Chapter 4

Long-Term Memory Deficits in Schizophrenia: Primary or Secondary Dysfunction?

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Abstract

Long-term memory impairment is often found in schizophrenia. The question remains whether this is caused by other cognitive deficits. One hundred eighteen first episode patients were compared with 45 controls on several memory tasks. The role of processing speed and central executive functions on memory performance was examined with regression analysis for all subjects and for patients separately. Deficits were found in general verbal learning performance and retrieval in episodic memory and semantic memory. Processing speed reduced disease related variance in all memory variables. Coordination, organization of information, and speed of processing were the best predictors for long-term memory deficits in patients. The amount of explained variance, however, is small, especially in general verbal learning performance.

1. Introduction

Although no single neurocognitive test or construct completely separates schizophrenic patients and controls (Heinrichs & Zakzanis, 1998), long-term memory impairment is often found in schizophrenia. Some researchers even suggest that schizophrenia patients have a specific deficit in long-term memory against a background of more generalized cognitive dysfunctioning (Saykin, Gur, et al., 1991; Saykin, Shtasel, et al., 1994). Memory impairments, especially impairments in long term memory, are also associated with a variety of functional outcome measures, such as vocational outcome, community functioning and quality of life, in schizophrenia (Green, 1996; Green, Keen, Braff & Mintz, 2000).

Memory, however, is not a unitary concept and can be divided into several systems and processes (Schacter & Tulving, 1994). Long-term memory can be divided into episodic and semantic memory systems. Episodic memory enables people to encode and retrieve personal information, which is encoded in relation to spatial and temporal context. Three processes can be distinguished in manipulating episodic information: encoding or learning of new information; storage of information; and explicit retrieval of information. The other long-term memory system is semantic memory, an organized amount of context-free knowledge, together with rules to manipulate this knowledge. Explicit retrieval processes can also play a role in the retrieval of information from semantic memory. In contrast to these explicit memory systems, there is also implicit memory, which deals with the automatic cognitive and motor processes, which do not require conscious attention.

Some diseases are characterized by specific memory deficits. Storage deficits in episodic memory, for example, are typical for patients with Alzheimer's or Korsakov disease. Impaired initiation of retrieval strategies on the other hand is typically found in patients with Huntington's and Parkinson's disease (Paulsen et al., 1995). In schizophrenia, however, impairments in explicit memory are prominent, while lesser impairments in implicit memory are found (e.g. Clare, McKenna, Mortimer & Baddeley, 1993; Goldberg, Hyde, Kleinman & Weinberger, 1993; Kazes et al., 1999). Many studies report problems in episodic memory, but most of them only find learning and retrieval deficits, while storage is relatively spared (e.g. Aleman, Hijman, de Haan & Kahn, 1999;

Brebion, Amador, Smith & Gorman, 1997; Hawkins Sullivan & Choi, 1997; Paulsen et al., 1995). Although the majority studied verbal memory only, visual memory impairments are found as well, and there is no evidence for a difference between both modalities (Aleman et al., 1999). There is also evidence for semantic memory deficits (McKay et al., 1996). This seems to be caused by inefficient access to the semantic store, which could be labeled as a retrieval deficit (Joyce, Collinson & Chrichton, 1996). In sum, the memory deficits found in schizophrenia are explicit, verbal as well as visual and mostly concern active memory processes, such as learning and retrieval processes in long term memory systems. These systems are at least partly dependent on other cognitive functions, such as speed of information processing, and central executive processes. Should the memory impairments in schizophrenia be understood as pure memory deficits or as the result of another underlying cognitive deficit? Because different brain regions mediate these cognitive functions, this is an important question in the search for basic mechanisms in schizophrenia.

Several studies have described a slowing of processing speed on a number of cognitive tasks as a major cognitive deficit in schizophrenia (Nelson et al, 1990; Schatz, 1997; Van der Does Dingemans, Linszen, Nugter & Scholte, 1996). Most studies make a distinction between sensorimotor speed and cognitive speed. The latter requires controlled information processing and is more impaired in schizophrenia than simple sensorimotor speed (Nelson et al., 1990; van Hoof, Jogems-Kosterman, Sabbe, Zitman & Hulstijn, 1998). The influence of processing speed on other cognitive functions has been studied extensively in aging research by Salthouse (1996). He found evidence that age-related slowing of processing speed influences other cognitive measures, such as memory. A few studies have examined the relation between processing speed and memory measures in schizophrenia. Brébion, Amador, Smith and Gorman (1998) and Brébion et al. (2000) concluded that memory deficits may be partly accounted for by a slowing of processing speed.

