Verbal memory deficit in patients with schizophrenia: an important future target for treatment

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Despite more than two-thirds of patients with schizophrenia showing reductions in delusions and hallucinations following optimum available treatment, many are left with crippling cognitive impairments. Neurocognitive deficit is a core feature of schizophrenia, but the question arises as to whether efforts should be geared towards ameliorating and normalizing these deficits. Verbal memory dysfunction is one of the most consistently reported cognitive deficits and among the best predictors of functional outcome in schizophrenia. Therefore, a better understanding of the nature of this deficit could lead to treatments that not only improve the specific systems mediating the impairment, but could also have wider implications for clinical and social outcome.

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Neurocognitive deficit is a primary feature of schizophrenia, with over 80% of patients being clinically impaired in one or more domains of cognitive function. Some authorities consider the remainder of patients as 'high functioning' or 'near normal' rather than normal [1–3]. Deficits are present in first episode schizophrenia and remain relatively stable over the course of illness, although there may be a more rapid decline in older chronic schizophrenia patients than in their normal counterparts [1,4–8]. The deficits appear to be independent of positive symptomatology and medication effects, and to some extent predate the onset of psychosis and are present in some healthy first-degree relatives of schizophrenic patients [9–13].

Verbal memory is one of the most impaired cognitive domains in schizophrenia [14–16]. It is among the strongest predictors of functional outcome, can differentiate between antipsychotic responder and nonresponder schizophrenic patients and is associated with a greater emotional discomfort, poorer quality of life, worse clinical and community outcome, improvement in work performance, inefficient social problem solving and worse performance of daily life skills [17–26].

Given the impact of memory deficits on everyday life in schizophrenia patients, a better delineation of the nature the deficit and of the molecular and neurobiological systems underlying it, has obvious therapeutic consequences. (For a broad overview on the topic, the reader is referred to a review by Cirillo and Seidman [14]). The issue of verbal memory deficits is put into context by introducing the concept of memory.

Outline of memory systems

A plethora of speculations concerning the classification and conceptualization of memory have been proposed, with distinctions between short- and long-term memory, declarative and procedural memory including their various subdivisions, being among the most influential [27–31]. A comprehensive description of memory is beyond the scope of this review. The interested reader is referred to Tulving and Baddeley [32,33].

Types of memory

Short-term memory is conceptualized as a limited-capacity system restricted in temporal duration and amount of storage. Long-term memory refers to several unlimited capacity subsystems of essentially unrestrictive temporal

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duration and storage ability [34]. Another influential distinction involves the classification of memory into declarative and procedural. Declarative memory represents the ability to acquire, integrate and remember information about facts, objects, concepts and events. Most research into memory in schizophrenia involves assessing this aspect of memory and the verbal component of this system constitutes the focus of this review. Procedural memory involves the implicit learning of skills, such as walking and talking. According to some authorities, declarative memory may be further subdivided into semantic and episodic memory [35,36]. The former relates to memory for general knowledge whereas the latter refers to memory for happenings in particular places at specific times [32]. The distinction between effortful and automatic memory refers to acquisition of new information involving conscious or effortful processing, such as that involved in declarative memory or passive (implicit) learning, for example that involved in nondeclarative memory.

Stages of memory

Memory processing can be separated into three stages: encoding, storage and retrieval. Encoding refers to the initial processing of information involving the active organization of the material to be learned. Immediate recall of a list of words or a passage is thought to tap into this stage of memory. The maintainance and consolidation of information is referred to as storage. Normally decay rates of stored information (i.e., forgetting) are assessed by calculating the percentage of information retained in a second trial in relation to the amount of information learned during the initial recall condition. Retrieval refers to the mental search processes required to access and recollect previously stored information. Impaired free-recall in a context of intact recognition suggests that the information cannot be accessed, probably due to inappropriate use of search strategies, even though it has been stored. This would suggest deficits at the retrieval stage.

Verbal memory deficit in schizophrenia

Evidence from a review on verbal declarative memory dysfunction in schizophrenia, a meta-analyses on memory and a quantitative review on neurocognitive deficits, converges to the conclusion that verbal memory is among the most impaired domains of cognitive function in schizophrenia [14–16]. It is impaired in first episode and chronic schizophrenia and appears to be present throughout the course of illness without being fully accounted for by changes in clinical state or medication effects (TABLE 1) [6,10,15,37,38].

Studies of first episode patients

First episode studies have an advantage over those research designs that examine patients at various stages of the disease because they avoid the secondary effects of chronic use of medication and hospitalization on cognition.

Schuepbach and colleagues investigated the course of clinical symptoms and neuropsychologic performance in a sample of neuroleptic-naive patients experiencing their first episode of psychosis [39]. The patients were followed for 5 weeks after the onset of treatment when most patients had recovered from acute psychosis. The authors found that a patient's performance in verbal learning and memory tests deteriorated after initiation of treatment, while controls showed modest increases on the follow-up assessment, presumably due to familiarity or practice effects. Changes in symptom profile were not associated with changes in memory and therefore, this could not have accounted for the memory decline in patients.

In another study, Bilder and colleagues compared the performance of a large sample of first-onset patients after initial stabilization of psychosis with that of a normal control group in a comprehensive battery of tests [6]. The patients had a large generalized neuropsychological deficit of the magnitude of 1.5 standard deviations (SDs) below the mean of the control group, with some further subtle impairment in memory (both verbal and visual) and executive processing. Correlations between clinical variables and neuropsychological scale scores showed that memory deficit correlated with alogia, global assessment scale, antipsychotic dose at testing and anti-Parkinson medication dose. This study had an advantage over other first episode studies, in that it assessed first episode patients after clinical stabilization. Therefore, the investigators attempted to measure underlying neuropsychological characteristics by minimizing effects associated with clinical presentation and medication. The authors argued that the pattern of deficit in their first episode sample resembled that found in studies of chronic schizophrenia groups, though the overall severity of the deficit is greater in the latter. As Bilder and colleagues highlight, it is not known whether the difference in magnitude usually found between chronic and first episode samples reflects a sampling bias, since only a portion of first episode patients will go on to a chronic course or whether it reflects cognitive decline.

