Working Memory Impairments in Schizophrenia: A Meta-Analysis.

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Working memory impairments in schizophrenia: A meta-analysis

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Abstract

Working memory (WM) deficit is a cardinal cognitive symptom of schizophrenia but the differences among the tasks and measures used to assess WM make it difficult to compare across studies. We conducted a meta-analytic review to address three major questions: 1) Do schizophrenia patients show WM deficits across diverse methodology? 2) Is WM deficit supramodal? and 3) Does the WM deficit worsen with longer delays? The results indicate that significant WM deficit was present in schizophrenia patients in all modalities examined. Increasing the delay beyond 1 second did not influence the performance difference between normal and schizophrenic subjects in WM. These results suggest that WM deficit in schizophrenia is modality-independent and that encoding and/or early part of maintenance may be problematic.

Schizophrenia is a complex brain disorder characterized by clinical heterogeneity and deficits of cognitive functions such as distractibility, perseveration and inability to inhibit irrelevant information or responses. Although much was already known about the neuropsychological profile of schizophrenia patients in the 1980s, it was not until the early 90s that researchers began to look towards the emerging field of cognitive neuroscience for a conceptual vessel that could integrate the diverse and seemingly heterogeneous neurocognitive deficits of schizophrenia with a focus on working memory.

Since the publication of the first article demonstrating the presence of working memory deficit in schizophrenia (Park & Holzman, 1992), working memory research has become central to studies of neurocognitive deficits in schizophrenia. Accumulating evidence indicates that working memory deficit is a core feature of schizophrenia (Cohen and Servan-Schreiber, 1992; Goldman-Rakic, 1994; Gold et al., 1997), but the source of the deficit is not yet clearly elucidated.

Baddeley (Baddeley, 1986) originally defined 'working memory' as an active short-term memory consisting of a central executive and modality-specific slave system. Since then, the concept of working memory has evolved into different forms, depending on the theoretical research framework. For example, Kieras, Meyer, Mueller, and Seymour (1999) regarded working memory as an entire system of temporary stored codes, human knowledge representation and procedures, whereas Ericsson and Delaney (1999) conceptualized working memory as a component of long-term memory system whose function is to maintain selective access to information that is needed to complete a task with unlimited capacity. Engle and his colleagues (Engle et al., 1999) also considered working memory as a system consisting of active long-term memory traces

active above threshold plus controlled attention. In neurophysiology or behavioral neuroscience literature, working memory is often defined as the system that maintains task-relevant information 'on-line' for a short period of time (e.g., Goldman-Rakic, 1991). Therefore, depending on the theoretical and empirical framework adopted, definitions, approaches and experimental paradigms concerning working memory in schizophrenia vary significantly across different studies.

Although some investigators in schizophrenia research have adopted working memory tasks developed in cognitive psychology or behavioral neuroscience, the more dominant trend in psychiatric and clinical fields has been to use available neuropsychological tasks that are hypothesized to tap working memory. However, most of the available neuropsychological tasks were not developed to probe working memory per se, and thus it is not so clear what function(s) they are testing. For example, the Wisconsin Card Sorting Task (WCST) has been used in several studies to measure working memory deficits in schizophrenia (Bertolino, Esposito, Callicott, Mattay, Van Horn, Frank, Berman, & Weinberger, 2000; Schroder, Tittel, Stockert, & Karr, 1996). Though working memory is important for successful performance in the WCST, there are several other cognitive functions necessary to perform the WCST, such as deducing a rule, planning, inhibition etc. Therefore, it is not easy to decide whether or not poor performance of schizophrenia patients in the WCST results from working memory deficits or other cognitive dysfunction. Considering diverse methodology and paradigms used to study working memory in schizophrenia, it is not surprising to find studies that have failed to show working memory deficits in schizophrenia. Yet, the field as whole has accepted working memory deficit as a fact without definitive quantitative evidence.

Therefore, it is necessary to investigate whether working memory deficits in schizophrenia do exist across very heterogeneous and diverse approaches and paradigms.

The present study was designed to evaluate the consistency and strength of working memory deficit in schizophrenia using quantitative meta-analytic review of published studies. The main research question we were interested in answering was whether schizophrenia patients show consistent working memory deficits. Two important aspects of the present study regarding this question were: 1) the reason for a quantitative review, and 2) how to refine the definition of working memory. Although it is generally accepted that schizophrenic patients show working memory deficits, there is no study that verifies the validity of this statement with a quantitative technique. Meta-analysis is a powerful quantitative tool that allows us to test hypotheses across diverse methods, techniques and paradigms (Cooper & Hedges, 1994). By focusing on the effect size, the meta-analysis provides a technique for examining the magnitude and the consistency of evidence (i.e., effect size d or r) across different studies instead of relying on the significance test of the findings. Effect size analysis allows us to avoid the pitfalls of null hypothesis-statistical significance testing, such as faulty conclusions about hypothesis that are based on a count of significant and non-significant studies. Variability of effect sizes across studies can be indexed by common statistics such as standard deviations and confidence intervals as well as the homogeneity test statistics of effect size estimates.

