

Working memory impairment as an endophenotypic marker of a schizophrenia diathesis

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ABSTRACT

This review focuses on the viability of working memory impairment as an endophenotypic marker of a schizophrenia diathesis. It begins with an introduction of the construct of working memory. It follows with a consideration of the operational criteria for defining an endophenotype. Research findings regarding the working memory performance of schizophrenia and schizophrenia-spectrum patients, first-degree relatives of schizophrenia patients and healthy controls, are reviewed in terms of the criteria for being considered an endophenotypic marker. Special attention is paid to specific components of the working memory deficit (namely, encoding, maintenance, and manipulation), in terms of which aspects are likely to be the best candidates for endophenotypes. We examine the extant literature regarding working memory performance in bipolar disorder and major depression in order to address the issue of relative specificity to schizophrenia. Despite some unresolved issues, it appears that working memory impairment is a very promising candidate for an endophenotypic marker of a schizophrenia diathesis but not for mood disorders. Throughout this review, we identify future directions for research in this exciting and dynamic area of research and evaluate the contribution of working memory research to our understanding of schizophrenia.

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1. Introduction

In this introductory section, we discuss alternative ways of conceptualizing working memory. We also describe the operational criteria for endophenotypic markers.

1.1. Cognitive components of working memory

Working memory (WM) is an active, limited-capacity, short-term memory system that temporarily maintains information, and supports human thought processes by providing an interface between perception, long-term memory and action (Baddeley, 2003). In Baddeley's model of working memory (2007), temporary maintenance of information is supported by a supervisory attentional control system called the "central executive" and modality-specific subsystems (e.g. phonological loop, visuospatial sketchpad) that feed into a multimodal episodic storage buffer with a capacity limit of approximately four chunks; see Fig. 1. The central executive is hypothesized to control the deployment and selection of attentional resources, selection of strategies, and coordination of information flow from the sub-systems. Without the central executive, behaviors would become distractible, stereotypic, perseverative and insensitive to context.

Due to capacity constraints, healthy humans are able to maintain internal representations of only three to four discrete items at any given moment in working memory (see Cowan, 2001, 2005, 2010). Cowan's model offers an alternative conceptualization of working memory that is helpful for understanding how a capacity limit arises. According to Cowan's "Embedded Process Model" (see Fig. 2), working memory is a subset of the long-term memory (LTM) system that is temporarily activated and accessible via focal attention. The capacity limit of working memory is a direct consequence of the limitation of our ability to pay attention to mental representations. Individual differences in working memory capacity might arise from structural or functional problems, i.e., the differences in the storage space or in the efficiency of attentional control that determines access to working memory.

Clearly, working memory provides the foundation for all forms of learning, including language. Therefore, working memory impairments are likely to cascade into difficulties in all aspects of cognitive performance and furthermore, into the social domain.

1.2. Neural basis of working memory

A complementary framework for understanding working memory is to focus on the neural correlates of temporal components such as encoding and maintenance rather than on the hypothesized structural components of working memory such as the central executive. In non-human primates, working memory has been studied most extensively with the delayed-response task (DRT), which can be subdivided into three clearly demarcated phases of encoding, maintenance and

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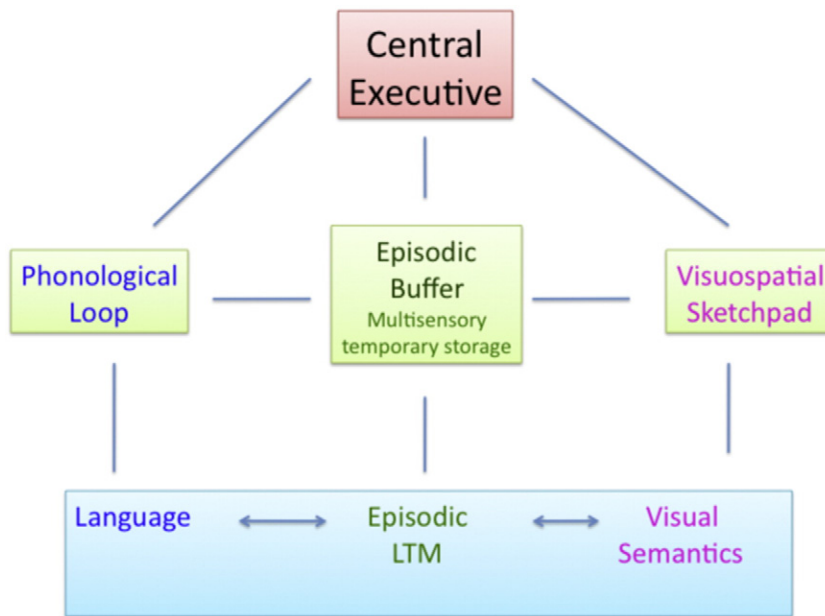


Fig. 1. Schematic diagram of Baddeley's Model of Working Memory.

retrieval. A prototypical DRT involves presentation of a stimulus (encoding), followed by a short delay (maintenance) and the subsequent presentation of response choices (retrieval). Much is known about the role of the dorsolateral prefrontal cortex (DLPFC) in working memory and its regulation of higher cognitive functions in non-human primates (Goldman-Rakic, 1987, 1999). The ability to perform DRTs is destroyed by lesions in the DLPFC (Funahashi et al., 1989, 1990, 1993). Neurons in the principal sulcus (PS, Area 46) maintain spatial information over time (Funahashi et al., 1989, 1990, 1993, Sawaguchi and Goldman-Rakic, 1991). When a saccade to a target is delayed, the neurons in PS increase and maintain firing during the delay, but as soon as the response is made, the firing decreases rapidly.

