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The psychopathology, neuropsychology, and neurobiology of associative and working memory in schizophrenia

M. Spitzer

Psychiatrische Universitätsklinik Heidelberg, Voss-Strasse 4, D-61115 Heidelberg, Germany

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Summary. A large number of psycholinguistic findings on how human beings store lexical information suggest the existence of associative memory, which may be characterized by a large capacity and a long duration. Its anatomical basis supposedly is, at least in part, the frontal lobes, and some of its functional characteristics have been tentatively linked to dopamine release. Working memory has a limited capacity, lasts only for seconds and is relevant for goal-directed behavior. Its anatomical basis in the frontal cortex is established and strong evidence suggests the involvement of dopaminergic pathways. Experimental evidence using several lexical decision tasks and a delayed response task is provided to demonstrate that some characteristic features of schizophrenic thinking – in particular the rapid shift of associations, the indirect relationship of associations, the overly abstract or overly concrete use of concepts, the lack of context-sensitivity and of general integrative function and intellectual capacity – can be explained in terms of an activation or disinhibition of associative memory, and of a dysfunctional working memory. The findings serve as an example of schizophrenia reserarch in a cognitive neuroscience framework.

Key words: Schizophrenia – Working memory – Associative memory – Lexical decision – Semantic priming – Delayed response task

Introduction

It is the aim of this paper to provide experimental evidence that some of the psychopathological characteristics of schizophrenic thought can be accounted for in terms of associative and working memory. These characteristics are loose associations, indirect associations, a lack of integrative function, and overly concrete and/or overly abstract thinking, as described and interpreted by a number of authors. After a brief sketch of the phenomena in question, the concepts of associative memory and of working memory will be introduced. A series of experiments is then reported in support of the view that pathological changes in both types of memory play a role in the formation of the symptoms under scrutiny. Finally, the implications of the findings will be discussed in the framework of present schizophrenia – and cognitive neuroscience – research.

The phenomena under investigation

Eugen Bleuler (1911) conceived schizophrenia as a disorder of associations. "The association disturbances were conceived of as being primary; from these we can derive the majority of secondary symptoms" (Bleuler 1911, p. 355). Bleuler's view was influenced by the strong association psychology tradition of his time. C. G. Jung, Emil Kraepelin, and Gustav Aschaffenburg, among others, had carried out a number of experiments in normal control subjects and in patients, which clearly showed abnormalities in the associations of schizophrenic patients (for a review, see Spitzer 1992). In the uttered thoughts of schizophrenic patients, "the associations tend to proceed along new lines" (p. 14), and "indirect associations [...] receive unusual significance" (p. 14). At the same time, thought can be slow, and numerous interruptions of the flow of thought can be present. Many schizophrenic patients suffer from a marked apathy and a lack of intentional thoughts and behavior. In present psychiatry, this view has been adopted, as can be seen from the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R, American Psychiatric Association 1987), where the characteristic features of schizophrenic thought are described as follows:

> "A disturbance in the form of thought is often present. [...] The most common example of this is loosening of associations, in which ideas shift from one subject to another, completely unrelated or only obliquely related subject [...]. There may be a poverty of content of speech, in which speech is adequate in amount, but conveys little information because it is vague, overly abstract, or overly concrete [...]" (DSM-III-R, p. 188).

In short, a *rapid shift* of associations, their *indirect* relationship, and an *overly abstract* or *overly concrete* use

of concepts are among the main features of schizophrenic thinking. Moreover, schizophrenic thought and behavior have been characterized by a *lack of integrative function,* i.e., by the lack of goal-directedness, context sensitivity, drive, and general intellectual capacity (cf. Kraepelin 1913).

These psychopathological features have been interpreted in terms of overinclusion and underinclusion of thought (Cameron 1939, Feinberg and Garman 1961), deformed mental structure and reduced affective drive (Janzarik 1968), a reduced intentionality (Mundt 1984), and in terms of basic deficits which were ultimately attributed to an underlying neurochemical disorder (Huber 1983). Such *interpretive* accounts of schizophrenic symptoms provide a means to bring order into the seemingly endless list of schizophrenic symptoms (by interpreting them as a result of a few "basic" processes). However, they are hard to relate to the growing literature on the "broken brains" of schizophrenic patients. What is needed are links between the observable clinical phenomena and supposedly underlying brain functions (cf. Callaway 1992). This paper attempts to represent an example of how such links can be established by the application of experimental psychological methods to psychiatric questions.

Associative memory

The way semantic information is stored in human beings has been unraveled to some extent by experimental psychological studies of the production and understanding of language. In particular, the "mental lexicon" where word meanings are stored, probably together with other features of words, has been investigated using tasks in which word associations play a major role (cf. Levelt 1989). For example, it is long known that a given stimulus word often produces a specific "associated" word, if the person is asked to name "just what comes to mind when hearing...". In this word-association paradigm, "black" produces "white", "lemon" produces "sour", and "sour" produces "sweet" (cf. Cramer 1968). However, for the study of specific types of word associations, this method of free associations is limited by the fact that the analysis of the type of association can only be made post hoc (i.e., the experimenter cannot specify a certain association and then test it). The technique of lexcial decision, in which the subject has to decide whether a given string of characters is a word or not, can be used to avoid this difficulty. In order to investigate specific types of associations, word pairs are presented either simultaneously or one after the other. Then, the effect of the relation between the words on the specific task of deciding wheter both of them are in fact words can be measured in terms of the time it takes to perform the task and the errors subjects make.

A robust phenomenon that has been discovered using this technique of lexial decision is *semantic priming* (cf. Meyer and Schvaneveldt 1971; Neely 1991). Whenever a word is shown first and then a string of characters is shown, with respect to which the subject has to perform a lexical decision, the response is faster, in case the character

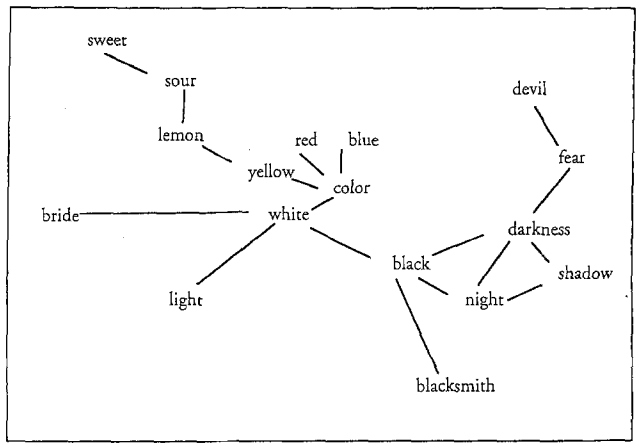

Fig. 1. Structure of associational (semantic) memory as suggested by research on word associations

string is a word, if the word is meaningfully related to the word shown immediately before. To give an example: "black" is recognized faster as a word if it is presented shortly after "white" as compared to being presented shortly after a non-related word such as "soft".

