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Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings

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Abstract

Working memory (WM) deficits are a persistent, disabling and relatively treatment-resistant feature of schizophrenia that may underlie many cognitive deficits and symptoms. They are associated with prefrontal cortex dysfunction. While most neuroimaging studies of WM demonstrate ''task-related hypofrontality'' in schizophrenic relative to healthy subjects, several recent studies have reported equal or *increased* prefrontal activity. These findings challenge central assumptions regarding cognitive deficits and prefrontal cortex dysfunction in schizophrenia. The goal of this review is to reconcile these seemingly discrepant findings. Methodological factors addressed include the use of intersubject averaging, WM task parameters and the reliability of the measures. Factors intrinsic to schizophrenia and their relevance to the selection of experimental methods and the interpretation of group data are also discussed. Both hypo- and hyperfrontality are hypothesized to be valid and informative reflections of prefrontal cortex dysfunction in schizophrenia. Due to the heterogeneity and variability of both performance and regional recruitment in schizophrenia, whether individual data is considered, the level and type of WM demands and the composition of the sample with regard to performance deficits all influence study outcome and contribute to discrepancies. Although the prefrontal cortex is consistently implicated in WM deficits, the basis of its dysfunction and its exact contribution remain unclear. Future work might focus on delineating the exact WM processes, domains and components that are deficient. In addition, variability in behavior and activation might best be regarded as intrinsic to schizophrenia and having a neural basis that requires explanation. In combination with other techniques, neuroimaging can identify the neural circuitry responsible for WM deficits and elucidate the contribution of each anatomical component.

Keywords: Prefrontal cortex dysfunction; Working memory; Schizophrenia

Working memory (WM) is the process of actively holding information ''on-line'' in the mind's eye and manipulating it in the service of guiding behavior (Baddeley, 1992). It is hypothesized to be a temporary store whose contents are continually updated, scanned and manipulated in response to immediate information processing demands. WM prolongs responses to events to allow linkages with past memories, lexical labels and other events (Mesulam, 1998). It is a critical building block of normal

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cognition that is essential for higher cognitive functions and goal-directed behavior. Daily activities, from mentally rehearsing a phone number to considering alternative perspectives and outcomes, depend on it.

In schizophrenia, WM deficits have been demonstrated in medicated, unmedicated and medication-naive patients (Barch et al., 2001; Carter et al., 1996; Park and Holzman, 1992). They are core features of the disorder that persist throughout the course of illness (Park et al., 1999) and are relatively resistant to pharmacotherapy (Goldberg and Weinberger, 1996), although some of the newer atypical agents may partially ameliorate them (Green et al., 1997; Keefe et al., 1999; Meltzer and McGurk, 1999). They are also present in healthy relatives of schizophrenic patients suggesting that they may be a behavioral marker of genetic liability for schizophrenia (Park et al., 1995). Some investigators have hypothesized that many of the cognitive deficits and symptoms of schizophrenia stem from deficient WM processes that lead to a failure to guide behavior on the basis of internalized representations such as schemata and ideas (Cohen et al., 1996; Goldman-Rakic, 1991). WM deficits may lead to behaviors that are stimulus-bound rather than guided by context, stereotypic and perseverative. Perhaps it is on this basis that WM deficits are consistently associated with poor functional outcome (Green et al., 2000).

The participation of the dorsolateral prefrontal cortex (DLPFC) in WM is well established on the basis of evidence from single unit recordings in nonhuman primates and from neuroimaging studies of humans (Friedman and Goldman-Rakic, 1994; Petrides et al., 1993). Although the neuroanatomic underpinnings of schizophrenia remain controversial, a wealth of data from clinical, neuropsychological and eye movement studies indirectly implicates prefrontal cortex dysfunction. Neuroimaging studies have provided complementary evidence of prefrontal cortex dysfunction during WM performance in schizophrenia. These studies have generally demonstrated ''task-related hypofrontality'' (Andreasen et al., 1992; Barch et al., 2001; Berman et al., 1986, 1992; Callicott et al., 1998; Carter et al., 1998; Menon et al., 2001; Weinberger and Berman, 1996; Weinberger et al., 1986, 1988; Yurgelun-Todd et al., 1996). Compared to healthy subjects, schizophrenic subjects show a relative physiologic hypoactivity of the prefrontal cortex during task performance. Hypofrontality was first demonstrated in schizophrenic subjects during rest (Ingvar and Franzen, 1974). These findings were not consistently replicated possibly due to the substantial variability of methods, patient samples and the resting state itself (for reviews, see Andreasen et al., 1992 and Weinberger and Berman, 1996). In addition, rest may not be the appropriate state in which to demonstrate a *functional* deficit of the prefrontal cortex. Findings of hypofrontality during WM activation paradigms have been far more consistent in spite of widely varying methods, patient status and tasks employed. However, several recent functional magnetic resonance imaging (fMRI) studies have reported either equal (Honey et al., 2002) or *increased* activation of the DLPFC in schizophrenia during WM performance (Callicott et al., 2000; Manoach et al., 1999, 2000).

