COGNITIVE AGING EFFECTS IN SCHIZOPHRENIA: A QUANTITATIVE REVIEW

by

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Abstract

Cognitive impairments are well-established in schizophrenia; however the impact of the aging process on cognition is controversial. Meta-analytic techniques were used to quantify the impact of aging in patients with schizophrenia on long-term memory (LTM). Fifty verbal memory effects from 49 studies and 30 non-verbal memory effects from 29 studies were identified with participants falling into the following age ranges: young (20-39), middle-aged (40-59), and old (60-79). Relative to controls, the oldest patient samples demonstrated greater LTM impairments for both verbal (d=-1.87) and non-verbal (d=-1.56) material. Middle-age patient samples showed equivalent impairments to that of young patients in verbal LTM (d=-1.02 and -1.14 respectively), but greater impairments in non-verbal LTM (d=-1.38 vs. -0.91). In conclusion, these results demonstrate that older patients with schizophrenia are significantly more impaired in LTM than younger patients and suggest that schizophrenic patients may be at increased risk for cognitive decline in late-life.

Dedication

To Tara, my soul mate, without whom I could not have completed this work.

And to my boys, Ainge and Sullivan for bringing joy into my life.

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Introduction

Cognitive impairment is a central feature of schizophrenia, the course of which is generally well understood through young and middle age. Typically, there are cognitive deficits present in the preclinical phase, which are followed by a notable drop in functioning at the onset of the disorder (Walker, Kesler, Bollini, and Hochman, 2004; McGlashan, 1999). Research has demonstrated that adult schizophrenia is characterized by heterogeneity in clinical course, in the severity of cognitive impairment, as well as on the relative impact on various cognitive domains (Hegarty et al., 2001; Gaebel and Frommann, 2000; Heinrichs and Zakzanis, 1998). Post-onset cognitive impairment is typically thought to be stable and non-progressive (Goldberg, Hyde, Kleinman, and Weinberger, 1993; Heaton et al., 2001; Goldstein, Allen, van Kammen, 1998), however some argue that schizophrenic patients show a decline in cognitive function beyond that seen in normal aging. In the earliest descriptions of schizophrenia by Kraepelin (1919), a central observation was that of continual cognitive decline over the course of the disorder. Indeed, there is some indication that there exists at least a subgroup of chronic patients that may be at risk for poor cognitive outcome (Ciompi, 1987; Keefe et al., 1996; Davidson et al., 1995). At present however, the post-onset course of cognition in schizophrenia is subject to debate. There are two main considerations that appear to contribute to this lack of consensus in this literature, the first being methodological differences between studies, and the second being differences in potentially moderating characteristics in the patients being studied. These points will be discussed in turn.

Methodological Issues

Cross-sectional studies

Conclusions regarding age-related cognitive decline in schizophrenia have been derived from various research designs, which may influence results. Cross-sectional studies of age in schizophrenia come in two basic designs, those with and those without a group of control participants. Both share the limitation of cohort effects, which are significant as patients are subject to different intervention strategies and educational opportunities across different eras. Several studies have compared older and younger schizophrenic patients in the absence of a healthy control comparison. Studies comparing patients across cohorts have shown impairment across all age groups, but have not reported age associated declines across most cognitive domains (Hyde et al, 1994; Goldberg, Hyde, Kleinman, and Weinberger, 1993; Mockler, Tonmoy, and Sharma, 1997). In contrast, cross-sectional studies looking at severely chronic patients have reported poorer functioning in older patients with schizophrenia (e.g., Davidson et al., 1995; Harvey et al., 1997; Harvey et al., 1999; Putnam and Harvey, 2000; Putnam and Harvey, 1999). However, whether this decline amounts to more than that seen in normal aging is indeterminate within the structure of these designs.

Cross-sectional studies that utilize a healthy control comparison have generally indicated no evidence for accelerated cognitive loss in schizophrenia. Fucetola et al. (2000) compared three cohorts of schizophrenics and control participants and found similar trajectories of cognitive loss across most cognitive domains except in abstraction ability, which showed increased impairment in the older schizophrenic group. Additional research used the Halstead Reitan Neuropsychological Test Battery (Reitan and Wolfson,

1993) to compare young and old schizophrenic patients divided into neurologically impaired and intact groups, to young and old control participants also in neurologically intact and impaired groups. This report revealed comparable age related impairments between the schizophrenia and control participants in the neurologically intact groups; however the neurologically impaired schizophrenic group showed a number of age associated interactions across neuropsychological measures, indicating a different and more severe aging process in this group (Goldstein and Zubin, 1990). Another study involving the comparison of older and younger groups of schizophrenic patients and control participants on several neuropsychological measures found that patients did not show greater age related deficits than controls (Chaikelson and Schzwartzman, 1983). However, participants in this study were all in the high average range of intellectual function, indicating that the patient groups were not representative. A report on patients and control participants between the ages of 40-85 years on the Dementia Rating Scale (Mattis, 1973) found similar age differences in cognitive impairment in both groups (Eyler Zorrilla et al., 2000). Heaton et al. (1994) compared young and old schizophrenic patients with late-onset schizophrenic patients and healthy controls. They found the three schizophrenic groups to be similar neuropsychologically, providing no evidence for age associated declines in cognitive function. In contrast, evidence has also been reported indicating accelerated decline in cognition in schizophrenia. An examination of patients and control participants across a wide age range found strong age related reductions in Quick Test estimated IQ (Mortimer and Bowen, 1999) in schizophrenic patients, but not in controls, indicating that age was associated with poorer performance relative to

normative data for patients on this measure (Kondel, Mortimer, Lees, Laws, and Hirsch, 2003).

Longitudinal studies

While longitudinal studies may be the best poised to examine cognitive decline, especially when a control group is included, limitations include selective attrition, practice effects, and limited follow-up intervals. Also, while the aging literature reports that age related changes in cognition typically do not occur until after the age of fifty (Schaie, 1994; Schaie, Willis, and O'Hanlon, 1993; Verhaeghen and Salthouse, 1997), the overwhelming majority of studies examining cognition have followed schizophrenia patients through their 30s and 40s, and have not included a healthy control group for comparison (e.g., Abrams and Nathanson, 1966; Hamlin, 1969; Klonoff et al., 1970; Schwartzman and Douglas, 1962; Smith, 1964; Waddington and Youssef, 1996). The majority of these studies have shown modest declines in cognitive functioning in patients over long (greater than 10 years) follow-up (Abrams and Nathanson, 1966; Hamlin, 1969; Schwartzman and Douglas, 1962; Smith, 1964; Waddington and Youssef, 1996). However, there have been contradictory findings reported. Klonoff et al. (1970) found improved Performance IQ in 66 chronic schizophrenia patients over an eight-year period. Although the authors note that it may have been an artifactual increase based on age correction of IQ scores, relative to the normative data the patients did not show a decline.

Other studies have examined the question of whether the syndrome of schizophrenia is consistent with a neurodegenerative disorder, and have examined patients longitudinally over relatively short follow-up times, making it difficult to detect age related cognitive decline. For instance in a one and two-year follow-up of chronic

schizophrenia patients using the Mini Mental Status Exam (MMSE; Folstein, Folstein, and McHugh, 1975), Harvey et al. (1995) found stable function in patients. Additional evidence for stable function comes from Heaton et al. (2001) as they followed patients and control participants with a wide age range over 1.6-year and 5-year intervals. In this study, both patients and controls showed improved performance at both follow-up points. However, in a 30-month follow-up of patients using the Clinical Dementia Rating Scale (CDRS; Berg, 1988), approximately 30% showed decline (Harvey et al., 1999). Risk factors identified with cognitive decline were older age, higher positive symptoms, and lower levels of formal education (Harvey et al., 1999).

Cross-sequential designs

One notable study used a cross-sequential design where several age cohorts were followed longitudinally over a 6-year period (Friedman et al., 2001). Participants included a chronic group of patients with schizophrenia between the ages of 20-80, as well as healthy control subjects between the ages of 50-80. In this study, the patients with schizophrenia showed greater decline in cognitive functioning on the CDRS compared to control participants at follow-up.

Patient characteristics and moderating variables

While each of the approaches to aging research in schizophrenia brings with it strengths and weaknesses, an overall consensus on age related cognitive changes remains elusive. Heaton and Drexler (1987) in a review of the aging literature concluded that schizophrenia is not consistent with a neurodegenerative condition, and that there was little evidence for age related cognitive declines. Others however argue that there are neurodegenerative elements present in schizophrenia (Lieberman, 1999; Knoll et al.,

1998; Ashe, Berry, and Bolton, 2001), and even two or more distinct diseases (Kirkpatrick, Buchanan, Ross, and Carpenter, 2001; Crow, 1985; Wagman, Heinrichs, Carpenter, 1987) with distinct neuropsychological patterns, courses, and outcomes. Several factors associated with poor outcome will now be examined as potential moderating factors for cognitive outcome in this disease including: chronicity, negative symptoms, educational achievement, and gender.

Chronicity. Highly chronic and severe illness courses in schizophrenia are associated with earlier symptom onset, higher levels of negative symptoms, more hospital admissions, and resistance to treatment (Kirkpatrick et al., 2001). These patients also described as *deficit* or *Kraepelinian*, have greater cognitive deficits (Roy et al., 2003; Buchanan et al., 1994), greater cerebral impairment (Buchsbaum et al., 2002; Davis et al., 1998), and poorer cognitive outcomes (McGlashan, 1988; Keefe et al., 1996), than less severe patients. Poor outcome chronic schizophrenia patients have shown significant age-associated ventricular enlargement longitudinally (Davis et al., 1998; Knoll et al., 1998), and cross-sectionally relative to healthy controls (Weinberger, Jeste, Wyatt, and Teychenne, 1987; Knoll et al., 1998). These patients have also shown impaired brain activation in the temporal lobes and cingulate relative to better outcome patients while performing a verbal memory task (Buchsbaum et al., 2002). Studies looking at older poor outcome patients have for the most part reported cognitive decline in this group (e.g., Davidson et al., 1995; Friedman et al., 2001; Harvey et al., 1999).