In an attempt to address this issue, Addington and Addington compared the neuropsychological performance of patients experiencing their first episode of schizophrenia with that of patients with an established course [4]. They examined a sample of 111 first episode patients and compared their performance with 76 outpatients on a range of measures. There was a similar pattern of neuropsychological impairment in both samples, with the multiepisode group showing a greater magnitude of deficit, although both groups were equally impaired in verbal memory. However, their finding of an association between negative symptoms and memory performance in both groups suggested that memory impairment could be due to negative symptoms. When they followed up the patients 1 year later, they found that compared with the multiepisode group, the first episode sample showed superior performance on verbal memory, although their performance was still impaired, being below the 30th percentile.

Overall, the most recent studies echo the findings of older investigations in that impairments in verbal memory are present in patients experiencing their first psychotic episode and, therefore, deficits cannot simply be attributed to the effects of hospitalization or chronic medication.

Table 1. Recent studies on cognition and schizophrenia.

Study design	Main results on memory	Ref.
First episode patients	Verbal learning and memory deteriorated after initiation of treatment	[39]
	Compared first with multiepisode samples. Both groups equally impaired on verbal memory, but memory impairment may be due to negative symptoms	[4]
	Large generalized impairments on several domains, with some further subtle impairments in verbal and visual memory	[6]
Chronic patients	Compared geriatric and nongeriatric chronic patients. Poor outcome patients appear to have a pattern of memory impairment that has features in common with cortical dementia	[38]
	Compared elderly patients with schizophrenia with patients with probable Alzeimer's disease. Both groups showed impairments with similar profiles	[40]
Longitudinal	Deficits remained stable over both a short-term (1.6 years) and long-term (5-year) period	[8]
	Followed first episode and recent-onset sample. Immediate recall improved over 5-year follow-up. Delayed condition remained the same	[41]
	Followed first episode sample over a period of 2–5 years. Patients showed deterioration on verbal memory, showing no benefit from repeated exposure to this assessment	[7]

Studies of chronic patients

Most neuropsychologic studies in schizophrenia are conducted in chronic samples. Numerous studies have been published in the last few years with most showing a verbal memory deficit in chronic schizophrenia. A few studies took a more novel approach [38,40].

Putnam and Harvey examined the verbal and visual learning and memory performance of geriatric and nongeriatric chronic schizophrenic patients [38]. As expected, associations were found between all aspects of memory and general cognitive ability, with the lower the general ability, the worse the memory performance. When the authors accounted for this, age effects were still present for most memory measures. Delayed recognition was as impaired as delayed recall for both groups but geriatric patients performed worse than their nongeriatric counterparts. The authors suggested that poor-outcome schizophrenic patients have a pattern of memory impairment that has some features in common with cortical dementia.

Another study that reached a similar conclusion is that by McBride and colleagues who compared cognitive performance in elderly patients with schizophrenia with that of patients with probable Alzheimer's disease [40]. Both groups showed impairments compared with controls with their profiles appearing remarkably similar, although Alzheimer's patients demonstrated a greater deficit in delayed recall of a word list and greater loss of stored information.

Longitudinal course of verbal memory deficits

Longitudinal studies follow patients during the course of the disease for periods ranging from a few months to several years. This has the advantage over cross-sectional studies, which compares two different groups at different points of the disease, of examining the same patients and, therefore, eliminating the variability that arises from assessing different samples.

Heaton and colleagues assessed a large sample of 142 outpatients with schizophrenia and 206 community controls on several domains of cognitive functions [8]. Neurocognitive impairment, including memory (verbal and visual), remained stable over both short-term (1.6 years) and long-term follow-up (mean 5 years) periods, suggesting that neuropsychologic impairment in schizophrenia is a stable trait-like dimension of the disorder. This study did not include chronically institutionalized patients and its findings may not be representative of that patient population.

Contrary to most longitudinal studies, Gold and colleagues used a first episode and recent-onset schizophrenia sample to examine the longitudinal course of cognitive performance [41]. In terms of verbal memory, They found that immediate recall improved over the 5-year follow-up period, although the delayed recall condition remained at the same impaired level [41]. Neither medication dose nor any of the symptom dimensions was associated with memory performance.

In another study that followed a first episode sample, Hoff and colleagues examined the change in pattern of cognitive abilities over a period of 2–5 years [7]. Patients with schizophrenia or schizophrenifom disorder were followed at annual intervals after initial hospitalization and assessed on various neuropsychologic and MRI measures. As anticipated, patients with schizophrenia performed 1–2 SDs below the normal mean throughout the follow-up period. When the authors examined the rate of change over time, patients showed deterioration compared with controls on verbal memory, showing no benefit from repeatedly participating in this assessment. This result contrasted with findings for other measures, which showed improvement over time. Again the findings were not related to medication or symptom effects.

Overall, verbal memory appears to be largely stable, perhaps with some small improvements in some aspects and deterioration in others, but does not change dramatically with

alterations in symptoms or medication. In general, the reviewed studies are in agreement with the results of a review on longitudinal studies by Rund [42].

Effects of symptoms

In a meta-analysis of 70 studies examining memory impairment, Aleman and colleagues concluded that only negative symptoms are associated with memory performance [15]. Their meta-analysis suggested no associations between the magnitude of memory impairment and positive symptoms. This conclusion appears to remain the case for most more recent studies, although a minority of studies report results, as is often the case with schizophrenia research, which is inconsistent.

