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# Similar verbal memory impairments in schizophrenia and healthy aging. Implications for understanding of neural mechanisms

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## ABSTRACT

Memory is impaired in schizophrenia patients but it is not clear whether this is specific to the illness and whether different types of memory (verbal and nonverbal) or memories in different cognitive domains (executive, object recognition) are similarly affected. To study relationships between memory impairments and schizophrenia we compared memory functions in 77 schizophrenia patients, 58 elderly healthy individuals and 41 young healthy individuals. Tests included verbal associative and logical memory and memory in executive and object recognition domains. We compared relationships of memory functions to each other and to other cognitive functions including psychomotor speed and verbal and spatial working memory. Compared to the young healthy group, schizophrenia patients and elderly healthy individuals showed similar severe impairment in logical memory and in the ability to learn new associations (NAL), and similar but less severe impairment in spatial working memory and executive and object memory. Verbal working memory was significantly more impaired in schizophrenia patients than in the healthy elderly. Verbal episodic memory impairment in schizophrenia may share common mechanisms with similar impairment in healthy aging. Impairment in verbal working memory in contrast may reflect mechanisms specific to schizophrenia. Study of verbal explicit memory impairment tapped by the NAL index may advance understanding of abnormal hippocampus dependent mechanisms common to schizophrenia and aging.

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## 1. Introduction

Verbal learning and memory, typically tested by the ability to learn lists of words or written passages, is severely impaired in schizophrenia (Aleman et al., 1999) and linked to deficits in real-world social functioning (Green, 1996) and poor performance on social competence tests (Bowie et al., 2008). However despite a long history of extensive research (Gold et al., 1992; Heaton et al., 1994; Cirillo and Seidman, 2003) it is still unclear whether any specific cognitive deficit can be detected within the extensive impairment characteristic of schizophrenia patients and whether some component processes within domains such as memory are affected more than others.

A recent comparison of diagnostic groups found cognitive impairments considered core features of schizophrenia in bipolar disorder patients and may reflect shared pathology (Reilly and Sweeney, 2014).

Memory impairments are a prominent feature of healthy aging. We recently reported that in well-functioning healthy individuals, age related impairment in the ability to learn new associations was distinct from the equally severe impairment in logical (item) memory and from memory in executive and object-recognition domains (Silver et al., 2012). This was consistent with the model (Shing et al., 2010) that memory decline involves two processes, one initially in the hippocampus (addressing binding) and the other in the prefrontal cortex (PFC, addressing strategic encoding and controlled retrieval) and with imaging evidence that age-related cognitive decline may involve distinct hippocampus and PFC-based patterns (Kramer et al., 2007). PFC and hippocampal abnormalities are also common in schizophrenia (Harrison et al., 2003; Harrison, 2004; Grace, 2012) (Razi et al., 1999; Gotthelf et al., 2000), raising the question whether similar mechanisms underlie memory disturbance in schizophrenia and healthy aging.

To examine this we studied verbal and nonverbal explicit memory performance in schizophrenia patients and elderly and young healthy individuals. In a previous study such a comparison elucidated dissociations between tests of the executive domain. When compared to young healthy individuals as reference, schizophrenia patients showed more impairment than old healthy

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individuals on inhibition of prepotent responses and abstraction but showed similar severe impairment under conditional exclusion (Silver and Bilker, 2013). Notably the convergent outcome resulted from distinct processing impairments in the two groups.

As we were interested in studying as far as possible the effects of “pure” aging processes, the elderly group was selected to include only active independent individuals with high levels of education and good cognitive and social function, minimizing potential confounds from early dementing processes or environmental impoverishment.

We asked two specific questions:

1. What are the relationships between verbal and other memory types in schizophrenia?
2. How does the pattern of memory in schizophrenia compare to that in healthy aging?

The planned analyses included comparisons of impairments in schizophrenia and old healthy individuals using young healthy group as reference and of the associations between them taking into account other cognitive factors.

## 2. Methods

### 2.1. Participants.

Participants included 77 (68 men 9 women) individuals with schizophrenia, 58 (38 men, 20 women) elderly healthy and 41 (37 men, 4 women) young healthy individuals.

Mean age in the schizophrenia group was 36.62 S.D.=10.10 years and mean education was 10.08 S.D.=2.27 years. Elderly group had mean age of 72.36 S.D.=6.73 years and mean of 14.64 S.D.=4.11 years of education. Mean age in the young healthy group was 33.90 S.D.=9.50 years (vs. schizophrenia  $p=0.20$ ) and mean=11.12 S.D.=1.82 years of education. Schizophrenia patients had significantly less education than those in the older ( $p < 0.001$ ) but not younger ( $p=0.07$ ) healthy group.