Neuroanatomical correlates of working memory in healthy humans have been studied extensively with functional neuroimaging methods. In general, it appears that brain regions, including the prefrontal cortex (PFC) and the posterior parietal cortex (PPC) are critical for the active maintenance of mental representations that

are necessary for goal-directed behavior across diverse working memory paradigms and modalities (Belger et al., 1998; Cohen et al., 1997; Curtis, 2006; Perlstein et al., 2001; Ragland et al., 1997; Curtis and D'Esposito, 2003; Jonides et al., 2008; Leung et al., 2002; Smith and Jonides, 1999). For example, the maintenance of spatial information in working memory during DRTs is supported by a robust activation of the middle frontal gyrus (MFG), and furthermore MFG activity is correlated with the memory load (Leung et al., 2002). The MFG is also recruited during the maintenance of phonological information during a verbal DRT (Kim et al., 2010). This finding of the relationship between MFG activity and working memory maintenance parallels the results from the single cell recording data from monkeys during DRTs (Funahashi et al., 1989, 1990, 1993). These results implicate the DLPFC directly in the maintenance process and in directing attention to the internal representations of sensory stimuli and motor plans that are stored in more posterior regions (Curtis, 2006; Curtis and D'Esposito, 2003). In addition, the working memory network extends to other cortical and subcortical areas including the inferotemporal cortex, the cingulate gyrus, the hippocampal formation and basal ganglia (Collette et al., 1999; Curtis and D'Esposito, 2003; Jonides et al., 1993; Manoach et al., 2000). Thus, working memory is not localized to a single brain region but may be thought of as an emergent property of the interactions between the PFC and other areas. This suggests the fundamental importance of functional and structural connectivity between these areas in mediating working memory (Gazzaley et al., 2004; Kim et al., 2003).

1.3. Operational criteria for an endophenotype

Endophenotypes are heritable, quantitative traits that are associated with disease liability and lie intermediate between the genotype and the phenotype (Gottesman and Gould, 2003). In order to qualify as a viable endophenotypic marker, the trait must be heritable. Endophenotypic traits are state independent, i.e., present regardless of whether the illness is active or remitted. The abnormality or deviance is found in clinically affected members (probands) and clinically unaffected family members at a higher rate than in the general population. Finally, within families, the anomaly and the illness co-segregate (Gottesman and Gould, 2003).

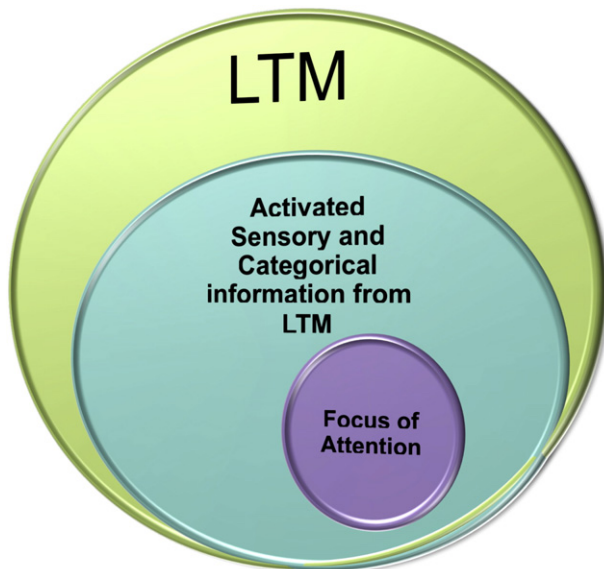


Fig. 2. Schematic diagram of Cowan's Model of Working Memory.

Other proposed requirements for endophenotypes are more controversial. Many investigators (Bearden and Freimer, 2006; Doyle et al., 2005; Waldman, 2005) assert that the putative endophenotype must demonstrate good psychometric properties (i.e., have internal consistency, be able to be reliably assessed) and be analyzable on a quantitative scale. An optimally informative candidate endophenotype would also involve homologies of expression across species, to enable development of animal models (Bearden and Freimer, 2006; Gould and Gottesman, 2006). To be most useful, the endophenotype should be related to neurobiological pathways and/or neural system models that have been implicated in the psychiatric disease, though there is controversy whether the genetic basis of the endophenotype is likely to be more, less, or equally complex as the genetics of the disease itself (Bearden and Freimer, 2006). Earlier definitions (see, for example, Preston and Weinberger, 2005) presumed that endophenotypes had a less complex genetic basis than the disease itself; indeed, it was thought that multiple endophenotypes would reflect different aspects of the genetic risk for the disorder (Kendler and Neale, 2010).

There are two different models for endophenotypes, namely, the liability-index (or ‘risk indicator’) model and the mediating variable model (Kendler and Neale, 2010). Although both endophenotype models predict that individuals with high scores are at elevated risk for the development of the psychiatric disorder, the models differ in terms of the hypothesized relationship between the endophenotypic trait and the candidate gene(s) underlying the disorder. As Kendler and Neale (2010) describe it, an endophenotype liability-index model is a model of pleiotropy whereby one set of genetic variants causes variation in both endophenotype and disease risk. In contrast, the mediational model for an endophenotype posits that the effects of a gene on the disorder are expressed, either partly or fully, through the endophenotype (Kendler and Neale, 2010; Waldman, 2005). The mediational model makes additional predictions and has additional requirements for endophenotypic markers; interested readers are referred to Doyle et al. (2005), Waldman (2005), and Jablensky (2010) for further explication.