Negative Symptoms. High levels of negative symptoms are also associated with poor outcome (Green, 1996) and deficits in various neuropsychological domains including memory (Brebion et al., 2000; Heinrichs and McDermid Vaz, 2004; Aleman et

al., 1999) and executive functioning (Berman et al., 1997; Chan, Chen, Cheung, and Cheung, 2004; Bryson Whelahan, and Bell, 2001; Nieuwenstien, Aleman, and de Haan, 2001). Negative symptoms also tend to increase with age (Harris, Jeste, Krull, Montague and Heaton, 1991; Sauer, Hornstein, Richter, Mortimer, and Hirsch, 1999). However null findings examining the difference between older deficit and non-deficit patients in cognition have been reported (Granholm and Jeste, 1994; Harris et al., 1991), leading some to suggest that symptomatic subtypes used to characterize patients may lose currency with age (Granholm and Jeste, 1994). Clarification of the issue is warranted.

Educational achievement. Educational attainment influences neuropsychological test performance (Lezak, 2004). Higher education has been shown to be a protective factor for cognition in late-life (Zhang et al., 1990; Stern et al., 1994). The educational attainment of many schizophrenic patients is curtailed due to onset of symptoms and therefore the lower educational level may place patients at risk for greater impairment later in life. The matching of patients on education is a significant issue in schizophrenia research, as the educational level attained may not reflect premorbid ability, and lead to mismatching with healthy controls (see Resnick, 1992 for discussion). Typically, estimates of premorbid ability are used to match patients and control participants. These include reading measures such as the National Adult Reading Test (NART) or the reading subtest of the Wide Range Achievement Test (WRAT; Wilkinson, 1993), which are relatively good indicator of premorbid functioning, and correlate well with premorbid Full Scale IQ (Lezak, 2004).

Gender. Male gender is associated with earlier onset, more severe course, and deficit syndrome in schizophrenia (Roy, Maziade, Labbe, and Merette, 2001), as well as

more severe neuropsychological impairment (Goldstein et al., 1998). Studies of gender in late life have revealed increased negative symptoms in male patients, but no differences between genders in cognitive impairments in poor outcome patients (Moriarty et al., 2001).

Brain reserve and the neurocognitive deficits of schizophrenia

A discussion about the interaction of a neurodevelopmental condition and the aging process is usefully framed by the theory of cognitive reserve. Cognitive reserve is a hypothesized mechanism developed to explain the observed disconnection between brain pathology and the behavioural manifestation of impairment, as well as the apparently protective nature of higher education, IQ, and brain mass against dementia (Stern, 2002; Satz, 1993). There are a number of consistently reported structural abnormalities in the schizophrenic brain such as lower brain volume, increased ventricle size, and temporal lobe structures bilaterally (Wright et al., 2000; Zakzanis, Poulin, Hansen, and Jolic, 2000), and reduced frontal lobe volume (Zakzanis and Heinrichs, 1999). Cognitive impairments are also consistently reported in nearly every cognitive domain including global cognition, memory, attention, and executive functions (Heinrichs and Zakzanis, 1998; Aleman et al., 1999; Johnson-Selfridge and Zalewski, 2001). Previous research has shown that persons with mild cognitive impairment are at much higher risk for dementia, and that memory impairments are particularly predictive of a future dementia diagnosis (Tuokko and Frerichs, 2000; Flicker, Ferris, and Reisberg, 1991; Bozoki, Giordani, Heidebrink, Berent, and Foster, 2001). Given these findings, and the fact that some of the brain abnormalities identified in schizophrenia affect the same neuroanatomical structures (e.g. enlarged ventricles, reduced temporal lobe volume) that are affected in

aging (Buchsbaum and Hazlett, 1997), one could posit an interaction with the aging process that would erode their low neurocognitive reserve and place them at greater risk for cognitive loss in late-life, with more severely affected individuals, presumed to have the least amount of reserve, at the highest risk.

Memory impairments in schizophrenia.

While schizophrenia is associated with global cognitive deficits there are neurocognitive domains that are particularly impacted. Long-term or secondary verbal free recall is one domain that is especially impaired in schizophrenia, with mean effect sizes ranging from d=-1.20 (Aleman, Hijman, de Haan, and Kahn, 1999) to d=-1.41 (Heinrichs and Zakzanis, 1998), where d is a measure of the number of standard deviations that the patient and control groups differ. Verbal memory is an important factor in predicting functional outcome (Green, 1996; Milev et al., 2005), and is a key feature of a diagnosis of dementia (American Psychiatric Association [APA], 2000). The deficits associated with non-verbal memory in schizophrenia are lesser in magnitude than the verbal memory deficits, yet still large (between –0.74 [Heinrichs and Zakzanis, 1998] and -1.09 [Aleman et al., 1999]). Memory performance also declines with age with reported effects ranging from d=-0.67 to -0.99 (Verhaeghen, Marcoen, Goossens, 1993; Verhaeghen and Salthouse, 1997). Memory deficits have been reported in older chronic schizophrenic patients (Putnam and Harvey, 1999), and aging studies of cerebral metabolism in schizophrenia have shown decreases in glucose metabolism in frontal and anterior temporal regions in older patients beyond that seen in healthy controls during a list-learning and memory task (Siegel et al., 1994; Buchsbaum and Hazlett, 1997).

Furthermore, age related slowing of myelination in the hippocampus has been reported in schizophrenics relative to healthy controls (Maier and Ron, 1996).

Hypotheses

The goal of this study is to undertake a quantitative review of the literature in order to examine age effects on memory deficits in schizophrenia. It is predicted that persons with schizophrenia will show deficits in memory relative to healthy controls across every age group, and that the magnitude of the difference will increase linearly with age, in a pattern consistent with accelerated aging. Due to the difference in magnitude between verbal and non-verbal memory deficits in schizophrenia they will be examined separately. There is no basis for differential predictions between verbal and non-verbal memory, and a similar trajectory is predicted based upon the fact that both types of memory are dependant upon the hippocampus (Sweatt, 2004), and bilateral hippocampal abnormalities are present in schizophrenia (Nelson, Saykin, Flashman, and Riordan, 1998; Heckers, 2001). It is further predicted that these age associated deficits will be most pronounced in more severely ill groups (i.e., highly chronic groups, higher negative symptoms). Other predicted moderators of increased memory impairment are an early age of onset (Tuulio-Henriksson, Partonen, Suvisaari, Haukka, and Lonqvist, 2004; Meltzer et al., 1997), lower educational achievement (Harvey et al., 1999), and male gender (Meltzer et al., 1997; Moriarty et al., 2001).

Methods

Study selection

Studies were obtained though a computerized search of Medline (1966-2004), PsycINFO (1887-2004) and Digital Dissertations (1861-2004) databases between the

years 1980 and 2004, using the following search terms: *cognition, neuropsychology, memory, WMS, CVLT, CERAD and schizo**. The year 1980 was chosen in order to maximize diagnostic reliability with the introduction of the Diagnostic and Statistical Manual (3rd ed. [DSM-III]; APA, 1980). In addition, an examination of the citations of major review articles in this area was conducted (e.g., Lieberman, 1999; Harvey, 2001; Cohen, 1990; Heaton and Drexler, 1987), and multiple volumes of journals which most frequently published articles in this domain were sampled. These journals included *Schizophrenia Research, Schizophrenia Bulletin, American Journal of Psychiatry, Archives of General Psychiatry,* and the *International Journal of Geriatric Psychiatry.* Articles published up to and including December 2004 were included, and were limited to those presenting results in English. All studies were inspected to ensure that they met the following inclusion criteria:

1. In order to be included in the analysis, studies required the inclusion of a secondary or long-term memory measure for a schizophrenic sample in a format that allowed for calculation of effects (i.e., means and standard deviations, F-statistic with one degree of freedom, t-test, or probability). A secondary memory task was defined as a task exceeding the capacity of working memory, such as a list, prose, or figure recall task (Stillings et al., 1987). In order to ensure independence among the studies included in the analysis, when multiple studies were based on the same sample of participants, the study including the best age groupings, and/or largest number of subjects was chosen for inclusion in the analysis (e.g., Fucetola, Seidman, Kremen, Faraone, Goldstein, and Tsuang, 2000 was included because it divided subjects into three age groups, Seidman, Kremen, Koren, Faraone, Goldstein and Tsuang, 2002; Seidman Lanca, Kremen,

Faraone, and Tsuang, 2003; Kremen, Seidman, Faraone, Toomey, and Tsuang, 2000; Kremen, Seidman, Faraone, and Tsuang, 2001 were not included).

Verbal memory and non-verbal memory measures were analyzed separately. Verbal memory measures included the California Verbal Learning Test (CVLT) and CVLT-II (Delis, Kramer, Kaplan, and Ober, 1987; 2000), the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941; Corwin and Bylsma, 1993), Logical Memory and Paired Associate subtests from the Wechsler Memory Scale (Wechsler, 1941) WMS-R (Wechsler, 1987) and WMS-III (Wechsler, 1997), and the Serial List Learning Test from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery (Morris et al., 1988). Non-verbal memory measures included the Rey-Osterrieth Complex Figure Test (Rey, 1941; Myers and Myers, 1993), the Visual Reproduction subtest of the WMS, WMS-R, and WMS-III (Wechsler, 1941; 1987; 1997), and a visual analogue of the paired associates task (Ragland et al., 1996). Effects were calculated only on measures of free recall and a single average effect for immediate and delayed recall was generated.