Neuroimaging findings (e.g., hypofrontality) continue to form the crux of many theoretical conceptualizations of schizophrenia. These recent, seemingly discrepant findings challenge central assumptions regarding prefrontal cortex function in schizophrenia by raising the question of whether task-related hypofrontality is characteristic of schizophrenia in general or restricted to particular subgroups or the use of certain methodologies. A better understanding of the factors influencing behavioral and neuroimaging outcome measures may lead to a more precise definition of the nature and complexities of WM and prefrontal cortex dysfunction schizophrenia.

Rather than providing a comprehensive review of all previous work, this manuscript addresses methodological issues pertinent to neuroimaging studies of schizophrenia. These include: the use of intersubject averaging; WM task parameters; group differences in motivation and task performance; and the reliability of the measures employed. Factors intrinsic to schizophrenic pathology, primarily its heterogeneity and variability, and their relevance to the selection of experimental methods and the interpretation of group data are also discussed. This review considers recent findings from both the normal and schizophrenia WM neuroimaging literatures to illustrate methodological considerations and, in so doing, presents an attempt to theoretically reconcile seemingly discrepant findings in schizophrenia.

1. Technical issues in neuroimaging: group averaging

Findings of hypofrontality may be an artifact of methodologies that require group averaging and for this reason mask possible structural and functional heterogeneity of the DLPFC. Group comparisons in neuroimaging studies often rely on data that is averaged across the individuals within each group. Averaging is used to enhance the signal-to-noise properties of the images. Using the averaged group data, images obtained during an experimental or task state are statistically compared to those obtained during a control or baseline state in order to reveal significant differences in regional brain activation attributable to the cognitive process of interest (contrastive methodology). Groups can then be compared on these analyzed images to determine differences in regional brain activation during task performance.

Until recently, most positron emission tomography studies depended on group averaging techniques for the power to discern significant differences in regional brain activation between conditions and between groups. fMRI studies, in contrast, usually have sufficient power to examine significant differences between conditions in individual subjects. This allows group comparisons to be made using indices of activation gleaned from both the individual subjects and from the group-averaged data.

In order to average across individuals, it is necessary to transform both the structural and functional brain images into a common space. Transformation requires the stretching and shrinking of the acquired images and may obscure individual differences in both anatomy and regional brain activation. For this reason, data derived from individual statistical maps vs. group-averaged maps methods may yield contrasting findings. This is illustrated by a recent study in which the group-averaged findings were consistent with hypofrontality—the schizophrenic group activated fewer DLPFC voxels than the healthy comparison group (Manoach et al., 2000). In the data derived from individual subjects, however, the schizophrenic subjects activated more voxels (although this difference was not significant) and showed a significantly greater magnitude of DLPFC activation. Further examination of this discrepancy between the group and the individual data revealed that the activation clusters of healthy subjects were almost three times more likely to overlap with their averaged group clusters than was the case for the schizophrenic subjects. Thus, the schizophrenic subjects were more heterogeneous in the spatial distribution of activation within the DLPFC. Because of the decreased overlap, averaging the functional images across subjects underestimated DLPFC activity in the schizophrenic subjects. Similar preliminary findings of increased spatial heterogeneity of activation in schizophrenia have been reported in motor regions during performance of a motor task (Holt et al., 1998) and in the DLPFC during performance of the *n*-back WM task (Holt et al., 1999).

There are several plausible explanations for the increased spatial heterogeneity of DLPFC activation in the schizophrenic group and work to date does not discriminate between them. The DLPFC is a highly evolved region and shows substantial variability in its location even in healthy subjects (Rajkowska and Goldman-Rakic, 1995). In imaging studies, this is compensated for, in part, by spatial normalization and image smoothing. Schizophrenic subjects may be even more variable than healthy subjects in the gross morphology and/or functional organization of the DLPFC on the basis of neurodevelopmental abnormalities. These abnormalities interact with the environment giving rise to anomalous experience that may further affect cortical development. This potential difference is difficult to measure and control in neuroimaging studies. Unlike other primates, the human DLPFC is not bounded by definitive sulcal landmarks. Because neuroimaging lacks the resolution to discern cytoarchitecture, the precise boundaries of the DLPFC cannot be identified. For this reason, the anatomic criteria applied to define the DLPFC are necessarily arbitrary and differ between studies. In addition, schizophrenics may be more variable and less efficient in their use of strategies to accomplish the task. This may also contribute to increased spatial heterogeneity.