The main advantage of an endophenotype is that it is presumed to provide a more reliable indicator of liability than clinical manifestations of the illness (i.e. the phenotype) (Gottesman and Shields, 1972). Endophenotypes are valuable in that they can assist us in terms of helping identify at-risk individuals for inclusion in genetic studies. They can also help elucidate the underlying pathophysiology of the disorder. Finally, endophenotypes can help delineate the boundaries of the disease spectrum, because presumably all related disorders would be expected to differ in terms of phenotype, but share an underlying diathesis, which would be indicated in part by similar deficits on a given cognitive, bio-behavioral, or physiological trait.

The purpose of this review is to evaluate the viability of working memory impairment as an endophenotypic marker of a schizophrenia diathesis. That is, we are evaluating the feasibility of working memory impairment as a risk indicator for schizophrenia.

2. Evaluation of working memory performance as an endophenotype

In order to evaluate the feasibility of working memory impairment as a risk indicator for schizophrenia, we will review findings from experimental psychopathology and cognitive neuroscience research pertaining to the working memory performance of schizophrenia and schizophrenia-spectrum patients, and first-degree relatives of schizophrenia patients and healthy controls in terms of each of the criteria for endophenotypic status. We extend the extant literature by taking an approach, which parses the working memory performance of schizophrenia patients in terms of its temporal components. We will also consider issues of diagnostic specificity and identify unresolved issues.

2.1. Working memory impairment is associated with schizophrenia in the population

In the past two decades since the publication of the first empirical study demonstrating the presence of working memory deficits in schizophrenia (Park and Holzman, 1992), this impairment has emerged as a cardinal feature of the illness. Impaired working memory is found in a disproportionate number of schizophrenia patients, though it is relatively rare in the normal population. Schizophrenia patients show working memory deficits across different modalities including spatial (e.g., Badcock et al., 2008; Choi et al., 2012; Haenschel et al., 2009; Park and Holzman, 1992, 1993; Park et al., 1999; Reilly et al., 2007), verbal/auditory (e.g. Barch et al., 2002; Bell et al., 2001; Conklin et al., 2000; Gold et al., 1997; Huguelet et al., 2000; Kim et al., 2010; Wexler et al., 1998), object (e.g. Coleman et al., 2002; Gooding and Tallent, 2004; Park and Lee, 2002; Spindler et al., 1997) and haptic (Park and Holzman, 1992).

An extensive meta-analysis of 125 studies published between 1992 and 2004 revealed a moderate effect size of 0.45 for the presence of working memory deficit in schizophrenia across a wide range of paradigms, and domains (Lee and Park, 2005). A selective meta-analytic review of first-episode schizophrenia patients ($n = 2$ studies) revealed a moderately large effect size of 0.79 (Mesholam-Gately et al., 2009). The results of these meta-analyses, along with more recent ones (c.f. Forbes et al., 2009), provide cogent evidence that the working memory impairment is consistently observed in schizophrenic patients. Overall, effect size estimates range from 0.45 to 1.29 (Forbes et al., 2009; Lee and Park, 2005; Mesholam-Gately et al., 2009), showing that these deficits are robust across different tasks, modalities and subject variables, though there appear to be more consistent and greater impairments in the visuospatial domain than other domains (Lee and Park, 2005).

A wide range of experimental paradigms is currently used to assess working memory. Depending on the task parameters, different subcomponents of working memory and associated cognitive and perceptual functions are recruited. On-line maintenance of information can be tested using delayed response or delayed discrimination tasks (e.g. Badcock et al., 2008; Cannon et al., 2005; Gooding and Tallent, 2003, 2004; Haenschel et al., 2007, 2009; Park and Holzman, 1992). Maintenance and manipulation of information can be assessed using N-back tasks (e.g. Barch et al., 2002; Callicott et al., 2003), digit span backward (Glahn et al., 2006; Pirkola et al., 2005), and letter-number sequencing tasks (e.g. Gold et al., 1997). Change detection tasks (Gold et al., 2003; Mayer et al., 2012) and the Sternberg paradigm (Manoach et al., 1999) among others have been used to estimate the capacity of working memory. At present it is not clear which components or subprocesses of working memory are the best endophenotypic marker for schizophrenia. Different paradigms are likely to be differentially effective in detecting the putative endophenotypic marker. This point becomes even more apparent in neuroimaging studies of working memory.

Neuroimaging studies of schizophrenia patients performing working memory tasks have typically demonstrated task-related hypofrontality (Barch et al., 2002; Cohen et al., 1997). However, there are also reports of hyperfrontality (Manoach et al., 2000) and anomalous frontal functional asymmetry (Kim et al., 2010; Lee et al., 2008; Walter et al., 2003) during working memory tasks. These contrasting results suggest that several additional factors, such as the task demand, manipulation of task parameters, and individual differences, must be considered in evaluating the activation patterns in the prefrontal cortex of patients with schizophrenia compared with healthy participants (Callicott et al., 2003; Manoach, 2003). Activating a system or network may not necessarily correlate with the behavioral performance and failure to engage a certain brain network (e.g. hypofrontality) is not necessarily linked to abnormal performance. Neural activation also depends on the degree of practice or expertise; inactivity of a network sometimes reflects a certain level of automaticity for that particular task and therefore mastery rather than failure. Given that there are many neural and cognitive routes to working memory errors, as well as the non-linear

nature of the brain-behavior relationship, it is important to parse the sources of memory errors in fMRI studies. Therefore, group comparisons must be interpreted in specific behavioral contexts in which errors arise (Lee et al., 2008). A network approach to understanding working memory deficits suggests that a broad network of frontal, parietal, temporal and subcortical systems is involved in schizophrenia (Barch and Csernansky, 2007; Driesen et al., 2008; Haenschel et al., 2009; Lee et al., 2008). Given this broad nature of network abnormalities, it might be practical and efficient to specify endophenotypic markers at the behavioral level, and elucidate which aspects or components of the working memory system are likely to be the best candidate(s). Below, we discuss briefly what is known about encoding, maintenance, manipulation and retrieval stages of working memory in schizophrenia.