For studies not reporting control participant data, normative data was utilized to calculate effect estimates. Norms were chosen based on samples matched for age, and educational level when available. Normative data was obtained from Spreen and Strauss (1998) and Mitrushina, Boone, and D'Elia (1999), the manuals for the California Verbal Learning Test (CVLT) and CVLT-II (Delis et al., 1987; 2000), manuals for the WMS-R (Wechsler, 1987) and WMS-III (Wechsler, 1997), and the Rey Complex Figure (Myers and Myers, 1993), as well as from Morris et al. (1988). Where multiple normative sets

were available, selection was made on the basis of those that were best matched first on age, then on gender and educational level of the sample.

2. Studies were included in the analysis if the age range of study subjects fell into one of three age categories based on conventions in the aging literature (Nichols, Rogers, Fisk, and West, 2001): "young" (18-39), "middle-aged" (40-59), and "old" (60+). If specific age ranges were not reported in the description of the sample, ranges were estimated based upon the mean age and standard deviation of the sample. An 80% confidence interval for age range was calculated for these studies by adding/subtracting 1.28x standard deviations to the mean, in order to predict that 80% of the sample would fall into that age range assuming a normal distribution of age in the sample. If the upper or lower limit of the study's age range exceeded the aforementioned age ranges by more than five years, the study was eliminated from the analysis (n=369).

3. Studies containing unmedicated patients were eliminated (one study: Saykin et al., 1991).

Based on these inclusion criteria, a total of 53 studies were identified, with 50 effects from 48 publications were identified for inclusion in the verbal memory analysis: 34 young, seven middle, and nine old (see Figure 1). Thirty effects from 29 studies were included in the non-verbal memory analysis, 23 young, two middle, and five old (see Figure 2). Three studies included two age groups that contributed independent effects to the analysis (Cartegena, 2001; Fucetola et al., 2000; Lindenmayer et al., 1997).

Demographic information for the studies sampled in the verbal memory study can be seen in Table 2. There were significant differences in the gender, $F(2, 46) = 15.01$, $p<0.01$, education, $F(2, 35)=8.55$, $p<0.01$, and age of onset, $F(2, 38)=32.41$, $p<0.01$,

between the age groups. Although there was overlap between the studies that contributed information to both verbal and non-verbal analyses, the demographic information for non-verbal studies was limited (see Table 3). Only one study from each of the middle and old groups contained length of illness and onset of illness information, making it impractical to analyze these variables. Education level differences between groups was non-significant, $F(2, 20)=2.27$; $p=0.11$)

Analysis

Effect-sizes were generated for each of the memory measures reported in the study by converting results into *d* using a random effects model (Hedges and Olkin, 1985). When mean and standard deviation information is provided, *d* is calculated by dividing the difference of the means of the patient and comparison groups by the pooled standard deviation in order to generate the number of standard deviations that the patient and control groups differ (see equation 1).

(Equation 1):

$$d=\frac{(m1-m2)}{\sigma}$$

These calculations were performed in DSTAT (Johnson, 1989). Calculation of *d* was also made from F-tests with one degree of freedom, t-test statistics, and probability statistics. These calculations were performed using the Effect Size software package (Shadish, Robinson, and Liu, 1999). When multiple memory measures were presented in a single study, a single effect was calculated by first averaging the effect of each test (i.e., averaging short free recall and long free recall on the CVLT), and then averaging across tests to generate a single effect for the study.

Effect sizes were coded so that a negative effect indicated worse performance for the schizophrenic group. Hedges procedure was used to adjust effects for the upward bias associated with small sample size (Hedges and Olkin, 1985), and to calculate an unbiased effect *g*. Comprehensive Meta-Analysis software (Borenstein and Rothstein, 2000) was used to calculate the overall point estimate for each age group. Where normative data was used, the effect weight was based on the sample of the schizophrenia group. The more conservative random effects model was used (Hunter and Schmidt, 2004). To determine whether the effects sizes could be assumed to originate from the same population, within group homogeneity was evaluated using a calculation of the homogeneity statistic Q_w, which has a chi-squared distribution with k-1 degrees of freedom (Hedges and Olkin, 1985). Contribution to group heterogeneity was a criterion for outlier exclusion. Some between group differences were analysed using the Q_b statistic, which is analogous to an F-statistic, to test between group heterogeneity and examine between group differences (Hedges and Olkin, 1985). SPSS was used for generation of *F*-tests and for the regression analyses of moderators.

Analysis of age effects was conducted in two ways: categorically based on age groupings, as well as associating each effect with the mean age of the sample for regression analyses. Regression analyses were also conducted to examine the contribution of various proposed moderators to the effect magnitude. Differences in verbal and non-verbal effect magnitudes were examined with a paired-sample *t*-test examining those studies that included both types of memory data. This was undertaken to avoid the differential age distribution of the two effect sets, with verbal memory containing older effects, which would push the effect in the predicted direction.

Moderators

Based on existent literature, several factors were identified as possible moderators of memory effects in schizophrenia. These factors were coded as follows:

Age. Memory difference between age groups was the primary interest of this study. Studies were coded into three groups using the aforementioned age groupings (i.e. young, middle, and old).

Chronicity. McGlashan (1988) identified four components of chronicity: length of manifest illness, treatment resistance, age of onset, and institutionalization. Due to limited reporting of all four aspects of chronicity, only a subset of these elements could be coded. Thus, length of illness, age of first contact with the mental health system, and percent of sample institutionalized were coded for each sample. Effects based on greater than 70% inpatients were coded as inpatient samples, and effects with less than 30% inpatients were coded as outpatient samples; samples falling between were coded as mixed. Inpatient groups were further subdivided into those coming from inpatient acute hospitals or long term inpatient tertiary hospitals. These variables were then combined into a single variable describing the average level of care that the sample was receiving: (1) represented an entirely outpatient sample, (2) a mixed inpatient/outpatient sample from an acute hospital, (3) all inpatients at an acute hospital, and (4) all inpatients at a tertiary or state hospital. Patients from group 4 were seen to have the highest level of chronicity. Analyses were undertaken to examine differences between this group and the other three groups. While all older patients who remain in contact with the mental health system are chronic to some degree, within the remainder of this paper the term chronic

will be used to describe those older patients with persistent symptoms and a severe disease course, however for younger patients define chronic.

Symptoms. Patients' severity of positive, negative and general symptoms were examined where possible by including scores from the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen and Olsen, 1982), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen and Olsen, 1982) the Positive and Negative Symptom Scale (PANSS; Kay, Fiszbein, and Opler, 1987), and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorman, 1962; Ventura, Green, Shaner and Liberman, 1993). In order to compare across different measures, the scales were standardized by dividing each sample's mean score by the number of items on each scale and the maximum possible value for each item on the scale, thereby producing a value for each study on a scale from 0 to 1, with 0 indicating that all subjects received the minimum score on every item on the scale and with 1 indicating that all subjects received the maximum score on every item on the scale. Positive, negative and general symptom scales were coded separately.

Educational level. Education is an important moderator for cognitive decline (Satz, 1993; Stern, 2002), and is known to be associated with performance on neuropsychological tests, and also has cohort effects (Lezak, 2004). The effect of level of education attained in years was examined. The discrepancy between patient and control levels of education was also calculated. Premorbid estimators such as the NART or WRAT were only included in about one third of studies, and could not be meaningfully examined.

Gender. Previous findings have indicated that patient gender is an important moderating factor (Roy et al., 2001; Goldstein et al., 1998). Gender was calculated for each sample as a proportion of male participants to total number of participants.

Results

Homogeneity and Outlier Analysis

Rosenthal (1995; Rosenthal and DiMatteo, 2001) suggests that planned comparisons be carried out despite significant within group heterogeneity, if attempts to account for the heterogeneity through identification of moderating factors fail. Outliers were identified by visual inspection and by their contribution to within group heterogeneity (Hedges and Olkin, 1985). In the verbal memory analysis, one large magnitude effect was eliminated from the middle age group (van Oostrom et al., 2003). This changed the overall effect by 0.12 and resulted in a homogeneous effect set. Two large outlying effects were eliminated from the young group (Lindenmayer et al., 1997 [young group]; Roxborough, Muir, Blackwood, Walker, and Blackburn, 1993) for the group comparisons. The overall change in weighted d was 0.07 (see Table 2), this group remained significantly heterogeneous ($p<0.01$). In the non-verbal analysis, one large outlying study was removed from the old group (Putnam and Harvey, 1999). This affected the overall mean d by 0.32, and resulted in a homogeneous effect set.

For the regression analyses, outlying studies were re-entered and an additional *multivariate* outlier analysis was conducted; studies were eliminated based on a large leverage value (above 0.4; Myers and Well, 2003). One effect was eliminated on this basis in the verbal memory study in the educational discrepancy regression (Lindenmayer et al., 1997 [young group]). No studies were eliminated in the regression of verbal

memory effects and gender or chronicity, or in the examination of non-verbal memory and educational discrepancy. There was not sufficient data to conduct an analysis of chronicity factors in the non-verbal data set. Deletion of outliers did not affect the direction or statistical significance of the results.

Age Analysis

Significant between group differences were found in for verbal memory with the old schizophrenia to healthy control effect magnitude significantly larger than the effect magnitudes of the middle schizophrenia to healthy control and the young schizophrenia to healthy control effects, Q_b (2, 44)=65.69; p<0.01. As shown in Table 2, the old group had a mean weighted effect magnitude of d=-1.87 (95%CI: -2.11– -1.63), compared with the middle and young groups d=-1.02 (-1.25 – -0.79) and d=-1.14 (-1.29 – -1.00) respectively. Young and middle age groups were not significantly different (t=0.193; p=0.85), and were therefore combined for comparison to the old group. The 95% confidence interval of the oldest age group showed no overlap with the other age groups (t=3.90; p<0.01). Figure 4 shows non-verbal memory effects which also revealed significant differences, Q_b(2, 26)=10.95; p<0.01. The young group had a mean weighted d of -0.91 (95% CI: -1.06 -- -0.76), the middle group d=-1.38 (95% CI: -1.86 -- -0.81), and the old group d=-1.56 (-1.95 -- -1.18). The young and old groups were significantly different from one another (t=2.88; p<0.01).