To summarize, group averaging rests on the assumption that general principles of functional brain organization will transcend transformation. This assumption may be less valid in highly evolved areas such as the DLPFC, particularly in pathological groups characterized by anomalous neurodevelopment. In schizophrenia, group averaging may mask structural and functional heterogeneity of the DLPFC. This increased interindividual variability may render

comparisons of averaged group data misleading. In our recent study, the apparent hypofrontality of the group-averaged data indicated that schizophrenic subjects activated fewer voxels in common, not that they activated less (Manoach et al., 2000). This finding clearly needs to be replicated to determine whether the hypothesis of increased variability is supported. It is important to note that several fMRI studies using data from individual subjects have also demonstrated hypofrontality (Barch et al., 2001; Callicott et al., 1998; Stevens et al., 1998). Thus, while the use of group-averaging techniques may contribute to hypofrontality in some studies, it clearly cannot explain the finding of hypofrontality in all studies. Other factors must also be considered to account for discrepant findings and these are discussed below.

2. Choice of tasks: processes, domains and components

The seminal studies that established a direct link between deficient cognition and reduced activity of the prefrontal cortex employed the Wisconsin Card Sort Test (WCST), a standard neuropsychological instrument that is sensitive to prefrontal cortex dysfunction (Berman et al., 1986, 1992; Weinberger et al., 1986, 1988). The WCST is the most widely employed measure of executive function in schizophrenia (Green, 1998). In addition to WM, successful performance of the WCST requires sustained attention, concept formation and task switching (e.g., Sullivan et al., 1993). Therefore, poor performance and differential activation cannot be definitively attributed to a WM deficit. In addition, the complexity of the task makes it difficult to design appropriate baseline tasks to isolate WM processes for contrastive neuroimaging analyses.

Recent studies have used paradigms that constrain task demands in order to isolate WM. However, WM is not a unitary construct. It involves both maintenance and manipulation and different tasks emphasize these processes to different degrees. Maintenance refers to holding information "on-line" in the mind's eye in the absence of external stimuli. Manipulation refers to operations conducted on materials held on-line (e.g., mental arithmetic). Some tasks (e.g., the delayed match-to-sample and Sternberg Item Recognition Paradigm, Sternberg, 1966) emphasize maintenance, while others (e.g., *n*-back, Tower of London and WCST) emphasize manipulation (Fig. 1). Manipulative processes include the updating, monitoring, reordering and temporal tagging of the contents of WM.

A

1. High WM Load	2. Low WM Load	3. Baseline
Learn These 0 2 1 3 8	Learn These 7 2	Arrows
6 (foil)	7	←
1 (target)	4	→
4	8	→
2	2	←
8	3	←

B

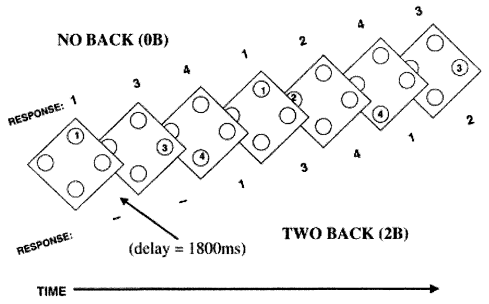

Fig. 1. (A) The Sternberg Item Recognition Paradigm (SIRP) as adapted for neuroimaging emphasizes the maintenance of information. In the working memory (WM) conditions (1 and 2), subjects memorize a set of digits (targets). This is followed by trials in which they are presented with a probe (single digit) and respond by indicating whether the probe is a target (a member of the memorized set) or a foil (not a member of the memorized set). The number of targets can be varied to produce high and low WM load conditions. Accurate responding is predicated on the internal representation of the targets in WM. In the baseline condition (3), subjects respond to the display of arrows pointing right or left by pressing the corresponding trigger. This condition has identical motor requirements but substitutes a visually guided for a memory-guided response. (B) The *n*-back WM task emphasizes manipulative processes. The no-back (0B) control task requires subjects to press a button corresponding to the currently seen number. The WM condition (2B) requires the subject to encode the currently seen number and to concurrently recall and respond to the number seen two trials previously by pressing the corresponding button. In addition to maintaining previously seen numbers, this task requires monitoring, updating and temporally tagging the contents of WM. Figure 1.(B) reproduced from Callicott et al. (2000) by permission of Oxford Univ. Press.