Executive functions are thought to play a role in effortful cognitive processes. Recent research suggests that the central executive has different component functions (Baddeley, 1996; 1998; Nathaniel-James, Brown & Ron, 1996; Salamé, Danion, Peretti & Cuervo, 1998), such as: coordination of performance; switching of strategies to handle a task; selective attention and inhibition,

organization of information. Although the central executive is thought to play an important role in schizophrenia (Goldman-Rakic, 1994), the results are not always consistent, probably due to a large variance in the patient group. And it is not clear what component of the central executive is related to memory in schizophrenia (Salamé et al., 1998). Organization of information however, is a good candidate because strategic processes, such as organization of to-be-learned information, play a role in the encoding of new information (Fletcher and Henson, 2001). Recall is better for word lists that can be organized in semantic categories for example, and a strategic approach in a visual copy and memory task, such as the Rey Complex Figure, leads to better results on the reproduction part of this task (e.g. Chiulli, Haaland, La Rue & Garry, 1995). Therefore organization of information might be an important determinant of memory performance within schizophrenia as well.
In this study, we examined long-term memory in a large group of first episode schizophrenia patients. Because slowing of processing speed is often found in schizophrenia, we analyzed the relations between long-term memory and basic cognitive functions to test our first hypothesis that differences in processing speed explain the differences in memory measures between patients and controls. Next we examined whether variance in memory measures within the patient group is explained by differences in central executive functions, especially organization of information.

2. Method

2.1. Subjects

The study included 118 patients who had recently experienced a first or a second psychotic episode according to DSM-IV (American Psychiatric Association, 1994) and received a diagnosis within the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizophreniform disorder). All patients participated in a Dutch multicenter study of the university hospitals of Groningen, Utrecht and Amsterdam. Diagnosis was based on a structured interview (SCAN; Wing et al., 1990 or CASH; Andreasen, Flaum & Arndt 1992). Exclusion criteria were mental retardation according tot DSM-IV

Table 1. Subject characteristics of patients by diagnosis

Subject characteristics	**All patients n = 118** M (SD)	**Schizophrenia (a), n = 84** M (SD)	**Schizophreniform (b), n= 19** M (SD)	**Schizoaffective (c), n = 15** M (SD)	**F** Post-hoc [c]
Age	23.30 (5.27)	22.45 (4.54)	26.63 (6.81)	23.80 (5.56)	5.30** a<b
Education (range 1-8)	4.0 (2.2)	3.8 (2.2)	4.7 (2.2)	4.1 (2.0)	1.37
PANSS (range 30-210)	61.85 (18.03)	65.24 (18.48)	51.53 (13.91)	56.20 (14.08)	5.75** a>b
Positive[a]	2.22 (1.06)	2.44 (1.07)	1.60 (0.85)	1.83 (0.85)	6.83** a>b
Negative	2.33 (0.95)	2.46 (1.02)	1.89 (0.72)	2.18 (0.63)	2.99
Disorganization	1.86 (0.68)	1.95 (0.72)	1.64 (0.56)	1.61 (0.46)	2.87
Depression	2.34 (0.95)	2.32 (0.93)	2.21 (1.09)	2.63 (0.89)	0.90
Excitement	1.61 (0.73)	1.69 (0.74)	1.44 (0.73)	1.40 (0.68)	1.53
MADRS (range 10-60)	14.13 (10.22)	14.39 (10.50)	12.06 (8.69)	15.20 (10.71)	0.48
Age at onset	22.18 (5.11)	21.26 (4.18)	26.28 (6.93)	22.01 (4.95)	7.98*** a<b
Sex m/f	87 / 31	66 / 18	12 / 7	9 / 6	3.57[b]

[a] Standardized PANSS ratings ranging from 1: absent to 7: extreme. [b] χ^2 test. [c] Tamhane. * $p < .05$. ** $p < .01$. *** $p < .001$.

2.2. Procedures and Instruments

Memory measures.