A large number of studies using lexical decision and related techniques suggests that semantic information is stored in the form of an associational network (see Fig. 1). According to current network models of semantic memory, semantic (and possibly other) features of words are represented as "nodes" (which have been called "logogens") in a neuronal network. In the course of an utterance, these semantic units become activated for a short period of time and thereafter either decay rapidly or are actively inhibited (Collins and Loftus 1975; Neely 1977, 1991). This model of lexical access further asserts that concepts activated in a semantic network by a prime serve as a source of activation that spreads to other related concepts. Such spreading of activation to nearby nodes in the semantic network lowers their thresholds of being activated. If one of these concepts is denoted by a word as target in a lexical decision paradigm, this target will be recognized faster because its processing is facilitated by its being already activated to some degree, i.e., semantic priming occurs.

In recent years, the concept of associational networks and the method of semantic priming in lexical decision tasks has been applied to the study of thought disorder in schizophrenic patients by a number of authors (Chapin et al. 1989; Fisher and Weinman 1989; Maher et al. 1987; Manschreck et al. 1988; see also Kwapil et al. 1990). Most notably, Maher and Manschreck discovered an *increased* semantic priming effect in schizophrenic patients who suffered from formal thought disorder, as compared with non-thought-disordered schizophrenic patients and normal control subjects. The authors interpret their results as evidence for an activated semantic network in schizophrenic patients, which is visible clinically as disordered thought and produces a larger priming effect as it allows word associations to spread faster. This is in line with the observation that schizophrenic patients are preoccupied with "too many of the semantic

features of a word" and produce "sentences according to [...] semantic features of previously uttered words rather than to a topic", as Chaika (1974) noted.

Little is known about the anatomical and physiological basis of associative memory. A number of rather large cortical areas have been implicated in the storage of associations between various kinds of stimuli and reactions, and verbal associations have been linked to areas in the left frontal, parietal and temporal lobes. However, studies using positron emission tomography (PET) have shown that when normal subjects generate the meaning of a word parts of the left inferior prefrontal cortex become selectively activated (Petersen et al. 1988; Posner et al. 1988). With respect to the involvement of neurotransmitters, it is noteworthy that Cohen and Servan-Schreiber (1992) have proposed a computational model of the effect of dopamine release on the working characteristics of associational networks which fits data on semantic priming in normal control subjects as compared to schizophrenic patients. In brief, the model suggests that dopamine alters the working characteristics of neural network neurons in that it increases the signal-to-noise ratio (cf. Servan-Schreiber et al. 1990). The activation becomes more focused and irrelevant information is either not activated or even suppressed. On the contrary, low-dopamine activation produces a pattern of activity in such a network which is less focused. In such a state of unfocused high activation, associations should spread fast and reach nodes which under "normal conditions" are either not activated or become activated to a lesser degree or at a later stage of information processing (leaving less time for these associations to become behaviorally relevant). One of the experiments reported below was specifically designed to test the assumption that associations spread further and faster in schizophrenia.

The concept of associative memory has been useful in describing a large number of psycholinguistic findings on how human beings store lexical information. Moreover, there is evidence that schizophrenic thought disorder is specifically related to an activation or disinhibition of associational memory. Finally, associative memory has a tentative anatomical basis in parts of the frontal lobes and some of its functional characteristics have been linked to dopamine release.

Working memory

Associational memory is established on the basis of repetitive exposure to appropriate stimuli (think of learning new words in another language, for example) to which responses have been formed. It is conceived to be stable over time. On the contrary, the most salient feature of working memory is its ever-changing character. In contrast to the seemingly unlimited capacity of associational memory and its enduring character, working memory has a limited capacity, and items are stored only for seconds. To give a simple example: when we want to call a close friend, we may use associational memory and retrieve his or her phone number, or we may look it up in a phone book, keep it in working memory in order to dial the number – and forget it immediately after we have dialed the number. Working memory has been compared to a "scratch pad", and to the random access memory of a computer which holds the most-needed information "on line".

Goldmann-Rakic and others have argued on the grounds of behavioral data from human subjects, patients, and animal research, and on the grounds of single cell recordings from monkeys that holding information "on line" over a short period of time involves the functioning of the frontal cortex (Funahashi et al. 1989; Goldman-Rakic 1990; Goldman-Rakic et al. 1990; Goldman-Rakic and Freedman 1991). In particular, the cooling of the dorsolateral prefrontal cortex in monkeys induces reversible deficits in performance of visual, tactual, and cross-modal delay tasks, which implies that this anatomical site is crucial for a supramodal short-term memory (Fuster 1991). Moreover, this type of short-term memory has been linked to dopamine activity in this brain area. Data from animal research and from a study on human subjects suggest that both types of the major dopamine receptors, D_1 and D_2, are involved (Luciana et al. 1992). Since dopamine functioning is clearly involved in the pathogenesis of schizophrenia (cf. Carlsson 1988; Davis et al. 1991) since frontal cortex dysfunction in schizophrenia has already been demonstrated by neuropsychological tests (such as the Wisconsin cart sorting task; cf. Shimamura et al. 1991; Litman et al. 1991; Braff et al. 1991) and brain imaging methods (cf. Weinberger et al. 1988), and since it is the essence of delayed response tasks to require the subject to guide his response by memory of information newly stored for each trial, such tasks seem suitable to tap working memory deficits in schizophrenic patients (cf. Goldman-Rakic 1991). Moreover, working memory deficits have already been demonstrated in schizophrenic patients using an oculomotor and a haptic version of a spatial delayed response task (Park and Holzman 1992).

In short, working memory has a limited capacity, lasts only for seconds and is relevant for goal-directed behavior. Its anatomical basis in the frontal cortex is established, it has been related to dopamine function in animal and in human subjects studies, and there is evidence of its dysfunction in schizophrenic patients.

Experiments

Semantic and indirect semantic priming

Several studies on semantic and indirect semantic priming have been conducted that will only briefly be summarized here (for details, cf. Spitzer et al. 1993a; see also Spitzer 1993).

Rationale and method. In one study, we set out to replicate the finding of Manschreck et al. (1988) of a comparatively larger amount of semantic priming in thought-disordered schizophrenic patients. In this study of 70 schizophrenic inpatients and 44 normal control subjects, a lexical decision task was used involving the recogni-

tion of words which were preceded (primed) by meaningfully associated, or non-associated words. Psychopathology was rated using the Brief Psychiatric Rating Scale (BPRS; cf. Overall and Gorham 1976), and the patient group was split into high and low thought disorder groups.

All subjects and patients were tested individually. They were told that they would be presented with pairs of words or strings of letters which would come together quite closely in time; their task was simply to read the first word, and then to decide as quickly and accurately as possible whether or not the second string of letters was a real German word.

Stimuli were presented on an Apple Macintosh Classic microcomputer (Apple, Cupertino, Calif.). All prime and target words were written in lower-case letters of 18-point Geneva font. Given a viewing distance of about 50 cm, each word subtended a visual angle of about 1–2° in width and 0.5° in height. Data collection (reaction times and errors) was also automatically controlled by the computer program. The subject's responses consisted of pressing one of two keys on the computer's keyboard ("N" for "no" or "non-word" responses, "B", relabeled as "J" for "ja" (yes) or "word" responses). Subjects used their dominant hand to indicate their responses and had their fingertips already placed on the respective keys. The experiments were all self-paced, i.e., the subjects and patients initiated each trial by depressing the computer's mouse button with their non-dominant hand, thereby proceeding through the experiment at a speed appropriate to each individual's capacity.