Moderator Analyses

Chronicity. In order to examine how chronicity was related to memory deficits, a comparison was undertaken between the most chronic and severe groups (inpatients in tertiary or state hospitals) and the combined less chronic groups. This comparison was

done in the young and old age groups only, as the middle age group did not include any groups in the highly chronic category (k=0). Table 4 reveals the results of this analysis, which show a clear division between the older groups in terms of their care-level, with more chronic older patients showing larger magnitude effect estimates than less chronic older patients, with no overlap in the 95% confidence interval ($p<0.01$). There were three chronic young effects (d=-1.25) to compare to the 26 young non-chronic effects (d=-1.09), and the difference in effect magnitude was non-significant (p=0.59). After the elimination of the chronic groups from the analysis, significant group differences remained were found in comparing the means of the three age groups ($Q_b(2, 31)=7.28$; $p<0.05$; see Figure 5), and the same pattern remained with the young and middle age groups not significantly different from each other (t=0.344; p=0.73), and both significantly different from the old group (t=2.48; $p<0.05$).

Other measures of chronicity were also examined in the verbal memory effect set. Length of illness was highly correlated with age (r=0.97; $p<0.01$) and the magnitude of the effect (r=-0.40; $p<0.01$). Age of onset held a significant relationship with current age (r=0.79; $p<0.01$) indicating that older patients tended to have later first hospitalizations than younger patients. The correlation between age of onset and effect magnitude was similarly significant (r=-0.30; $p<0.05$), albeit in the opposite direction predicted. This is likely due to a cohort effect, and marks the finding that older groups had later first contact with the mental health system. Because age, length of illness, and onset of illness are linearly dependant, (i.e., age of onset + length of illness = current age), the regression of both age of onset and length of illness added a similar and non-significant amount of predictive power to a regression equation of age and effect magnitude (p=0.70).

Symptoms. Symptom severity, especially negative symptoms, was a predicted moderator of cognitive decline. However, correlational analysis shown in Tables 5 and 6 revealed that positive, negative, and general symptoms were not significantly related to the effect magnitude or to age in either the verbal or non-verbal effect set.

Gender. Table 5 shows two potential confounding variables that were related both to age and to the effect magnitude in verbal memory: gender proportion of the sample and educational level. Older samples tended to have a higher proportion of females (r=-0.54 for verbal and -0.49 for non-verbal data sets; both $p<0.01$). Because women generally outperform men on tests of verbal memory (Kimura, 1999; Herlitz, Nilsson, and Backman, 1997) this finding was predicted to be operating in opposition to the age relationship. Nonetheless, a regression analysis was undertaken to examine its potential contribution to the effect magnitude. Removal of the variance due to gender proportion did not affect the significance of the age or age squared term, and gender did not significantly contribute to the prediction of the effect magnitude (p=0.10). As shown in Table 6, gender distribution was significantly related to age in the non-verbal memory effect set (r=-0.49; $p<0.01$) but was not significantly related to the effect magnitude (r=0.13; p=0.25).

Education. Education was confounded both with age and effect magnitude in both the verbal and non-verbal memory effect sets. Educational matching is a complex issue in schizophrenia research, as educational attainment is frequently curtailed by disease onset, and is generally viewed as a poor indicator of premorbid functioning (Resnick, 1992). Nonetheless, it is associated with neuropsychological test performance. Educational discrepancy between the healthy control and patient groups was also found to relate

significantly with both age and effect magnitude in verbal memory (r=0.61 and r=-.54 respectively; both p<0.01), and non-verbal memory (r=0.52; p<0.01; r=-0.43; p<0.05). This indicates that older patient and control participant samples tended to be more mismatched on education than younger samples. In order to address this confound, a regression analysis was undertaken to examine the age effect after the effect of educational discrepancy was removed. Educational discrepancy had significant predictive power on effect magnitude for verbal memory (R=0.61; p=0.01), and non-verbal memory (R=0.53; p=0.01). Nonetheless, age added a significant amount of predictive power to the regression equation both for verbal memory (R=0.63; p<0.05) and non-verbal memory (R=0.67; p<0.01). The non-linear age-squared term was entered in the analysis and marginally added predictive power to the equation in the verbal memory effect set (R=0.69; p=0.052). The age-squared term did not add a significant amount of predictive power to the equation in the non-verbal memory effect set (p=0.44), indicating a linear relationship.

Verbal/Non-verbal magnitude differences

Verbal and non-verbal memory differences were examined in a paired t-test of the 25 studies that included both types of memory effects. Mean effect size for verbal memory was d=-1.27, non-verbal memory was d=-0.99. Results indicated that the verbal memory deficits were significantly larger in magnitude than the non-verbal memory deficits (t=-2.86; p<0.01).

Supplementary Analysis

The possibility of differences between effects derived from study reported control participant groups and those from normative data sets was examined. There was no

difference in the overall effect magnitude effects based on healthy controls and those based on normative data (d=-1.29 vs. -1.36 respectively, p=0.67), nor between control and normative studies at any of the age groups (young control -1.23 vs. normative -0.97; p=0.15; middle age control -1.16 vs. normative -1.01; p=0.36; old control -1.79 vs. normative -1.97; p=0.75).

Discussion

The purpose of this investigation was to evaluate age effects on memory functioning in schizophrenia. The results of this meta-analysis support previous findings that schizophrenia is associated with memory impairment across all age groups (Aleman et al., 1999; Heinrichs and Zakzanis, 1998; Saykin et al., 1991). Furthermore, results support the hypothesis that long term memory shows an age related increase in impairment in late life schizophrenia. Verbal memory deficits showed age associated increases following a non-linear pattern, with young and middle groups relatively stable, with a significant loss in the old group. This pattern proved to be moderated to some degree by chronicity. Highly chronic older groups showed more severe memory impairment than less chronic older groups. However after excluding the chronic groups from the analysis, the pattern of memory impairment in the oldest group remained significant, showing more severe impairment than the young and middle aged groups. This non-linear pattern was not consistent with the prediction of a linear accelerated age effect, and parallels the cognitive pattern seen in a diagnosis of mild cognitive impairment (MCI). As noted previously, persons with a diagnosis of mild cognitive impairment are at much higher risk for dementia, and memory impairments are particularly predictive of decline (Tuokko and Frerichs, 2000; Flicker, Ferris, and

Reisberg, 1991; Bozoki, Giordani, Heidebrink, Berent, and Foster, 2001). Disorders such diabetes (Verhaegen, Borchelt, and Smith, 2003) and hypertension (Posner et al., 2002) have been linked to MCI and the current findings indicate that older persons with schizophrenia could be another group at high risk for possible dementia.

As predicted, the impairments found in non-verbal memory were not as severe as those seen in verbal memory. Non-verbal memory deficits increased in a linear fashion, with the oldest group showing the most severe impairment. The difference in pattern noted between verbal and non-verbal memory was also counter to the predicted hypothesis. There are several possible explanations for this difference in findings. The first is that verbal and non-verbal memory age differently. There is little evidence to suggest that this is the case. Greene, Baddeley, and Hodges (1996) in a study of healthy elderly and persons with mild and moderate AD, found no differences in verbal and non-verbal memory impairment in either healthy control or AD groups. However, it is possible that schizophrenia may interact to alter the normal pattern of aging. A more likely explanation is of a statistical nature. The middle age group in the non-verbal analysis is composed of only two studies, and hence is of low reliability, as evidenced by the wide confidence interval (-1.86 - -0.814). While the fact that the older group performs more poorly than the young group relative to age matched control participants on non-verbal memory recall measures can be reliably concluded, the overall pattern of age related impairment is tentative. Nonetheless, taken together the results of both verbal and non-verbal memory analyses indicate that relative to age-matched healthy control subjects, older schizophrenic patients do indeed show an increase in memory impairment that goes beyond that expected in normal aging.

A comparison between the more chronic and less chronic patients in the old age group indicated a clear separation between these two groups and supports previous reports that have linked chronicity to poor outcome (Ciompi, 1987; Huber, 1997; Keefe et al., 1996). Removal of the most chronic samples did not affect the significance of age relationship to verbal memory impairment, indicating that even relatively good outcome older patients demonstrate increased memory losses when compared to healthy controls. Several other reported markers of poor outcome such as longer length of illness, and lower educational level were also shown to be associated with greater memory deficits. Some of these moderating factors were also associated with age in what emerged as several clear cohort effects noted in the data set, and potentially confounding the observed age effect. Older samples tended to be more female, less educated, more mismatched relative to educational levels of their control participants, and they also tended to have a later first hospitalization. Nonetheless, age remained significantly related to memory impairment over and above education level and educational difference between control and normative groups, and the gender distribution proved to be non-predictive of memory impairment.

Age of first mental health contact was found to be associated with memory impairment in an opposite fashion than predicted, as a later age of first contact was associated with poorer memory performance. Previous research has shown that early age of onset is a predictor of illness severity and poor treatment response (Schurhoff et al., 2004; Tuulio-Henriksson, Partonen, Suvisaari, Haukka, and Lonnqvist, 2004). There are two possible explanations for this finding, both related to cohort effects between groups. Firstly, the finding may have been related to the higher levels of female patients in the

older samples, as female patients tend to have later onset of symptoms (Meltzer et al., 1997). In the present study this relationship between proportion of males in the study and age of onset was found in the expected direction ($r=-0.52$; $p<0.01$). In addition, a recent trend toward earlier diagnosis and treatment has also been reported (DiMaggio, Martinez, Ménard, Petit, and Thibaut, 2001), as current thinking in the area holds that early and aggressive treatment limits the cognitive impact of schizophrenia. These findings were also corroborated in this study with a significant positive relationship found between age and age at onset of illness ($r=0.78$; $p<0.01$). Longer duration of untreated illness has also been found to be associated with verbal memory deficits (Ho et al., 2003).