All patients were tested after being on stable medication for at least six weeks. Table 2 gives an overview of the memory measures. The Dutch translation of the California Verbal Learning Tests (CVLT; Delis, Kramer, Kaplan & Ober, 1987) was used to asses long-term verbal episodic memory. The CVLT is a list-learning task in which 16 words from 4 categories (list A) are presented over 5 immediate recall trials. Following the five trials, a second list (B) is presented for one interference trial. Directly after this presentation, short delay free and cued recall of list A are assessed. After 20 minutes long delay free and cued recall are assessed, immediately followed by a yes-no recognition task with 28 distracters. The total sum of words over the first five learning trials was taken as a measure of general verbal learning performance. The difference between long-term free recall and immediate recall trial on 5 was taken as a measure of storage. Retrieval was computed by subtracting the standardized score of long term free recall from the standardized score on the recognition task. Because it is difficult to find a visual memory task with measures for encoding, storage and retrieval, and there is no evidence for a difference between verbal and visual memory in schizophrenia, we decided to use the recall measures from the Rey

(American Psychiatric Association, 1994) and a known systemic or neurological illness. Subject characteristics of patient are given for the entire group and the three different diagnostic groups in table 1. No differences in memory or cognitive measures were found between the diagnostic categories. Accordingly they were treated as one group. Ninety-five subjects had their first episode, 23 subjects experienced their second episode. Twenty-five patients used typical antipsychotics, seventy-five were on atypical antipsychotics and eighteen patients did not use antipsychotic medication. Ten patients also used anticholinergic medication. Twenty-eight patients had a diagnosis for alcohol abuse, 55 for cannabis abuse and 16 for other drug abuse. No significant differences on memory measures between patients with and without a substance abuse diagnosis were found, except for the patients with alcohol abuse, who performed significantly better on general verbal learning performance: $F(1,117) = 7.76$, $p = .006$. Forty-five healthy controls were included in order to establish standard scores on memory tests. Thirty-eight males and seven females were included. Mean age was 24 years (SD 6.4). There were no significant differences between patients and controls for sex: χ^2 (1, 1 63) = 2.10, ns, or age: $F(1, 161) = 0.29$, ns. Patients and controls were not matched on education level. The Dutch educational system differentiates already after primary school into four levels, therefore we have chosen a coding system rather than years of education. This goes from 1: primary school up to 8: university or graduate school. Because thirty seven percent of the patients still received education, we took the level they were aiming at minus half a point. Mean education level for controls was 5.9 (SD 1.5). There was a significant difference between patients and controls: $F(1.161) = 30.45$, $p < .000$. The most likely explanation is that a number of patients quit school before finishing one of the four different high school levels, due to prodromal symptoms. Therefore they only received the code for primary school. All control subjects finished at least one of the additional high school options. Although subjects from both groups are represented at the highest level (university or graduate school), the mode of the control group is at a higher level than that the mode of the patients group. Therefore education is entered as a covariate in the analyses of the differences between patients and controls and it is treated as a possible confounder in the regression analyses.

Complex Figure Test (RCFT; Rey, 1964) only. Subjects were administered a copy trial, an immediate recall and a delayed recall trial in which they had to draw the complex figure. The RCFT was scored using explicit scoring criteria from Duley, Wilkins, Hamby and Hopkins (1993) based on the method developed by Osterrieth (1944). The mean percentage correct from the immediate and the delayed recall (recall: copy x 100) was used as a visual memory measure. Retrieval from semantic memory was measured with a category fluency task in which subjects had to name as many words from one category (animals and professions) as possible in one minute. Although it cannot be denied that frontal functions play a role in category fluency, several studies also prove that the performance on category fluency is also influenced by the contents of the semantic store or semantic memory or the access to the semantic store. (Joyce et al., 1996; Chertkow & Bub, 1990).

Basic cognitive variables that may influence memory.

These additional measures were collected in the same test session (see table 2). The time in seconds on word reading and color naming of a computerized STROOP task were taken as measures of processing speed. A modified version of the Trailmaking Test (Vink & Jolles, 1985) was administered as a second task for processing speed. This version consists of three parts. In part A, the subject must connect consecutively numbered circles from 1 to 26. In part B, the subject must connect circles with the letters A through Z. In part C the subject must connect 26 consecutively numbered and lettered circles, by alternating between the two sequences. Time on part A and part B were taken as measures of processing speed. All speed measures correlated highly with each other in the total group of subjects (r ranging from .50 to .91, with $p < .000$). Therefore they were averaged after a z-transformation, to create one processing speed score. Five different measures were used in order to examine different component processes of the central executive. The Continuous Performance Task used in this study (CPT; Van den Bosch, Rombouts & Asma, 1996) is a double stimulus version, with a memory load, in which a subject has to react when the number seven appears on a computer screen after the number 3. Patients have to remember the last stimulus, the task instruction, and stay alert to react to the new stimulus. The sensitivity index (d') of this double-stimulus CPT was used to assess the ability to coordinate the allocation of processing