Prior to the initiation of each trial, the computer screen was blank. Once a trial was initiated, a fixation point was displayed in the center of the screen for 700 ms, followed by presentation of the prime for 200 ms. Then the screen again went blank for either 0, 200, or 500 ms[1], and then the target was presented until the response was made. Both primes and targets were presented in the middle of the screen, centered over where the fixation point had been. Following the subject's response, the screen again went blank and a new trial could then be initiated by the subject (see Fig. 2).

In a second study (Spitzer et al. 1993a), indirect associations between words have been investigated in schizophrenic patients using the same methodology as just described. In indirect, or mediated, word associations, such as "chalk–(white)–black", or "lemon–(sour)–sweet", the connection between prime and target is obvious only via a mediating associated word: The target is an association to an association of the prime. Up to the present, only a few studies, all on normal subjects, have been carried out on such indirect associations (Balota and Lorch 1986; DeGroot 1983; McNamara and Altarriba 1988). They have produced evidence of a limited indirect semantic priming effect in normal controls under certain boundary conditions (i.e., the effect was small, not robust, and its existence depended upon experimental conditions, and the timing of stimuli). According to the network model of semantic priming as described above, the spreading of activation is postulated to dissipate with distance, and there is empirical evidence that such an inverse relationship between semantic distance and the amount of activation exists (Den Heyer and Briand 1986).

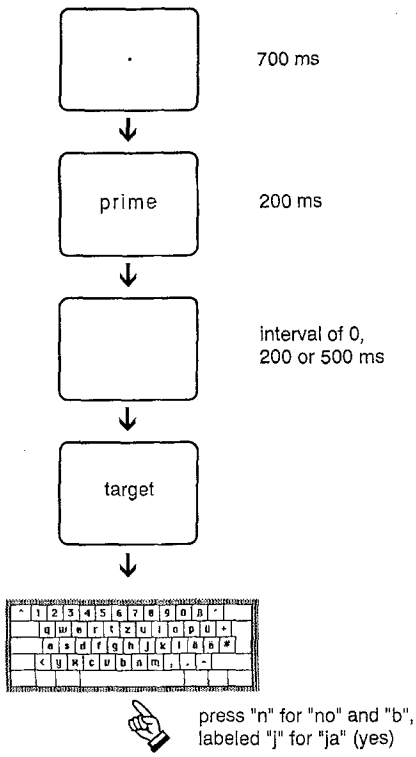

Fig. 2. Sequence of events in a single trial of the lexical decision task

Guided by clinical experience, we proposed that there should be differences in indirect associations between schizophrenic patients and normal control subjects, and that these differences should be detectable by the method of lexical decision. In particular, according to the hypothesis of activated associations in schizophrenia, there should be more indirect priming in schizophrenic patients than in normal control subjects.

Two versions of a lexical decision experiment (i.e., two stimulus lists) were designed with the following relations between prime and target:

1. indirectly semantically related words (e.g., lemon-sweet);
2. semantically related words (e.g., hen-egg);
3. unrelated words (e.g., sofa-wing);
4. word-nonword (e.g., drift-kribe).

Each stimulus list was set up twice, once with an interstimulus interval (ISI) of 0 ms and once with an ISI of 500 ms. Subjects and patients were assigned to Stimulus Set (2) by ISI (2) combinations on a random basis, with the constraints that each subject received each stimulus set and each level of ISI and that, over the entire experiment, there would be an equal number of subjects at each of the four possible combinations. The order of ISI

[1] In order to determine the exact time course of the activational phenomena under scrutiny, three intervals between the prime and the target (= inter stimulus intervals, ISI) were used.

presentation was varied pseudorandomly across subjects. The order of items within each stimulus set was initially randomized but then remained constant for all presentations of that set across all ISIs and across all subjects.

Before the actual two experiments were run, a small practice experiment was performed with no results measured. Additionally, five practice word pairs were presented at the beginning of each stimulus set to allow the subjects to make any short-term adjustments which may have been necessary due to resuming the experiment or as a result of the changed ISI. The procedures were the same as in the previous experiment, except that only two experiments per subject/patient were run with the two ISIs of 0 and 500 ms.

Results and discussion. In both experiments, each subject's mean reaction times (RTs) and percent-error rates per condition were treated as raw data and subjected to further statistical analysis. Mean RTs were calculated from the correct responses only and data were trimmed such that RTs that were greater than twice a given subject's mean RT for a particular condition and ISIs were omitted from further analyses (this procedure resulted in the exclusion of 3.5% of all reaction times in patients and 1.0% in controls in the first experiment, and of 3.3% and 1.2% of all reaction times in the second experiment, respectively). Semantic priming was operationalized as the difference score of RTs between the unrelated and the related condition. Accordingly, indirect semantic priming was operationalized as the difference in RTs of the unrelated and the indirectly related condition.

The main result of the first experiment consists in a significantly larger semantic priming effect in thought-disordered schizophrenic patients (148 ms) as compared to non-thought-disordered schizophrenic patients (74 ms) and normal control subjects (63 ms; see Fig. 3). The experiment directly replicated the finding of Maher et al. (1987), and provided further support for the hypothesis of an activated associative memory in schizophrenia, in particular, in patients who suffer from formal thought disorder.

It should be kept in mind that the related stimuli are strongly related word pairs, i.e., words which are associated by normal people in word association tests. Such associations between prime and target lead to a faster recognition of the target in normal subjects. Schizophrenic patients gain even more by semantic relatedness, i.e., in schizophrenic patients, normal associations are more readily available. The finding therefore implies that schizophrenic thought is *not* characterized by new and different associations, but rather by an increased and inappropriate availability of *normal* associations.

In order to provide further evidence in favor of this view, the mean semantic priming effect of each related word pair was calculated by subtracting the mean RT of the three groups for each related word pair from each group's mean RTs of all non-related word pairs. This procedure allows to compare the priming effects of each word association between the three groups. If schizophrenic patients had a totally different associational network, then the same word pair should produce different priming effects in the three groups, i.e., a particular word pair should prime in one group but not in the other. In order to assess the structure of the entire network as probed by the 63 related word pairs of the experiments, we ordered the word pairs separately for each group according to their priming effects and calculated rank correlations between the three groups (see Fig. 4). These correlations turned out positive and significant. The rank correlation between the control subjects and the non-TD patients was 0.362 ($P = 0.0044$) and the correlation between the controls and the TD patients was 0.347 ($P = 0.0062$). In order to put these correlations into perspective, we used data from a previous study in which we had tested 40 normal controls twice with a delay of about 6 weeks between the tests (Spitzer et al. 1993b). Here the rank correlation between the priming effects of the same word pairs was 0.493 ($P = 0.0001$). Given the fact that this correlation was obtained using data from the same subjects, the correlations between the groups appear high enough to exclude any major differences between the associational networks of (non-thought-disordered *and thought-disordered*) schizophrenic patients and normal controls.