One pivotal aspect of our review concerns the concept of working memory. As described above briefly, the definition of working memory depends on one's theoretical framework. However, it is of the utmost importance to define what working memory is

for the purpose of this meta-analysis, because the definition of working memory directly determines which studies are included or excluded. Miyake and Shah (1999) tackled definition of working memory by comparing the existing 10 models of working memory in terms of basic mechanisms and the nature of representations. These leading theories of working memory indicate that the core part of working memory is the system or procedure of maintaining mental representation for further processing of the representation. In this paper, we focused on the definition of working memory as a system or mechanism where information is represented, maintained, and updated for a short period of time. This definition emphasizes the process of maintaining representation active above threshold, so that the activation of information relevant to the current task can be maintained under the focus of attention, particularly when individuals experience interference from internal or external events. Maintaining the mental representation under the focus of attention in the presence of distraction, internal or external, also requires updating of the representation. This definition separates working memory from 'traditional' short-term memory by emphasizing the maintenance of representation the focus of attention. Short-term memory, which is closely related to working memory, is a more passive system where items (either encoded or transferred from long-term memory and activated) decay quickly, especially when interference is present (i.e. Cowan, 1988). Indeed, short-term memory tasks such as forward digit and spatial span tasks, despite their surface similarity to some working memory tasks do not necessarily tap working memory (Engle, Tuholski, Laughlin, & Conway, 1999).

By choosing a more process-oriented definition, we can further focus on other yet equally important questions of working memory deficits in schizophrenia: 1) whether

schizophrenia patients show differential deficits in working memory task depending on which kind of material, the modality of information (i.e. verbal, visuospatial), is primarily required to be maintained in a specific task, and 2) to what extent the delay, the period when representation should be kept in working memory, affects performance of schizophrenia patients. A few previous studies implemented working memory tasks in more than one modality (e. g., Park & Holzman, 1992; Spindler, Sullivan, Menon, Lim, & Pfefferbaum, 1997; Barch et al., 2002; Fossati et al., 1999; Pukrop et al., 2003), but it is not clear whether schizophrenia patients show differential deficits in tasks based on the modality of information in working memory. For example, Pukrop et al. (2003) measured verbal and visuo-spatial working memory by using letter number span and visuo-spatial delayed response task, respectively, but they did not examine whether schizophrenia patients showed more severe deficit in one modality compared to the other. This question is also important for understanding the biological mechanism of working memory deficits in schizophrenia, considering that different parts of the prefrontal cortex are involved with each modality of representation in working memory (i.e. D'Esposito, Aguirre, Zarahn, Ballard, Shin, & Lease, 1998; Goldman-Rakic, 1999). For example, Smith and Jonides (1999) suggest that domain specificity in working memory may be reflected in the lateralization of activation (e.g., language related information activates left frontal lobe and spatial information activates right frontal lobe). Therefore, it is of interest to examine whether modality-specific systems are differentially impaired in schizophrenia to understand the role of working memory deficits in schizophrenia comprehensively and bridge the gap between cognitive dysfunction and neurobiological abnormalities in schizophrenia.

In addition to examining the effect of modality, we examined how the duration of delay may affect working memory deficits of schizophrenia patients. The delay periods vary widely across the studies of working memory and may have differential effects on schizophrenic patients compared with normal controls. Lengthier delays may result in greater working memory deficits in schizophrenic patients because the likelihood of disrupting mental representation or being distracted by internal or external events (e.g., hallucination or noise) may increase with time especially if they are disproportionately vulnerable to interference. It is also possible that there is temporal gradient of vulnerability to disruptions during the delay. The time course of vulnerability to distraction may change such that disruptions may be more detrimental at the beginning of the delay period where the mental representation is not yet fully consolidated (Vogel, Woodman, & Luck, in press; Woodman & Vogel, in press). However, it is also possible that increasing the delay may have no incremental effect on working memory errors in schizophrenia patients. If internal representations are not formed during the encoding stage, then there will be a working memory error regardless of the duration of the delay Similarly, if a wrong stimulus is encoded, the result would be an error no matter how short or long the delay period may be. Finally, even if longer delays increase errors in schizophrenic patients, normal subjects may also be equally vulnerable such that the group difference (i.e., the extent of the deficit) may remain stable. We examined the effects of the length of the delay on working memory in schizophrenia patients across studies in our review in order to further elucidate the nature of working memory deficits in schizophrenia.