Maintenance and manipulation may not be entirely dissociable since maintenance may require strategic processing with increasing load (D'Esposito et al., 1998). In addition, some degree of manipulation may be necessary respond to a probe (e.g., mentally scanning the contents of WM and decision processes). There is some evidence suggesting that these processes may be mediated by different prefrontal circuitry. Dorsal regions are hypothesized to be preferentially recruited for manipulation and ventral regions for maintenance (D'Esposito et al., 1999; Petrides, 1995). However, there are numerous studies that report DLPFC activation in healthy subjects during performance of WM tasks that emphasize maintenance (e.g., delayed response tasks and variations of the Sternberg Item Recognition Paradigm) (Awh et al., 1999; Jansma et al., 2001; Manoach et al., 1999, 2000; Zarahn et al., 1999) and the degree of DLPFC recruitment is related to the number of items maintained in WM (Manoach et al., 1997; Rypma et al., 1999). These studies suggest that the DLPFC also contributes to the performance of maintenance tasks, but do not reveal the timing or nature of its contribution. Using event-related fMRI, investigators are beginning to identify unique patterns of regional activation associated with the temporally separated encoding, delay and response components of WM performance. Some event-related stuides have demonstrated that DLPFC activity is specifically associated with maintenance during the delay period (Cohen et al., 1997; Zarahn et al., 1999) while other work has demonstrated that DLPFC activity follows the delay and is temporally associated with the response to the probe (Rowe et al., 2000). Two studies have demonstrated that during the delay period, the DLPFC is active in both maintenance and manipulation trials but is significantly more active for trials requiring manipulation, even when matched for difficulty (D'Esposito et al., 1999; Postle et al., 1999). These studies support a relative functional specialization of the DLPFC for manipulative processes.

In addition to distinctions in WM *processes* and *components*, there may be regional specialization for different *domains* of information within prefrontal cortex. However, this remains a subject of debate. While some neuroimaging studies demonstrate spatial segregation of prefrontal cortex activation based on domain (see review, D'Esposito et al., 1998), others provide evidence that the same prefrontal regions subserve WM for both domains (Nystrom et al., 2000; Owen et al., 1998; Postle et al., 2000). The literature on single unit recording in nonhuman primates also provides contrasting evidence of both anatomical subdivision (Levy and Goldman-Rakic, 1999; Wilson et al., 1993) and the same neurons participating in WM for both domains (Rao et al., 1997).

Thus, functional specialization in the prefrontal cortex may exist for both processing requirements and domains (Fletcher and Henson, 2001; Petrides, 2000). Recent neuroimaging work suggests, however, that these functional distinctions may be more a matter of degree of participation than an absolute segregation (Haxby et al., 2000; Nystrom et al., 2000; D'Esposito et al., 1999; Postle et. al., 1999).

In schizophrenia, the specific WM processes, domains and components that are deficient and the networks that subserve them remain to be delineated. If there are selective rather than generalized impairments of WM, differences in the processing requirements and domains of the tasks employed may contribute to contrasting findings. Conversely, if WM processes, domains and components are anatomically segregated within the prefrontal cortex, they may be differentially affected in schizophrenia. The prefrontal cortex is not functionally uniform. Different prefrontal regions have unique patterns of connection with the rest of the brain that likely influence information processing. The identification of spared and impaired WM functions in schizophrenia may implicate specific neural circuitry and aid investigations of its pathophysiology. Suggestive evidence for selective deficits comes from a report of verbal WM deficits in the context of normal performance on a more difficult task of WM for auditory tones (Wexler et al., 1998).

3. Performance differences: motivation and capacity

Amotivation is a prominent feature of schizophrenia and represents a possible confound in studies of cognitive performance (Schmand et al., 1994). When a subject performs poorly, it is often difficult to determine whether this reflects a true information processing deficit or that the subject was unwilling or unable to exert the effort necessary for optimal performance. In addition, tasks differ in the amount of

effort required and suboptimal motivation may be more detrimental to some tasks than to others. There are few satisfactory solutions to ameliorating motivational deficits. One approach is to provide a monetary reward for correct responses. Monetary reinforcement has had mixed success in improving WCST performance in schizophrenia (Green et al., 1992; Hellman et al., 1998; Summerfelt et al., 1991). Two studies that employed a monetary reward found hyperfrontality during WM performance (Manoach et al., 1999, 2000). The investigators hypothesized that the reward enhanced motivation, task performance and activation. This is consistent with the finding that monetary reward increases DLPFC activation in healthy control subjects during performance of a task involving both inhibition and working memory (a delayed motor go no-go task) (Thut et al., 1997). It is also consistent with single unit recordings from nonhuman primates demonstrating that the activity of neurons in the principal sulcus depends on the motivational context of a task (Watanabe et al., 2002) and increases during WM delays in anticipation of a preferred reward (Watanabe, 1996). A potential contribution from motivational deficits to performance and activation differences in schizophrenia is difficult to exclude.