In a recent study, Hughes and colleagues longitudinally examined the cognitive and symptom profile of people with chronic schizophrenia [9]. At the first assessment, severity of negative symptoms predicted poor neuropsychologic scores, including performance in verbal memory. However, this relationship was not maintained on the second evaluation which followed 6 months after the baseline assessment, prompting the authors to argue against a causal relationship between the improvement in symptoms and neuropsychologic performance. The authors suggested that the relationship between symptoms and cognition varies with illness progression, with first episode and recent-onset patients showing improved cognitive functioning as symptoms improve, but chronic patients showing no cognitive benefits following amelioration in symptoms. This may be because chronic patients represent a distinct subgroup with different etiology and/or level of cognitive functioning or it could be due to the chronic effects of an interaction between various factors including treatment history and hospitalization.

In the discussed first episode schizophrenia study, Bilder and colleagues explored the relationship between neuropsychologic performance and various clinical measures, including symptoms [6]. They examined the relationship between neurocognitive and symptom ratings made at study entry before initialization of treatment and close to the time of the neuropsychologic examinations. They found no correlations greater than 0.30 between neuropsychologic scores and psychosis and disorganization dimensions at baseline. However, they did find associations of more than 0.30 between affective flattening and memory (this included both verbal and visual memory). Global clinical assessments and ratings on negative symptoms correlated more strongly with cognitive tests, including tests on memory, at the follow-up.

Using a different approach, Vaz and Heinrichs separated patients into memory impaired and unimpaired and found that memory impaired schizophrenia patients experience significantly more positive symptoms and a poorer quality of life compared with patients with no memory impairments [20]. In contrast, Addington and Addington found no associations between positive symptoms and cognitive functioning in first episode and multiepisode samples [4]. However, like others, these authors reported several significant associations between negative symptoms and cognitive functioning. For the multiple episode group, negative symptoms were associated with a measure of executive function and delayed verbal memory. For the first episode group, negative symptoms were also associated with a measure of executive function and visual and verbal memory at the initial assessment and with executive function and verbal memory in the 1-year follow-up.

What is the nature of the verbal memory deficit?

Establishing the precise nature of the verbal memory deficit by isolating the exact stage(s) during which the failure occurs is important if we want to identify the neuronal systems subserving these impairments. In a review of the literature on declarative verbal memory, Cirillo and Seidman concluded that the impairment is mainly due to a deficit at the encoding stage (learning), with a further mild impairment reflected as an increase in the rate of forgetting [14].

In a recent study, Chan and colleagues examined the performance of acute and chronic patients on encoding, retention and retrieval processes, by using word lists presented randomly or in clusters [43]. Patients showed impaired learning (encoding) but both patient groups appeared able to retain most of the newly acquired information, regardless of the presentation format after a 30 min delay. Semantic clustering (organizing information based on conceptual features) appeared to facilitate retention of information in both groups.

A similar conclusion was reached by Gold and colleagues [44]. They initially found marked impairments in immediate and delayed recall and percentage retained in schizophrenic patients compared with normal comparison subjects. However, when they matched patients and controls on level of initial recall, they had similar delayed recall scores. This suggests a primary deficit in the initial acquisition of information rather than an accelerated rate of forgetting in schizophrenia. Their data are consistent with the view articulated a few decades ago by Koh that encoding impairments appear to be the primary cause of memory failure in schizophrenia [45].

In a study focusing on encoding, Brebion and colleagues investigated the effect of processing speed and selective attention on different types of memory impairment (superficial vs. deep encoding) [46]. In the patient group, processing speed was related to superficial (e.g., serial learning of items) and deep encoding (e.g., organization of the recalled words according to semantic categories) and global verbal memory score. Selective attention (ability to inhibit nonrelevant information) only contributed to the superficial encoding processes and, therefore, had little impact when information was encoded based on semantic properties.

In a study comparing verbal and nonverbal memory performance in schizophrenia, Tracy and colleagues reported that patients had deficits in both modalities compared with age-matched controls [47]. On the verbal task, retrieval processes, in addition to encoding processes, were disrupted. On the nonverbal task, the deficits were restricted to encoding. Therefore, while encoding was compromised irrespective of material, test of retrieval processes revealed material-specific effects.

Is the verbal memory impairment primary or secondary?

Recently, a few papers have been published examining various parameters that may be the primary cause of the verbal memory deficits in schizophrenia. Wexler and colleagues used an experiment that was designed to bypass early perceptual processing of verbal material and determine if patients continue to show impaired performance on verbal memory tasks [48]. The authors provided clear evidence that verbal memory deficits are independent of the sensory processing of verbal stimuli and therefore, the latter cannot explain the apparent verbal memory impairment. Similarly, Brebion and colleagues found that distractability, which is known to impede the holding and rote rehearsal of sequences of items, does not appear to be a major contributing factor in the memory deficits found in schizophrenia [49]. However, there is some preliminary evidence to suggest that verbal memory deficits may be secondary to depression and slowness [49,50]. In addition, processing speed appears to be related to both superficial encoding and the efficiency of deep encoding. There are some suggestions that if schizophrenic patients were not slow, they would not be impaired on serial learning and would be better able to encode information [49].

It is possible that many factors, such as slowness and depression, may exacerbate the memory deficit in schizophrenia. However, verbal memory deficits are also found in healthy relatives of schizophrenic patients who do not experience such symptoms. This suggests that verbal memory deficit is not an epiphenomenon but rather a core symptom of schizophrenia.

Family & high-risk studies

Evidence from family and high-risk designs converges to suggest that cognitive impairment may be a marker for liability to schizophrenia with verbal memory being among the best candidates [11,12,51,52]. The authors found evidence that familial, presumed genetic, liability to schizophrenia may be expressed as dysfunction in verbal memory and that verbal memory may be selectively impaired in relatives of schizophrenic patients compared with other functions such as visual memory and executive processing [11,12].