In summary, this meta-analysis study intended to quantify the general, qualitative statement of working memory deficits in schizophrenia. By choosing the process-oriented definition of working memory, we tried to untangle confusion over diverse methodology in the field. Three main questions we addressed were: 1) are working memory deficits in schizophrenia consistent cross studies? 2) if so, do working memory deficits in schizophrenia vary depending on the modality of the task used in studies or are they independent of the modality of working memory task? And 3) do schizophrenia patients show differential deficits in working memory task depending on the length of delay?

Method

Literature Search

To identify relevant articles, literature searches were conducted with searches of computerized database including PsychInfo and Medline and manual searches of the bibliographies of recent review (Park & Lee, 2002). Since the main question of the present article is whether the qualitative statement of working memory deficits in schizophrenia can be held through a meta-analysis, the terms for the literature search were selected to include the maximum number of articles of working memory and schizophrenia. In this study, working memory is considered as a system or mechanism where information is represented, maintained, and updated for a short period of time. The tasks that are thought to measure working memory are the followings: the delayed-response task, the delayed-matching-to-sample-task, the n-back task, the 'span' task (digit and spatial backward span tests, reading span, speaking span, letter-number span and mathematical span), AX-continuous performance test with a delay, and spatial

working memory task from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Based on these tasks, the followings terms were used to locate relevant articles in the computerized search: working memory and schizophrenia, verbal span and schizophrenia, spatial span and schizophrenia, and continuous performance task (or test) and schizophrenia. The articles located by the computer and manual search were limited to peer-reviewed articles written in English.

Among nearly 600 studies found with two methods, the following criteria were applied to select articles for this review: First, studies must be published between 1980 and September 2004. The year 1980 was chosen as a year of publication criterion because it corresponded roughly to the introduction and use of more systematic and reliable diagnostic criteria for schizophrenia such as the Diagnostic and Statistical Manual of Mental Disorders (DSM, 3rd edition, American Psychiatric Association, 1980). The year 2004 was chosen as an upper limit to ensure maximal coverage of the literature by the computer-based journal database. Studies must also have a research design with a control group comprising healthy participants and an experimental group consisting of patients with schizophrenia. Schizophrenic patients must meet diagnostic criteria for either the DSM (3rd or 4th edition, American Psychiatric Association, 1980, 1994) or the International Classification of Disease (ICD-9 or 10, World Health Organization, 1978, 1992) and have satisfied these criteria on the basis of a structured clinical interview or the diagnosis of psychiatrists. Additionally, studies must include one of the working memory tasks listed above. The studies were further specified based on which modality of representation is required to perform the task: verbal and visuo-spatial. And finally, studies must include statistics convertible to effect size r (e.g., mean, standard deviation,

F, t or the significance value). If studies met the previous three criteria, but did not present statistics, a direct contact to author(s) via e-mail was conducted to request statistics[1]. Among articles found through the search of computerized databases and the manual search, 124 studies were selected for this review after applying these criteria[2].

Coding of Study Characteristics

Recorded variables for every article used in meta-analyses included the journal name, author(s), and the date of publication of the articles, the number of subjects in each group (schizophrenia group and healthy control group), working memory tasks used in studies, and the statistics that are convertible to effect size.

Calculation of Effect sizes and Data Analysis

Effect size (r) was calculated based on reported statistics (Rosenthal, 1991). When means and standard deviations in each group were reported, Cohen's d was calculated with these statistics first and Cohen's d was converted to effect size r. If studies did not report means and standard deviations, effect size r was calculated with reported t, F statistics or the significance values.

A number of studies included in this review used several measures to examine working memory in schizophrenia, and therefore it was possible to calculate more than one effect size estimates for one study. In addition the same research team may conduct a series of studies included in this review so the participants may be overlapped across studies. Because the measures of each subject are correlated, the effect size estimates

[1] Studies where we were not able to contact the authors and/or access their data were excluded from this review.

[2] 124 studies included in this review were indicated with an asterisk in a reference section.

from these studies are likely to be correlated within studies or among studies. There are several approaches to resolve dependencies among effect size estimates (i.e., Gleser & Olkin, 1994). If the estimates of the covariance structure among the correlated effect sizes are known, a multivariate method can be applied to produce the most precise effect size among the estimated effect sizes (Gleser & Olkin, 1994). However, none of the studies included in the review provided the covariance structure of correlated effect sizes, nor were published covariance structure among several measures of working memory tasks available. Therefore, when several effect size estimates were computed within studies, two decisions were made based on the research question of interest. To examine the general working memory deficits and the effect of stimulus modality on working memory deficits in schizophrenia, the median of all possible effect size estimates was selected in each modality of working memory task within individual studies. However, no correction was applied to potentially correlated effect size estimates from studies that were conducted by same research groups (therefore possibly using overlapping set of subjects) because of lack of available information on covariance structure. For the relationship between the length of the delay and working memory deficits in schizophrenia, the median effect size estimate was chosen for each delay (if more than one delay was used) per each study.