capacity (Coordination). In another study of our group (Broerse, Holthausen, van den Bosch & den Boer, 2001), significant correlations were found between CPT d' and the percentage of inhibition errors on an antisaccade task, which is an established frontal executive task. The interference score of the Trailmaking Test (interference = C- ½ (A + B) / ½ (A + B)) was taken as a measure of the ability to switch between search strategies (Switching). The STROOP interference score (STROOP color word – STROOP color naming) was used to assess selective attention and inhibition (Selective attention). We had two measures for organization. The semantic cluster score from the CVLT was taken as a measure of organization of verbal information. Regarding visual memory we decided to take the method of drawing as a measure of organization. We used a binary approach wherein a drawing strategy in which the main figure was drawn first was coded as normal and a drawing strategy with a fragmented approach was labeled as abnormal (Chiulli et al., 1995; Lezak, 1983).

Psychopathology.

Symptoms were rated on the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein & Opler, 1987) within the same week as the neuropsychological assessment. These ratings were used to obtain dimensional scores by calculating the sum scores loading high on the positive, negative, disorganization, depression and excitement dimensions as described in Lindenmayer, Bernstein Hyman, Grochowski and Bark (1995). Depressive symptoms were also rated with the Montgomery Åsberg Depression Rating Scale(Montgomery and Åsberg, 1979). Symptom ratings are given in table 1.

3. Results

All variables were inspected to see if they resembled the normal distribution. If not, log transformations were performed. This was the case for STROOP interference and the positive and disorganization dimensions from the PANSS. Differences between patients and normal controls on all memory and cognitive variables were tested with ANCOVA with education as covariate. If the effect of the covariate was significant, estimated marginal means are given, which are

corrected for education (with raw means in parentheses). Effect sizes were computed for the differences between controls and patients on all memory and cognitive measures using Cohen's d, with the standard deviation of the control group (table 2). Patients performed significantly worse on all long term memory measures, except storage of verbal information, which was left out of further analyses. The effect sizes showed that general verbal learning performance and semantic memory were especially disturbed, with large effect sizes (according to Cohen, 1969). Patients also performed significantly worse on most basic cognitive measures, with large effect sizes except for Trail Making interference (small) and CVLT semantic clustering (medium).

Table 2. Long-term memory and other cognitive variables in patients and controls.

Cognitive measures	Controls n = 45 M ± SD	Patients n = 118 M ± SD	F-value	Effect sizes Cohen's d
Memory Measures				
CVLT trial 1-5	56.38 ± 8.52	45.69 ± 9.21	45.59****	-1.25
CVLT storage	-0.68 ± 1.49	-1.15 ± 2.25	1.66	-0.32
CVLT retrieval	0.11 ± 1.65	1.18 ± 1.77	12.01**	-0.65
RCFT immediate recall	70.50 ± 16.21	61.71 ± 20.19	5.86*	-0.54
RCFT delayed recall	68.39 ± 16.46	61.31 ± 18.37	5.11*	-0.43
Category fluency	22.68 ± 5.09	18.06 ± 4.27	33.96****	-0.91
Estimated marginal means[a]				
STROOP names (time)	38.33 ± 4.59 (36.76)	47.29 ± 9.91 (47.91)	28.70****	-1.95
STROOP colors (time)	33.77 ± 5.68 (34.42)	44.72 ± 9.14 (45.27)	32.55****	-1.58
Trailmaking A (time)	26.71 ± 7.54 (25.13)	38.13 ± 15.08 (38.88)	19.81****	-1.51
Trailmaking B (time)	26.87 ± 9.68 (24.62)	37.19 ± 15.78 (38.38)	14.85****	-1.07
CPT d '	4.14 ± 0.55 (4.29)	3.60 ± 0.77 (3.53)	17.23****	-0.98
CVLT semantic clustering	2.05 ± 0.99 (2.05)	1.61 ± 0.66 (1.57)	8.98**	-0.44
Raw means				
Trailmaking interference	41.51 ± 30.05	48.31 ± 44.31	1.11	-0.23
STROOP interference	7.43 ± 5.17	11.59 ± 11.44	2.17*	-0.80
RCFT organization type (% normal)	84%	62%	7.50[b]**	-

[a] Means adjusted for the covariate education, raw means without adjustment are shown within parenthesis.
[b] χ^2 test. * p < .05. ** p < .01. ***p < .001. **** p < .0001.