2.2. Components of working memory deficit in schizophrenia

Although it is helpful to parse working memory, componential analysis depends on the theoretical framework adopted. One conventional way of parsing working memory is to divide it into the central executive and modality-specific components (e.g. Baddeley, 2003). Functions of the central executive include allocation of attention and coordination of modality-specific subsystems. Cognitive control, as indexed by the N-back and CPT-AX tasks and mediated by the PFC, is clearly impaired in schizophrenia patients (see Barch and Ceaser, 2012). Attentional orienting to external (or internal) targets that is necessary for encoding, is mediated by the posterior parietal cortex (Awh et al., 2000; LaBar et al., 1999). Directing and allocating attention, mediated by the dorsal visual processing system that includes the DLPFC and posterior parietal cortex is abnormal in schizophrenia (Sharma et al., 2011).

To understand how attention interacts with working memory, it is useful to study the temporal components of working memory. Componential analysis of working memory based on the temporal course of events indicates that several processes are responsible for working memory impairment (Haenschel et al., 2009; Park and Lee, 2002; Park and O'Driscoll, 1996). Successful working memory performance depends on accurate encoding, maintenance of internal representation, inhibition of irrelevant distractors, and initiation of appropriate responses. Failure to facilitate any of these hypothetical components can result in working memory errors.

2.2.1. Encoding problems

There is ample evidence for impaired encoding in schizophrenia patients (Haenschel et al., 2007; Hahn et al., 2010; Hartman et al., 2002; Mayer and Park, 2012; Mayer et al., 2012, 2014; Tek et al., 2002) but the precise reason for impaired encoding is not clear. Encoding problems that lead to reduced working memory capacity are thought to arise from a selective impairment of top-down attentional control in schizophrenia patients who demonstrate preserved stimulus-driven attentional capture (Mayer et al., 2012). Hahn et al. (2010) suggest that an inability to overcome salient distractors during encoding is a large factor. While healthy individuals benefit from increased target salience during working memory encoding (Mayer et al., 2011), patients with schizophrenia fail to do so. Overall, these findings suggest a difficulty in directing resources to appropriate items during encoding.

There is mixed evidence for sensory problems during encoding in schizophrenia with some finding early visual deficits that contribute to encoding difficulties (Dias et al., 2011; Haenschel et al., 2007) and others finding no reduction in the precision of encoding (Badcock et al., 2008). These discrepancies may partly be due to diverse difficulties underlying encoding problems. Encoding deficits may arise from different reasons: (a) Degraded or imprecise encoding (impaired perceptual analysis) or (b) Encoding of incorrect item/feature owing to impaired attentional orienting to the task-relevant information. Degraded encoding versus selecting the wrong item at encoding have different consequences. Degraded encoding will result in reduced confidence in

response but choosing the incorrect item to encode may result in confident response and false memory. Working memory performance in schizophrenia patients and their unaffected first-degree relatives is characterized by increased false memory errors in a spatial delayed response task, but bipolar individuals do not make false memory errors (Mayer and Park, 2012).

2.2.2. Maintenance and manipulation

Even when encoding is optimized, residual working memory deficits remain, especially in the spatial modality (Kim et al., 2006; Lencz et al., 2003; Tek et al., 2002). This suggests that successful encoding does not necessarily lead to successful maintenance or retrieval. What characterizes the working memory deficit displayed by individuals in the schizophrenia-spectrum may be a specific pattern of errors that suggests either encoding and/or early maintenance problems (Badcock et al., 2008; Lee and Park, 2005; Mayer and Park, 2012).

Maintenance is an active process that requires deployment and orienting of attention to internal representations. Just as we move our attention to external targets in space, we also move attention to mental representations in working memory (Griffin and Nobre, 2003; Nobre et al., 2004). This is why pitting manipulation versus maintenance is somewhat misleading: they are not segregated in neurophysiological studies of single cells in PFC (Rao et al., 1997) or in neuroimaging data (Leung et al., 2002). A central element of manipulation in working memory is a *continued orienting of attention to the internal representation of the target*. Although orienting spatial attention to external targets has been studied extensively for decades, not much is known about orienting attention to internal representations (Griffin and Nobre, 2003). Viewed in this way, active engagement of attentional focus and resources play a key role in maintenance. There are several factors that influence maintenance. Whatever pulls attention away from the internal representation will reduce or abolish maintenance. Maintenance deficits may be caused in part by impaired functioning of the DLPFC that is vulnerable to interruptions of the ongoing, sustained activation of memory representation.

While maintenance has been pitted against manipulation in working memory (e.g., Cannon et al., 2005; Tan et al., 2005), our review of the evidence suggests that maintenance and manipulation are not necessarily independent, conceptually or empirically. In neurophysiological studies of neurons that support working memory, manipulation and maintenance are indistinguishable and are supported by the same cells (Funahashi et al., 1989, 1990, 1993). Similarly, human neuroimaging data suggest that the same circuits support these two functions (Leung et al., 2002). Maintenance in working memory is *active* and *requires attention*; active attention is also a hallmark of 'manipulation'. Thus, it may be more useful to study the allocation and deployment of attention in working memory as significant aspects of manipulation that allow us to maintain information over time.