Findings of hypofrontality have been challenged as a possible artifact of poor task performance (Ebmeier et al., 1995). Hypofrontality and poor performance may arise from a failure of the prefrontal cortex to support behavior. Alternatively, poor performance may reflect inattention, poor motivation, the use of an inappropriate strategy or that the task was simply too difficult and for these reasons result in hypofrontality (Frith et al., 1995). Schizophrenic subjects generally perform significantly worse than healthy subjects on WM tasks both in terms of reaction time and accuracy. These performance differences are likely to be reflected in regional brain activation. There is accumulating evidence suggesting that whether a study finds hypo- or hyperfrontality depends, in part, on task performance in the schizophrenic vs. the comparison group. Task performance depends on WM load, the time allotted for a response and the degree of cognitive impairment. WM load can be defined as the level of task demand with regard to the amount of information that has to be maintained and the manipulative processes required.

In healthy subjects, DLPFC activation increases parametrically with WM load (Braver et al., 1997). However, when WM load exceeds an individual's capacity to manage this material, DLPFC activation decreases (Callicott et al., 1999; Goldberg et al., 1998). These findings suggest a nonlinear relationship between DLPFC activation and WM load (Fig. 2). A

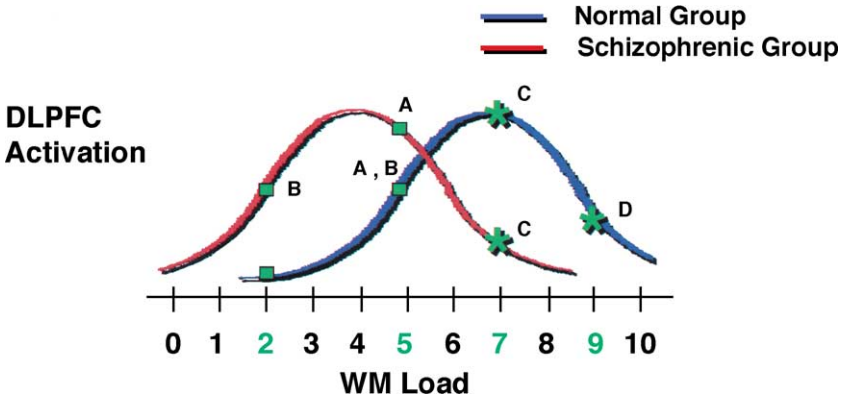

Fig. 2. A depiction of the hypothetical relationship of DLPFC activation to working memory (WM) load in the healthy and schizophrenic groups. This figure also provides a schematic illustration of relevant findings from Manoach et al. (1999, 2000). (A) Schizophrenics show increased DLPFC activation in the high WM load condition (five targets) relative to healthy subjects. (B) When task performance is matched by comparing the schizophrenics in the low WM load condition (two targets) to healthy subjects in the high WM load condition (five targets), DLPFC activation does not differ. (C) If WM load was increased, one would expect relative hypofrontality in the schizophrenic group. These data points are represented by an asterisk as they have not yet been tested. (D) One might also expect that if the WM capacity of normal subjects were exceeded, they too would show reduced DLPFC activation.

similar model has been proposed elsewhere (Callicott, 2001). Increased WM load leads to increased DLPFC activation, but only up to the point that task demands are manageable. When the demands exceed capacity, either in terms of WM load or the pace of stimulus presentation, subjects may engage cognitive and affective processes that are unrelated to WM and DLPFC activation may diminish. These processes may include error-monitoring, attempts at compensation, disengaging from the task, feeling overwhelmed and guessing.

Several studies reported increased DLPFC activation when schizophrenic subjects performed above chance but worse than healthy subjects (Callicott et al., 2000; Manoach et al., 1999, 2000). Increased DLFPC activation and poorer performance may reflect that given identical task demands, performance is more effortful or less efficient. In other words, WM capacity is reduced. As a reflection of this reduced capacity, in the proposed model, the curve that describes the schizophrenia group's DLPFC activation as a function of WM load is shifted to the left (Fig. 2). The findings of the Manoach et al. studies are consistent with this model. Using the Sternberg Item Recognition Paradigm, the schizophrenic group was hyperfrontal relative to the comparison group at a WM load of five digits (Fig. 2A) (Manoach et al., 1999, 2000). Under conditions of matched performance, the magnitude of DLPFC activation did not differ (Manoach et al., 2000). Matching for performance was achieved by comparing groups across WM loads (e.g., healthy subjects at five digits were compared to schizophrenic subjects at two digits, Fig. 2B). Three other recent studies have reported equivalent prefrontal activation with matched performance using the *n*-back task, two by comparing across WM loads (Callicott et al., 2000; Perlstein et al., 2001) and one by comparing groups at a low WM load (Honey et al., 2002). The proposed model predicts that hypofrontality would be the likely outcome of using WM loads that exceed the capacity of schizophrenic but not control subjects (Fig. 2C). In schizophrenia, this would lead to a breakdown of performance and decreased DLPFC activation. In control subjects, the increased demand would render the task more challenging, but not overwhelming. It would be associated with decreased performance and increased DLPFC activation. Preliminary findings using the *n*-back task support these predictions (Jansma et al., 2002). WM was tested over a range of loads in healthy control and schizophrenic subjects. Relative to controls, schizophrenic subjects exhibited equal or increased DLPFC activation at low and intermediate WM loads and decreased activation at a high load. Previous studies that employed tasks with high WM demands may have exceeded the WM capacity of schizophrenic subjects and consequently found hypofrontality. One might also expect reduced DLPFC activation to result from exceeding the WM capacity of healthy subjects (Fig. 2D). This is consistent with the findings of an 'inverted-U' shaped neurophysiological response in DLPFC as WM load increases (Callicott et al., 1999). Healthy subjects, however, might be expected to show a more gradual decline in performance and activation than schizophrenic subjects in response to increasing WM load. This difference would be expected on the basis of their increased ability to invoke strategies to manage the increasing load (e.g., skipping certain stimuli).