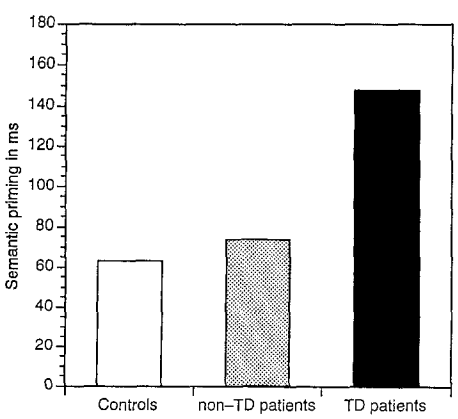

Fig. 3. Semantic priming in control subjects, little or non-thought-disordered (non-TD) and in thought-disordered (TD) schizophrenic patients

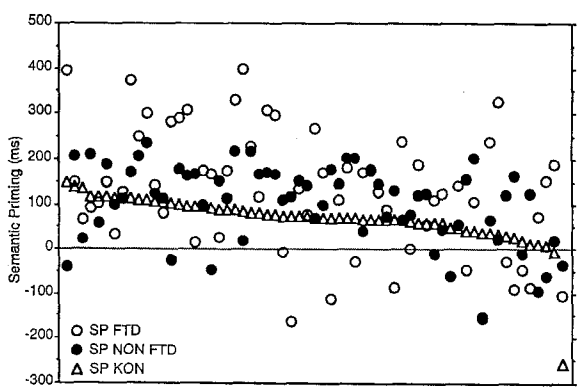

Fig. 4. Semantic priming effect of each single related word pair; the data of all three groups-formal thought-disordered schizophrenic patients (FTD), non-formal thought-disordered schizophrenic patients (NON-FTD), and normal controls (KON) are ordered according to the decreasing priming effect in the control group, such that general trends are visible (from Spitzer et al. 1993b)

Table 1. Demographic and clinical characteristics of the three groups participating in the delayed response task

	Schizophrenic patients	Psychiatric controls	Normal controls
n	25	9	12
Gender (male/female)	16/9	3/6	7/5
Age (years)	29.9 (± 7.9)	35 (± 11.2)	28.6 (± 4.6)
Education (years)	11.0 (± 1.7)	10.4 (± 1.9)	12.3 (± 1.6)
BPRS total	44.9 (± 9.8)	33.8 (± 6.9)	–
BPRS item no. 4 (formal thought disorder)	3.6 (± 1.9)	1 (± 0)	–

The main finding of the second experiment consists in a larger indirect semantic priming effect in schizophrenic patients (58.5 ms) at the short ISI of 0 ms as compared to the control group (12.8 ms). At the longer interval between prime and target (ISI = 500 ms) significant indirect semantic priming was obtained in both groups. The fact that the larger indirect semantic priming effect in schizophrenic patients occurred at 0 ms indicates that it must be mainly due to *automated* processes. With respect to the hypothesis of an activated associational network in schizophrenic patients, this result of increased indirect semantic priming at a short ISI seems to be particularly relevant for the following reasons:

1. The comparatively larger (direct) semantic priming effect obtained in thought-disordered schizophrenic patients (see above) could be interpreted as a non-specific result of the overall slowness of the schizophrenic patients, increasing not only the absolute values of RTs but also the differences. However, if indirect priming and direct priming is measured, the three relevant conditions – related, indirectly related and non-related – produce a *different pattern* of responses instead of a single difference. Hence, the criticism that the increased priming effect are merely due to non-specifically inflated differences is no longer sustainable.

2. While the study of Kwapil et al. (1990), who used error rates and no RTs at all, supports the idea of increased facilitation of word recognition in a semantically related condition and is not subject to the criticism just mentioned (the authors did not use RT as the dependent variable), the experiment does not allow to discern automated vs. controlled processes. Subjects and patients were required to recognize visually degraded words, and may engage in various (and in fact, different) strategies in order to solve the task. On the contrary, using RTs allows distinctions between automated and controlled processes, and therefore provides more information.

3. From a network theory point of view of associative (semantic) memory, it is questionable whether the (most) common association – used as prime in the associated condition to produce semantic priming – is the best probe for the general activation of the network. In normal controls *focused* activation may lead to the activation of the closest adjacent associations (nodes in the semantic network), and hence, produce semantic priming and little, if any, indirect semantic priming (at short ISIs). In contrast, the *unfocused* general activation supposedly present in schizophrenia may not only lead to a more pronounced activation of close associations (nearest nodes), as suggested by Maher et al. (1987) and Manschreck et al. (1988), but may also lead to the activation of more distant nodes.

Delayed response task

Subjects and methods. Twenty-five schizophrenic patients, 9 psychiatric control subjects and 12 normal control subjects participated in the delayed response task. Demographic and clinical characteristics of the three groups are reported in Table 1. The psychiatric controls consisted of patients with the following diagnoses: obsessive-compulsive disorder (1), chronic alcoholism (2), depressive episode (1), manic-depressive disorder (1), benzodiazepine withdrawal (1), and personality disorder (3). Some of the patients were treated with psychotropic agents. All patients were inpatients. All schizophrenic patients received neuroleptic medication. Diagnoses were made by the physician on the ward, supervised by the chief of service, by means of clinical records and actual psychopathology according to the ICD-10 classification system.

The delayed response task was developed to match closely the task used by Luciana et al. (1992). The stimulus material consisted of 16 black dots about 0.7 cm (visual angle: 0.6°) in diameter displayed on a white screen, to which the subjects had to point as accurately as possible. The viewing distance from the screen was about 50 cm[2], and was enforced by accurate placement of the chair only to allow maximal comfort for the subjects during the experiment. Stimulus presentation and data acquisition was controlled by a microcomputer (Apple Macintosh LC II) with a touch-sensitive monitor[3] (a 489 × 640 pixel screen, 32.5 cm in diameter, set to black and white).

During each trial, the screen was blank for 3000 ms and then the subject observed a central fixation cross (visual angle: 1.2°) for 700 ms. Then a black dot appeared in one of the positions specified in Fig. 5 for 200 ms. The positions of the dots were about 10° from the center of the screen. Then the screen either went blank and allowed

[2]Multiple measurements were taken during pilot runs showing a range viewing distances from about 40 to 60 cm. The reported visual angles were calculated using 50 cm

[3]A "Touchstar™ Touchscreen" by Troll Technology, set to the drag mode with no offset and quick averaging, was used