Correlations between all memory and cognitive variables and education for all subjects and for the patient group separately are given in table 3 and 4.

Table 3: Correlations between memory measures and cognitive measures for the whole group (patients and controls, N = 163)

	2	3	4	5	6	7	8	9	10	11	12
1.Verbal learning	.223**	.347***	.365***	.415***	.460***	.362***	.160*	.061	.419***	.300***	.277***
2. Verbal storage	-	.465***	.184*	.245**	.176*	.189*	.074	.128	.178*	.303***	.086
3. Verbal retrieval		-	.197*	.369***	.357***	.300***	.137	.185*	.297***	.257**	.181*
4. Visual memory			-	.231**	.323***	.301***	.095	.076	.129	.346***	.148
5. Semantic memory				-	.571***	.423***	.125	.064	.335***	.255**	.288***
6. Speed of processing					-	.577***	.236**	.040	.340***	.289***	.436***
7. Coordi-nation						-	.159*	.136	.245**	.262**	.429***
8. Selective attention							-	.139	.089	.100	.159*
9. Switching								-	.055	.096	.109
10. Verbal organization									-	.265**	.299***
11. Visual organization										-	.213**
12. Education											-

* p < .05. ** p < .01. ***p < .001.

There are significant correlations between all memory measures in the whole subject group, and between most memory measures in the patient group. As for the cognitive measures, speed, coordination and verbal and visual organization are significantly associated. Correlations between memory variables and psychopathology measures were computed. Only two significant correlations were found for semantic memory and the negative and disorganization dimensions respectively ($r = .262$, $p = .005$; $r = .228$, $p = .014$)

In order to examine whether speed explains the difference in memory measures between patients and controls, we used the method suggested by Salthouse (1996). In the original method, which is based on regression analysis, group is first entered as a predictor, to calculate the amount of variance predicted by group membership for each memory measure, the so-called disease related variance. Secondly, in a new analysis, speed is entered as a first predictor before group, to see if the amount of variance explained by group is reduced considerably. We altered this method slightly to control for the possible confounding effect of education. First group is entered as a predictor, as in the original method. Secondly education was entered after group.

Table 4. correlations between memory measures and cognitive measures for patient group (n = 118)

	2	3	4	5	6	7	8	9	10	11	12
1.Verbal learning	.200*	.231*	.337***	.294**	.222*	.242**	.118	.018	.236*	.189*	.188*
2. Verbal storage	-	.297**	.191*	.151	.127	.186*	.036	.079	.193*	.303**	.083
3. Verbal retrieval		-	.178	.301**	.248**	.255**	.098	.151	.255**	.189*	.109
4. Visual memory			-	.153	.318**	.314**	.054	.060	.046	.298**	.099
5. Semantic memory				-	.436***	.382***	.090	.008	.228*	.173*	.240**
6. Speed of processing					-	.439***	.239*	.129	.234*	.203*	.310**
7. Coordi-nation						-	.140	.136	.144	.204*	.319***
8. Selective attention							-	.113	.060	.086	.232*
9. Switching								-	.045	.078	.046
10. Verbal organization									-	.150	.207*
11. Visual organization										-	.175
12. Education											-

* p < .05. ** p < .01. ***p < .001.

If the coefficient of group changed more than 10 %, education was treated as a confounder. This was the case for visual and semantic memory. For these variables we conducted two separate analyses. In the first group was entered after speed, to see how much the disease related variance is reduced by speed. In the second group was entered after education to see how much the disease related variance is reduced by education (table 5). Entering processing speed in the model reduced disease-related variance in all memory variables.

Table 5: Reduction of disease related variance after entering speed and education as a first predictor for the whole group (patients and controls, N = 163).

Memory Measures	***Disease related variance*** R^2 group	**Δ R^2 for group, after speed as a first predictor**	**Δ R^2 for group, after education as a first predictor**
Verbal learning	.22 ****	.07****	-
Verbal retrieval	.07****	.01	-
Visual memory	.04 *	.00	.02
Semantic memory	.18 ****	.01	.11****

* p < .05. ** p < .01. ***p < .001. **** p < .0001.

