



# Declarative memory in unaffected adult relatives of patients with schizophrenia: A systematic review and meta-analysis

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## Abstract

Despite evidence for diverse neuropsychological impairment in schizophrenia, verbal declarative memory has emerged as a core deficit in the disorder. Similar but less marked impairments have been demonstrated in unaffected biological relatives of patients with schizophrenia, but the nature and extent of the memory impairment in relatives compared to controls is unclear. We have conducted a systematic review and meta-analysis of the literature investigating declarative memory in unaffected biological relatives of schizophrenics and controls, with the aim of quantifying memory deficits in relatives. The standardised mean difference between groups was calculated for nine measures of declarative memory and two measures of intellectual ability, based on 21 studies of several hundred relatives of schizophrenics and controls. Unaffected relatives showed poorer performance relative to controls on all tests of memory examined. Small to moderate effect sizes, with overlapping 95% confidence intervals, were greatest on immediate (trial 1) list recall (0.65), followed by immediate (0.53) and delayed story recall (0.52). Verbal and general IQ showed smaller standardised mean differences as the latter tests, while the smallest standardised mean difference was shown on delayed visual recall (0.32). Results suggest greater deficits on tests of increasing memory load or which place demands on effective encoding processes but more studies with these tasks are needed. Investigation of sub-groups within these cohorts (e.g. age groups within or beyond the maximum age of risk) is recommended in order to identify deficits specific to the disease process.

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## 1. Introduction

Neuropsychological impairments in schizophrenia are diverse (Bildler, 1996; Heinrichs and Zakzanis,

1998), but deficits in the domains of executive function and memory are now considered especially prominent (Aleman et al., 1999; Cirillo and Seidman, 2003; McKenna et al., 1990; Saykin et al., 1991, 1994). Moreover, although verbal memory impairment in schizophrenia has not been established as a differential deficit, several studies have reported larger effect sizes for verbal memory than for other cognitive

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functions (Saykin et al., 1991, 1994; Touloupoulou et al., 2003a,b). Interestingly, this has been additionally shown in unaffected relatives of schizophrenic patients (Sitskoorn et al., 2004). Verbal memory could therefore be considered a core deficit of the disorder.

Investigation of individuals at an enhanced genetic risk for the disorder has allowed for the elucidation of underlying cognitive trait abnormalities of schizophrenia. These assessments are freed from some of the more difficult confounds such as stage of illness, symptom types and medication effects, due to the fact that none of the sample are actually ill (and are unlikely to become ill if over the age of 45). Indeed, cognitive impairments in this group, based on a comparison with a matched control group, are inherently subtle and performance would not generally be classified as sub-normal. This makes differences in performance between groups even more compelling. Impairments found in unaffected relatives of schizophrenics, relative to healthy controls, which are both stable and milder than but consistent with impairments found in schizophrenia, may qualify as ‘vulnerability’ deficits or reflections of a predisposition to the disorder.

While a recent meta-analysis quantified general cognitive impairment in non-psychotic relatives of schizophrenics (Sitskoorn et al., 2004), none have investigated memory performance specifically in this group when compared to controls. The purpose of this review therefore is to systematically and quantitatively review the literature investigating declarative verbal and non verbal memory performance in healthy, non-psychotic, first degree relatives of schizophrenic patients, when compared with normal controls, in order to clarify the nature and magnitude of the memory impairment. In addition, effect sizes are also derived for measures of intellectual function acquired in the included studies, as a means of qualitatively comparing relative global intellectual performance with memory ability.

In a meta-analysis of cognition in schizophrenics and controls, Heinrichs and Zakzanis (1998) organised measures of memory into one of two categories: global memory, which included summed trial recall and general learning indices, and selective memory, which included specific scores such as intrusion rate, forgetting, recognition and recall on specific trials.

Aleman et al. (1999) more discretely calculated separate effect sizes for verbal and non-verbal cued and free recall and recognition, and digit span backwards and forwards, and showed greatest effect sizes in total recall and free and delayed verbal recall. Most recently, Sitskoorn et al. (2004) combined scores on three tests of verbal memory—the Rivermead Behavioural Memory Test (RBMT), the California Verbal Learning Test (CVLT) and the Wechsler Memory Test (WMS)—to derive one effect size for verbal memory in relatives of schizophrenics compared to controls. In this quantitative review, we sought to refine these estimates for specific declarative memory tests. We have therefore looked at performance on individual tests of short and long-term declarative episodic and semantic memory, which have been used consistently throughout the literature to compare relatives of schizophrenic patients with controls.

## 2. Methods

### 2.1. Criteria for inclusion

Case control and cohort studies published between 1965 and July 2004 were considered for inclusion where neuropsychological assessments were performed on a sample of no less than 10 non-psychotic first or first and second degree relatives of schizophrenic patients and 10 healthy non-psychiatric control participants. Studies examining participants under the age of 16 were not included. This was based on similar factors to those outlined by Kremen et al. (1994). Aside from not yet being within the maximum risk age period for development of the disorder, children will also have been at a different developmental stage from adults at the time of testing. Both groups will have different life and educational experiences and some test formats will be less familiar to and less appropriate for children than for adults, thus restricting meaningful comparisons across groups (Kremen et al., 1994). It was also necessary that studies had used at least one of the memory tests listed in Table 1, ensuring that only measures of memory derived from the same groups of tests were included in the analysis. Note that we did not seek or include studies of (auditory or spatial) working memory.

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