An unweighted average effect size estimate and corresponding 95% and 99% confidence intervals (CI), the coefficient of robustness (CR), and a measure of effect size homogeneity, the Q statistic, were calculated across studies (Rosenthal, 1991, 1995; Shadish & Haddock, 1994). CI's that excluded zero were considered significant. CR, the mean effect size divided by the standard deviation, provides an index of the stability and

replicability of the average effect size. The Q statistic has a chi-square distribution with (k-1) degrees of freedom, where k is the number of effect sizes being combined. The critical alpha for the Q statistic was set at .05.

Insert Table 1

Result

Effect Sizes, Significance Testing and the Effect of Modality

124 studies published between 1980 and 2004 were included in the present study and 129 effect size estimates were computed based on statistics reported in studies (Table 1). Table 2 contains a stem and leaf display of the effect size of the studies in the meta-analysis. Table 3 contains additional information about central tendency, variability, significant tests, and confidence intervals.

Insert Table 2

Insert Table 3

All results showed a positive effect size for the working memory impairment in schizophrenia. The unweighted mean effect size from all working memory tasks was .452, and the result of t-test for mean effect size was significant. This significant t-test of effect size estimates indicates that schizophrenic patients showed deficits in working memory. The 95% confidence interval suggests the likely range of effect sizes to be from .106 to .798. The Q statistic showed the heterogeneity among effect size estimates included in this review.

To investigate whether schizophrenia patients show differential deficits depending on the modality of working memory tasks, studies were classified and compared. These categories and their respective results are displayed in Table 4. Z test was performed to find whether differences in modality of working memory task would lead to disparate results. The contrast analysis (visuospatial WM vs. verbal WM, Z=. 011) showed no significant difference among modalities of working memory tasks. The size of the coefficient of robustness, however, suggests that there are more consistent impairments in visuospatial working memory tasks than in verbal working memory task in schizophrenia patients.

Table 4

The Length of the Delay and Working Memory Deficit

To examine whether increasing the duration of the delay period may increase working memory deficits in schizophrenia, 65 effect size estimates from studies, which specified the delay component, were included in this analysis. When several working memory tasks were used in a study, the median value of effect size estimates was chosen for each specific delay period. Correlation analysis showed that increasing the delay did not increase working memory deficits in schizophrenia beyond one second, which was the shortest delay duration reported in these studies (see Figure 1.)

Figure 1

File Drawer Analysis

It is likely that studies with non-significant results would be less published. Due to this 'file drawer problem', studies included in this meta-analysis are not likely to be a random sample of all studies actually conducted on working memory and schizophrenia. For the probability for this meta-analysis to become non-significant ($p>.05$), there would have to be 1560 studies with mean probability of .05 remaining squirreled away in the file drawer (Rosenthal, 1991).

Conclusion and Discussion

To our knowledge, this is the first quantitative meta-analytic study of working memory deficits in schizophrenia. The result of the meta-analysis showed that working

memory deficits in schizophrenia are reliably found across very diverse methods and approaches. Furthermore, the present study indicates that working memory deficit is present in schizophrenia independent of the specific modality of the task. This suggests that common cognitive process necessary to perform working memory tasks may be abnormal in schizophrenia in addition to any problems that may be specific to the modality-specific systems. Although there was no significant difference in the effect sizes in relation to the modality of working memory, visuo-spatial working memory deficit in schizophrenia seems to be more consistent and robust than deficits found in verbal working memory, as observed in the size of the coefficient of robustness. Finally, increasing the duration of the delay beyond 1 second did not result in greater working memory deficit in schizophrenia patients compared with normal controls.

The consistent finding of working memory deficits across 124 studies strongly supports the important role of working memory deficits in unraveling the mystery of schizophrenia. This study clearly showed that working memory deficit is not an artifact of specific characteristic of a task. That is, working memory deficits were present regardless of specific stimulus modality of tasks or the duration of the delay periods. In addition, working memory deficits have been found in biological relatives of schizophrenia patients (Park et al, 1995a; Myles-Worsley & Park, 2002; Conklin et al., 2000) and healthy individuals with schizophrenia characteristics (Park et al., 1995b; Park & McTigue, 1997; Tallent & Gooding, 1999). These studies as well as the results of the present study suggest that working memory deficit is a strong candidate of endophenotype marker of schizophrenia patients.