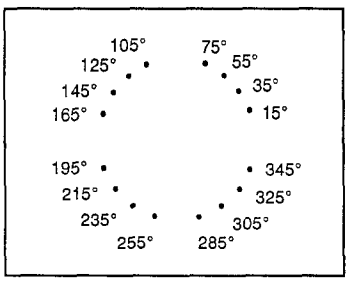

Fig. 5. Positions of the stimuli as used in the task

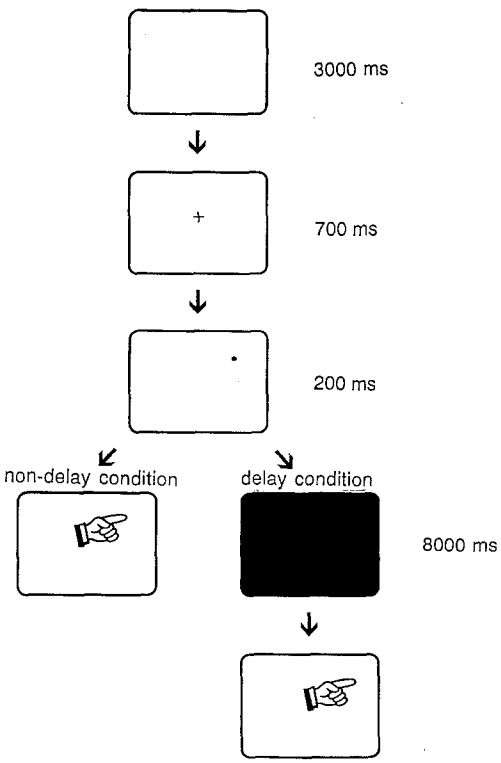

Fig. 6. Sequence of events in a single trial of the delayed response task

for an immediate touch response or it went black for 8 s, after which it went blank, allowing for the delayed touch response (see Fig. 6). Subjects were instructed to make the response as accurately as possible with the index finger of their dominant hand. When the screen was touched, it went black for 100 ms in order to indicate that a response was made and recorded. Then the next trial began with a blank screen (i.e., a pause) for 3000 ms.

In each run, the first four trials were practice trials (two with a delay and two without a delay) and responses were not recorded. After the four trials, subjects were asked if there were still any questions and if this was denied, 32 trials (16 trials with delay and 16 trials without delay) followed such that every stimulus point was presented once in each condition. Condition (delay vs. non-delay) and localization were randomized initially and remained constant in all the experiments.

The computer recorded the x- and y-coordinates of each response. Response errors were calculated using a

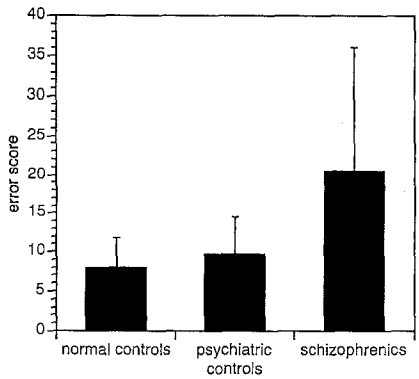

Fig. 7. Mean delay-induced error scores of normal control subjects, psychiatric controls and schizophrenic patients

"spreadsheet program" (Microsoft Excel 4.0), which was set up to provide the accurate positions of each stimulus dot, and calculated the distance of each response from the correct position of the dot using the Pythagorean theorem. The mean of all distances for both the delayed and the non-delayed condition was calculated and the difference (delay condition minus non-delay condition) was calculated. This difference represents the effect of the delay, and is independent of general accuracy or any other general response biases. It is reported here as it was measured by the computer in pixel coordinates.[4]

Results and discussion. The main result of the delayed response study consists of a significant deficit in working memory displayed by schizophrenic patients, as shown in Fig. 7. An ANOVA revealed a significant group effect [$F(2; 43) = 5.723$, $P = 0.0063$] with significant ($P < 0.05$) differences between the schizophrenic patients and the psychiatric as well as the normal control group.

While the limited size of the groups does not allow for any fine-grained analysis of the effect of the delay condition in relation to various clinical features, it seems noteworthy that the correlation between the error score and the BPRS item no. 4 (formal thought disorder) was 0.51. Moreover, as the psychiatric controls represent the oldest and least educated group, the delayed response task does not seem to be influenced by the age and the educational level of the subjects/patients.

Concretism as an exemplary case

Rationale. A bias in the semantic preferences of schizophrenic patients towards the more abstract and/or the more concrete meaning of a word or an utterance has been reported by a number of authors. Although the term "concretism" is hard to find in modern textbooks, clinicians use it to refer to instances of "concrete think-

[4] In order not to introduce rounding errors and to keep data analysis as simple as possible, we refrained from converting the measurements as taken by the computer in actual metric distances before data analysis. According to multiple calibration measurements that were performed with a ruler on the actual screen, a distance of 27 units is equivalent to 1 cm

Table 2. Demographic characteristics of control subjects and patients

Group	Gender (male/female)	Age (years)	Educational level (years of school education)
Normal controls ($n = 43$)	13/30	28.1 (± 10.8)	11.1
Schizophrenic patients ($n = 35$)	24/11	34.4 (± 12.4)	10.5

Table 3. Conditions in the "concretism" experiment

Condition	German example, as used in the study (auditory prime: "Sie hängt alles an die große Glocke")	Similar English example (auditory prime: "He is skating on thin ice")
Concretely related	Klingel	Snow
Abstractly related	Klatsch	Risk
Non-related (concrete noun-abstract noun)	Tisch/Liebe	Chair/grief
Non-word	Tosch	Toble

ing" in cases of schizophrenia and organic mental disorder.

Normal people are capable of *thinking abstract*, which was characterized by Goldstein (1944, p. 19) as voluntary, active, shifting from one aspect to another, keeping in mind simultaneously various aspects, grasping the essential of a given whole, planning, taking possibilities into consideration, detachment from immediate given items. In contrast, concrete thinking is characterized by immediate experience, rather than abstractions (cf. Stone 1988). The meanings of words and expressions are taken in the literal sence, and metaphors are misunderstood, i.e., not taken as metaphors at all.

A failure of schizophrenic patients to take the "abstract attitude" (Goldstein 1944), i.e., a preference for the literal (denotative) meaning as opposed to the metaphorical (connotative) meaning of words in tasks such as interpreting proverbs or selecting word pairs that "fit" together has been reported by a number of authors (Chapman 1960; Cutting and Murphy 1990; Holm-Hadulla and Haug 1984; Meadow et al. 1953). Contrary to such an "underinclusive" bias, the tendency to overgeneralize a given concept, i.e. "overinclusive" thinking, has been noted as a characteristic feature by several authors (Cameron 1939; Payne 1962, 1966). Overinclusive thinking was characterized "by an inability to preserve conceptual boundaries, so that ideas which are only distantly related, or even irrelevant to a concept become incorporated into it [...]. Because of this, thinking becomes more abstract and less precise" (Payne 1966, pp 78–79).

Subjects and methods. The demographic characteristics of the control subjects and patients are shown in Table 2. Only patients with a clearly established diagnosis of schizophrenia participated in the study. All patients were inpatients and received neuroleptic medication. Diagnosis of schizophrenia was made by the physician on the ward, supervised by the chief of service, by means of clinical records and actual psychopathology according to the ICD-10 classification system.