Severity of negative symptoms was not found to be associated with memory deficit or with age. Previous research has found that negative symptoms were predictive of memory deficits (Aleman et al., 2001; Pelletier, Achim, Montoya, Lal, and Lepage, 2005; Pantelis, Stuart, Nelson, Robbins, and Barnes, 2001), and that negative symptoms and 'deficit syndrome' increase with age (Harris et al., 1991; Sauer et al., 1999) as well as with male gender (Roy et al., 2001). An association between positive symptoms and age related cognitive deficits in geriatric schizophrenia has also been reported (Harvey et al., 1999), but was not corroborated in the present findings. As noted in the introduction, previous symptom based examination of cognition in older patients has not revealed significantly different outcomes (Granholm and Jeste, 1994; Harris et al., 1991). One possible explanation for this lack of finding is that deficit and non-deficit patients become more symptomatically similar with age, as the positive symptoms associated with schizophrenia tend to 'burn out' over time, leaving the more enduring negative symptoms. The lack of any significant finding related to symptoms in this study may be

due to the relatively small number of studies reporting symptom information in the sample. A more direct analysis of symptom and age related changes in schizophrenia may shed light on the situation.

Consistent with previous findings, the effect magnitude reported for older schizophrenic patients in the present study (d=-1.87) does not approach that reported for memory impairment in AD (d=-3.2; Zakzanis, 1998; Heaton et al., 1994; Granholm and Jeste, 1994). Given that normal age related cognitive losses are of the order of one standard deviation (Verhaeghen and Salthouse, 1997; Nilsson, 2003), the present finding that older schizophrenic patients are approximately two standard deviations below this level nonetheless represents a substantial level of memory impairment. Previous research has shown that severe cognitive impairment in schizophrenia is not associated with increased AD neuropathology (Arnold et al., 1998; Purohit et al., 1998), and neuropsychological findings even in severely chronic patients do not support a primary progressive dementia model of impairment in late-life schizophrenic (Friedman et al., 2001; Harvey et al., 1995). The results of the present study, when discussed in terms of reserve theory are consistent with some type of late-life interaction that occurs in the schizophrenic brain, where a low level of cognitive or brain reserve allows the normal effects of age to cross a threshold, resulting in memory impairment. Due to the large number of neurological and cognitive abnormalities associated with schizophrenia, as well as lower levels of educational attainment (Resnick, 1992), and increased lifetime institutionalization, which is arguably a less cognitively stimulating environment, it is reasonable to believe that schizophrenic patients possess reduced reserve and would be at greater risk of age-related cognitive decline (Arnold, 2001). Given the numerous

cognitive impairments associated with schizophrenia, previous findings showing no apparent cognitive reduction in old age (e.g., Mockler et al., 1997; Chaikelson and Schwartzman, 1983; Goldstein et al., 1998; Heaton et al., 1994) appeared to run contrary to this theory. While the present study does not evaluate the underpinnings of the increased memory impairment associated with age in schizophrenia, one possible identified mechanism is the abnormal myelination of the hippocampus in older schizophrenics. While healthy people see myelination in the hippocampi continue throughout their lifetime, Maier and Ron (1996) found significantly lower increases in the rates of choline, a building block of myelin, in the hippocampi of older schizophrenic patients relative to control participants. Increasing age would increase the differences in the integrity of the hippocampi between schizophrenics and healthy controls, and older schizophrenics have been shown to have impairments in hippocampal function during memory tasks (Buchsbaum and Hazlett, 1997).

Limitations

The age analysis used in this study is cross-sectional and while this is a commonly used methodology in aging research it cannot speak directly to age changes in verbal memory over time. It was clear in the results of this study that there were numerous cohort differences between the groups in educational level, and even the age of first contact with the mental health system. Longitudinal research, or ideally cross-sequential research, in this area would help to answer this question.

A related limitation of this study has to do with the ability to generalize the results to all older schizophrenic patients and the issue of age cohort equivalence. At issue is whether the patients in the old group can be considered to be psychiatrically equivalent to

the patients in the young and middle-aged groups. Due to the possibility that a certain percentage of patients are successfully stabilized early in their illness course, some patients composing the young schizophrenic group may lose contact with the mental health system in a systematic fashion biasing the middle and older samples toward more severe patients, who had not shown the same recovery. Consequently, an illness severity bias (i.e., selection bias) may be operative that could dispose the old group to greater memory impairments. Additionally, the current results likely cannot be generalized to those people that live as outpatients in the community with little or no contact to the mental health system.

Another source of bias in the sample is related to increased mortality in schizophrenia that is well established, with a suicide rate 6-8 times higher than a matched cohort (Harris and Barraclough, 1998; Brown, 1997). Therefore, the patients that do survive to old age may introduce a survivor bias into the results of research of old age schizophrenia. Bias in the healthy controls that participated in the studies as control participants is another possible biasing factor, as the results indicated they were more highly educated than the patient groups, and were possibly also healthier than average to survive to old age.

While the area of research into old age and schizophrenia has certainly expanded in the last decade, it is clear from the results of this study that the number of independent neuropsychological studies in this population is relatively small. Due to the heterogeneity that is inherent in the disorder more research must be undertaken with a wider variety of older patients to improve our understanding in this area. As noted in the introduction, much of the research in this area is published by large research groups looking at a single

long-term sample of chronic and severe patients, and at issue is whether the present results can be generalized to all older patients with schizophrenia. While the results of this study have shown that less chronic patients show age related memory impairments, it remains unclear whether these same deficits would be found in patients not captured in the clinical samples.

In conclusion, persons with schizophrenia are at risk for age related declines in their memory, and perhaps in cognition more generally. An understanding of the general late-life cognitive outcome in schizophrenia is important for this population because they are showing the same demographic shift into older age that the general population is experiencing (Heaton et al., 1994). Given the increasing numbers of elderly mental health patients at risk for cognitive impairment, it is important that these patients have increased structural support in place to support them in late life, as well as increased intervention strategies throughout the course of their illness in order to possibly ameliorate cognition and improve outcome.

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Figure 1: Verbal Memory Effects Summary

agegroup	Citation	N1	N2	AGE	Effect	Lower	Upper
1. young	Albus et al., 1996	40	40	30.80	-1.39	-1.89	-.89
1. young	Baare et al., 1999	14	14	28.50	-1.67	-2.59	-.75
1. young	Bacon et al, 2001	19	19	31.70	-.69	-1.36	-.01
1. young	Beatty et al, 1993	13	20	33.20	-.95	-1.72	-.18
1. young	Braff et al, 1991	40	40	29.70	-1.46	-1.97	-.96
1. young	Brewer et al., 1996	26	19	31.80	-.87	-1.51	-.23
1. young	Bruder et al, 2004	22	26	30.90	-1.82	-2.52	-1.12
1. young	Buchanan et al, 1994	39	30	33.71	-1.56	-2.11	-1.00
1. young	Chen et al, 2000	23	26	33.20	-.58	-1.17	.01
1. young	Egeland et al, 2003	53	50	31.50	-1.23	-1.66	-.80
1. young	Ehmann et al, 2004	37	37	30.00	-.63	-1.11	-.16
1. young	Fucetola et al., 2000	23	39	30.00	-2.11	-2.77	-1.45
1. young	Gold et al., 1999	54	54	29.00	-1.98	-2.45	-1.51
1. young	Goldstein et al., 1994	44	44	27.00	-.56	-.99	-.13
1. young	Hawkins et al, 1997	17	17	29.56	-.92	-1.66	-.18
1. young	Hill et al., 2004	45	33	28.09	-.75	-1.22	-.28
1. young	Kareken et al, 1996	29	29	29.38	-1.73	-2.35	-1.10
1. young	Landro et al., 2001	33	33	25.40	-.53	-1.03	-.03
1. young	Lindenmayer et al, 1997	20	20	34.20	-2.89	-3.83	-1.95
1. young	Malla et al, 2001	87	87	32.90	-.98	-1.30	-.66
1. young	Matsui et al, 2004	15	15	28.10	-1.52	-2.38	-.66
1. young	Moritz et al, 2001	25	25	30.76	-1.00	-1.60	-.39
1. young	Nagasawa et al, 1999	20	40	24.20	-1.37	-1.98	-.77
1. young	O-Leary et al, 2000	122	164	31.20	-1.34	-1.60	-1.08
1. young	Pollice et al, 2002	44	44	33.40	-1.77	-2.27	-1.27
1. young	Rosmark et al, 1999	14	14	32.80	-.87	-1.69	-.05
1. young	Roxborough et al, 1993	30	30	29.30	-2.32	-3.00	-1.64
1. young	Rushe et al, 1999	58	53	33.60	-1.10	-1.50	-.69
1. young	Seidman et al, 1998	35	25	28.70	-.84	-1.39	-.29
1. young	Seltzer et al, 1997	36	36	30.60	-.90	-1.40	-.41
1. young	Semkovska et al., 2004	27	27	27.20	-.95	-1.53	-.37
1. young	Sweeney et al, 1991	44	44	28.50	-1.02	-1.48	-.57
1. young	Torres et al, 2004	107	107	30.90	-.86	-1.14	-.58
1. young	van Beilen et al, 2004	50	25	28.60	-1.15	-1.67	-.62
1. young (34)		**1305**	**1326**		**-1.21**	**-1.36**	**-1.05**
2. middle	Altshulter et al, 2004	20	22	50.00	-1.10	-1.78	-.43
2. middle	Fucetola et al., 2000	38	27	41.10	-1.17	-1.72	-.63
2. middle	Lancaster et al, 2003	40	40	47.00	-1.23	-1.72	-.74
2. middle	Roy et al, 2003	36	36	44.03	-.51	-.98	-.03
2. middle	Soni et al., 1993	40	40	49.80	-1.39	-1.89	-.89
2. middle	Tuulio-Henriksson, 2004	237	237	45.20	-.91	-1.10	-.72
2. middle (6)		**411**	**402**		**-1.02**	**-1.25**	**-.79**
3. old	Fukunishi et al., 1990	39	40	68.80	-1.49	-1.99	-.98
3. old	Gab-Johnson et al., 2003	12	12	71.00	-2.10	-3.20	-1.01
3. old	Harvey et al., 2003	147	147	71.30	-1.81	-2.08	-1.54
3. old	Hyde et al., 1994	11	11	65.40	-1.68	-2.74	-.62
3. old	Kurtz et al., 2001	32	32	75.10	-2.32	-2.98	-1.67
3. old	Lindenmayer et al, 1997	25	25	66.70	-1.41	-2.05	-.77
3. old	McBride et al., 2002	44	44	75.50	-2.33	-2.88	-1.77
3. old	Putnam & Harvey, 1999	36	36	75.93	-2.26	-2.86	-1.65
3. old	Stookey, 1996	21	21	60.80	-1.48	-2.19	-.77
3. old (9)		**367**	**368**		**-1.86**	**-2.11**	**-1.62**
Combined (49)		**2083**	**2096**		**-1.30**	**-1.44**	**-1.16**

