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Use of a sequencing task designed to stress the supervisory system in schizophrenic subjects

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ABSTRACT

Background. We investigated whether schizophrenic subjects are impaired in non-routine behaviour because of the dysfunction of a general executive component labelled, in neuropsychological terms, the supervisory system.

Methods. A specific verbal sequencing test was designed for this purpose. Subjects had to perform sequential reasoning with verbal material. Each test sequence consisted of a series of words presented in jumbled order. The construction of some sequences had to be done using familiar routine associations (valid conditions). In contrast, some other sequences required the overriding selection of familiar routine associations, which were inappropriate within the general context of the task (invalid conditions). Twenty verbal sequences (10 valid–10 invalid) were administered. Thirty-seven DMS-IV schizophrenic patients and 21 normal volunteers matched for age and educational level were recruited.

Results. Compared to the control group the schizophrenic group was impaired in both valid and invalid conditions. The number of 'capture errors' specific to supervisory system failure was significantly higher in the schizophrenic group and only the schizophrenic patients had significantly fewer correct sequences in invalid conditions than in valid conditions. Poor performance in invalid conditions alone was observed only among the schizophrenic subjects without a general cognitive defect.

Conclusions. These findings suggest that sequencing procedures requiring an executive input are impaired in schizophrenia.

INTRODUCTION

Clinicians have frequently observed that schizophrenic subjects have difficulties in generating and implementing plans or solving problems whose solutions are not readily apparent (Elliot & Sahakian, 1995; Weinberger, 1996). To elucidate the basis for this deficit, interest has recently focused on cognitive operations thought to be involved in a 'supervisory system'. The frontal lobes are assumed to play a major role in programming, regulating and verifying activity (Luria, 1966). The model developed by Norman & Shallice (1986) (Burgess & Shallice, 1994) seems to be particularly relevant to Luria's theory. The assumption in this model is that the processes involved in the cognitive control of action and thought operations can be divided into two levels (Shallice, 1988; Shallice & Burgess, 1991*a*). The first level is related to routine activities where selected learned triggering procedures are sufficient to carry out the task satisfactorily. Basic cognitive operations are carried out in modules controlled by routine programs (Schemata) for the control of over-learned skills. Competition between schemata is controlled by a lateral inhibitory mechanism (contention scheduling). The second level, known as the supervisory system and consisting

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of many component processes, is needed when routine operations are insufficient. Stuss *et al.* (1995) have indicated that this system is required in the following four circumstances: when there is no known solution to the task at hand; when weakly activated schemata are evoked; when specific selection among schemata is necessary; and, when inappropriate schemata must be inhibited. One role of the supervisory system is to adjust contention scheduling, particularly when a routine schema elicited by a strong environmental trigger must be over-ridden. 'Capture errors' or failures in appropriate selection of responses occur if the supervisory system is inoperative when an incorrect schema becomes strongly activated in contention scheduling.

To determine whether or not the supervisory system is operative, it is possible to use sequencing tasks such as picture or sentence arrangement tests (Wechsler, 1981; Kaplan, 1991). Good performance in this type of test is related to the frontal lobe (Petrides & Milner, 1982; Stuss *et al.* 1994), which plays a significant role in the ability to see relationships between events, establish priorities and order activities chronologically. Della Malva *et al.* (1993) hypothesized that sequencing tasks in which routine associations must not be over-ridden would not necessitate intervention of the supervisory system. In contrast, sequencing tasks which require over-riding selection of familiar routine associations (when these are inappropriate within the general context of the task) necessitate the intervention of the supervisory system to prevent capture errors. Results of the Della Malva study indicate that patients with focal frontal lobe lesions perform significantly less well than normal control subjects and patients with posterior brain lesions in conditions that may lead to capture errors.

The aims of this study were to compare the performance of schizophrenic patients and healthy subjects in two versions of a verbal sequencing task, only one of which was designed to elicit the supervisory system.

METHOD

Population

Thirty-seven French-mother-tongue psychiatric patients who satisfied the DSM-IV criteria (American Psychiatric Association, 1994) for chronic schizophrenia were evaluated in the Memory Center of Nice University Department of Psychiatry with their informed consent. Patients with an organic brain disorder, mental retardation, a history of severe head trauma or a history of alcohol or drug abuse/dependence were excluded from the study. None of the patients had acute exacerbations during the previous month. Ten patients were drug-free, nine were on neuroleptics and 18 were receiving a neuroleptic plus an anticholinergic agent. All the patients on treatment had to have been on stable doses for at least a month. Symptoms were rated using scales for the assessment of negative (SANS) and positive (SAPS) symptoms (Andreasen, 1983*a*, *b*). Furthermore, factorial analysis of these two scales (Andreasen *et al.* 1995) made it possible to evaluate separately the negative, productive and disorganized dimensions.