Manipulation has not yet been extensively investigated in schizophrenia. An obvious way to examine manipulation ability is through the study of mental imagery. All mental imagery involves working memory (Kosslyn, 1980) and they share overlapping neural circuitry (Slotnick et al., 2011). Imagery manipulation in working memory such as imagery generation and mental rotation seems to be intact or even enhanced in schizophrenia in spite of their working memory maintenance deficit (Benson and Park, 2013; Matthews et al., 2014; Thakkar and Park, 2012). In healthy people, mental imagery manipulation and maintenance abilities are highly correlated (Baddeley and Andrade, 2000; Matthews et al., 2014) but they are dissociated in schizophrenia patients (Matthews et al., 2014; Thakkar and Park, 2012). Thus, when no working memory maintenance is required, the control of mental representation seems intact or enhanced in schizophrenia.

It is puzzling as to why better imagery manipulation ability in schizophrenia does not translate to better working memory overall, as it does in healthy participants. One possibility is that abnormal

connectivity of frontal and parietal cortices in schizophrenia (Karlsborg et al., 2008; Shergill et al., 2007) results in relative functional independence of these two regions. Interestingly, increased working memory demand results in suppression of the temporoparietal junction (TPJ) activity in healthy people (Todd and Marois, 2004; Todd et al., 2005), and greater TPJ de-activation during encoding predicts better working memory performance (Anticevic et al., 2013). The TPJ is recruited during body mental imagery and egocentric transformation (Blanke et al., 2005). It is possible that relatively independent parietal regions, including the TPJ, enhance mental imagery activity at the expense of working memory encoding.

Thus, reduced working memory capacity (impaired encoding and maintenance) coupled with enhanced imagery could underlie abnormal cognition in schizophrenia through such links. Furthermore, this profile of deficits and enhancement might be a better signature of the schizophrenia endophenotype than a diffuse deficit in working memory. This hypothesis should be evaluated in future research.

2.3. Working memory deficit is heritable in schizophrenia

There is ample evidence of working memory deficit in the first-degree relatives, including data from twin studies. For example, Glahn et al. (2003) examined spatial working memory performance in 17 probands with 8 monozygotic co-twins and 13 dizygotic co-twins, and 42 healthy twins. Working memory performance declined according to the degree of genetic overlap with the schizophrenia proband. Pirkola et al. (2005) compared 46 schizophrenia patients, 32 of their unaffected co-twins, 22 bipolar patients, 16 of their unaffected co-twins, and 100 control twins. They found that schizophrenia patients and their unaffected co-twins performed significantly worse than healthy controls on the spatial working memory task. Only the schizophrenia patients performed significantly worse than healthy controls on the verbal working memory task, which suggests that verbal working memory deficits might emerge with the expression of the disorder itself. In contrast, neither bipolar patients nor their unaffected co-twins differed from the healthy controls on working memory. Taken together, these findings from twin studies (Glahn et al., 2003; Pirkola et al., 2005) support the hypothesis that spatial working memory deficits are an index of genetic liability for schizophrenia but not for bipolar disorder.

There have been a few pedigree studies that have permitted calculations of heritability estimates for working memory. In nonclinical twin samples (Ando et al., 2001; Hansell et al., 2005), heritability estimates for verbal and spatial working memory ranged from 0.41 to 0.49. Based upon their investigation of schizophrenia patients and their families, Tuulio-Henriksson et al. (2002) estimated heritability for working memory to be 0.42. In a mixed sample of 605 probands, and first- and second-degree relatives, Greenwood et al. (2007) obtained a heritability estimate for verbal working memory of 0.39, whereas Glahn et al. (2007) obtained a higher estimate ($h^2 = 0.46$) for spatial working memory in their Latino sample of 266 patients and siblings. Overall, these studies provide sufficient support for Gottesman and Gould's criterion that a candidate endophenotype for an illness be heritable.

2.4. Working memory impairment is state independent

One requirement of endophenotypic traits is that they are manifest in the person whether or not the illness is active, though the trait may be age-normed and might need to be elicited by challenge (Bearden and Freimer, 2006; Gottesman and Gould, 2003). Working memory deficits are observed in both acutely ill (Carter et al., 1996; Park et al., 1999; Zanello et al., 2009) and more stable outpatients, regardless of their clinical symptoms (Gooding and Tallent, 2001; Haenschel et al., 2009; Park et al., 1999; Reilly et al., 2007; Zanello et al., 2009). Importantly, prodromal or 'at-risk' mental state individuals show working memory deficits prior to the onset of the first psychotic episode (Choi et al., 2012;

Pflueger et al., 2007; Simon et al., 2007; Smith et al., 2006; Wood et al., 2003).

It has been shown that working memory deficit can best distinguish the 'at-risk', prodromal subjects from healthy controls (Pflueger et al., 2007), as well as differentiate the 'at-risk' subjects who convert to psychosis compared with 'at-risk' individuals who do not (Pukrop et al., 2007). Past the prodromal state, working memory deficits are present from the first episode (e.g., Reilly et al., 2007; Schneider et al., 2007; Zanello et al., 2009) to chronic stages (e.g., Haenschel et al., 2009; Park et al., 1999; Reilly et al., 2007; Zanello et al., 2009).