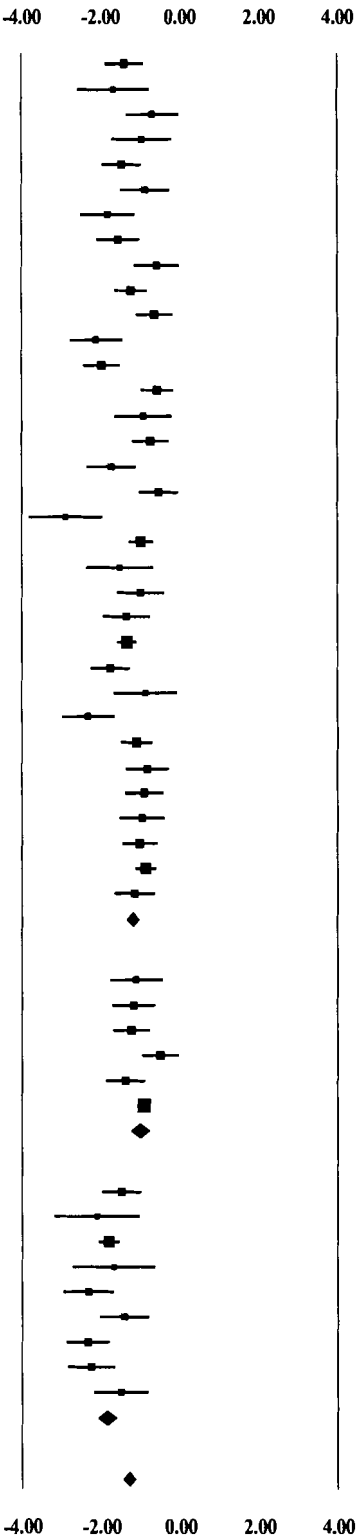


Figure 2: Non-Verbal Memory Effects Summary

agegroup	Citation	N1	N2	AGE	Effect	Lower	Upper
1. young	Albus et al., 1996	40	40	30.80	-.50	-.95	-.05
1. young	Baare et al., 1999	14	14	28.50	-1.22	-2.08	-.36
1. young	Bacon et al, 2001	19	19	31.70	-.84	-1.53	-.15
1. young	Braff et al, 1991	40	40	29.70	-.90	-1.36	-.43
1. young	Bruder et al, 2004	22	22	30.90	-.72	-1.35	-.09
1. young	Buchanan et al, 1994	39	30	33.71	-1.25	-1.78	-.72
1. young	Cuesta et al., 1998	69	36	28.61	-.82	-1.25	-.40
1. young	Egeland et al, 2003	53	50	31.50	-1.61	-2.07	-1.16
1. young	Ehmann et al, 2004	37	37	30.00	-.63	-1.11	-.16
1. young	Gold et al., 1999	54	54	29.00	-1.25	-1.67	-.83
1. young	Goldstein et al., 1994	49	49	27.00	-.71	-1.13	-.30
1. young	Hawkins et al, 1997	17	17	29.56	-.01	-.71	.69
1. young	Hill et al., 2004	45	33	28.09	-.76	-1.24	-.29
1. young	Landro et al., 2001	33	33	25.40	-.57	-1.07	-.07
1. young	Malla et al, 2001	87	87	32.90	-1.51	-1.85	-1.17
1. young	Matsui et al, 2004	15	15	28.10	-.29	-1.04	.46
1. young	Nagasawa et al, 1999	30	30	24.20	-.72	-1.26	-.19
1. young	O-Leary et al, 2000	146	104	31.20	-1.02	-1.29	-.75
1. young	Ragland et al, 1996	30	30	31.00	-.87	-1.41	-.33
1. young	Rushe et al, 1999	58	53	33.60	-1.28	-1.70	-.87
1. young	Seidman et al, 1998	35	25	28.70	-.96	-1.52	-.41
1. young	Seltzer et al, 1997	36	36	30.60	-1.06	-1.56	-.55
1. young	Semkovska et al., 2004	27	27	27.20	-.56	-1.12	.00
1. young (23)		**995**	**881**		**-.91**	**-1.06**	**-.75**
2. middle	Altshulter et al, 2004	20	22	50.00	-1.19	-1.87	-.51
2. middle	Cartagena, 2001	19	13	57.50	-1.56	-2.40	-.71
2. middle (2)		**39**	**35**		**-1.34**	**-1.86**	**-.81**
3. old	Cartagena, 2001	8	39	73.00	-1.36	-2.20	-.53
3. old	Gab-Johnson et al., 2003	12	12	71.00	-1.52	-2.50	-.54
3. old	Kurtz et al., 2001	22	22	75.10	-1.96	-2.71	-1.20
3. old	Putnam & Harvey, 1999	30	30	75.93	-3.21	-4.00	-2.41
3. old	Stookey, 1996	21	21	60.80	-1.39	-2.09	-.69
3. old (5)		**93**	**124**		**-1.89**	**-2.57**	**-1.20**
Combined (30)		**1127**	**1040**		**-1.04**	**-1.21**	**-.87**