In order to investigate the nature of schizophrenic concretism in detail, the method of lexical decision was used to probe for the activation of literal and metaphoric meanings of metaphoric statements. Normal control subjects and schizophrenic patients had to perform a visual lexical decision task shortly after they had listened to a proverb. The stimulus material consisted of 60 metaphorical statements as primes, and of the following targets (see Table 3): 10 concretely related words (to the last or to the most prominent word of the proverb), 10 metaphorically (abstractly) related words, 10 non-related words (5 of which were concrete words and 5 of which were abstract words), and 30 non-words. For each metaphoric statement 3 words and 3 non-words were selected and different versions of the test were set up, such that each prime sentence was followed by each of the targets. The order of the conditions in each experiment was randomized initially and then remained constant. The different versions were used at random for patients and subjects in order to exclude the effects of particular stimulus words.

Auditory stimuli were generated using sound-digitizing hardward (MacRecorder) and software (SoundEdit) for sampling the sentences spoken by a female voice at 22 kHz with 8-bit sampling. Visual stimuli were set up in 18-point Geneva font using a graphics program (Superpaint). Presentation of stimuli and data acquisition was carried out by a Microcomputer (Apple Macintosh Classic with a 512 × 342 pixel black and white screen 22.5 cm in diameter) and the MacLab program. Target words were displayed in black on a white background. Given a viewing distance of 50 cm, targets appeared at a horizontal visual angle of 1–2° and at a vertical visual angle of approximately 0.5°. Data collection (reaction times and errors) was also automatically controlled by the computer program. The subject's responses consisted of pressing one of two keys on the computer's keyboard ("N" for "no" or "non-word" responses, "B", relabeled as "Y" for "yes" or "word" responses). Subjects used the index and middle finger of their right hand to indicate their responses. The experiments were all self-paced, i.e., the subjects initiated each trial by depressing the computer's mouse button with their left hand.

Prior to the initiation of each trial, the computer screen was blank. Once a trial was initiated, the computer replayed the proverb while the screen was blank. 800 ms after the offset of the auditory prime a fixation point was displayed in the center of the screen for 400 ms, followed by presentation of the target in the middle of the screen until the response was made (in the pilot experiment there was no 800-ms interval between the auditory prime and the fixation point). Following the subject's response, the screen again went blank and a new trial could then be initiated by the subject. A set of 15 practice trials was presented before the actual experiment, which itself contained five practice trials

Table 4. Reaction times and % error (means and standard deviations) of normal controls ($n = 43$) and schizophrenic patients ($n = 35$)

	Normal controls		Schizophrenic patients	
	RT (ms)	% error	RT (ms)	% error
Concretely related word	682.2 (116.4)	1.86 (4.50)	944.3 (280.6)	2.00 (4.73)
Abstractly related word	678.7 (117.4)	1.63 (3.74)	1020.4 (374.6)	2.57 (5.61)
Non-related concrete word	712.0 (148.4)	3.08 (7.19)	1037.6 (360.8)	6.37 (13.55)
Non-related abstract word	721.6 (195.5)	1.16 (5.33)	1023.5 (388.2)	2.67 (8.24)
Non-related word	716.6 (163.8)	2.09 (4.66)	1028.9 (355.3)	4.86 (9.81)
Non-word	764.9 (215.7)	2.32 (3.75)	1074.8 (345.8)	4.98 (8.91)
Concrete semantic priming effect	34.4 (77.01)	0.23 (7.07)	84.6 (142.99)	2.85 (8.25)
Abstract semantic priming effect	37.9 (83.42)	0.47 (5.32)	8.5 (204.48)	2.28 (11.40)

at the beginning, from which responses were not recorded.

Results and discussion. RTs were calculated from the correct responses of the subjects. RTs that were greater than twice a given subject's mean RT for a particular condition were omitted from further analyses. This trimming criterion resulted in the exclusion of 0.34% and 1.80% of all RTs in the control group and the patient group, respectively, from further analysis. Each subject's mean RTs (and %-error rates) per ISI and condition were treated as raw data and subjected to further statistical analysis. Reaction times and error rates are presented in Table 4.

Semantic priming in both the concrete and the abstract condition was operationalized as the difference score of RTs between the unrelated and the related condition. Separate ANOVAs were performed on both data sets (controls and patients) to test for possible interaction effects of stimulus list with prime-target relation (condition) on the RTs of subjects. No list effect was detected.

Further analysis focused on the priming effects in the two groups. *t*-tests were used to test for specific effects of the abstract and concrete conditions compared to the non-related word condition (i.e, the semantic priming effects) in control subjects and in schizophrenic patients. Significant semantic priming effects for the concretely related words were found in both groups (34.4 ms; $t = 2.931$; $P = 0.0054$; 84.6 ms; $t = 3.499$; $P = 0.0013$). The abstractly related word condition produced a significant priming effect only in the control subjects (37.9 ms; $t = 2.978$; $P = 0.0048$).

In order to exclude an effect of the kind of word (abstract vs. concrete) in the absence of any priming condition, RTs to the abstract and concrete words in the non-related condition were calculated separately. Two *t*-tests did not reveal a significant effect of abstractness/concreteness per se in both normal control subjects and schizophrenic patients (14.1 ms; $t = 0.37$; $P = 0.714$; 9.51 ms; $t = 0.516$; $P = 0.609$). The negative value of the difference of the effect is to indicate that, contrary to the control group, the patients were (non-significantly) faster in recognizing the non-related abstract words than the non-related concrete words. Hence, the differences between the abstractly and concretely related words cannot be interpreted as effects of abstractness or concreteness (and related variables, such as word frequency, which tends to be higher for concrete words).

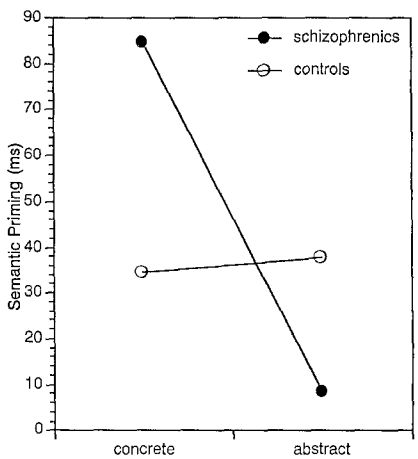

Fig. 8. Concrete and abstract priming effects in normal control subjects and in schizophrenic patients

The abstract and concrete priming effects in both groups are displayed in Fig. 8. A two-factor ANOVA with group (controls vs. patients) and condition (abstract vs. concrete) as within subject factor showed a significant interaction [$F(1;76) = 5.786$, $P < 0.05$], indicating a group-dependent difference in the priming effect of concrete and abstract meanings. Whereas in normal control subjects both, the concrete and the abstract meaning produce a significant priming effect, in schizophrenic patients only a concrete priming effect could be detected.

As there were significant differences between the controls and the patients with respect to education and gender, we calculated the priming effects separately for males and females, and for subjects scoring high, medium, and low on education for both groups. Separate one-way ANOVAs did not reveal any significant differences due to these variables. Likewise, two two-way ANOVAs with group (controls vs. patients) and gender

and with group (controls vs. patients) and education (high, medium, and low) as independent variables and with abstract and concrete priming as dependent variables neither showed any significant effects of gender and education nor any significant interactions.