The working memory impairment observed in schizophrenia appears to be independent of medication. Working memory deficits are present in unmedicated patients with schizophrenia (Carter et al., 1996). Impaired working memory does not seem to be normalized by antipsychotic treatment as the majority of schizophrenic patients on medication show working memory deficits (e.g., Park et al., 1999; Reilly et al., 2006). Although there are at least two reports of some beneficial effects of atypical antipsychotic medication (risperidone) on verbal working memory (Green et al., 1997; Honey et al., 1999), findings of successful remediation of working memory deficits with antipsychotic drugs are exceedingly rare. Reilly et al. (2006) observed an exacerbation of spatial working memory deficits when risperidone was given to first episode patients. On the other hand, McGurk et al. (2005) observed an improvement in spatial working memory with risperidone treatment and worsening with clozapine over a period of 29 weeks in schizophrenic patients in a large-scale, multi-site study. However, the cognitive improvements reported in these clinical trials are consistent in magnitude with practice effects observed in healthy controls (Goldberg et al., 2007), suggesting that these improvements may reflect practice effects (e.g., exposure, familiarity, procedural learning) rather than medication effects.

Lastly, the fact that unaffected, unmedicated first-degree relatives of schizophrenia patients show working memory deficits suggest that this problem is probably not caused by antipsychotic medication. Overall, working memory deficits observed in schizophrenia patients may be minimally modulated by antipsychotic treatments; to date, the core deficit seems largely unaffected by pharmacotherapy.

2.5. Working memory deficits are found in the unaffected relatives of schizophrenia patients at a higher rate than in the general population

Unaffected biological relatives of schizophrenia patients show working memory deficits, albeit to a lesser degree than schizophrenic probands (Bachman et al., 2008; Brahmabhatt et al., 2006; Cellard et al., 2010; Conklin et al., 2000; Glahn et al., 2003; Mayer and Park, 2012; Myles-Worsley and Park, 2002; Park et al., 1995a). In their meta-analytic review of 58 studies of first-degree relatives of schizophrenia patients, Snitz et al. (2006) observed effect sizes that ranged from small to medium (mean Cohen's $d = 0.24$ to 0.55). They concluded that, on average, relatives of schizophrenia patients demonstrate poorer working memory performance than controls. Even when healthy first-degree relatives show intact working memory performance, accompanying hyperfrontal activity suggests a compensatory mechanism that differentiates the relatives from healthy controls (Choi et al., 2012). Moreover, patterns of working memory errors observed in schizophrenia patients are also found in their first-degree relatives, such as increased false memory errors, which is not present in healthy participants or bipolar patients (Mayer and Park, 2012) and an increased susceptibility to distraction (Cellard et al., 2010). Overall, these studies suggest that working memory deficit meets Gottesman and Gould's (2003) criterion for the anomaly to be associated with unaffected family members. Although it is clear that first-degree relatives of schizophrenia patients show working memory deficits at a higher rate than in the general population, it is unknown whether working memory impairment and schizophrenia co-segregate within families. Multigenerational, family studies are needed to answer this question.

2.6. Working memory deficits show relative diagnostic specificity

Some investigators (e.g., Skuse, 2001) assert that the endophenotypic trait should be relatively specific to a given disorder. Although many earlier discussions of endophenotypes (e.g. Iacono, 1998) focused on specificity and their association with categorical disease phenotypes, with the advent of the DSM-5 (American Psychiatric Association) and the NIMH Research Domain Criteria (RDoC), it is less likely that many will continue to insist upon this criterion. Moreover, others (e.g., Bearden and Freimer, 2006; Jablensky, 2010) argue against the requirement of diagnostic specificity, because sets of genes may influence susceptibility to disease across traditional nosological boundaries, or several disorders may share common underlying neurobiological substrates.

2.6.1. Working memory performance in schizophrenia-spectrum disorders

Working memory deficits are also observed in individuals with schizophrenia-spectrum disorders, such as schizotypal personality disorder (Goldstein et al., 2011; McClure et al., 2008; Roitman et al., 2000), schizophreniform disorder (Bertolino et al., 2003; Sacchetti et al., 2008) and schizoaffective disorder (Gooding and Tallent, 2002). There is also growing evidence of the presence of working memory deficits in individuals in the prepsychotic, prodromal phases of the illness, prior to their conversion to schizophrenia, as summarized above in Section 2.4. Finally, nonclinical individuals with schizotypal characteristics identified on the basis of their psychometric profiles, also show working memory deficits relative to nonschizotypal comparison groups (Choi et al., 2012; Gooding and Tallent, 2003; Matheson and Langdon, 2008; Park and McTigue, 1997; Park et al., 1995b; Schmidt-Hansen and Honey, 2009; Tallent and Gooding, 1999).

2.6.2. Working memory performance in bipolar disorder

Park and Holzman (1992) found no spatial working memory deficits in floridly psychotic bipolar subjects. In at least two investigations of spatial delayed response task performance by bipolar outpatients (Gooding and Tallent, 2001; Park and Holzman, 1993), no impairments were observed. However, others have reported deficits in spatial working memory in mania (McGrath et al., 2001) and bipolar disorder (Glahn et al., 2010).

This discrepancy between different studies may be due to acuity of manic symptoms, the presence of psychotic features, and/or specific components of working memory under investigation (Glahn et al., 2006; McGrath et al., 2001). For example, Glahn et al. (2006) compared individuals with bipolar disorder with schizophrenic subjects on the backward digit span and spatial delayed response performance. They found that both bipolar and schizophrenic subjects regardless of psychotic features were impaired on backward digit span, (thought to tap verbal working memory) but only those with a history of psychosis showed deficits on the spatial delayed response task. Thus, backward digit span performance may be a marker that cuts across diagnostic categories whereas spatial working memory performance clearly distinguishes non-psychotic bipolar patients from schizophrenic patients and bipolar patients with psychotic features. On the other hand, Allen et al. (2010) reported that visuospatial working memory was impaired in bipolar disorder regardless of the presence of psychotic features. Overall, the existing literature on working memory function in bipolar disorder does not yield an unambiguous conclusion of the presence of a deficit. Moreover, it is unknown whether working memory function fluctuates across different mood states within subjects because longitudinal data are currently unavailable. Effects of medication on working memory function in bipolar subjects are also largely unknown.