Similarly, in a study that examined parents of schizophrenic patients, Appels and colleagues found that verbal memory was among the most impaired domains of cognitive function [53]. This is in agreement with some earlier studies, including those by Laurent and colleagues who found that a higher proportion of relatives compared with controls had deficits in verbal fluency and verbal memory, and by Faraone and colleagues who suggested that verbal memory is a stable trait determined by a gene or genes that also increase liability to schizophrenia [54,55].

Using a high-risk design, Erlenmeyer-Kimbling evaluated childhood predictors of adult schizophrenia-related psychoses and found that childhood deficits in verbal memory identified 83% of the subjects who later developed such psychoses [56]. Verbal memory had the highest predictive power of any cognitive domain. In an interesting study following young people at high risk for schizophrenia, Cosway and colleagues found that the development of psychotic symptoms is preceded by a decline in intelligence quotient and memory [57].

In summary, there is a great deal of evidence that verbal memory impairments are present in relatives and high-risk subjects, suggesting that genetic liability to the disorder can be expressed as verbal memory deficit.

Neuroimaging studies in verbal memory

Determining the neural circuitry underlying verbal memory deficit could lead to the development of drugs that target the neurotransmitter systems responsible for these deficits. A growing number of neuroimaging studies on verbal memory in normal and schizophrenia populations have been published over the last few years. A review of this literature is beyond the scope of this paper and the interested reader is referred to papers by Weiss and Heckers, who reviewed the neuroimaging literature on declarative memory in schizophrenia [58]. In addition, Buckner and Koutstaal conducted functional neuroimaging studies concerning encoding, priming and explicit memory retrieval, and Cabeza and colleagues who examined the neural correlates of episodic memory. See also Nyberg and colleagues and Cabeza and colleagues [59–65]. Here an outline of what has emerged in the literature regarding functional neuroimaging studies of verbal memory is given.

One of the empirical regularities which has been derived from functional neuroimaging studies on episodic memory, is referred to as the HERA (hemispheric encoding/retrieval asymmetry) model [32]. According to this, the left prefrontal cortex is differentially more activated compared with right during the encoding phase, whereas the opposite is true during memory retrieval. According to the model, episodic encoding processes usually require retrieval of semantic information, semantic retrieval is also facilitated by the left frontal lobe [32].

However, it is clear that prefrontal brain regions constitute only a part of a wider functional network. Fernandez and Tendolkar, who reviewed the literature on normal human declarative memory, suggested that memory formation involves integrated brain activity requiring specific mnemonic operations subserved by the medial temporal lobe and other semantic/perceptual processes mediated by the prefrontal cortex [66]. The authors speculated that within this broad network, there are subregions that support formation of specific types of memory (e.g., relational vs. nonrelational). The idea that certain subregions or networks are involved in different forms of memory is also supported by Habib and colleagues who found that different neural networks are active during verbal memory encoding of novel and familiar information [67].

Even though findings of distinct regions subserving specific processes within memory are emerging, the opposite situation, where the same networks are involved in more than one cognitive function, may also be true. Buckner and Koutstaal suggested that verbal encoding is associated with activation of brain regions including the left inferior and dorsal prefrontal cortex, areas that are also activated during working memory and effortful word generation tasks [59]. Furthermore, explicit retrieval appears to be mediated by the same regions as in encoding and word generation tasks. However,

Buckner and Koutstaal argued that explicit retrieval also engages other brain regions, such as the right anterior prefrontal cortex.

A series of studies by Cabeza and colleagues further support the hypothesis that different cognitive functions may involve overlapping brain regions [60,65]. Cabeza and colleagues reported on a common fronto–parietal–cingulate–thalamic network for verbal episodic retrieval and visual attention [65]. In addition, they reported similar activation of the medial temporal regions during both processes. In another study, Cabeza and colleagues found a common fronto–parieto–cerebellar network for verbal episodic recall and working memory [60]. However, in both studies, several subregions were also differentially involved for each function suggesting that there are distinct processes within these cognitive domains.

Clearly, functional neuroimaging will help to elucidate the cerebral correlates of the various memory components and processes which are involved in verbal memory. In addition to studies on memory in normal populations, several investigations have been conducted in disease samples, including schizophrenia. Overall, memory impairment in schizophrenia appears to involve a disconnectivity between the prefrontal cortex and three brain regions that are known to be important in normal learning and memory: the hippocampus, thalamus and cerebellum [58]. This appears to be the case even when patients perform at a level comparable with that of normal healthy subjects.

Hofer and colleagues found that even though the patients performed well in a word recognition task, they showed less activation in the right dorsolateral and anterior prefrontal cortex, right anterior cingulate and left lateral temporal cortex, during word encoding compared with controls [68]. Similarly, after corrections for performance on behavioral recognition to avoid bias related to lower task performance, Jessen and colleagues reported disturbed hippocampal function in patients during performance in verbal encoding and recognition tasks [69].

In another recent study, Weiss and colleagues examined the effect of interventions designed to facilitate performance, on verbal retrieval-related hippocampal activity in patients with schizophrenia and community controls [70]. The interventions were associated with hippocampal recruitment in controls during word retrieval but with prefrontal activation in patients. Patients with schizophrenia showed intact memory performance following encoding interventions even though they did not activate the hippocampus, thus suggesting a dissociation of the normal function–structure relationship in schizophrenia.

Therefore, the neural substrates of the various subcomponents of verbal memory are just beginning to be understood and there is clearly considerable scope for a better characterization of the deficit in schizophrenia as the available techniques, methodologies and cognitive measures become more refined and sophisticated.