The proposed model can also be invoked to resolve discrepancies in the observed relations of activation to performance within the schizophrenia group. While Manoach et al. (1999, 2000) found that poor performance was associated with decreased prefrontal activation, Callicott et al. (2000) found it to be associated with increased activation and Perlstein et al. (2001) and Honey et al. (2002) found no relationship between performance and prefrontal cortex activation. Manoach et al. interpreted the decreased activation of poor performers to reflect that, in these subjects, the DLPFC was less able to support WM. In contrast, Callicott et al. interpreted the increased activation of poor performers to reflect cortical inefficiency. These findings and interpretations are not necessarily incompatible as illustrated in Fig. 3. The level of WM load and the composition of the sample with regard to WM capacity may determine both the direction of difference between healthy comparison and schizophrenic groups and whether inverse, direct or no relations between activation and performance are observed.

Clearly, the relation of activation to performance and to task demands is complex, especially in the context of pathology. It may involve a number of variables (i.e., the possibility of recruiting compensatory neural circuitry) that remain to be elucidated. In addition, the shift of the curve to the left may be too simple an explanation for deficient WM performance and activation in schizophrenia. There is also evidence

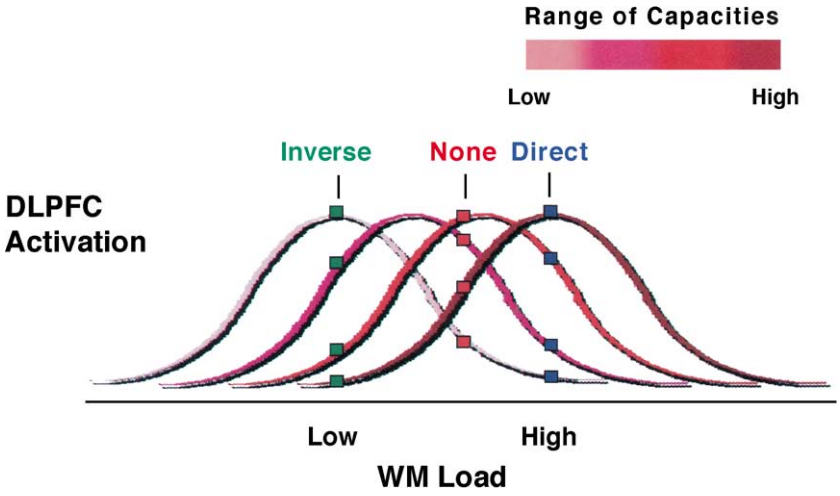

Fig. 3. This hypothetical model illustrates how the direction of the relation of performance to DLPFC activation within the schizophrenic group may vary as a function of both WM load and capacity. Each curve represents a single subject. Variations in the location and color of the curves represent a range of WM capacities. Subjects with higher WM capacity (curves shifted to the right) perform the task better. The colored squares represent a measurement of DLPFC activation at a particular WM load for each subject. An inverse relation is depicted by the green squares. The subjects with the highest capacity activate the least at a low level of WM load. At a high level of WM load, the inverse is true (blue squares), resulting in a direct relation. At a moderate level of load (red squares), the model predicts that no relation between activation and performance will be found for a group of subjects with this range of capacities.

of qualitative differences in task performance (e.g., differential ability to invoke strategies as described above and increased variability as described below). In addition, hypofrontality has been observed even in the context of intact WM performance (Stevens et al., 1998). Although the proposed model is oversimplified, it provides a basis for understanding and reconciling discrepant findings. Its explanatory power and limitations could be further evaluated by studying subjects on the same task across a range of within and above capacity WM loads and carefully characterizing activation and performance (cf., Callicott et al., 1999, 2000; Jansma et al., 2002). Consideration of such models may shift the focus of attention from hypofrontality vs. hyperfrontality to understanding the physiological basis of prefrontal cortex dysfunction.