And although education is a confounder for disease related variance in visual and semantic memory, speed still reduced more of the disease related variance than education.

Finally, with hierarchical multiple regression analysis with forced entry, the best fitting regression model for the whole group is computed, using all cognitive variables: speed, coordination, selective attention, switching, verbal and visual organization. Education was also entered in the model to examine for possible confounding. There was no confounding, so education was left out of the analyses. Results are presented in table 6.

Table 6: Hierarchical multiple regression analyses for long term memory variables in all subject (n = 163), schizophrenic patients (n = 118) and controls (n= 45)

Memory measures	Predictors	B	β	R^2
All subject (N = 163)				
Verbal learning	Speed	2.58	.38 ****	.30 ****
	Organization[a]	3.93	.31 ****	
Verbal retrieval	Speed	0.41	.30 ****	.20 ****
	Organization[a]	0.46	.20 *	
	Switching	0.01	.19 *	
Visual memory	Organization[b]	3.93	.29 ****	.17 ****
	Speed	3.41	.24 **	
Semantic memory	Speed	2.08	.54 ****	.35 ****
	Organization[a]	0.88	.14 *	
Patients (n = 118)				
Verbal learning	Organization[a]	3.26	.23 *	.10 **
	Coordination	2.31	.20 *	
Verbal retrieval	Coordination	0.51	.22 *	.11 **
	Organization[a]	0.60	.22 *	
Visual memory	Speed	1.47	.26 **	.18 ****
	Organization[b]	3.47	.23 *	
Semantic memory	Speed	1.41	.38 ****	.25 ****
	Coordination	1.10	.20 *	
Controls (n = 45)				
Verbal learning	Organization[a]	0.46	.46**	.39****
	Speed	0.49	.37**	
Visual memory	Organization[b]	1.05	.39 **	.16**
Semantic memory	Speed	2.63	.40**	.16**

[a] Organization of verbal material (CVLT semantic clustering). [b] Organization of visual material (RCFT organization type). * p < .05. ** p < .01. ***p < .001. **** p < .0001.

A combination of processing speed and organization made the best prediction for all memory variables.

Secondly we analyzed the influence of basic cognitive variables on long term memory within the patient group with hierarchical multiple regression analyses

with forced entry, using all cognitive variables (speed, coordination, selective attention, switching, verbal and visual organization). Because the role of disease severity on memory is not clear, psychopathology dimensions were also entered in the model. Results are presented in table 6. The coordinating component of the central executive (CPT d') is the best predictor for both general verbal learning performance and verbal retrieval. Processing speed is the best predictor for visual memory and semantic memory, but CPT d' still explains additional variance of these variables. Organization is a significant predictor for all three episodic memory measures but not for semantic memory. As for the role of disease severity, the psychopathology dimensions were not significant predictors.
The influence of basic cognitive variables on long-term memory within the control group was also analyzed with hierarchical multiple regression analyses with forced entry. Results are presented in table 6. Organization is the best predictor for general verbal learning performance and visual memory. Speed is the best predictor for semantic memory and also explains some variance in general verbal learning.

4. Discussion

The long-term memory deficits in schizophrenia found in this study correspond to a large extent with those reported in other studies (e.g. Aleman et al., 1999; Paulsen et al., 1995), in which learning and retrieval deficits were reported but no storage deficits. In contrast with the results of two large meta-analyses (Aleman et al.; Heinrichs & Zakzanis, 1998) verbal memory deficits in our patients appeared more severe than visual memory deficits. Although some studies suggest a differential deficit in verbal learning and memory in schizophrenia (e.g. Saykin et al., 1991) most of these studies, including ours, used a non-verbal memory task that is not comparable to word list learning. A recent study of Tracy et al. (2001) showed similar results on verbal and non-verbal memory tasks in schizophrenia with a non-verbal memory task, which produced the same memory component measures as the CVLT. Therefore we think that the difference in effect sizes on verbal and visual memory measures are caused by differences in task characteristics and not by modality specific

deficits. There were also significant differences between patients and controls on basic cognitive variables, thought to influence memory. These differences were most apparent for processing speed and the coordinating component of the central executive. Although significant, the differences were less pronounced for the selective attention and the organization components of the central executive. There was no significant difference between patients and controls on the switching component of the central executive, suggesting that a distinction between different central executive components is valid indeed. Although there was a difference in education between patients and controls in this study, the differences in cognitive variables were still clearly significant after controlling for the effect of education.