Furthermore, the consistency of working memory deficit in schizophrenia across the stimulus modality of the tasks suggests a potentially fruitful strategy for disentangling the etiology of this impairment. Rather than focusing on the modality-specific subsystems as described by Baddeley, it may be much more useful to parse cognitive process necessary for successful performance in working memory task into dissociable, temporal components. To perform a working memory task successfully, one has to 'encode' the target, internally represent the target, maintain the mental representation of the target while inhibiting irrelevant information, and retrieve the mental representation at the right moment. Dysfunction in one of these sub-processes may result in impaired performance. Recently several studies reported that poor encoding may contribute to the working memory deficits of schizophrenia patients. Tek et al. (2002) showed that impaired perceptual processing in schizophrenia patients mediates their visuo-spatial working memory deficits. In addition, Hartman and his colleagues (2002) showed that increasing stimulus presentation duration improved the performance of schizophrenia patients in visuo-spatial working memory task. We also found a facilitation of working memory in schizophrenia patients when we increased the attentional salience of the targets (Park et al., 2001; Lee et al., 2002). Thus, inefficient encoding seems to be partly responsible for visuo-spatial working memory deficits in schizophrenia. Similar analysis of components of verbal working memory suggests an equally important role of imprecise encoding in verbal working memory deficits in schizophrenia. Future studies are needed to test this hypothesis in detail. As to what factors cause imprecise encoding, there are several possibilities. Schizophrenia patients may just simply need more time to form a mental representation as suggested by Hartman et al (2002). In addition,

schizophrenia patients may have imprecise encoding because they have difficulties in selecting relevant information or they are unable to deploy attention to the relevant feature efficiently (e.g., Braver et al., 1999; Adler et al., 1998). Such difficulties may result in imprecise encoding as well as encoding wrong stimuli. To understand what causes poor encoding, it is necessary to specify how impairments in perceptual and attentional processes may contribute to working memory deficits. However, it is also important to note that degraded or imprecise encoding alone cannot fully account for working memory deficits in schizophrenia because as Tek et al (2002) point out, even when encoding is optimized, they still observed spatial working memory deficits. In other words, working memory maintenance and retrieval also present significant problems in schizophrenia patients and future studies are necessary to specify the roles of each component in working memory deficits of schizophrenia patients.

This study showed that increasing the length of the delay was not associated with the effect-sizes of working memory deficit. That is, after 1 second delay, increasing the duration of the delay did not increase the working memory deficit further. This result suggests perhaps the importance of encoding and the early part of the delay in maintaining mental representation. If schizophrenia patients have difficulties forming mental representation that is impervious to disruptions in the first place, they may be more vulnerable to interference especially at the early stages of the delay. However, if they can maintain the representation for the crucial few seconds at the beginning, then the neural circuits that support the maintenance may have enough signal strength to continue. In other words, it may be possible that even partially consolidated images from poor encoding could be remembered. Unfortunately, merely comparing the effects of different

delay intervals does not allow us to fully investigate the temporal dynamics of working memory process. These possibilities can be explored empirically in future studies by comparing the effect of delay with optimized encoding (stable representation) versus poor encoding (degraded representation).

The length of delay did not affect the effect sizes of working memory deficit in schizophrenia. First, it is important to note that this result does not imply maintenance is unimpaired in schizophrenia. This finding shows that the group differences in working memory performance, as indexed by the effect size estimates of working memory deficit, remained stable across different delay durations. In other words, it means that schizophrenic patients make more working memory errors than normal controls at all delays but the size of this deficit is fairly stable regardless of the length of the delay. Second, there were not enough studies with variable delays in the current database to perform a comprehensive delay-related meta-analysis so this finding may not be generalized. Third, most studies included in the meta-analysis of the effect of a delay included a delay of less than 10 seconds and many of the experiments, including the N-back tasks, used delays of 1 second (Figure 1). The restricted range of the delays may contribute to the statistically insignificant relationship between the length of a delay and the magnitude of effect size estimates. A future meta-analytic study that includes various ranges of delays in working memory tasks is needed to test this hypothesis.

Our results render support for the growing view that cognitive and perceptual abnormalities may be just as important as clinical symptoms in schizophrenia. Neurocognitive deficits have been the better predictor of the social function and outcome of schizophrenia (e.g. Green, 1996) and at present, remediation of cognitive deficits is a

major goal of treatment of atypical antipsychotic drugs. Heinrichs (2001) demonstrated the strength and consistency of cognitive deficits in schizophrenia in a comprehensive and integrated synthesis of neurobiological and psychological studies of schizophrenia using meta-analytic methods. In his review, the most powerful and consistent findings in schizophrenia research were cognitive and perceptual differences between schizophrenia patients and healthy people, such as learning, reasoning, visual or auditory attention, and expressive language. Working memory is a key component of many of the tests that he included in his meta-analysis, and we augment his finding by providing the presence of working memory deficit in schizophrenia patient independent of the stimulus modality. Heinrich's findings and our finding emphasize the importance of understanding the nature of cognitive abnormalities in solving the riddle of schizophrenia.