Genes & verbal memory

Recently, researchers have also turned their attention to understanding the deficit at the molecular level. Research has been performed to investigate the effects of common functional variants of genes, such as *COMT* and *BDNF* on cognitive function and some interesting findings have emerged. In a recent report, Egan and colleagues investigated the effects of a single nucleotide polymorphism (*Val66Met*) of the human brain-derived neurotrophic factor gene and found that those with the met allele showed poorer episodic memory [71]. Furthermore, Hariri and colleagues demonstrated that those with the met substitution showed relatively diminished hippocampal activation compared with val homozygotes during both encoding and retrieval processes [72].

Predictive validity of verbal memory deficits

Memory appears to be one of the strongest predictors of functional outcome in schizophrenia. In a review of the literature, Green and colleagues reported that verbal memory was reliably related to every outcome domain examined. A positive association was found between the two domains in 13 out of the 18 studies considered [17]. Immediate verbal memory was associated with psychological skill acquisition. The author's own meta-analyses suggested that verbal memory had a medium-to-large predictive power on social outcome, a greater predictive power than any other cognitive domain.

More recently, a study by Verdoux and colleagues found a dose-response association between verbal and visual memory performance at first admission and clinical outcome over a 2-year follow-up [21]. Their results suggested that the worse the score on memory, the higher the risk of exhibiting psychotic symptoms and rehospitalization. Cognitive performance was a better predictor of clinical than social outcome in this first episode sample, prompting the authors to argue that the relationship between neurocognitive deficits and poor social outcome may hold more in chronic samples than in first episode patients.

Another recent study suggests that the cognitive abilities needed for initial improvement in work performance differ from those that are necessary in later vocational development. For example, while attention is more important for initial success, verbal memory is necessary for sustained work improvement [24]. Taking a novel approach, Rempfer and colleagues examined the relationship between cognition and performance on daily living skills in a natural setting and found that shopping efficiency was associated with better performance on several cognitive tasks, including verbal memory [26]. Similarly, Fujii and Wylie recently reported that verbal memory significantly predicted functional outcome [22]. Due to these observations, the current thinking is that normalizing these deficits may improve the functional and clinical outcome of schizophrenia.

Treatment of verbal deficit

Since cognitive impairment is a core feature of schizophrenia, with an established effect on long-term functional outcome, no intervention can be considered totally effective unless it also targets this aspect of the disorder [1,10,73]. Although different patients present with different profiles of cognitive dysfunction, four-fifths fall below the median in global verbal memory,

constituting the highest percentage in any cognitive domain [16]. This and its relevance in daily life and to long-term clinical and functional outcomes, such as employment and social skill acquisition, should render verbal memory as one of the most important cognitive targets for treatment [14].

An expanding number of studies have examined the effect of medication on cognitive function in schizophrenia. For critical reviews on the issue see Green and Harvey, Keefe, Meltzer and McGurk, and Keefe and colleagues [10,74–76].

The vast majority of these studies examine the effect of an existing antipsychotic medication on neurocognitive function. However, the dissatisfaction with available treatments in terms of their effects on cognition has led to a few studies investigating the addition of other compounds to standard antipsychotic treatment in the hope that this would improve cognitive function.

Overall, the available data suggest that second-generation atypical drugs, though associated with small neurocognitive advantages compared with conventional antipsychotics, do not normalize patients performance [10,75]. In addition, it is not known if the benefits of the atypical antipsychotics are restricted to those studies which compared them with high dosages of conventional treatments [10]. It is not clear if cognitive amelioration is caused by the treatment effects of the newer medications or by release from inappropriate, often high-dose, conventional treatment [74].

It is clear from reviews of the literature that until 1998, the research methodology used was not consistent with clinical trial methods [10,74,76] . In addition, most research has been financed by industrial companies with an obvious interest in particular outcomes [74]. Since methodological weaknesses limit the interpretability of findings, great caution should be exercised in evaluating research in this area. The interested reader is referred to the study by Keefe and colleagues which reports on the newly established standards for research designs and to the article by Harvey and Keefe on the issues that should be considered when interpreting research findings [74,76].

A second conclusion that has emerged from the literature is that different atypical antipsychotic medications have different neurocognitive profiles, with certain medications improving specific aspects of cognition [75]. Therefore, in the future, it may be possible to prescribe a medication on the basis of a patient's neuropsychological profile [10].

In terms of verbal memory, Cuesta and colleagues found that patients on olanzapine (Zypreza®, Eli Lilly & Co., IN, USA) compared with those on typical neuroleptic medication, showed greater improvement in verbal memory and negative symptomatology at baseline and in the 3- and 6-month follow-up assessments [77]. However, when groups were matched on cognitive baseline scores, the benefit on verbal memory was lost. Similarly, melperone (Janssen-Cilag, NJ, USA), an atypical antipsychotic drug, was also not associated with amelioration of verbal memory [78]. Verbal memory improvements were seen in patients taking quetiapine (Seroquel®, AstraZeneca, London, UK) and risperidone (Risperdal®, Janssen-Cilag, NJ, USA) [79,80]. In addition, clozapine (Clozaril®, Novartis Pharmaceutical Corp., Basel, Switzerland) does not appear to be associated with the verbal memory deficits found with conventional neuroleptic treatments and compared with haloperidol, clozapine significantly improves performance on delayed verbal memory [81,82].

In terms of adjunctive treatments to antipsychotic medications, tandospirone, a serotonin$_{1A}$ agonist, was found to improve verbal memory function in schizophrenia while donepezil (Aricept®, Pfizer Inc., NY, USA) a cholinesterase inhibitor, was not associated with any improvement in any domain of cognitive function [83,84]. Taking a novel approach, Newcomer and colleagues found preliminary evidence suggesting that improvement in memory performance in patients with schizophrenia followed increases in circulating glucose availability [85].