4. Measurement issues: reliability and heterogeneity

Discrepant findings call into question the reliability of fMRI findings of prefrontal cortex dysfunction in schizophrenia. Demonstrating reliability has become particularly important since some atypical antipsychotic medications (e.g., Risperidone) purportedly improve WM deficits (Green et al., 1997) and associated prefrontal dysfunction as measured by repeated fMRI studies (Honey et al., 1999) (literature reviews and commentary on the differential effects of atypical antipsychotic drugs on cognition, including working memory, can be found elsewhere (Keefe et al., 1999; Meltzer and McGurk, 1999; Meltzer et al., 1999). Defining the neurocircuitry of this improvement is of paramount importance to further progress in understanding and treating WM deficits in schizophrenia. fMRI is a noninvasive low-risk tool that readily lends itself to repeated studies within individuals. Repeated fMRI studies have the potential to identify brain activity changes in response to interventions and thus provide a powerful technique for the assessment of efficacy in clinical trials. To evaluate the findings of repeated studies, however, it is crucial to know the test–retest reliability of the measures employed. A recent study reported highly reliable WM task performance (both accuracy and RT) in both healthy and clinically stable schizophrenic subjects (Manoach et al., 2001). Although mean RT did not change significantly from test to retest for either group, the schizophrenic subjects were more heterogeneous than

healthy subjects with regard to both the magnitude and direction of RT change across sessions. In addition, individual subjects showed greater variability of RT during each session as measured by coefficients of variation. Using activation indices derived from individuals, schizophrenics showed essentially no relation of activation across sessions and were significantly less reliable than healthy subjects in regions associated with cognition (DLPFC, intraparietal sulcus, insula). Schizophrenic subjects were comparable to healthy subjects with regard to reliability in primary motor cortex, better in supplementary motor area and worse in the lateral premotor area, regions associated with motor function.

Measurement confounds that disproportionately affected the schizophrenic group (e.g., motion) probably contributed to unreliable activation. However, they are unlikely to fully explain the findings in schizophrenic subjects given that their reliability in motor areas was comparable to that of healthy subjects. Variability of regional brain recruitment and behavior in individual subjects may be intrinsic to schizophrenia. Test–retest unreliability has been reported even for the simple demonstration of manual preference in a paper entitled, "Re-examining handedness in schizophrenia: now you see it—now you don't!" (Nelson et al., 1993). Increased variability of regional recruitment during WM performance has been demonstrated in both group (Meyer-Lindenberg et al., 2001) and individual subject data (personal communication with Dr. Meyer-Lindberg) and for performance of a simple motor task with associated decreased motor activation (Schroder et al., 1999).

Although repeated fMRI studies have the potential to detect clinically significant changes in brain activation, it is critical to understand sources of variation (both artifactual and intrinsic) and to develop reliable measures. Despite limited test–retest reliability among schizophrenic subjects as individuals, averaged over the group, the identical network of structures were activated at both sessions (Manoach et al., 2001).

5. A theory of WM deficits in schizophrenia: deficient automation

One speculative explanation of reduced capacity and increased variability is that schizophrenics fail to automate WM task performance. Automation refers to using experience to shape the optimal spatiotemporal pattern of activity in neural circuitry. Automation leads to increased efficiency and decreased variability of behavior. In the motor system, the DLPFC and striatum are activated while learning a task (Jueptner and Weiller, 1998). DLPFC activation is no longer present after the task becomes automated (overlearned) as a result of practice but returns if subjects must again attend to the task (Jueptner and Weiller, 1998). While frontostriatal circuits are usually associated with the regulation of voluntary movement, accumulating evidence suggests that they are also intimately involved in regulating cognition and, in particular, WM (Alexander et al., 1986; Houk, 1997, 2001; Houk and Wise, 1995).

Striatal neurons have extremely high degrees of convergence from cortical afferents, making them well suited for contextual event detection. In addition, striatal neurons receive input from dopamine neurons that appears to adjust the weights of their corticostriatal synapses (Wickens and Kotter, 1995). Dopamine neurons signal predictions of reward (Schultz et al., 1997). Under these influences, striatal neurons could learn to recognize contexts that are associated with reward and to disinhibit prefrontal-thalamic modules whose firing contributes to reward attainment (Houk and Wise, 1995).