While we interpret the results of the meta-analysis as providing evidence for the important role of working memory deficit in schizophrenia, others may argue that this result is an indicative of a generalized deficit. Many of the studies, especially those from cognitive neuroscience tradition, included control tasks to rule out other cognitive, perceptual and motor deficits that are not inherent components of working memory. These studies demonstrate that working memory deficits are present in schizophrenia patients even when other cognitive and perceptual functions are intact. In addition, working memory deficit was still found even when schizophrenic patients and the controls were matched on IQ and education (e.g., Park & Holzman, 1992). Of course, it can still be argued that the fact that schizophrenic patients perform normally on control tasks does not rule out the possibility of generalized deficit since some control tasks may not have comparable discriminating power (Strauss, 2001) but this argument seems

weakened when we consider the fact that psychometric schizotypal undergraduates show specific working memory deficits (e.g., Park et al., 1995; Park & McTigue, 1997; Tallent & Gooding, 1999), because these undergraduate students had normal or above normal IQ, showed intact performance on other neuropsychological tests, and were enrolled and taking courses at highly competitive universities (e.g., Northwestern, Cornell, Wisconsin), which suggests that they did not have generalized cognitive deficits. In other words, in individuals who carry latent liability for schizophrenia, working memory deficit is found without generalized deficits and this working memory deficit seems to be correlated with schizotypal personality traits. While this argument does not rule out the possibility of a generalized deficit as a primary cause of working memory deficits in schizophrenia and schziotypy, it suggests that it is possible to have pockets of working memory deficits without having deficits in all aspects of cognition. It seems that further work is needed to determine whether working memory deficit in schizophrenia is a differential deficit or a generalized deficit. To do so, it will be useful to focus on theoretically constrained models of cognitive deficits and parse them into testable components.

Although the results of our meta-analysis are clear, there are some caveats. First, in this review, we applied theoretically constrained and stringent inclusion criteria for working memory tasks. The concept of working memory in this study emphasizes the role of actively maintaining mental representation “on-line” while inhibiting interference or distraction. These criteria may be regarded as limited by other investigators; however, our reasons for using these strict inclusion/exclusion criteria are explicit and therefore we do not intend to generalize our finding beyond the scope of this particular analysis.

Secondly, a vast majority of the studies included in this meta-analysis examined medicated patients. Working memory deficit in schizophrenia is probably not a mere artifact of antipsychotic medication, as some studies included in this review examined unmedicated patients and still found working memory deficits (i.e. Carter, Robertson, Nordahl, Chaderjian, Kraft, & O'Shora-Celaya, 1996). Furthermore, there is also a report of beneficial effects of atypical antipsychotics on verbal working memory in schizophrenia (Green et al., 1997). However, we cannot entirely rule out the possible effects of antipsychotic medication on working memory over time. In the future, it may be possible to examine the results from studies that include only unmedicated patients to examine whether effect sizes of working memory deficit are related to medication status but at present, we do not have enough data. Third, consistent working memory deficits across diverse methods suggest working memory deficit as a possible endophenotype of schizophrenia. Several studies showed working memory deficits in healthy, unmedicated relatives of schizophrenia patients (Park et al., 1995a; Myles-Worsley & Park, 2002; Conklin et al., 2000) and healthy psychometric schizotypals (Park et al., 1995b; Park & McTigue, 1997; Tallent & Gooding, 1999). However, it was not possible to conduct a meta-analysis for those studies because there are not yet enough studies on individuals who may carry latent liability for schizophrenia. Further studies of relatives of schizophrenia patients and healthy schizotypals are necessary.

To summarize, a meta-analysis of the 124 studies on working memory deficit in schizophrenia suggests that working memory deficit in schizophrenia is robust and modality-independent. Our results support the idea that working memory deficit in

schizophrenia is consistent across different tasks and paradigms, and suggest that working memory is an integral part of the schizophrenia endophenotype.

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Table 1. Summary Table of Studies