The main findings of this experiment may be interpreted as follows: a comparatively large concrete priming effect in schizophrenic patients is in line with the above-mentioned result of lexical decision studies on semantic and indirect semantic priming. Hence, this large concrete semantic priming effect may be taken as one more piece of evidence in favor of the activated semantic associations network hypothesis. The concrete meaning of a metaphoric statement is not only more prevalent relative to the abstract meaning (because the abstract meaning has not been produced by the patient), but also is activated to a higher degree than in normal controls. This might explain the clinical observation that schizophrenic concretism is somewhat different from concretism displayed by "organic" patients in that schizophrenic patients may focus on a concrete aspect of a remote feature of a concept (Holm-Hadulla 1982). The finding of a significant abstract priming effect only in normal control subjects corresponds directly to the clinical observation of concretism in schizophrenic patients. The study has clearly demonstrated that little or no abstract meaning is activated in schizophrenic patients more than a second after a metaphoric statement has been uttered; instead, one or a few concrete meanings are highly active. Data from a similar previous study (for details, cf. Spitzer et al. 1993c) which had pilot character, may shed more light on the results. Forty normal control subjects (15 males, 25 females; mean age; 26.85 ± 9.15 years; mean educational level; 11.0 years of school) performed a task almost identical to the one of the experiment just reported. The difference consisted in the interval between prime and target which was only 400 ms (i.e., there was no 800-ms blank between the offset of the auditory prime sentence and the onset of the fixation point). Under these conditions, a significant concrete priming effect, but no significant abstract priming effect was obtained (only a trend was detectable). This corresponds with already established differences in decoding time of literal and metaphoric speech (cf. Chaika 1990, pp. 108–116) and suggests that the metaphoric meaning needs some time to "build up" (only then being effective as a prime) in normal control subjects. During this time, the meanings of the words have to be kept in mind – a task which supposedly involves working memory. Therefore, we propose that while the prominent concrete priming effect in schizophrenic patients indicates an overactive associative memory, the lack of a significant abstract priming effect signifies a deficit in working memory.

General discussion

In this discussion, first, the above-mentioned phenomena of schizophrenic thought pathology will be reconciled with the concepts of working and associative memory in an attempt to provide a unified explanation for a number of seemingly unrelated phenomena. Secondly, the theoretical and practical implications of the findings will be discussed. Finally, the paradigmatic function of this work

Table 5. Features of associative and working memory, and their possible involvement in schizophrenic thought pathology

	Associative memory	Working memory
Capacity	High	Limited
Duration	Years	Seconds
Relevant task	Word association test lexical decision task with related or indirectly related primes	Delayed response task
Anatomy	Frontal lobe, as demonstrated by PET studies	Frontal lobe, as demonstrated by single cell recordings, lesion studies and PET in animals
Involvement of dopamine	Likely	Demonstrated in animals and human beings
Effect of dopaminergic activation/deactivation	Increased focus (i.e., suppression of irrelevant associations)/decreased focus (i.e., lack of inhibition of irrelevant associations)	Improvement/deterioration
Role in normal thought	Stores semantic (and possibly other) features of lexical items	Holds immediately relevant information "on line", plans, executes goal-directed motor behavior
Dysfunction in schizophrenia	Unfocused (heightened) activation or lack of inhibition	Reduced capacity and/or accessibility

for schizophrenia research within a cognitive neuroscience framework will be highlighted. Before this is done, a look at Table 5 may serve to briefly recall some of the salient features of associative and working memory.

A parsimonious explanation for a plethora of phenomena

We have provided experimental evidence that a variety of schizophrenic symptoms related to thought processes can be explained in terms of associative and working memory. A heightened or disinhibited associative memory as experimentally demonstrated by more semantic priming and automatic indirect semantic priming fits nicely with the clinical observations of "strange", oblique and often non-related associations and thought processes in schizophrenic patients. Even if only the second next node is reached in the semantic network (for example: from "lion" to "tiger" to "stripes"), it may not be possible to reconstruct the path of thought for the listener, and he therefore may speak of unrelated thoughts following one another with no logical or meaningful connecting thread, as was already suspected by Bleuler (1911, P. 26): "I suspect that only the lack of sufficient observation has been responsible for our inability to demonstrate them more frequently in the thought-processes of our patients."

"Overinclusive" thinking may also be easily explained in terms of an activated semantic network in which associations proceed quickly thereby transgressing the usual boundaries of concepts. In contrast to the focused activity of the network in normal thought, its unfocused activity may lead to the activation of remote aspects of a concept and impedes the establishment of clear-cut meanings. However, the quick accessibility of "remote" aspects of things/concepts may be helpful: in problem-solving tasks that require the unusual use of an object, schizophrenic patients actually do *better* than normal control subjects (Poljakov 1973).[5]

The lack of integrative function, goal-directedness, adequate attention, drive, and general intellectual capacity can be directly related to working memory dysfunction. If less information can be held "on line" for immediate use, complex tasks cannot be performed and behavior will generally be guided to a greater extent by immediate perceptual cues rather than internally generated, and kept, goals. Beringer (1924, 1926) described the "diminished intentional span" of schizophrenic patients as most characteristic of the patient's deficits, which may be interpreted as merely another way of referring to a reduced capacity and/or accessibility of working memory in these patients. The "underinclusive" use of a concept, i.e., the disregard of several of its meanings relevant to a given task, may also be explained as a failure to keep all these aspects in working memory simultaneously.

In addition to the clinical correlates of dysfunctions of associative memory and dysfunctions of working memory, a number of features of schizophrenic thought may be best explained by a combined dysfunction of both types of memory. As we have already seen, the peculiar kind of schizophrenic concretism, i.e., the tendency to take a remote aspect of a concept overly concrete, can easily be explained as the combined effect of a disinhibited (unfocused) associative memory and a reduced capacity of working memory. Furthermore, the clinically highly relevant aspect of schizophrenic thought and behavior, the patients' ubiquitous lack of sensitivity to context (cf. Chapman et al. 1964; de Silva and Hemsley 1977), can easily be accounted for in terms of working and associative memory. The patients' failure to make appropriate use of contextual evidence in the production and understanding of language as well as in goal-directed behavior may be caused by the inability to keep relevant information "in mind" while pursuing a certain project. This relevant information has to be represented in working memory, since it has to be permanently used to guide behavior in the absence of immediate perceptual cues or even despite perceptual cues that suggest some alternative behavior.

Some implications for future research and clinical practice

For decades, psychologists have tried to go beyond the "surface" of overt pathological behavior of schizophrenic patients. Behavioral methods have been widely used, such as the determination of RTs and error rates in tachistoscopic paradigms. In most of these paradigms, the patients tended to display longer RTs, more errors, and a greater variation of the data compared to normal subjects (cf. Goldberg et al. 1991). Because little could be inferred from such non-specific or even trivial findings, theories of the underlying processes in schizophrenia suffered from a lack of critical appraisal and tended to come and go like "fashions of thought". As has been correctly pointed out, it was only too easy to add another concept or subsystem or "box" through which the information flows (cf. Shallice, in Hemsley 1992). Moreover, findings from other, non-psychological areas of research, such as the involvement of the neurotransmitter dopamine established by psychopharmacological studies, could not be linked to the psychopathological level. Given this state of affairs, the only plausible reserach strategy seemed to consist of attempts to *correlate* various psychological measures of "deficit" with measures of spontaneous overt behavior (i.e., clinical ratings) and with biological measures.