Because of the difference in education between patients and controls, the possible confounding effects of education were examined for all regression analyses. Education only was found to be a confounder for disease related variance in visual and semantic memory. However, education was not a confounder for the regression of cognitive variables on memory measures in the whole group. Our first hypothesis was partly confirmed. Processing speed did reduce the disease-related variance in all memory variables, suggesting that part of the differences in long-term memory performance between schizophrenic patients and controls could be due to a slowing of processing speed in schizophrenia. Although education reduced part of the disease related variance in visual and semantic memory, speed still reduced a larger part of the disease related variance than education. For general verbal learning performance, group membership, however, still explained some of the variance after entering processing speed as first predictor. This remained significant even after entering organization as a second predictor. This could point to a special role of verbal learning deficits in schizophrenia. Processing speed still was the best predictor for all verbal memory measures in the total subject group, and second to organization for visual memory. Switching was the only central executive measure with additional predictive power, in this case for verbal retrieval. The total amount of variance explained is limited to a maximum of 35 % for semantic memory.

Our second hypothesis was also partly confirmed. The combination of coordination and organization of information gave the best prediction for long-term verbal episodic memory measures in patients. Processing speed together

with coordination and organization respectively gave the best prediction for semantic memory and visual memory. The other central executive components, on which patients performed almost at a normal level, did not predict long-term memory in schizophrenia. This suggests that only central executive components that are affected by the disease, mediate memory performance in schizophrenia. An additional analysis of the control group, which performed well on all central executive measures, revealed that the coordination component did not influence memory performance; organization however did. An association between organization of information and encoding in normal subjects is found in other studies as well (Fletcher, Shallice & Dolan, 1998). We suggest a differential influence of central executive components on long-term memory, in which some components, such as organization, always influence long term memory performance, while others, such as coordination only have a negative influence when they break down. One should keep in mind, however, that the amount of explained variance in the patient group is modest, especially for episodic memory performance, suggesting that basic cognitive functions only have a limited influence on long-term memory functions. Data presented in other publications confirm our results. Brébion et al. (1998) presented correlations of processing speed and working memory with long-term memory measures ranging from .39 to .50, indicating a maximum of 25 % explained variance in long-term memory.

Psychopathology did not influence memory performance in this study. This is in contrast with the general trend that shows a moderate influence of negative symptoms on memory performance (Aleman et al., 1999). Some correlational longitudinal studies found memory measures to be partly related to active episodes (Censits, Ragland, Gur & Gur, 1997; Hoff et al., 1999). This could explain our negative results, because symptom ratings were rather mild, and patients were in a relatively stable phase of the disease.

Organization of information, coordination and especially speed were the best predictors for long-term memory in this study. This raises the question what is meant by “speed of processing”. The neurophysiology behind this construct is still unknown. Simple reaction times tend to be long relative to transduction and transmission times (Hanes and Schall, 1996). Speed could refer to efficiency of information processing, and therefore is likely to reflect some kind of executive process. Speed and central executive components were correlated in this study

but they explained different parts of the variance in long-term memory. These speed related "executive processes" probably operate in such a short time interval that they are almost impossible to assess with executive tasks. Electrophysiological and functional imaging studies could help to clear this issue.

The main conclusion is that the influence of more basic cognitive deficits on long-term memory in schizophrenia is modest, especially for verbal learning. It seems that the long-term memory deficits in schizophrenia are primary deficits. The question remains what sub processes of memory are to be held responsible. Because learning of information is most impaired, the early perceptual encoding of stimuli or the establishment of memory traces are the most likely candidates.

Imaging studies of verbal encoding point to a special role for the prefrontal cortex and the medial temporal regions including the hippocampus (Cabeza & Nyberg, 2000). In an excellent review of neuropathological and functional studies, Harrison (1999) postulates that the pathofysiology of schizophrenia reflects aberrant activity in, and integration of, the components of a distributed circuitry involving the prefrontal cortex, hippocampus and certain subcortical structures. Although the concept of localized dysfunctions still dominates research in schizophrenia, a growing body of evidence indicates that deficits in connectivity between and within the different components of the suggested circuitry, which are supposed to be involved in coordination and organization of information, are more likely. Because the process of establishing memory traces depends on the coordinated forming of associations between several features it is conceivable that deficits in connectivity also cause memory deficits, especially in the phase of encoding of information.

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