The patients were clinically stable inpatients who could cooperate with computerized testing. They were diagnosed with schizophrenia or schizoaffective disorder ( $N=4$ ), by consensus among treating and research clinicians who were all senior psychiatrists and who used clinical interviews, observations, and case notes to determine the DSM-IV diagnosis. Individuals with neurological disorders, substance abuse or medical conditions which could compromise cognitive function were excluded. Clinical characteristics were: SANS total mean score=57.74 S.D.=20.33, SAPS total mean score=23.81 S.D.=18.86, age of first hospitalization mean=26.57 S.D.=8.90 years, illness duration mean=9.12 S.D.=9.33 years, number of hospitalizations mean=5.13 S.D.=6.41.

All patients received antipsychotic treatment, 21 of second generation type (risperidone,  $N=6$ , mean dose=4.43 mg/day, olanzapine  $n=8$ , mean dose=16.3 mg/day, clozapine ( $N=3$  mean dose=491.7 mg/day, ziprasidone  $N=4$  mean dose 17.5 mg/day) and the rest first generation, usually in long acting injectable form. Some patients received more than one antipsychotic drug and/or additional psychotropic drugs (biperiden or SSRI antidepressant). As a condition of entry, antipsychotic treatment was continuous for at least 3 months and drug doses unchanged for at least 2 weeks prior to the study onset.

The healthy participants included an elderly group of selected high-functioning individuals living independently in the community and a younger group of volunteers drawn from the same community or hospital staff. Extensive questioning excluded individuals with medical problems, history of neurological disorders,

drug or alcohol abuse or medication that could significantly affect cognitive performance.

The details of the healthy population are fully described in Silver et al. (2011) which also included some of the test data and are summarized here for convenience. The elderly healthy group were individuals living in the community, recruited specifically for the study by personal contact and local community advertisement. Entry criteria required that they be living independently in their own homes and running the household with no social services support, and by their own initiative be active socially and in the community. Most were retired, but some were still fully or partially employed. The majority belonged to a synagogue congregation of which one of the assessors (C.G.) was a member and their high level of personal and social function was verified by personal observation and collateral reports.

The mean age of the younger group was 37.73 years (S.D. 10.71, range 18–60) and of the older group, 72.28 years (S.D. 6.76, range 61–85). The mean education level was 11.94 years (S.D. 1.57, range 8–20) in the younger group and 14.72 years (S.D. 4.12, range 7–25) in the older group ( $p=0.001$ ). The greater educational achievement in the older group was due to a substantial number of older individuals with multiple tertiary academic degrees.

General cognitive function in the older group as measured by the Mini Mental State Examination did not differ significantly from the younger group (MMSE, older mean=29.10 S.D.=1.14, younger mean=29.22 S.D.=1.26  $p > 0.05$ ) and showed high consistency between groups as evidenced by the 95% CI(28.81–29.40 older vs. 28.82–29.22 younger), range of scores (25–30 older vs. 23–30 younger) and number of individuals with scores  $< 28$  ( $n=6$  in each group).

### 2.2. Neuropsychological assessment

Verbal memory was assessed with the logical memory and easy and hard paired associates subtests from the Wechsler Memory Scale Revised (WMS R) (Wechsler, 1987). The logical memory subtest requires subjects to remember items contained in the story read by the examiner. In the paired associates subtest the subject has to recall pairs of words, some forming easy associations (easy list) and others not readily associated (hard list). To create a measure of the ability to form new associations with minimal influence from other memory processes, we calculated the new associative learning (NAL) index using the formula:  $NAL = (\text{Paired Associates easy list score} - \text{Paired Associates difficult list score}) / (\text{Paired Associates easy list score} + \text{Paired Associates difficult list score})$  (Silver et al., 2012). This results in a unit less measure which can be compared with indexes of memory in other domains and across groups. Smaller NAL values indicate better ability to form new associations.

Executive function was tested with the Abstraction, Inhibition, and Working Memory task (AIM) designed as a measure of abstraction and concept formation with and without additional memory load (Glahn et al., 2000). It presents subjects with five shapes: two in the upper right and two in the upper left corner of a computer screen, with a fifth target object appearing in the center of the screen, below the other stimuli.

The participants' task is to pair the target object with the objects on either the left or right. In half the trials, an additional requirement for working memory maintenance is superimposed on this basic module by adding a delay between the presentation of the target and other objects. The Executive memory index (CSTAIM) was calculated using the formula:  $CSTAIM = (\text{Abstraction with no memory} - \text{Abstraction with memory}) / (\text{Abstraction with no memory} + \text{Abstraction with memory})$ .

Object recognition was assessed with the Visual Object Learning Test (VOLT) (Glahn et al., 1997). It uses 20 Euclidean shapes as

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