Studies	Modality	SZ (N)	Normal (N)	r	Zr
Abi-Dargham et al.2002	verbal	16	16	0.496	0.543
Anil et al.2003	verbal	53	236	0.414	0.440
Bagner et al.2003	verbal	27	28	0.223	0.227
Barch et al.2001	verbal	14	12	0.568	0.645
Barch et al.2002	verbal	38	48	0.316	0.327
Barch et al.2002	visuospatial	38	48	0.329	0.341
Barch et al.2003A	verbal	72	49	0.545	0.612
Barch et al.2003B	verbal	38	49	0.316	0.327
Barch et al.2003B	visuospatial	38	48	0.313	0.324
Bertolino et al.2003	verbal	24	24	0.298	0.307
Bollini et al.2000	visuospatial	29	19	0.374	0.393
Brebion et al.1998	verbal	44	40	0.214	0.217
Bruder et al.2004	verbal	17	26	0.904	1.494
Burglen et al.2004	visuospatial	25	25	0.408	0.433
Cadenhead et al.1999	verbal	20	20	0.384	0.405
Callicott et al. 2000	verbal	13	18	0.418	0.445
Callicott et al.1998	verbal	10	10	0.705	0.878
Callicott et al.2003	verbal	14	14	0.388	0.409
Cameron et al.2003	visuospatial	48	46	0.385	0.405
Carter et al.1996	visuospatial	18	15	0.441	0.473
Carter et al.1998	verbal	8	8	0.773	1.026
Carter et al.2001	verbal	17	16	0.137	0.138
Chen et al.2000	verbal	23	26	0.322	0.334
Chey et al.2002	visuospatial	15	16	0.458	0.495
Cohen et al.1999	verbal	53	25	0.967	2.042
Coleman et al.2002	visuospatial	28	31	0.435	0.465
Condray et al.1996	verbal	11	11	0.243	0.247
Conkins et al.2000	verbal	52	73	0.276	0.284
Danion et al.2001	verbal	48	24	0.247	0.252
Dolan et al.2004	visuospatial	22	28	0.167	0.169
Dreher et al.2001	visuospatial	18	18	0.762	1.002
Egeland et al.2003	verbal	53	50	0.501	0.550
Elliott et al.1998	visuospatial	12	12	0.181	0.183
Fallgatter et al.2003	verbal	31	31	0.231	0.235
Fleming et al.1995	verbal	15	13	0.451	0.486
Fleming et al.1997	visuospatial	32	27	0.505	0.555
Fossati et al.1999	verbal	14	20	0.317	0.329
Fossati et al.1999	visuospatial	14	20	0.465	0.504
Fraser et al.2004	visuospatial	21	16	0.494	0.541
George et al.2002	visuospatial	31	45	0.445	0.478

Glahn et al.2000	verbal	64	64	0.398	0.422
Glahn et al.2003	visuospatial	17	42	0.346	0.361
Gold et al.1997	verbal	36	30	0.564	0.639
Gold et al.2003	visuospatial	20	18	0.356	0.372
Goldberg et al. 1998A	verbal	13	23	0.494	0.541
Goldberg et al. 1998B	verbal	15	15	0.783	1.052
Goldberg et al.2003	verbal	74	68	0.259	0.265
Gooding & Tallent, 2004	visuospatial	65	29	0.408	0.433
Gooding et al.2001	visuospatial	34	30	0.570	0.647
Gooding et al.2002	visuospatial	34	30	0.592	0.681
Granholm et al.1997	verbal	24	32	0.415	0.441
Hartman et al.2002	visuospatial	16	16	0.811	1.130
Honey et al. 1999	verbal	10	10	0.408	0.433
Honey et al.2002	verbal	20	20	0.240	0.245
Honey et al.2003	verbal	30	27	0.433	0.464
Huguelet et al.2000	verbal	24	24	0.375	0.394
Hutton et al.1998	visuospatial	30	30	0.566	0.642
Hutton et al.2004	visuospatial	109	59	0.387	0.408
Jacobsen et al. 2004	visuospatial	13	13	0.277	0.284
Jansma et al.2004	visuospatial	10	10	0.503	0.553
Javitt et al.1997	verbal	18	17	0.243	0.247
Joyce et al.2002	visuospatial	136	81	0.484	0.528
Keefe et al.1995	visuospatial	42	17	0.460	0.497
Keefe et al.1997	visuospatial	18	28	0.542	0.606
Keifer et al.2002	verbal	24	24	0.218	0.221
Kim et al.2003	visuospatial	12	12	0.262	0.269
Kim et al.2004	visuospatial	16	16	0.310	0.320
Kim et al.2004	verbal	16	16	0.266	0.273
Kindermann et al.2004	visuospatial	10	12	0.329	0.341
Kravariti et al.2003	visuospatial	42	43	0.384	0.405
Landro et al.2001	verbal	33	33	0.148	0.149
Leiderman et al.2004	visuospatial	15	14	0.676	0.822
Lencz et al.2003	visuospatial	57	22	0.262	0.269
Leudar et al.1992	verbal	46	22	0.448	0.482
Low et al.2000	visuospatial	12	12	0.473	0.514
Manoach et al.1999	verbal	10	12	0.590	0.677
Manoach et al.2000	verbal	9	9	0.561	0.634
McGrath et al.2001	visuospatial	19	19	0.645	0.767
Mendrek et al.2004	verbal	10	10	0.708	0.884
Menon et al.2001	verbal	11	13	0.626	0.735
Meyer-Lindenberg et al.2001	verbal	13	13	0.571	0.649
Morice et al.1996	verbal	17	17	0.492	0.539
Moritz et al.2002	verbal	25	70	0.360	0.377
Morris et al.1997	verbal	29	35	0.432	0.463