However, intact behavioral performance does not necessarily mean the neural network that supports working memory is intact. Townsend et al. (2010) conducted an fMRI study of n-back in bipolar disorder and control subjects. Bipolar patients were in manic, euthymic or depressed

states. There was no difference in accuracy among the 4 groups. Therefore, bipolar patients were not impaired on the n-back task. However, the brain activity pattern was different. Interestingly, bipolar subjects in all mood states showed a significant reduction in activation in right BA9/46 and right BA40. This suggests that despite behaviorally normal working memory performance, patients with bipolar disorder exhibit significantly reduced activation in working memory circuits, independent of mood state. This pattern suggests that bipolar subjects may be using alternative strategies to perform working memory tasks. In support of this idea, the authors found additional frontal and temporal activation in bipolar subjects. Similarly, another fMRI study of n-back and Sternberg task in euthymic bipolar patients (Monks et al., 2004) found no behavioral deficit in working memory in bipolar patients but different activation patterns compared with healthy controls; during the 2-back task, bipolar patients showed reductions in bilateral frontal, temporal and parietal activation, and increased activations with the left precentral, right medial frontal and left supramarginal gyri. The authors concluded that bipolar disorder patients' failure to engage "fronto-executive function" is what underlies their core neuropsychological deficits. However, considering that the performance of the bipolar patients on the working memory tasks was well within normal limits, it seems premature to propose working memory impairment as a core cognitive deficit that characterizes bipolar disorder because there is no evidence of a clear deficit.

A recent study investigated neural correlates of working memory in the first-degree relatives of bipolar patients (Thermenos et al., 2010). They found that working memory is affected by activity in emotion-regulatory circuits in bipolar patients and their unaffected relatives. Based on these results, the authors concluded that altered activity in the frontopolar cortex and insula during a working memory task might represent biomarkers of genetic risk for bipolar disorder. On the other hand, a twin study by Pirkola et al. (2005) with 46 schizophrenic patients, 32 of their unaffected co-twins, 22 bipolar patients, 16 of their unaffected co-twins, and 100 control twins, did not reveal working memory deficits in bipolar patients nor in their unaffected twins. The authors concluded that "spatial working memory might effectively reflect an expression of genetic liability to schizophrenia but less clearly to bipolar disorder" (p. 930). Similarly, Hamilton et al. (2009) concluded from an fMRI study of working memory in bipolar disorder and schizophrenia that although schizophrenia and bipolar disorder may share some diagnostic, and genetic features, there are differences in working memory-related cortical activity patterns between schizophrenic and bipolar patients, which suggests diagnostic specificity.

Finally, a recent study of the offspring of individuals with schizophrenia or bipolar disorder presents an intriguing picture (Diwadkar et al., 2011). The offspring of schizophrenia patients, but not the offspring of bipolar patients, showed impairments in working memory when compared with control subjects, indicating a unique deficit in the schizophrenia-spectrum. Conversely, the offspring of bipolar patients but not those of schizophrenia patients significantly differed from controls on attention tasks (Diwadkar et al., 2011). In order to satisfy the criteria for an endophenotype, the trait must be present in at least some of the first-degree relatives of the affected probands (Gottesman and Gould, 2003). The findings of Diwadkar et al. (2011) suggest that working memory deficits may not serve as an endophenotype for bipolar disorder. Clearly, more family data are needed to help resolve this issue. It would also be helpful to obtain longitudinal data regarding working memory performance in bipolar disorder patients, across various affective states and/or clinical stages. The results of Diwadkar et al. (2011) are also consistent with the core impairment of attention but not of working memory observed in unmedicated bipolar patients reported by Harmer et al. (2002) and point to the utility of attentional impairments as an endophenotypic marker in the case of bipolar disorder rather than working memory.

2.6.3. Working memory performance in major depression

There does not seem to be a significant deficit in working memory in major depression (Barch et al., 2003; Channon et al., 1993; Townsend et al., 2010) although some investigators have observed specific working memory deficits in inpatients with depression (Harvey et al., 2004; Rose and Ebmeier, 2006). Severely depressed inpatients showed deficits in the *n*-back task compared to control subjects (Harvey et al., 2004; Rose and Ebmeier, 2006), though they were unimpaired in tasks assessing the working memory maintenance and attention (Harvey et al., 2004). This suggests that severely depressed inpatients show deficits in executive control, updating or inhibitory components of working memory. If a difficulty with working memory is detected in depressed subjects, it appears to be linked to affect. Depression was associated with intrusions from irrelevant negative material into working memory (Joormann and Gotlib, 2008). Overall, evidence for the working memory deficit in depression is very weak and even if an impairment is observed, it may be state-related, (i.e., linked to their affective symptomatology), which fails to meet Gottesman and Gould's criterion (2003) for state independence.