Twenty-four healthy French-mother-tongue normal volunteers matched with the schizophrenic population for age and education formed the control group. Major social class-of-origin mismatches were excluded on the basis of an interview. All the subjects were screened with a medical questionnaire and physical examination to rule out previous neurological or psychiatric disease, significant head injury and alcohol or drug abuse.

Experimental sequencing task

Basically, sentence arrangement is a verbal analogue to picture arrangement. This test examines the capacity to perform sequential reasoning with verbal material and to make syntactically correct constructions. The words of a sentence are laid out in scrambled order with instructions to deduce a correct sentence. The overall experimental task consist of a series of 20 written sentences to be constructed. Each sentence is composed of six words and each word is presented on a separate card. Each sentence includes a strong association based on meaningfulness or frequent occurrence between the information on two of the cards. For example, word pairs such as '*téléphone sonne*' and '*citron pressé*' have a strong semantic association in French. Some associations were valid in the context of the sentence while others were invalid. Invalid associations, which had to be broken to complete the task correctly, were

called 'capture' sequences (Della Malva *et al.* 1993). An example of a capture sequence with an association that had to be separated to make a correct response is: '***sable/chaud***/*fait/car il/le/brûle*', which gives; '*le* ***sable*** *brûle car il fait* ***chaud***' (an example in English used by Della Malva is: 'of/full/the/was/**coffee/cup**', which gives, 'the **cup** was full of **coffee**'). An example of a valid (non-capture) association is: '***feu/vert***/*passent/les/voitures/au*', which gives; '*les voitures passent au* ***feu vert***' (**green/light**/pass by/cars/the/at', which gives, 'cars pass by at the **green light**').

After a training sentence (without word association) to ensure that the subject understood the instructions, the 20 sequences were presented (10 with valid and 10 with invalid associations). The first four sequences included valid associations to induce the use of routine schemata. The fifth included an invalid association and the last 15 sequences were presented in random order. The maximum time allowed to find the correct answer was 180 seconds.

The words and associations were selected in the following way for each sequence. All the words were sampled from the Brulex word frequency norms (computerized lexical data base for the French language, 1990). No words with frequencies lower than 3·95/1000000 (corresponding to the French word 'crab') were used.

The abstractness of each word was evaluated with a Likert-style questionnaire administered to 30 normal subjects (16 with more and 14 with less than 12 years of education). A word was dropped if more than one-third of the group judged it as being abstract.

The affective valence (positive, negative, neutral or ambiguous) of each sentence was evaluated in the same way by the same control group to ensure a balance between the valid and invalid sequences. To eliminate competitive associations within the sentences themselves, a Likert-style questionnaire was administered to 42 normal, test-naive French-speaking men and women (21 with more and 21 with less than 12 years of education). Combination word pairs were derived from each sentence, i.e. the associated pair (valid or invalid); and other possible combinations of word pairs were derived from the sequence (nouns, verbs, adverbs and adjectives). For example, three combination word pairs derived from the sentence '*tu décroches quand le téléphone sonne*' were: '*téléphone–décroches*'; '*sonne–décroches*'; '*téléphone–sonne*' ('When the telephone rings you pick it up': 'telephone–pick-up'; 'rings–pick up'; 'telephone–rings'). The results obtained with this normative population sample supported the preponderance of the target association within the valid and invalid sequences.

Dependent measures consisted of: (1) the number of correct sequences (correct valid sequences/correct invalid sequences); (2) the number of specific (CE) 'capture errors' (when the subject is unable to break a strong association) and non-specific (NSE) errors (when the error is due to another mistake which is not specific to the processes studied in the invalid conditions, i.e. syntactic or grammatical errors, sentences not constructed before the default time score, etc.) in the invalid conditions; (3) the difference (IVdif) between the number of correct responses in the invalid conditions minus the number of correct responses in the valid conditions; (4) the mean total time required to complete the 10 sequences with valid conditions (valid time) and the 10 sequences with invalid conditions (invalid time).

Neuropsychological assessment

The following complementary tests were administered: (1) IQ was estimated with a short-form (Silverstein, 1982) of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), including the vocabulary, block design, arithmetic and picture arrangement subtests; (2) digit span; and (3) Trails Making Test A and B (Reitan, 1958). The battery of tests usually took 2 hours to complete and was administered in 1 day. The subjects rested when they felt the need to do so.

