x	Increased inferior P, right T
Penner et al.	2003	MS	fMRI	attention, n-back	14	x	—	x	**
Sweet et al.	2004	MS	fMRI	n-back	15	x	—	x	Less activation outside WM areas
Sweet et al.	2006	MS	fMRI	n-back	15	x	—	—	Less activation outside WM areas
Staffen et al.	2002	MS	fMRI	PVSAT	21	x	x	—	Increased P
Wishart et al.	2004	MS	fMRI	n-back	10	—	—	x	Increased medial F, P
Chang et al.	2004	HIV	fMRI	visual attention	18	x	—	—	Increased right P
Chang et al.	2001	HIV	fMRI	n-back	11	—	x	—	Increased motor cortex
Ernst et al.	2002	HIV	fMRI	n-back	10	—	x	—	—
Ernst et al.	2003	HIV	fMRI	n-back	14	x	—	—	—
Caseras et al.	2006	CFS	fMRI	n-back	17	—	—	x	Increased medial F (at low loads)
Cook et al.	2007	CFS	fMRI	mPASAT	9	—	x	—	Increased Cerebellar, PCG, T
Lange et al.	2005	CFS	fMRI	mPASAT	7	x	x	—	—
Desmond et al.	2003	ETOH	fMRI	DMS	10	—	x	—	Increased cerebellum
Pfefferbaum et al.	2001	ETOH	fMRI	Spatial n-back	7	—	x	—	less DLPFC
Schweinsburg et al.	2005	ETOH	fMRI	Spatial M	15	x	—	—	Decreased L inferior F, medial F, ACC

Note. *data apply to encoding portion of recognition task only, ** in mild but not severely impaired MS.

Summary of the 33 studies reviewed, with Table 1a reporting a primary finding of increased PFC (either VLPFC, DLPFC, or both) and/or ACC involvement in the clinical sample. Table 1b consists of those studies where a primary finding was not increased PFC activity.

Abbreviations: ACC = anterior cingulate cortex, CBF = cerebral blood flow, CFS = chronic fatigue syndrome, CISSMS = clinically isolated syndrome suggestive of MS, DAI = diffuse, axonal injury, DMS = delayed match to sample task, DLPFC = dorsolateral prefrontal cortex, ETOH = alcohol abuse, F = frontal, fMRI = functional magnetic resonance imaging, IFG = inferior frontal gyrus, PVSAT = paced visual serial addition task, TBI = traumatic brain injury, T = temporal, PCC = posterior cingulate cortex, PCS = post concussion syndrome, VLPFC = ventrolateral prefrontal cortex.

determined in order to clarify this issue is the basic relationship between activation and performance in PFC.

If the recruitment of PFC resources observed in clinical samples is a natural support mechanism (e.g., cognitive control), one would also expect that this “natural” mechanism can be reliably elicited in healthy adults. In fact, examiners have repeatedly documented, that as WM load increases and performance diminishes, there exist parallel increases in PFC activation (Braver et al., 1997; D'Esposito et al., 1999;

Manoach et al., 1997; Mostofsky et al., 2003; Rypma et al., 1999). Work by Perlstein et al. (2004) comparing individuals with mild TBI and healthy adults is consistent with these reports: the investigators observed attendant changes in PFC in direct response to changes in task load irrespective of group membership. Moreover, investigations of healthy adults have demonstrated that as performance improves and a task routine is formalized, activation in PFC decreases (presumably because of diminished demand on cognitive control

Table 1b. Studies where increased PFC and/or ACC activity not found

Author	Year	Sample	Method	Task	N	Findings
Chen et al.	2003	TBI-mild	PET	spatial WM	5	mTBI had a smaller % increase in CBF in IFG
Chen et al.	2004	TBI-mild	fMRI	spatial WM verbal WM	16	less activation in the right DLPFC and a negative correlation between the BOLD and PCS severity
Newsome et al.	2007	TBI-severe	fMRI	n-back	10	greater "dispersion" of activation
Tapert et al.	2004	ETOH	fMRI	spatial WM	10	diminished BOLD in right P, right middle F, right postcentral gyrus, left superior F

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resources) (Anderson et al., 2004; Qin et al., 2004; Sohn et al., 2003; Sohn et al., 2005). One important caveat to this discussion regarding practice, learning, and activation in healthy adults is that, whereas PFC activation may diminish, the role of the ACC may increase as performance improves (Fincham & Anderson, 2006). Consistent with this, in a study directly examining cognitive control in individuals with TBI, Scheibel and colleagues (2007) revealed that poorer performance in individuals diagnosed with TBI was associated with less ACC involvement. Thus, if findings in clinical samples represent a natural support mechanism similar to what is observed in healthy adults, we would anticipate that PFC as opposed to ACC should be differentially recruited during tasks of WM. In many of the studies summarized here this is the case (see Table 1).