Conclusion

Verbal memory constitutes one of the most impaired domains of cognitive function in schizophrenia. It is a core characteristic and independent of hospitalization, medication or symptom effects and it is present in some healthy first-degree relatives of patients with schizophrenia. Impairments are present in first episode and chronic schizophrenia and persist throughout the course of the illness. The first stage of memory processing that involves organization of information, known as encoding, appears to be the most impaired with some further deficits related to retention of information.

Verbal memory is vital to everyday life, in schizophrenia impairment in this domain is among the most accurate predictors of long-term functional outcome. The financial and emotional costs related to this dysfunction are enormous and none of the available treatments can normalize the deficit.

Expert opinion

Verbal memory deficit in schizophrenia has been established in a large proportion of the schizophrenic population. From now on, we need to focus on samples that show the impairment to:

- Delineate the precise components that contribute to the verbal memory dysfunction
- Identify the specific brain regions that subserve this
- Understand its molecular and cellular basis

Key issues

- Verbal memory is vital to daily life.
- Verbal memory is among the most impaired domains of cognitive function in schizophrenia.
- It is a core feature of schizophrenia and not an epiphenomenon of medication, hospitalization or symptoms.
- Verbal memory is among the best predictors of functional outcome in schizophrenia.
- Currently there is no available treatment.

This will enhance our chances of treating the verbal memory deficit. Inevitably, the field will progress only as our basic knowledge of the memory systems of the normal human brain increases. Consequently, we need to create more platforms for communication between cognitive psychologists, neuroscientists and schizophrenia experts.

Five-year view

In terms of treatment, no drug is currently available that has been designed to specifically enhance cognitive deficits, including verbal memory, in schizophrenia. There are studies underway that explore the adjunctive effects of cognitive enhancers in schizophrenia. The results of these studies will become available within the next few years and it is possible that some of these drugs will produce significant ameliorations in memory. In addition, there is a huge effort to develop drugs to improve memory in other conditions such as Alzheimer's disease, therfore, it is conceivable that patients with schizophrenia may benefit from any advances found.

Information resources

- Tulving E, Craik FIM (Eds). *The Oxford Handbook of Memory*. Oxford University Press, NY, USA (2000).
- Baddeley AD. *Essentials of Human Memory*. Psychology Press Hove, UK (1999).
- Tulving E. Episodic memory: from mind to brain. *Ann Rev. Psychol*. 53, 1–25 (2002).
- www.schizophrenia.com (Accessed December 2003)
- www.nimh.nih.gov/publicat/schizmenu.cfm (Accessed December 2003)
- www.exploratorium.edu/memory/ (Accessed December 2003)
- http://psiexp.ss.uci.edu/ (Accessed December 2003)

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Hoff AL, KremenWS. Neuropsychology in schizophrenia: an update. *Curr. Opin. Psych.* 16, 149–155 (2003).

2 Palmer BW, Heaton RK, Paulsen JS *et al*. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology* 11, 437–446 (1997).

3 Allen DN, Goldstein G, Warnick E. A consideration of neuropsychologically normal schizophrenia. *J. Int. Neuropsychol. Soc*. 9, 56–63 (2003).

4 Addington J, Addington D. Cognitive functioning in first episode schizophrenia. *J. Psych. Neurosci*. 27, 188–192 (2002).

5 Riley EM, McGovern D, Mockler D *et al*. Neuropsychological functioning in first episode psychosis – evidence of specific deficits. *Schiz. Res.* 43, 47–55 (2000).

6 Bilder RM, Goldman RS, Robinson D *et al*. Neuropsychology of first episode schizophrenia: initial characterization and clinical correlates. *Am. J. Psych.* 157, 549–559 (2000).

7 Hoff AL, Sakuma M, Wieneke M *et al*. Longitudinal neuropsychological follow-up study of patients with first episode schizophrenia. *Am. J. Psych.* 156, 1336–1341 (1999).

8 Heaton RK, Gladsjo JA, Palmer BW *et al*. Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen. Psych.* 58, 24–32 (2001).
•• Large study involving 142 schizophrenic outpatients and 206 controls. Shows that neuropsychological impairment remains stable, regardless of baseline characteristics and changes in clinical state.

9 Hughes C, Kumari V, Soni W *et al*. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. *Schiz. Res.* 59, 137–146 (2003).

10 Green MF. Recent studies on the neurocognitive effects of second-generation antipsychotic medications. *Curr. Opin. Psych*. 15, 25–29 (2002).
•• Critically evaluates the literature on the cognitive effects of antipsychotic medication.

11 Toulopoulou T, Morris RG, Rabe-Hesketh S, Murray RM. Selectivity of verbal memory deficit in schizophrenic patients and their relatives. *Am. J. Med. Gen.* Part B – *Neuropsychiatric Genetics* B116, 1–7 (2003).

12 Toulopoulou T, Rabe-Hesketh S, King H, Murray RM, Morris RG. Episodic memory in schizophrenic patients and their relatives. *Schiz. Res.* 63, 261–271 (2003).

13 Cannon TD, Huttunen MO, Lonnqvist J *et al*. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *Am. J. Hum.* Gen. 67, 369–382 (2000).

14 Cirillo MA, Seidman LJ. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychol. Rev.* 13, 43–77 (2003).
•• Comprehensive review of the literature on verbal declarative memory.

15 Aleman A, Hijman R, de Haan EHF, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am. J. Psych.*156, 1358–1366 (1999).

16 Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* 12, 426–445 (1998).

17 Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the 'right stuff'? *Schizohr. Bull*. 26, 119–136 (2000).

18 Joober R, Rouleau GA, Lal S *et al*. Neuropsychological impairments in neuroleptic-responder verses – nonresponder schizophrenic patients and healthy volunteers. *Schiz. Res.* 53, 229–238 (2002).

