Schizophrenia Research: Cognition 1 (2014) 127–136

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: http://www.schizrescognition.com/

Working memory impairment as an endophenotypic marker of a schizophrenia diathesis

Sohee Park [a,*], Diane C. Gooding [b,*]

[a] Departments of Psychology and Psychiatry, Vanderbilt University, 111, 21st Avenue South, Nashville, TN 37240, USA
[b] Departments of Psychology and Psychiatry, University of Wisconsin-Madison, 1202 West Johnson Street, Madison, WI 53706, USA

ARTICLE INFO

Article history:
Received 22 July 2014
Received in revised form 14 September 2014
Accepted 18 September 2014
Available online 12 October 2014

Keywords:
Risk for schizophrenia
Genetic liability
Spatial delayed response tasks
Bipolar disorder
Neurocognitive deficits

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.

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

* Corresponding authors.
E-mail addresses: sohee.park@vanderbilt.edu (S. Park), dcgooding@wisc.edu (D.C. Gooding).

http://dx.doi.org/10.1016/j.scog.2014.09.005

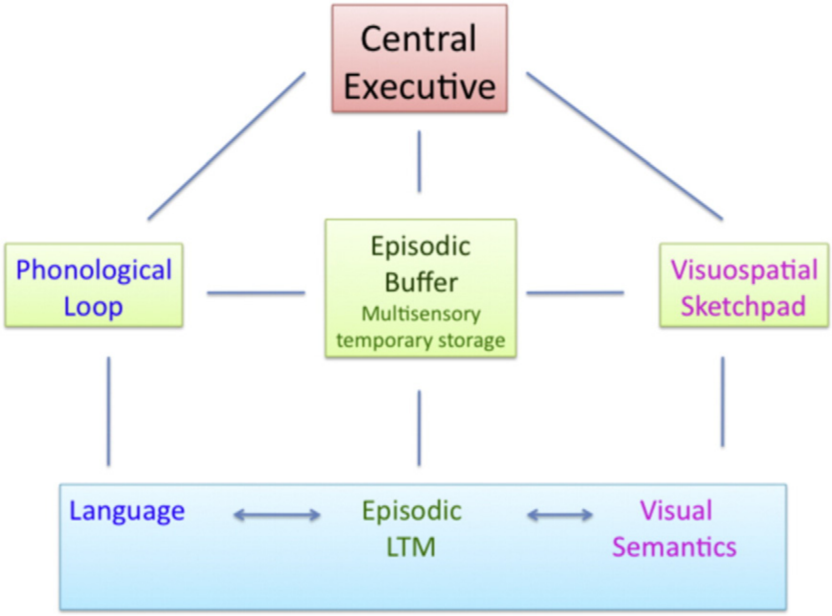

Fig. 1. Schematic diagram of Baddeley's Model of Working Memory.

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

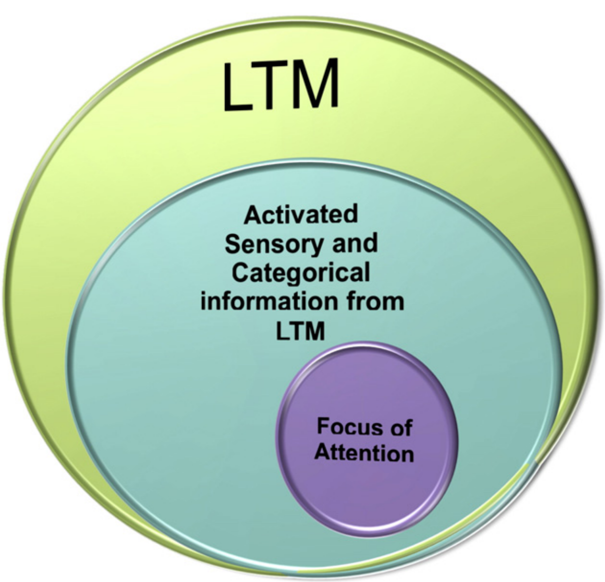

Fig. 2. Schematic diagram of Cowan's Model of Working Memory.

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).