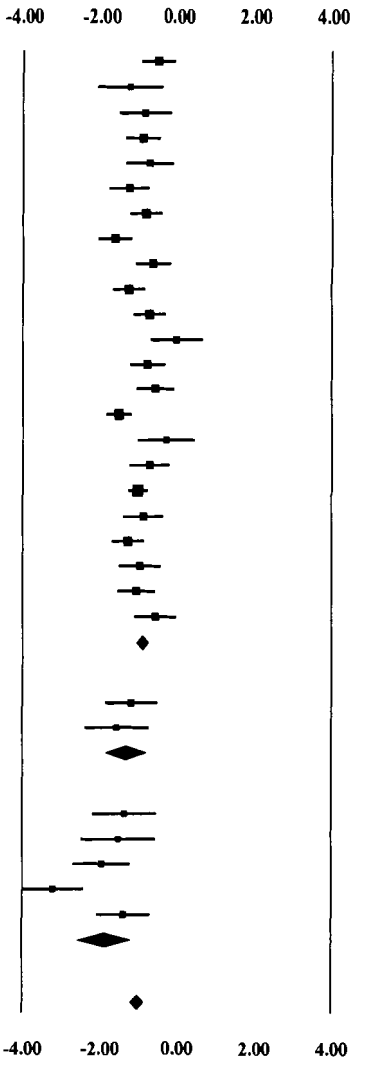


Figure 3: Verbal Memory Effects by Age

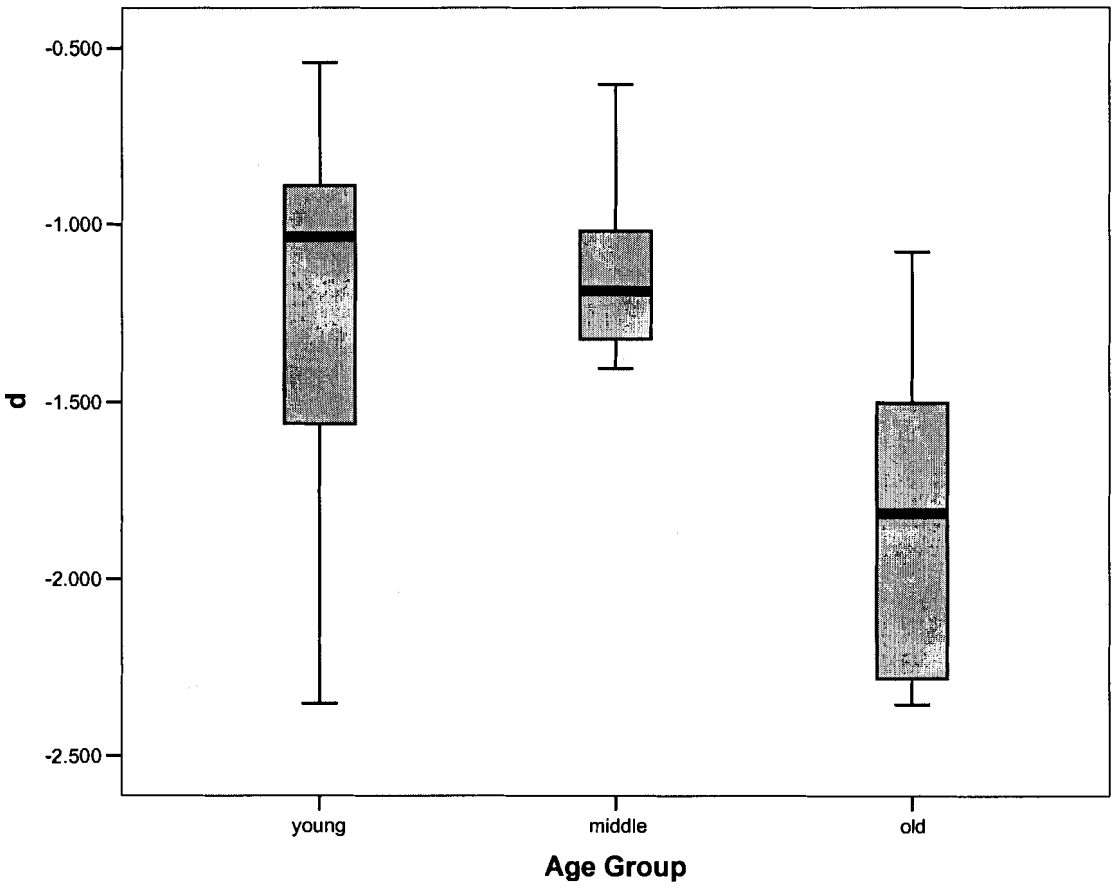
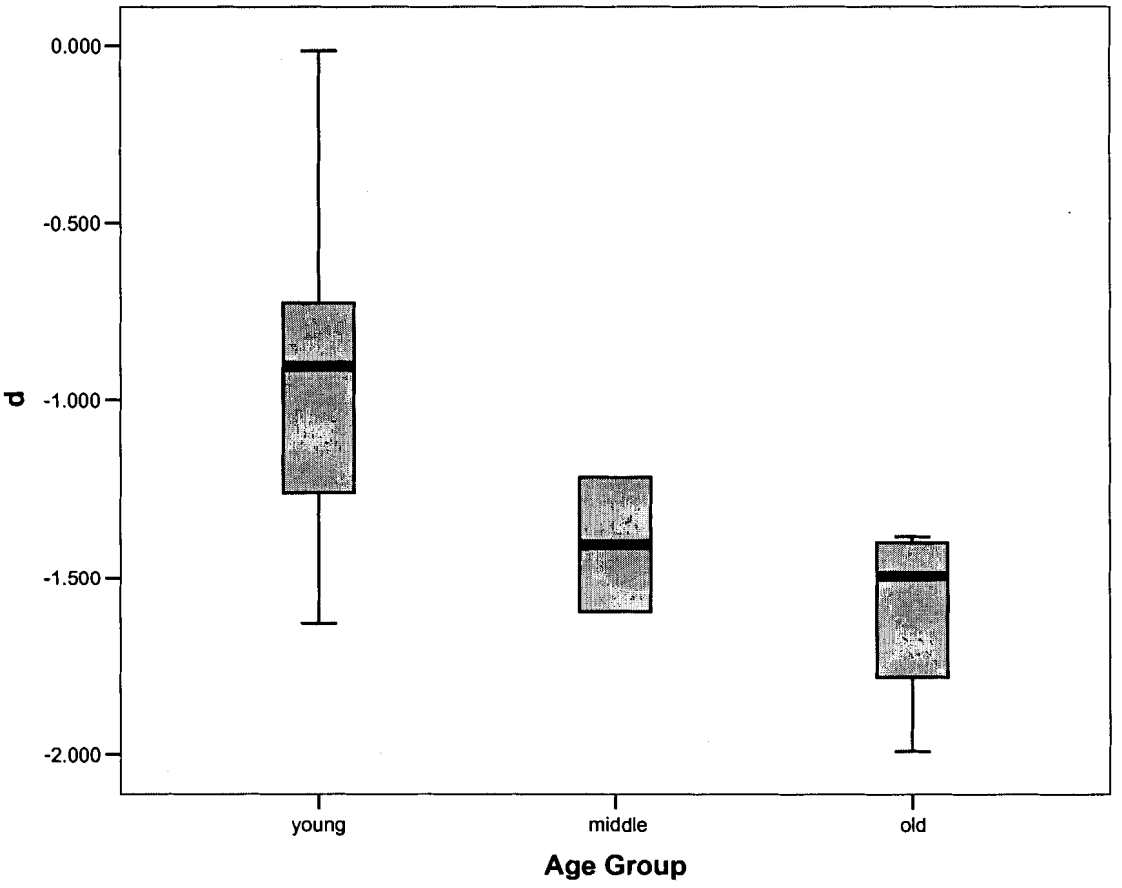


Figure 4: Non-Verbal Memory Effects by Age



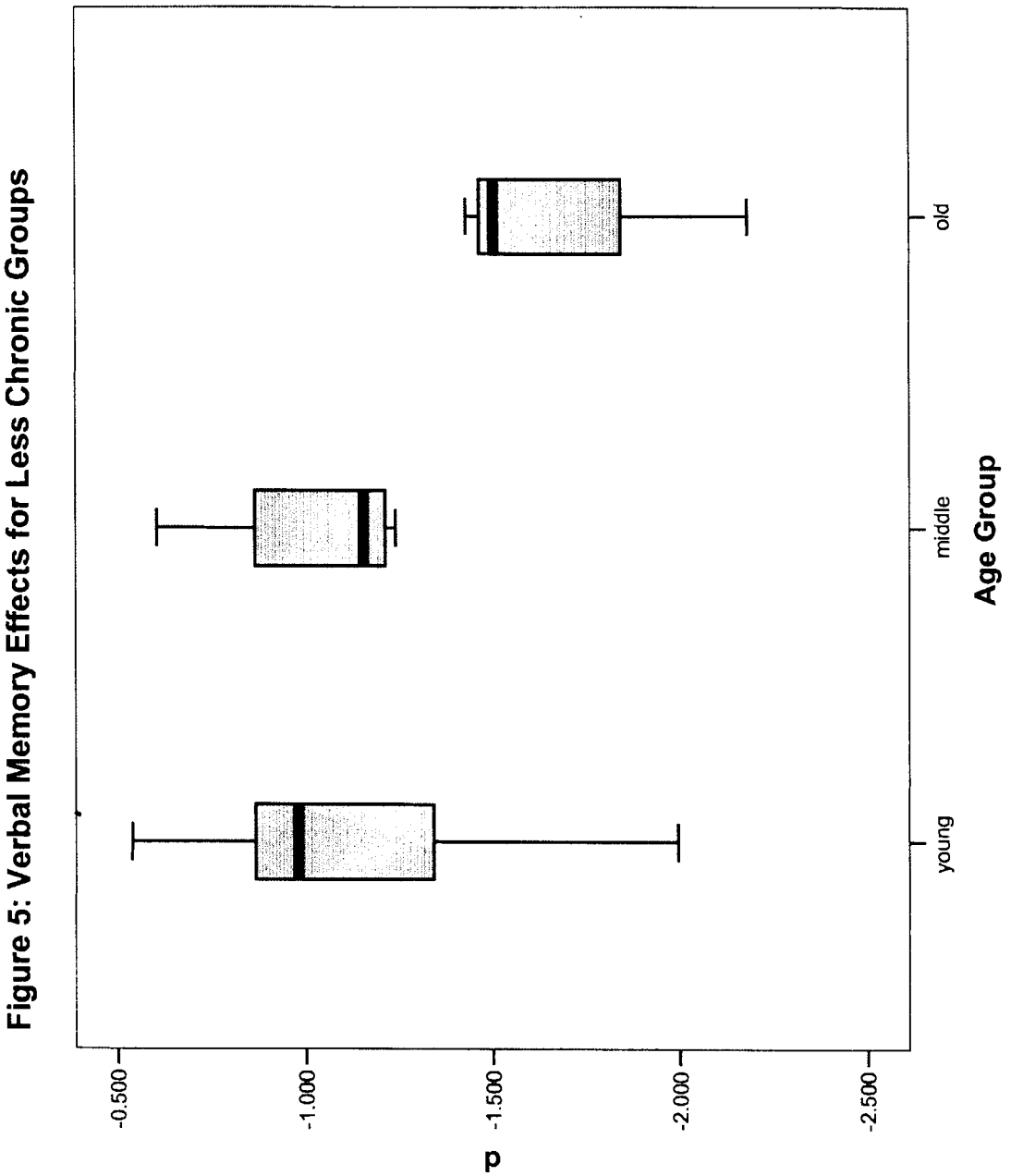


Figure 5: Verbal Memory Effects for Less Chronic Groups
-0.500
-1.000
-1.500
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p
young
middle
old
Age Group

Table 1: Cognitive Aging Literature in Schizophrenia

Cross sectional studies no control

Study	Study Design	Findings
Davidson et al. (1995)	SC patients from 25-85+ assessed with the MMSE	MMSE scores declined with age; larger decline than seen in normative groups; negative symptoms associated with cognitive impairment
Harvey et al. (1997)	Memory and verbal fluency measured in old and young SC patients	Memory and letter-fluency showed age-related decline; category fluency did not
Harvey et al. (1999)	Elderly SC patients followed-up over 30 months with the Clinical Dementia Rating Scale	30% of sample showed decline; 7% improvement
Hoffman et al. (1987)	Patients evaluated for symptoms of PD, TD, and NP function	Age did not predict NP deficits
Hyde et al. (1994)	Cross-sectional comparison of 5 age cohorts of SC patients on NP battery	No decline seen across cohorts, except with the Boston Naming Test

Mockler et al. (1997)	Cross-sectional comparison of 5 age cohorts of SC patients on IQ and RBMT	No age associated reductions in IQ or memory were found.
Putnam and Harvey (1999)	Examination of memory in older and younger SC patients	Age was negatively associated with memory performance however, young and old groups perform at a similar levels relative to normative data
Putnam and Harvey (2000)	Old and young SC patients assessed with NP measures	Age was associated with worse performance also, patients with high negative symptoms performed worse
Sachdev et al. (1996)	SC patients assessed for TD and tested on NP measures	Risk of TD increased with age