Myles-Worsley&Park,2002	visuospatial	32	19	0.410	0.436
Nienow & Docherty,2004	verbal	52	52	0.419	0.446
Oie et al.1999	verbal	19	30	0.028	0.028
Okada et al.2002	visuospatial	22	22	0.377	0.397
Pantelis et al.1997	visuospatial	36	31	0.538	0.601
Park & Holzman, 1992	visuospatial	12	12	0.922	1.599
Park & Holzman, 1992	verbal	12	12	0.497	0.545
Park et al., 1999	visuospatial	34	39	0.380	0.399
Park et al.1995A	visuospatial	18	18	0.710	0.887
Park et al.2003	visuospatial	28	33	0.473	0.513
Park, 1999	visuospatial	33	29	0.573	0.653
Park, et al. 1993	visuospatial	18	40	0.559	0.632
Park.1997	visuospatial	14	15	0.743	0.956
Perlstein et al.2001	verbal	17	16	0.312	0.323
Perry et al.2001	verbal	50	50	0.565	0.640
Perlstein et al., 2003	verbal	16	15	0.368	0.386
Pukrop et al.2003	verbal	66	45	0.341	0.355
Pukrop et al.2003	visuospatial	66	45	0.259	0.265
Quintana et al.2001	visuospatial	8	8	0.335	0.349
Quintana et al.2003	visuospatial	8	8	0.389	0.411
Ross et al.2000	visuospatial	10	10	0.748	0.969
Sabri et al.2003	verbal	11	10	0.092	0.092
Salgado-Pineda et al.,2004	verbal	14	14	0.893	1.438
Schlösser et al., 2003	verbal	6	6	0.592	0.680
Schwartz et al., 2003	verbal	24	24	0.414	0.440
Servan-Schreiber et al. 1996	verbal	11	11	0.336	0.350
Shelley et al.1996	verbal	11	13	0.692	0.851
Silver et al.2003	verbal	27	38	0.536	0.598
Snitz et al.1999	visuospatial	42	54	0.296	0.306
Spindler et al.1997	visuospatial	14	12	0.460	0.497
Spitzer, 1993	visuospatial	25	12	0.270	0.277
Stevens et al.1998	verbal	14	14	0.454	0.490
Stone et al.1998	verbal	18	15	0.620	0.725
Stratta et al.1997	verbal	30	25	0.618	0.721
Stratta et al.1999	visuospatial	25	25	0.601	0.695
Stratta et al.2000	verbal	20	20	0.556	0.627
Stratta et al.2001	visuospatial	25	35	0.579	0.661
Straube et al.2002	verbal	30	20	0.665	0.802
Suwa et al. 2004	verbal	36	25	0.501	0.551
Tek et al.2002	visuospatial	30	20	0.507	0.559
Thoma et al., 2003	verbal	20	15	0.673	0.816
Toulopoulou et al. et al.2003	visuospatial	70	66	0.359	0.376
Ueland et al., 2004	verbal	22	31	0.383	0.404
Zuffante et al.2001	visuospatial	23	23	0.361	0.377

Table 2. Stem and Leaf Plot of Effect size (r)

Stem	Leaf
.9	0 2 6
.8	1 9
.7	0 0 1 4 4 6 7 8
.6	0 1 2 2 4 6 7 7 9
.5	0 0 0 0 0 3 3 4 4 5 5 6 6 6 6 7 7 7 7 9 9 9
.4	0 0 0 1 1 1 1 1 1 2 3 3 3 4 4 4 5 5 5 6 6 6 7 7 8 9 9 9 9 9
.3	0 1 1 1 1 1 2 2 2 3 3 4 4 5 5 6 6 6 7 7 7 8 8 8 8 8 8 8 9
.2	1 1 2 3 4 4 4 4 5 5 6 6 6 7 7 7 9 9
.1	3 4 6 8
.0	2 9

Table 3. Statistical Summary (based on r)

Statistics	Value
Central tendency	
Unweighted mean	.452
Proportion >.00	100
Significant test	
t test for mean r	29.08
Variablity	
Maximum	.967
Quartile 3 (Q3)	.564
Median (Q2)	.432
Quartile 1 (Q1)	.329
Minimum	.028
Q3 – Q1	.235
σ [.75(Q3 – Q1)	.176
SD[a]	.177
SE[b]	.016
CR (M/SD) [c]	2.553
Q[d]	490.01*
CI for r[e]	
95 %	106 - 798
99 %	- 004 - 908

† [a] SD = standard deviation; [b] SE = standard error; [c] CR = coefficient of robustness; [d] Q = the homogeneity test statistics; [e] CI = confidence interval

†† * <.01

Table 4. Mean effect sizes ($\underline{r}$) for working memory (WM) deficits

Modalities	$k_{\underline{r}}$	$M_{\underline{r}}$	$SD_{\underline{r}}$	CR	Q	95% CI
Visuo-spatial	59	.459	.157	2.923	121.25*	.152 - .766
Verbal WM	70	.446	.193	2.310	368.77*	.068 - .824

† ** <.01

Figure Caption

Figure 1. Relationship between the effect size estimates of working memory deficit and the duration of the delay

FIGURE 1. Delay and Effect Size Estimate