

Verbal and visual memory: Characterizing the clinical and intermediate phenotype in schizophrenia

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Abstract

Background: Verbal and visual memory deficits are prominent trait markers for schizophrenia, with impairments also observed in first-degree relatives [Snitz, B.E., Macdonald, A.W., 3rd, & Carter, C.S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull*, 32(1), 179–194]. It remains unclear whether deficits lie in encoding or savings, and whether the deficit is heritable.

Objective: To determine which features of memory performance are impaired in both patients and their healthy siblings, possibly reflecting shared genetic effects.

Method: We tested episodic memory using Logical Memory (LM) and Visual Reproduction (VR) tasks of the Wechsler Memory Scale (Revised). Participants included patients with schizophrenia ($n=162$), their nonpsychotic siblings ($n=146$), and controls ($n=205$), recruited for the “CBDB/NIMH Sibling Study”. We assessed immediate encoding and 30 minute and 24 hour delayed recall as well as savings scores for the “short delay” (immediate to 30 min) and “long delay” (30 min to 24 h) intervals.

Results: We observed marked verbal recall deficits in both patients and siblings compared to controls for all stages ($p<.0001$). Only patients experienced significant verbal and visual savings deficits over short delays ($p<.0001$) as well as verbal deficits over long delays ($p<.005$). In siblings, no saving score difficulty was apparent for either measure.

Conclusions: Our results confirm shared impairment in verbal learning, but not memory, for both patients and siblings, therefore marking it as a potential schizophrenia-associated intermediate phenotype. The results implicate neural systems involved in immediate encoding and stabilization of memory representations in genetic risk for schizophrenia. In contrast, visual recall and savings impairments appear to be illness, i.e. state, deficits.

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1. Introduction

Multiple meta-analytic studies have demonstrated that impairments of episodic memory are among the most profound cognitive deficits documented in schizophrenia research literature (Heinrichs and Zakzanis, 1998). Substantial impairments have been described for both immediate and 30 minute recall of verbal and visual materials, with effect sizes of $d=1.27$ and 1.00 for immediate encoding and $d=1.2$ and 1.09 for 30 minute recall in verbal and visual tasks, respectively (Aleman et al., 1999). Given robust impairment in patients, measures of episodic memory are attractive as potential intermediate phenotypes, i.e. nondiagnostic indicators of genetic liability for the illness. Indeed, meta-analytic reviews of the cognitive performance of family members of patients have shown that verbal memory impairments are among the most reliable deficits (Snitz et al., 2006). Visual memory has been studied less frequently than verbal memory in patients (Snitz et al., 2006), and impairments in the visual domain among family members appear to be somewhat less severe than in the verbal domain (Delawalla et al., 2006; Heinrichs and Zakzanis, 1998; Whyte et al., 2005).

On the Wechsler Memory Scale (Revised), subjects are presented with stories or visual figures and are asked for immediate recall of encoded information. This “immediate encoding” performance is likely to involve a mix of material from short- and long-term memory. Thus, in order to assess long-term memory *per se*, it is necessary to examine delayed recall and savings over time.

The literature examining delayed recall in schizophrenia is far less extensive and consistent than the immediate encoding literature. Most studies have examined verbal memory following 30 minute delays and calculated savings scores (delayed recall/immediate encoding) and found that patients indeed retained less than controls (Calev et al., 1991; Cirillo and Seidman, 2003; Heinrichs and Zakzanis, 1998; Touloupoulou et al., 2003b). However, longer delay intervals produce less evidence of impairment (Braff et al., 1991). Thus, the evidence for impaired savings in schizophrenia, and whether impairment spans both verbal and visual materials, is surprisingly sparse. The savings issue has rarely been studied in relatives. Two studies (Laurent et al., 1999; Cirillo and Seidman, 2003) found immediate encoding, but not savings score deficits, in relatives. Thus, available evidence suggests that the deficit in relatives may be confined to immediate encoding and spare actual savings/memory.

Our analyses were designed to address the limitations of the available patient and family member literatures by examining immediate encoding as well as 30 minute and 24 hour recall and savings for both verbal and visual materials. The analysis of patient performance for long delays was intended to further define the clinical memory phenotype. The analysis of sibling performance was intended to explore which aspects of the impairments observed in patients also occurred in siblings and might therefore be considered as marking an intermediate phenotype. Based on the literature, we predicted that logical memory measures would likely be intermediate phenotype markers. Our approach to visual reproduction performance was exploratory as the literature does not support a clear prediction. We expected the strongest shared deficits to occur in the immediate encoding and short delay savings, with the expectation that long delay savings might be intact in relatives, and possibly patients.

While our focus is on behavior, the distinction between immediate encoding and long delay savings may have important implications for understanding neurobiological and genetic mechanisms. Specifically, there is a great deal of evidence from studies of long-term potentiation – a cellular model of memory – that the mechanisms implicated in the induction of LTP differ from those implicated in the long delay maintenance of LTP (Pastalkova et al., 2006). Glutamatergic transmission and stimulation of NMDA and AMPA receptors are thought to play a critical role in the initial induction of LTP, whereas long-term maintenance involves protein synthesis and structural modification of synapses (Bekinschtein et al., 2007; Raymond, 2007). Behavioral evidence of impairment limited to either short or long delay memory may have important implications for understanding the genetic architecture implicated in schizophrenia.

2. Experimental methods

2.1. Participant inclusion

Participants were recruited to be a part of the “CBDB/NIMH Sibling Study” (D. Weinberger, PI). After complete description of the study to the subjects, written informed consent was obtained. Egan et al. (2001) and Goldberg et al. (2003) provide more detail of methods and possible ascertainment biases. Briefly, we tested schizophrenic patients, their siblings, and healthy controls between 18 and 60 years of age who had a premorbid IQ greater than 70. Participants in all groups were included in the analysis reported below if they passed a rigorous set of

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