19 Lysaker PH, Bell MD, Greig TC, Bryson GJ. Emotional discomfort and impairments in verbal memory in schizophrenia. *Psych. Res.* 97, 51–59 (2000).

20 Vaz SAM, Heinrichs RW. Schizophrenia and memory impairment: evidence for a neurocognitive subtype. *Psych. Res.* 113, 93–105 (2002).

21 Verdoux H, Liraud F, Assens F, Abalan F, van Os J. Social and clinical consequences of cognitive deficits in early psychosis: a two-year follow-up study of first-admitted patients. *Schiz. Res.* 56, 149–159 (2002).

22 Fujii DE, Wylie AM. Neurocognition and community outcome in schizophrenia: long-term predictive validity. *Schiz. Res.* 59, 219–223 (2003).

23 Liddle PF. Cognitive impairment in schizophrenia: its impact on social functioning. *Acta Psych. Scand.* 101, 11–16 (2000).

24 Bryson G, Bell MD. Initial and final work performance in schizophrenia: cognitive and symptom predictors. *J. Nerv. Mental Dis.* 191, 87–92 (2003).

25 Addington J, Addington D. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schiz. Res.* 44, 47–56 (2000).

26 Rempfer MV, Hamera EK, Brown CE, Cromwell RL. The relations between cognition and the independent living skill of shopping in people with schizophrenia. *Psych. Res.* 117, 103–112 (2003).

27 Baddeley AD. *Working Memory.* Oxford University Press, Oxford, UK (1986).

28 Tulving E. How many memory systems are there? *Am. Psych.* 40, 385–398 (1985).

29 Craik FIM. Human memory. *Ann Rev. Psych.* 30, 63–102 (1979).

30 Atkinson RC, Shiffrin RM. *The Psychology of Learning and Motivation.* Spence KW, Spence JT (Eds). Academic Press, London, UK (1968).

31 Waugh NC, Norman D. Primary memory. *Psych. Rev.* 72, 89–104 (1965).

32 Tulving E. Episodic memory: from mind to brain. *Ann Rev. Psychol.* 53, 1–25 (2002).

33 Baddeley AD. *Essentials of Human Memory.* Psychology Press, Hove, UK (1999).

34 Lezak MD. *Neuropsychological Assessment.* Oxford Univerisity Press, Oxford, UK (1995).

35 Tulving E. Memory: performance, knowledge and experience. *Eur. J. Cog. Psychol.* 1, 3–26 (1989).

36 Tulving E. Episodic memory: from mind to brain. *Ann Rev. Psychol.* 53, 1–25 (2002).

37 Bilder RM, Volavka J, Czobor P *et al.* Neurocognitive correlates of the COMT Val (158)Met polymorphism in chronic schizophrenia. *Bio. Psych.* 52, 701–707 (2002).

38 Putnam KM, Harvey PD. Memory performance of geriatric and nongeriatric chronic schizophrenic patients: a cross-sectional study. *J. Int. Neuropsychol. Soc.* 5, 494–501 (1999).

39 Schuepbach D, Keshavan MS, Kmiec JA, Sweeney JA. Negative symptom resolution and improvements in specific cognitive deficits after acute treatment in first episode schizophrenia. *Schiz. Res.*53, 249–261 (2002).

40 McBride T, Moberg PJ, Arnold SE *et al.* Neuropsychological functioning in elderly patients with schizophrenia and Alzheimer's disease. *Schiz. Res.* 55, 217–227 (2002).

41 Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in first episode and recent-onset schizophrenia. *Am. J. Psych.* 156, 1342–1348 (1999).

42 Rund BR. A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophr. Bull.* 24, 425–435 (1998).

43 Chan AS, Kwok IC, Chiu H *et al.* Memory and organizational strategies in chronic and acute schizophrenic patients. *Schiz. Res.* 41, 431–445 (2000).

44 Gold JM, Rehkemper G, Binks SW III *et al.* Learning and forgetting in schizophrenia. *J. Ab. Psychol.* 109, 534–538 (2000).

45 Koh SD. Remembering of verbal materials by schizophrenic young adults. In: *Language and Cognition in Schizophrenia*. Schwartz S (Ed.). Erlbaum, NJ, USA (1978).

46 Brebion G, Smith MJ, Gorman JM *et al.* Memory and schizophrenia: differential link of processing speed and selective attention with two levels of encoding. *J. Psych. Res.* 34, 121–127 (2000).

47 Tracy JI, Mattson R, King C *et al.* A comparison of memory for verbal and nonverbal material in schizophrenia. *Schiz. Res.* 50, 199–211 (2001).

48 Wexler BE, Donegan N, Stevens AA, Jacob SA. Deficits in language-mediated mental operations in patients with schizophrenia. *Schiz. Res.* 53, 171–179 (2002).

49 Brebion G, Groman JM, Malaspina D, Sharif Z, Amador X. Clinical and cognitive factors associated with verbal memory task performance in patients with schizophrenia. *Am. J. Psych.* 158, 758–764 (2001).

50 Brebion G, Amador X, Smith M *et al.* Depression, psychomotor retardation, negative symptoms and memory in schizophrenia. *Neuropsych. Behav. Neurol.* 13, 177–183 (2000).

51 Egan MF, Goldberg TE, GscheidleT *et al.* Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Bio. Psych.* 50, 98–107 (2001).

52 Erlenmeyer-Kimling L, Rock D, Roberts SA *et al.* Attention, memory and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project. *Am. J. Psych.* 157, 1416–1422 (2000).

53 Appels MCM, Sitskoorn MM, Westers P, Lems E, Kahn RS. Cognitive dysfunctions in parents of schizophrenic patients parallel the deficits found in patients. *Schiz. Res.* 63, 285–293 (2003).