In summary, working memory impairment is associated with risk for schizophrenia and schizophrenia-spectrum disorders. However working memory deficits are not necessarily disease-specific; individuals with Parkinson's disease, for example, display working memory deficits (Owen et al., 1997). Nonetheless, for bipolar disorder and depression, working memory impairments are unlikely to meet the Gottesman and Gould's (2003) criteria for an endophenotypic marker. There is no unambiguous evidence that bipolar or depressed patients have detectable, permanent, and stable working memory deficits, even if some studies have shown altered brain activity during working memory tasks. More importantly, there is no evidence that working memory performance is state-independent in mood disorders or that it is present at a significantly higher rate in the unaffected relatives than in the general population.

3. Summary, integration, and future directions

In this final section of the review, we summarize the current status of the research, illustrate how working memory research has yielded insights about schizophrenia, and make recommendations for future research directions.

3.1. Summary of current status of working memory research

Working memory deficits, particularly in terms of impaired encoding and maintenance, are found in a disproportionate number of schizophrenia patients. Studies indicate that impaired working memory is a trait characteristic in schizophrenia and present from the prodrome to the chronic stages of the disorder. There is also evidence that working memory impairment is genetically transmitted. Working memory deficits have been consistently observed in unaffected relatives of schizophrenia probands at a higher rate than in the general population. There's also evidence that working memory deficits are displayed by a disproportionate number of persons in the schizophrenia-spectrum (i.e., those with schizotypal personality disorder, schizophreniform disorder, schizoaffective disorder). It is not presently known whether or not working memory dysfunction cosegregates with the disorder within families of schizophrenia patients. In contrast to the corpus of data regarding working memory and schizophrenia, evidence for a working memory deficit in the mood disorders is weak, or mixed at best. Based on these observations, we conclude that, despite some unresolved issues, working memory impairment is an excellent candidate for endophenotypic marker status in terms of schizophrenia liability.

3.2. Working memory research contributes to our understanding of schizophrenia

Working memory research has dramatically grown in parallel with the rapid developments in methods and techniques in cognitive neuroscience, neuroimaging and molecular genetics. Consequently, working memory research has contributed tremendously to our understanding of the etiology and sequelae of cognitive deficits in mental illness. Working memory tasks have been extensively utilized as behavioral probes to investigate the dynamics of higher brain functions in relation to genetic mechanisms, using molecular genetics and neuroimaging methods. Moreover, by identifying neurobiological pathways associated with working memory and executive control, it has become increasingly possible to understand individual differences in personality traits that are related to the risk for neuropsychiatric disorders. For example, neurogenetics research on the prefrontal circuits associated with working memory and executive function has revealed heritable traits relevant to cognitive deficits in schizophrenia (e.g. Egan et al., 2001; Goldberg et al., 2003, 2013; Karlsgodt et al., 2011; Tan et al., 2009). A common functional polymorphism of catechol-*O*-methyltransferase (COMT), an enzyme that metabolizes synaptic dopamine (Weinshilboum et al., 1999), is relevant to all disorders that are associated with catecholamine-related abnormalities including schizophrenia, bipolar disorder, and ADHD. Understanding the genetic variation in dopaminergic systems (e.g., COMT, DAT, AKT1) and the interaction between these individual differences and functional neuroanatomy could lead to efficacious, individualized treatment, whether pharmacological, behavioral, or a combination of the two approaches.

Working memory research has also led to confirming the significance of specific neural pathways, such as the role of the prefrontal involvement and the importance of frontoparietal and frontotemporal circuits. With the advance of neuroimaging methods, it is now possible to investigate how different brain regions are recruited and the time course of their interactions using a family of functional connectivity analyses (e.g., Meda et al., 2012; Repovš and Barch, 2012). These analyses reveal that schizophrenia is associated with a widespread, global abnormalities of functional connectivity along with more circumscribed and context-dependent alterations that are associated with transient states of hyper- and/or hypo-connectivity (Fornito et al., 2012). Future research should lead to a better conceptualization of behavioral profiles that corresponds to these network abnormalities.

3.3. Future directions for clinical research in working memory

Despite the considerable amount of clinical research that has focused on working memory, unresolved issues remain. For example, there is a dearth of multigenerational family studies of working memory, so it is unknown whether working memory impairment and schizophrenia-spectrum disorders co-segregate within families. More research into the manipulation ability of schizophrenia patients seems warranted, particularly in terms of the observed pattern of working memory deficits coupled with enhanced mental imagery. Given the compelling evidence supporting working memory impairment as an endophenotypic marker for schizophrenia liability, the logical next step then is to move toward a dynamic neurocognitive profile. That is, our next goal should be to specify impaired, intact and enhanced sub processes within working memory as the endophenotypic marker for schizophrenia, rather than resorting to a blunt construct of unitary working memory deficit.

Future research is also necessary to glean insights into the relationship between schizophrenia and the affective psychoses. Given that working memory dysfunction is present in other disorders (e.g. Parkinson's disorder), further study is warranted regarding the shared underlying neurobiology of other disorders in which certain genes and/or neural systems (e.g. fronto-striatal tracts) are implicated.

Furthermore, it is imperative that future research moves beyond simply characterizing individuals as displaying poor working memory. Individuals with a low working memory span may have fewer storage slots, or they may be unable to gate distractors. Both cases will result in working memory space becoming saturated to capacity with task-irrelevant information (Kane et al., 2001; Vogel et al., 2005), and in either case, the outcome is the same (i.e. reduced capacity). However, these two cases are distinct with respect to underlying cognitive and neural mechanisms and thus, there are distinct implications for potential remediation strategies. This highlights the importance of probing specific underlying causal mechanisms for behavioral impairments. Future studies should capitalize on the recent progress in cognitive neuroscience to uncover and refine separable components of impairments that define the schizophrenia-spectrum.

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Conflict of Interest

The authors have no conflicts of interest to report.

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