Longitudinal studies no control

Abrams and Nathanson (1966)	SC patients followed up between 6- and 10-years with IQ	Patients showed a significant decline in IQ related to length of hospitalization
Foulds et al. (1962)	Subtypes of SC patients compared by gender and length of hospitalization on Raven's PM and Mill Hill Vocabulary Scale	An age associated decline on Raven's PM was seen in both male and female patients; no decline was found in Vocabulary

Ginett and Moran (1964)	SC patients followed up 13-years with WB Vocabulary subtest	No decline in vocabulary performance over 13-years
Hamilton (1963)	SC patients IQ assessed at 2-year interval	Moderate improvement was noted 2-years post
Hamlin (1969)	Older paranoid and younger non-paranoid SC patients assessed after 8- and 14-years with IQ	Younger patients showed improvement over 14-year follow-up; older paranoid patients test stability, some decline in PIQ after age 60
Harvey et al. (1995)	Elderly SC patients followed-up 1 and 2 years with the MMSE	No change over 1 or 2 year follow-up
Klonoff et al. (1970)	SC patients with and without neurological dysfunction assessed with the HRB and at 8-year intervals with IQ	Patients showed improvement in IQ scores over 8-years
Schwartzman and Douglas (1962)	Hospitalized and non-hospitalized SC patients assessed at 10-year intervals with Army intelligence measure	Patients showed decline; hospitalized patients showing larger decline, while controls showed improvement; age and lower education associated with decline
Schwartzman et al. (1962)	Hospitalized and non-hospitalized SC patients tested at 11- and 17-year intervals	Patients showed a linear rate of decline; hospitalized patients showed an increase at 11-years, modest decline at 17-years.

	with Army intelligence measure	
Smith (1964)	IQ of two groups of SC patients followed up over 8 years	Younger hebephrenic/catatonic patients showed modest improvement; Older paranoid patients showed modest decline
Waddington and Youssef (1996)	Longitudinal followup of chronic SC patients over 10 years	Modest decline shown over 10-year follow-up; largest in patients with TD
Cross-sectional study with control		
Cartegena (2001)	Elderly SC patients compared to healthy controls over 2 year follow-up	Patients showed decline on WAIS-R Block Design
Chaikelson and Schwartzman (1983)	Older and younger SC patients compared to controls on verbal fluency, maze learning, tapping, and picture anomalies	No evidence for exaggerated decline in SC group; age differences were larger in the control group
Cohen et al. (1988)	Older and younger patients compared to older healthy controls	Older patients perform worse than other groups: possibility of age related decline
Fucetola et al. (2000)	Cross-sectional comparison of young, middle, and old SC patients and healthy	SC patients showed age-related decline in executive functions beyond that seen in healthy controls

	controls	
Goldstein and Zubin (1990)	SC patients with and without neurological dysfunction compared to controls	SC patients without neurological dysfunction showed age-related cognitive decline comparable to healthy control group; SC group with neurological dysfunction showed greater age-related decline than controls
Goldstein et al. (1991)	Age, education, and length of hospitalization correlated with NP performance	Age significantly related to level of NP impairment
Goldstein et al. (1998)	SC patients separated into groups with and without cognitive impairment were compared to controls	SC patients without significant cognitive impairment showed age-associated decline similar to controls; those with severe impairment showed no decline with age
Heaton et al. (1994)	Older and younger SC patients compared healthy controls on NP battery	No relationship between age and NP functions.
Heaton et al. (2001)	SC patients and healthy controls followed up with NP over an average 3 years	Comparable decline to controls over short (1.6 year) and long (5-year) follow-ups
Hijman et al. (2003)	SC patients and controls compared on 4 WAIS subtests	WAIS Picture arrangement showed a decrease with age; Vocabulary tended to increase with age

Kondel et al. (2003)	SC Patients and controls across a wide age range tested with IQ and reading measures	Age was negatively correlated with IQ and reading in SC patients but not controls
Palmer et al. (2003)	Comparison of early-onset older SC patients with late-onset SC, AD, and healthy controls over 2 years	Early-onset SC patients showed similar rates of decline to healthy controls and late-onset SC; AD patients showed greater decline

Cross-sequential studies with control

Friedman et al. (2001)	SC patients from 20-80 and healthy controls from 50-80 were followed over 6 years with the CDR	After age 70, SC patients showed a significantly higher risk of cognitive decline than did healthy controls

SC=schizophrenic; NP=Neuropsychological; TD=tardive dyskinesia; PD=Parkinson's disease; CDR=Clinical Dementia Rating Scale; DRS=Mattis Dementia Rating Scale; MMSE=Mini-Mental State Exam; IQ=Intellectual Quotient; PIQ=Performance IQ; Raven's PM=Raven's Progressive Matrices; WB=Wechsler-Bellvue; RBMT=Rivermead Behavioural Memory Test

Table 2. Demographic Summary of Verbal Memory Studies

All Studies Included									Outliers Removed		
Age	Number of Studies (k)	Number of Subjects (N)	Mean Age	Mean Age of Onset	Mean Length of Illness (y)	Mean Education Level	Gender (% male)	Mean weighted effect size (d)	Within Category Homogeneity Statistic (Qw)	Number of Studies (k)	Mean weighted effect size (d)	Within Category Homogeneity Statistic (Qw)
Young (20-39)	34	2631	30.2 (2.41)	22.55 (2.62)	7.19 (3.47)	12.30 (1.06)	69.04 (12.13)	-1.206	106.64***	32	-1.141	80.26***
Middle-Age (40-59)	7	853	47.6 (4.90)	24.58 (3.69)	23.00 (4.81)	11.86 (1.06)	72.56 (28.89)	-1.042	15.15**	6	-1.018	8.74
Old (60-79)	9	735	70.1 (5.15)	33.30 (4.52)	37.46 (6.35)	10.46 (0.71)	38.83 (14.52)	-1.865	12.33	9	-1.865	12.33
			p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.05			p<0.01	

***p<0.01
**p<0.05

Table 3: Demographic Summary of Non-Verbal Memory Studies

All Studies Included								Outliers Removed		
Age	Number of Studies (k)	Number of Subjects (N)	Mean Age (SD)	Educational Level	Mean weighted effect size (d)	95% Confidence Interval	Within Category Homogeneity Statistic (Qw)	Number of Studies (k)	Mean weighted effect size (d)	Within Category Homogeneity Statistic (Qw)
Young (20-39)	23	1876	29.5 (1.97)	12.38 (1.14)	-0.905	-1.056 -- -0.754	50.122***	23	-0.905	50.122***
Middle-Age (40-59)	2	74	53.8 (5.30)	12.20 (0.28)	-1.337	-1.859 -- -0.814	0.497	2	-1.337	0.497
Old (60-79)	5	157	69.6 (7.72)	11.20 (1.06)	-1.890	-1.953 -- -1.175	15.27***	4	-1.564	1.601
				n.s.	p<0.01				p<0.01	

***p<0.01
**p<0.05

Table 4: Verbal Memory Comparison Between Chronic and Less Chronic Groups

		Young (20-39)	Middle (40-59)	Old (60-79)
Less Chronic	Q_b=7.28**	*d*=-1.12 (-1.28 – -0.96) k=26	*d*=-0.99 (-1.35 – -0.63) k=4	*d*=-1.52 (-1.85 – -1.20) k=4
More Chronic	Q_b=22.90***	*d*=-1.25 (-1.93 – -0.57) k=3	—	*d*=-2.24 (-2.56 – -1.91) k=4

— indicates that no very chronic samples were available in the middle age range.
**p<0.05
***p<0.01

Table 5: Correlation Matrix for Verbal Memory Effects

	Age	Effect	General Symptoms	Positive Symptoms	Negative Symptoms	Gender (% Male)	Length of Illness	Age of Onset	Educati on	Education Difference
Effect	-.525*** k=47	—								
General Symptoms	-.141 k=15	.410* k=15	—							
Positive Symptoms	-.033 k=21	.168 k=21	.331 k=11	—						
Negative Symptoms	.260 k=22	.114 k=22	.659** k=10	.797*** k=20	—					
Gender (% Male)	-.545*** k=47	.261** k=47	.117 k=15	-.035 k=21	-.312* k=22	—				
Length of Illness	.972*** k=41	-.401*** k=41	.121 k=12	-.013 k=19	.208 k=20	-.402*** k=41	—			
Age of Onset	.786*** k=41	-.303** k=41	.476 k=12	.014 k=19	.344* k=20	-.531*** k=41	.621*** k=41	—		
Education	-.585*** k=38	.334** k=38	-.164 k=11	.226 k=16	.205 k=15	.296** k=38	-.544*** k=33	-.370** k=33	—	
Education Difference	.608*** k=34	-.539*** k=32	-.179 k=10	-.441* k=12	-.313 k=12	-.145 k=32	.650*** k=27	.454*** k=27	-.423*** k=32	—
IQ	-.405* k=15	.209 k=15	-.074 k=4	-.215 k=7	-.060 k=8	-.271 k=15	-.372 k=12	-.011 k=12	.385* k=14	-.269 k=12

Note. All tests one-tailed
*** p<0.01 **p<0.05 * p<0.10

Table 6: Correlation Matrix for Non-Verbal Memory Effects

	Age	Effect	General Symptoms	Positive Symptoms	Negative Symptoms	Gender (% Male)	Education
Effect	-.597*** k=29	—					
General Symptoms	-.391 k=11	.182 k=11	—				
Positive Symptoms	.144 k=12	.128 k=12	.267 k=7	—			
Negative Symptoms	.099 k=13	.072 k=13	.536 k=7	.714*** k=12	—		
Gender (% Male)	-.490*** k=29	.132 k=29	.284 k=11	-.139 k=12	-.405* k=13	—	
Education	-.312* k=25	.409** k=25	-.226 k=9	.070 k=10	-.069 k=10	.081 k=25	—
Education Difference	.519*** k=21	-.426** k=21	-.365 k=8	-.631 k=9	-.767*** k=9	-.012 k=21	-.073 k=21

*** $p<0.01$
**$p<0.05$
*$p<0.10$