54 Laurent A, Moreaud O, Bosson JL *et al.* Neuropsychological functioning among nonpsychotic siblings and parents of schizophrenic patients. *Psych. Res.* 87, 147–157 (1999).

55 Faraone SV, Seidman LJ, Kremen WS *et al.* Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. *J. Ab. Psychol.* 108, 176–181 (1999).

56 Erlenmeyer-Kimling L, Rock D, Roberts SA *et al.* Attention, memory and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project. *Am. J. Psych.* 157, 1416–1422 (2000).

57 Cosway R, Byrne M, Clafferty R *et al.* Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psych. Med.* 30, 1111–1121 (2000).

58 Weiss AP, Heckers S. Neuroimaging of declarative memory in schizophrenia. *Scand. J. Psych.* 42, 239–250 (2001).

59 Buckner RL, Koutstaal W. Functional neuroimaging studies of encoding, priming and explicit memory retrieval. *Proc. Natl Acad. Sci. USA* 95, 891–898 (1998).

60 Cabeza R, Dolcos F, Graham R, Nyberg L. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage* 16, 317–330 (2002).

61 Nyberg L, Marklund P, Persson J *et al.* Common prefrontal activations during working memory, episodic memory and semantic memory. *Neuropsychologia* 41, 371–377 (2003).

62 Nyberg L, Forkstam C, Petersson KM, Cabeza R, Ingvar M. Brain imaging of human memory systems: between systems similarities and within system differences. *Cog. Brain Res.* 13, 281–292 (2002).

63 Cabeza R, Locantore JK, Anderson ND. Lateralization of prefrontal activity during episodic memory retrieval: evidence for the production-monitoring hypothesis. *J. Cog. Neurosci.* 15, 249–259 (2003).

64 Cabeza R, Nyberg L. Special issue on functional neuroimaging of memory. *Neuropsychology* 41, 241–244 (2003).

65 Cabeza R, Dolcos F, Prince SE *et al.* Attention-related activity during episodic memory retrieval: a cross-function fMRI study. *Neuropsychology* 41, 390–399 (2003).

66 Fernandez G, Tendolkar I. Integrated brain activity in medial temporal and prefrontal areas predicts subsequent memory performance: Human declarative memory formation at the system level. *Brain Res. Bull.* 55, 1–9 (2001).

67 Habib R, McIntosh AR, Wheeler MA, Tulving E. Memory encoding and hippocampally-based novelty/familiarity discrimination networks. *Neuropsychology* 41, 271–279 (2003).

68 Hofer A, Weiss EM, Golaszewski SM *et al.* An fMRI study of episodic encoding and recognition of words in patients with schizophrenia in remission. *Am. J. Psych.*160, 911–918 (2003).

69 Jessen F, Scheef L, Germeshausen L *et al.* Reduced hippocampal activation during encoding and recognition of words in schizophrenia patients. *Am. J. Psych.* 160, 1305–1312 (2003).

70 Weiss AP, Schacter DL, Goff DC *et al.* Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. *Bio. Psych.* 53, 48–55 (2003).

71 Egan MF, Kojima M, Callicott JH *et al.* The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112, 257–269 (2003).

72 Hariri AR, Goldberg TE, Mattay VS *et al.* Brain-derived neurotrophic factor val(66)met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J. Neurosci.* 23, 6690–6694 (2003).

73 Kasper S, Resinger E. Cognitive effects and antipsychotic treatment. *Psychoneuroendocrinology* 28, 27–38 (2003).

74 Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am. J. Psych.* 158, 176–184 (2001).

•• Discusses issues to consider when interpreting studies in which cognitive changes are reported in patients with schizophrenia following novel antipsychotic treatment.

75 Meltzer HY, Mcgurk SR. The effects of clozapine, risperidone and olanzapine on cognitive function in schizophrenia. *Schizophr. Bull.* 25, 233–255 (1999).

76 Keefe RSE, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr. Bull.* 25, 201–222 (1999).

77 Cuesta MJ, Peralta V, Zarzuela A. Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. *Schiz. Res.* 48, 17–28 (2001).

78 Sumiyoshi T, Jayathilake K, Meltzer HY. The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. *Schizophr. Res.* 59, 7–16 (2003).

79 Velligan DI, Prihoda TJ, Sui D *et al.* The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. *J. Clin. Psych.* 64, 524–531 (2003).

80 Kern RS, Green MF, Marshall BD *et al.* Risperidone versus haloperidol on secondary memory: Can newer medications aid learning? *Schizophr. Bull.* 25, 223–232 (1999).

81 Perez-Gomez M, Junque C. Clozapine: neuropsychological and neuroimaging studies. *Actas Espanolas de Psiquiatria* 27, 341–346 (1999).

82 Potkin SG, Fleming K, Jin Y, Gulasekaram B. Clozapine enhances neurocognition and clinical symptomatology more than standard neuroleptics. *J. Clin. Psychopharmacol.* 21, 479–483 (2001).

83 Sumiyoshi T, Matsui M, Yamashita I *et al.* The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. *Bio. Psych.* 49, 861–868 (2001).

84 Friedman JI, Adler DN, Howanitz E *et al.* A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. *Bio. Psych.* 51, 349–357 (2002).

85 Newcomer JW, Craft S, Fucetola R *et al.* Glucose-induced increase in memory performance in patients with schizophrenia. *Schiz. Bull.* 25, 321–335 (1999).

86 Stip E, Lussier I. The heterogeneity of memory dysfunction in schizophrenia. *Can. J. Psych.* 41, S14–S20 (1996).

87 Stip E. Memory impairment in schizophrenia: perspectives from psychopathology and pharmacotherapy. *Can. J. Psych* 41, S27–S34 (1996).

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