If the PFC recruitment observed in clinical WM studies does represent brain reorganization, what remains unclear is why the "reorganization" is so consistent given the distinct pathophysiology, disease/injury severity, and lesion constellation across clinical samples. The lack of specificity again points to a common neural support mechanism evoked during periods of cerebral challenge. If recruitment of PFC in these clinical studies is a common neural support mechanism, then it should be more closely tied to behavioral performance than the magnitude or site of pathophysiology. There is evidence that this could be the case. In one of the few MS studies to integrate information about the degree of neuropathology with functional imaging results, work by Mainero and colleagues (2004) demonstrated that lesion load, regardless of its neuroanatomical origin, was correlated with right DLFC recruitment. These findings are very similar to work using pMRS and fMRI in conjunction to examine HIV; metabolic abnormalities found in several brain regions, including right frontal white matter, midfrontal gray matter, and basal ganglia, were correlated with PFC recruitment during a WM task (Chang et al., 2004). As noted above, in MS and moderate and severe TBI, subjects with the poorest performance have been shown to exhibit the greatest right DLPFC recruitment (Chiaravalloti et al., 2005; Christodoulou et al., 2001; Hillary et al., 2003) and increased right DLPFC activity in TBI has been tied to

monotonic increases in task load (see Perlstein et al., 2004). Thus, increased PFC involvement in these studies seems to be directly influenced by task performance but it is essentially unaffected by the etiology of neurological insult or even the specific neuroanatomical substrate that is affected. Moreover, WM requires the involvement of multiple neural substrates including the ACC, parietal areas, and cerebellum, yet these areas have not been common sites of neural recruitment; regardless of the task or clinical sample, the most consistent finding has been increased PFC activity.

Taken together, there appears to be greater evidence for a general mechanism in PFC (e.g., cognitive control) that provides transient support during periods of cerebral challenge, as opposed to permanent, injury-specific changes in the functional neural networks representing WM functioning (i.e., brain reorganization). In other words, the increased activation in PFC observed in the studies summarized here may be no different from the transient waxing and waning demand on PFC resources occurring day-to-day or even moment-to-moment in healthy adults as task demands continuously change.

Testing Brain Reorganization Hypotheses

It has been proposed thus far that there are at least three mechanisms that could explain the role of PFC recruitment in WM dysfunction in the literature reviewed here. The first, brain reorganization, supposes that additional PFC recruitment reflects underlying changes in the brain structure and/or changes in the functional network associated with WM tasks. This change is presumably permanent and the recruited neural resources maintain a positive relationship between activation and performance. A second mechanism, neural compensation, as it has been defined in this literature, operates similarly to brain reorganization, (it has a positive performance/activation relationship), but, unlike brain reorganization, it does not imply permanent changes in the neural network. The difference between these two explanations is subtle and linked almost exclusively to the presumed permanence of these changes. A third explanation is that the "aberrant" PFC recruitment is neither abnormal nor permanent; it

is the same process that is observed in healthy adults, albeit at a lower threshold. For example, in work by Sweet and colleagues (2006), healthy adults recruited nearly identical right PFC resources as the MS sample but only after increases in task load. The third explanation thus offers that PFC recruitment is a native support mechanism. Based on these three explanations for the recruitment of PFC resources in WM, I propose several testable predictions:

Prediction 1

If the recruitment of PFC resources represents either brain reorganization or neural compensation, then with practice of a task, PFC activation should remain the same or increase as task facility increases.

Prediction 2

If the recruitment of PFC resources represents either brain reorganization or neural compensation, the most impaired subjects in any clinical group should demonstrate the least involvement of PFC resources.

Prediction 3

If the recruitment of PFC resources represents brain reorganization, then recruitment of neural resources should be initiated at the outset of recovery and should increase over the course of recovery as task performance improves.

The following two sections focus on methodological considerations for examining WM dysfunction and testing the predictions offered here.

Direct Examination of Performance-activation Relationships

In order to examine the predictions offered here, it is critical that one understands the basic relationship between activation and performance. This can be achieved by manipulating task load and directly examining the interaction between alterations in the task and the associated neural activity (as in Perlstein et al., 2004), or by using behavior (e.g., accuracy, RT) as a regressor during analysis. These methods permit the separation of baseline neural network from components in the neural network that modulate task performance. Additionally, such manipulations allow one to determine if there are between group differences in how an identical neural substrate is moderating performance (Perlstein et al., 2004). Thus, manipulation of task load and direct examination of task/performance relationships provide the opportunity to assess the nature of between group differences (as opposed to simply reconfirming that the groups are different).

As noted throughout this paper, much of the work to date infers that the resources recruited in PFC operate to facilitate WM performance. That is, increased involvement of PFC allows individuals sustaining neurological insult to perform comparably when compared to healthy adults. With

the exception of the work in normal aging (Davis et al., 2007; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000), however, there are virtually no WM studies to date, in healthy or clinical samples, that have demonstrated this relationship. Unfortunately, less than 1/3 of the studies reviewed here directly examined the relationship between WM performance and neural activity. If PFC recruitment in WM dysfunction does facilitate performance, we would anticipate that, in clinical samples, practicing a task would increase PFC involvement (consistent with Prediction #1). The effects of practice on neural activity have not been directly examined in clinical studies of WM dysfunction. As noted, in healthy adults it has been demonstrated that when engaged in tasks of attention, speeded processing, and WM increased task facility results in diminished, and not increased, PFC involvement (for review see Kelly & Garavan, 2005). If PFC recruitment in WM dysfunction is reflecting the need for greater attentional resources (i.e., cognitive control) as the task is more slowly processed, we would anticipate that demand on these resources would diminish as one practices the task (contrary to Prediction #1).