Based on analogy with the motor system, if a cortical neuron repeatedly responds to its basal ganglionic inputs by firing in a particular manner, it should learn intracortical associations capable of causing the neuron to fire in a rapid, automatic manner whenever the same circumstances are repeated (Houk, 2001). As the intracortical mechanisms acquire automatic responding, the participation of the basal ganglia is expected to diminish. If automation was to occur for a well-practiced WM task, the task might become increasingly mediated by intracortical connections. If difficulty increased or task demands changed, one might expect to see a return of prefrontal and striatal activation as is seen in the motor system (Jueptner and Weiller, 1998). This might explain observations of basal ganglia activation in healthy subjects during WM performance in association with increased task difficulty (Barch et al., 1997; Owen et al., 1996). This model is also consistent with findings of decreased DLPFC activation and improved performance in

healthy subjects during a practiced (more automatic) vs. novel version of the Sternberg Item Recognition Paradigm (Jansma et al., 2001) and the spatial delayed match-to-sample task (Garavan et al., 2000).

Frontostriatal neural circuitry is dysfunctional in schizophrenia (e.g., Buchsbaum et al., 1992) and this dysfunction has been hypothesized to account for WM deficits (Pantelis et al., 2001). A failure of automation during WM performance in schizophrenia can be invoked to explain recent findings (Manoach et al., 2000, 2001). It may be reflected in findings of worse and more variable task performance and increased recruitment of basal ganglia which may, in turn, recruit the DLPFC to a greater degree and in more variable locations relative to healthy subjects (Manoach et al., 2000). Evidence consistent with defective automation in schizophrenia is also found in studies of visual and auditory perception. Although schizophrenia subjects can process information to which the visual system is "hard-wired" to respond, they are deficient in consolidating novel, unstructured information into memory traces. This limits the generation of top-down strategies to guide further processing that, in healthy subjects, quickly become automated (Knight et al., 2000; Knight and Silverstein, 1998; Silverstein et al., 1996a, 1998). Studies of auditory processing similarly reveal that schizophrenic subjects have an intact ability to group auditory stimuli on the basis of their physical characteristics but an impairment in using contextual information to guide their perceptual processes (Silverstein et al., 1996b).

6. Conclusions

Findings of both hypo- and hyperfrontality during WM performance are likely valid and informative reflections of prefrontal dysfunction in schizophrenia. They are consistent with clinical and neuropsychological studies that implicate the prefrontal cortex in a range of symptoms and cognitive deficits. Whether a particular study finds hypo- or hyperfrontality may depend on a number of variables. Methodological factors include: whether individual as well as group data is considered; WM task parameters with regard to the domain of information represented and the processes required; whether an incentive is provided; and the level of WM load. Variables intrinsic to schizophrenia include the degree of WM impairment (capacity) and the heterogeneity and variability of the cognitive manifestations of schizophrenia. Schizophrenic samples are hypothesized to be more heterogeneous than healthy comparison groups with regard to the structure of DLPFC, the magnitude and location of DLPFC activation and the strategies used to accomplish a task. Individuals with schizophrenia show more variable task performance within sessions and less consistent recruitment of critical brain regions across sessions. This review has not addressed the potentially important contributions of medication effects, symptom presentation and chronicity to the heterogeneity of schizophrenic samples and to discrepant findings.

The findings reviewed suggest that group-averaging techniques may be misleading in schizophrenia and that repeated fMRI studies should demonstrate that the measures employed are reliable in schizophrenic as well as healthy subjects. Even the consideration of individual data may present challenges. For example, in event-related fMRI studies, it remains to be seen whether schizophrenics show increased temporal variability of hemodynamic responses. This would lead to decreased amplitude of the averaged hemodynamic response. The findings also emphasize the importance of minimizing artifactual sources of variability (e.g., motion) (Weinberger et al., 1996) and accounting for group differences in task performance. Future studies might focus on delineating the exact WM processes, domains and components that are deficient in schizophrenia. Delineating selective deficits may aid investigations of neuropathology and identify intact function and circuitry for rehabilitation. Finally, rather than treating variability as a measurement confound, it may be more productive to regard it as intrinsic to schizophrenia and having a neurological basis that requires explanation.

The findings reviewed consistently implicate abnormal prefrontal function in WM deficits in schizophrenia, but the basis of this abnormality is not well understood. This review has only touched on the important issue of interactions of the DLPFC with other brain regions subserving WM. WM deficits are more likely to reflect dysfunctional neural circuitry rather than pathology at a single site (e.g., the DLPFC). This is consistent with recent fMRI findings suggestive of altered functional connectivity in WM

networks (Meyer-Lindenberg et al., 2001). In addition, research investigating the relations of WM deficits to markers of structural integrity of the prefrontal cortex (Callicott et al., 2000), genotype (Egan et al., 2001) and symptom presentation (Andreasen et al., 1992; Menon et al., 2001; Perlstein et al., 2001) may illuminate their neural basis. While neuroimaging identifies brain regions associated with task performance, it does not reveal which regions are critical or their exact contribution. In combination with other techniques (e.g., transcranial magnetic stimulation and magnetoencephalography), neuroimaging can identify the anatomical components of the neural circuitry responsible for WM deficits in schizophrenia and elucidate their contribution.

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