This has changed with the advent of clearly and narrowly defined cognitive tasks whose anatomical and even neurochemical bases are known by research on animal models or by functional brain imaging techniques. With respect to schizophrenia in particular, tasks which depart from the lesion-based "deficit model" so widely employed

[5] In most everyday tasks, however, a focused activity of associative memory is required. In fact, clinical improvement is accompanied by an increased focus of activity, as can be demonstrated by a reduced semantic priming effect on improvement (cf. Spitzer et al. 1993b) and, for example, by a study of Storms (1977), who found that clinical improvement of good premorbid schizophrenic patients was accompanied by an increase in word association commonalities, i.e., by an increase of more "normal" associations in the word association test

in neuropsychological schizophrenia research, are of special interest (cf. Hemsley 1992). This is why the hypothesis of an activated or disinhibited associative memory in schizophrenia deserves further studies. For example, with appropriate timing and stimulus material, it should be possible to construct test procedures in which normals show no facilitation while schizophrenic patients display major facilitatory effects. Using such supposedly rather robust paradigms, clinical correlates of facilitatory effects should be investigated. Ultimately, results from such tests may turn out to be better independent variables for research purposes than clinical ratings or diagnoses derived from the use of diagnostic manuals. As Maas and Katz (1992) pointed out in a recent editorial on the relation between neurobiology and psychopathology, the point of reference in this research is the symptomatology of schizophrenia, not the diagnostic category of schizophrenia.

While the delayed response task only produces another "deficit", it is important to realize that this deficit is specific to the delay (since everthing else is equal and the delay-induced intra-individual difference is taken as the dependent variable). Moreover, the delayed response task is among the most thoroughly investigated neuropsychological tasks with a clear anatomy, physiology, and neurochemistry. The very fact of its simplicity makes it suitable for animals and humans, and provides the additional advantage that in humans it is unlikely to be influenced by intelligence and cultural background. Finally, the delayed response task cannot be learned, as opposed to, for example, the Wisconsin cart sorting technique, which could not be performed on a daily bases (e.g. for monitoring purposes).

With respect to the linkages between experimental psychological findings and neurobiological data, the following points are of special interest: While many aspects of the involvement of dopamine in mental processes, and in particular in the genesis of schizophrenia are still unknown, some remarks may be made. Cohen and Servan-Schreiber's (1992) model of how a down regulation of dopaminergic activity in the frontal lobe decreases the functional focus of cortical neuronal networks and hence, reduces their ability to keep relevant contextual information "on line", may be regarded as a preliminary attempt to relate psychological functioning to biologically plausible mathematical models of neuronal circuits (cf. Kosslyn and König 1992). In line with one of the assumptions made in this model, i.e., that low dopaminergic cortical activation causes unfocused functioning of neuronal networks, are studies of word associations on awakenings from REM sleep (which is characterized by a *low* dopamine/high acetylcholine activation).

The result of a comparatively larger semantic priming effect on awakenings from REM sleep can be interpreted as evidence for the involvement of dopamine in focuses associative functioning (see Spitzer et al. 1991, 1992). Moreover, Luciana et al. (1992) have demonstrated that the D_2 agonist bromocriptine *increases* working memory in normal controls (i.e., improves performance in a delayed response task similar to the one used in the experiment reported in this paper). This is in line with the hypothesis proposed by several authors that negative symptoms in schizophrenia are due to a *decrease* in dopaminergic activity rather than an increase (Crow 1980; Mackay 1980; Davis et al. 1991; Grace 1991). In particular, Davis et al. (1991) have proposed that negative symptoms are caused by low prefrontal dopamine activity, which leads to excessive dopamine activity in mesolimbic dopaminergic neurons, which may eventually lead to positive symptoms. Similarly, Grace (1991) has suggested that schizophrenic patients suffer from a diminished "tonic" dopaminergic striatal dopamine release, consecutive up-regulation of striatal postsynaptic dopamine receptors and hence, increased responses to "phasic" striatal dopaminergic activation due to environmental stress. This would result in both, low dopaminergic negative symptoms and stress-related hyperdopaminergic positive symptoms.

In order to clarify many of these issues (including the short-term and long-term effects of medication on the measures we have discussed), experimental approaches with normal subjects should be further employed to study the effects of dopamine agonists and antagonists on working memory in normals and schizophrenic patients. In particular, as it is known that the D_2 agonist bromocriptine has beneficial effects in some chronic schizophrenic patients (Levi-Minzi et al. 1991), it should be investigated whether delayed response tasks can be used, possibly together with neurohumoral measures (such as the prolactin response to haloperidol challenge; cf. Keks et al. 1992) to assess dopamine/frontal lobe functioning in schizophrenic patients.

In addition, the signal-to-noise ratio of all the tests described in this paper can be improved by adequate timing of the adequate stimulus material, using the methods which have already been developed to choose the most sensitive items for paper and pencil tests and rating scales. Of course, data on the specificity of the methods and on the sensitivity to psychopathological states and other possibly relevant data (e.g., demographic characteristics of the subject) need to be collected.

Concluding remarks: cognitive neuroscience and schizophrenia research

Within the last few years, our understanding of how the brain performs the multitude of computations necessary to face and act upon reality has dramatically increased. "Cognitive neuroscience" is but the latest name for the continuing effort to relate brain and mind. Like in "physiological psychology", "behavioral neuroscience", and "neuropsychology", the aim of "cognitive neuroscience" is to carve the mind at its joints. It was the aim of this paper to show that by putting behavioral data – reaction times and error rates – into the right perspective, more can be gained than merely correlations between some "deficit" with some psychiatric diagnostic category, or some supposedly underlying malfunctioning brain process, respectively. Several phenomena and several experiments were discussed in a cognitive neuroscience framework, in which, by definition of the term "cognitive neuroscience", neurobiological, information-theoretical and psychological data are related in such a way

to allow mutual constraints. This means that *arguments,* and not mere correlations, can go from overt behavior to transmitters and neurons – and back. Such arguments not only can produce parsimonious explanations of seemingly unrelated clinical phenomena. This is what "interpretive" psychopathological accounts of schizophrenic symptoms were able to do for long. The advantage of the cognitive neuroscience approach to psychopathology is that psychological and neurobiological data can be related in a fruitful way. Most importantly for the near future, new hypotheses, such as the involvement of dopamine activity in the functioning of associative and working memory, can be directly subjected to laboratory tests. In the long run, the understanding of psychopathological phenomena in neurocognitive terms may provide us with new diagnostic and possibly even therapeutic insights.

There is still a long way to go from the present state of experimental psychopathological findings in schizophrenia to the application of such methods in clinical practice. However, we have a much clearer view of how this way looks now than we did a decade ago.

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