A separate consideration is that the influence of PFC involvement in any clinical sample may also be deduced by examining within-group variance in the BOLD response (Prediction #2). This is an important consideration, given the significant methodological hurdles involved in making between group comparisons in clinical samples. For example, according to Prediction #2, if PFC recruitment does represent brain reorganization or neural compensation, then subjects demonstrating the greatest cognitive impairment should show the least PFC involvement. Very few studies reviewed in Table 1 engage in this type of analysis and in studies where the investigators specifically provide data for the most cognitively impaired subjects (e.g., Audoin et al., 2005; Chiaravalloti et al., 2005) the opposite was shown to be true (i.e., the most impaired subjects demonstrated the greatest PFC and parietal cortex involvement). Larger sample sizes in future studies of clinical WM will permit this type of within-group analysis.

Verification of Brain Reorganization using Longitudinal Designs

If the PFC recruitment observed in this literature does represent permanent brain changes in the neural network (i.e., brain reorganization), we would anticipate that, over the course of recovery, increased involvement of PFC would operate to facilitate performance (Prediction #3). Examining the same subject during the recovery period offers the opportunity to document the consistency and permanence of the brain changes following diagnosis.

An important advantage of using longitudinal designs is that within-subject comparisons eliminate many of the methodological problems inherent in between-subjects designs, including the daunting task of guaranteeing identical performance between the clinical and comparison groups. Longitudinal designs also permit data interpretation with fewer

statistical comparisons (e.g., second level, or group analysis is often unnecessary). Given the enormous number of statistical comparisons used to determine what is and what is not “active” in each of the group representative images; without appropriate statistical control, between-group comparisons may reflect activation differences that are statistical artifact (Price et al., 2006). Therefore, in clinical studies, longitudinal designs eliminate the effects of within-group heterogeneity on statistical comparisons and provide the opportunity to examine within-subject change over time.

In addition to reducing the likelihood of obtaining spurious findings and simplifying data interpretation, longitudinal designs may help to characterize the nature of the differences that have been observed in clinical samples. It has been proposed here that transient, innate mechanisms such as cognitive control can account for many of the findings in PFC. However, this explanation is based on the current cross-sectional data that provide a “snap-shot” at one time point during recovery. What remains to be determined is the interplay between natural support mechanisms and injury/disease induced changes in WM networks over the course of recovery. This relationship is likely to be very fluid and, therefore, quite challenging to disentangle. Ultimately, cognitive control may play an important role in determining where and how plasticity is expressed in WM (Kelly & Garavan, 2005) and within-subject designs permit the opportunity to examine alterations in the neural network that are transient *versus* those that are permanent.

Finally, longitudinal methods may be useful for clarifying inconsistent or nuanced findings in the literature. For example, it has occasionally been observed that neural activity in parts of a relevant network actually *decreases* in cases of neurologic insult. The current review has focused almost solely on the increased activation typically observed in PFC and support regions for WM and processing speed. Several studies, however, have shown decreased activation in the baseline neural network when comparing clinical samples and healthy adults (Chang et al., 2001; Wishart et al., 2004). One hypothesis to be tested is that the failure to “activate” similar baseline networks may be indicative of neural disconnection, requiring an increased role of cognitive control resources. Separately, in the case of very severe pathology (e.g., late stages of Alzheimer’s disease), neural recruitment may be impossible because of significant gray matter loss and the eradication of viable neural networks. In cross sectional work, therefore, imaging results may be highly dependent upon the time elapsing between diagnosis and MRI data collection. Longitudinal designs thus allow the opportunity to examine the evolution of neural change/recovery, including potentially competing effects such as neural disconnection and the natural recruitment of cognitive control resources. Ultimately, future studies must emphasize longitudinal designs not only to definitively test brain reorganization hypotheses (such as the predictions offered here), but to address important questions regarding the time course, magnitude, and nature of the altered brain activation in clinical samples.

CONCLUSION

Clinical imaging studies have advanced our understanding of the influence of brain injury and disease on neural networks. It was the goal of this paper to integrate one specific literature and offer an interpretation that accounts for the findings to date. It has been proposed that in functional imaging studies of WM dysfunction, important methodological concerns obscure the meaning of existing findings and that the compensatory and brain reorganization hypotheses presented thus far may not fully capture the convergent data. It has been argued that a natural mechanism, cognitive control, may account for many of the findings in this literature and that this phenomenon must be accounted for in order to begin understanding brain reorganization processes in cases of brain injury and disease.

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