Data analysis

Within each group, the mean and standard deviation were calculated for each continuous demographical, clinical and neuropsychological variable. Data were transformed when assumption of normality or homogeneity of variance was violated. The mean total time and number of correct sequences were analysed with two-way ANOVA with a between-subjects factor (group) and a within-subjects factor (valid/invalid conditions) with a *post hoc* test. Capture

errors (CE) and differences between the number of correct responses (IVdif) were analysed with one-way ANOVA. The same type of analysis was performed on a high-IQ schizophrenic subpopulation composed of subjects not on treatment and normal subjects with an IQ < 105 (105 represents the highest IQ score obtained in the subgroup of medication-free schizophrenics). Other data were subjected to *t* tests. A Pearson correlation coefficient matrix was calculated for clinical dimensions and neuropsychological tests.

RESULTS

Table 1 summarizes the demographic and neuropsychological characteristics of the schizophrenic and control groups. There were no group differences in age and education but schizophrenic subjects had significantly lower performances than the control subjects in all the neuropsychological tests with the exception of the digit span. In the schizophrenic group the mean duration of illness was 5 years 4 months, the SANS total score was 56·7 (S.D. = 17·7) and the SAPS total score was 35·3 (S.D. = 21).

Table 2 shows the results of the sequencing task. The schizophrenic group produced significantly fewer correct sequences than the control group in both valid and invalid conditions; group effect *F* ratio (30·33; $P = 0.0001$ and condition effect *F* ratio (10·53); $P = 0.002$ (group × condition: *F* ratio (5·03) $P = 0.027$). IVdif, the number of CE and NSE errors in invalid conditions were significantly higher in the schizophrenic group than in the control group. Both groups took longer to complete the sequencing task in invalid conditions (condition effect: *F* ratio (35·5) $P < 0.001$); in addition, whether the associations were valid or invalid the schizophrenic group took longer to complete

Table 1. *Age, sex, number of years of education and neuropsychological test results in schizophrenic patients and normal subjects (mean and standard error)*

	Normal controls $N = 21$	Schizophrenic subjects $N = 37$
Age (years)	31·2 (8·4)	30·1 (8·1)
Sex	8 F//13 M	10 F//21 M
Years of education	10·5 (2·3)	10 (2·5)
IQ	103 (7·9)	83·9 (12·3)***
Order digit span	5·63 (1·3)	4·41 (0·9)
Trail Making Test A (time in seconds)	25·3 (9·4)	45·3 (20·2)***
Trail Making Test B (time in seconds)	61·6 (23·5)	134·9 (52·3)***

*** $P < 0.001$.

Table 2. *Patterns of verbal sequencing test results in the schizophrenic and control groups (mean and standard error)*

	Control subjects $N = 21$	Schizophrenic subjects $N = 37$
Correct valid sequences	9·9 (0·3)	8·9 (1·2)***
Correct invalid sequences	9·6 (0·5)	7·4 (2·2)***
Valid time	74·1 (27)	139·3 (74·1)***
Invalid time	153·8 (61·9)	262·4 (126·8)***
Capture error	0·23 (0·29)	1·7 (0·21)
	one-way ANOVA	*F* ratio (16·6; $P = 0.0001$
IVdif	−0·28 (0·37)	−1·56 (0·27)
	one-way ANOVA	*F* ratio (7·63); $P = 0.008$

*** $P < 0.001$.

Valid time = time to complete the 10 sequences with valid conditions.

Invalid time = time to complete the 10 sequences with invalid conditions.

IVdif = difference between the number of correct responses during the invalid conditions minus the number of correct responses during the valid conditions.

Table 3. *Age, years of education, IQ and patterns of verbal sequencing test results in a subgroup of treatment-free schizophrenic patients and a subgroup of control subjects with IQ < 105 (mean and standard error)*

	Control subjects $N = 12$	Schizophrenic subjects $N = 10$
Age	30·7 (7·9)	29·7 (9·1)
Years of education	9·7 (2·3)	10·2 (2·8)
IQ	97·5 (5·6)	90·3 (13·7)
Correct valid sequences	9·8 (0·3)	9·4 (1)
Correct invalid sequences	9·4 (0·6)	8 (1·9)*
Valid time	78·7 (30·4)	104·6 (35·2)
Invalid time	154·1 (45)	241·2 (127·7)*
Capture errors	0·41 (0·33)	1·6 (0·37)
	one-way ANOVA	*F* ratio (5·59); $P = 0.02$
IVdif	−0·4 (0·31)	−1·4 (0·34)
	one-way ANOVA	*F* ratio (4·52); $P = 0.04$

* $P < 0.05$.

IVdif = difference between the number of correct responses during the invalid conditions minus the number of correct responses during the valid conditions.

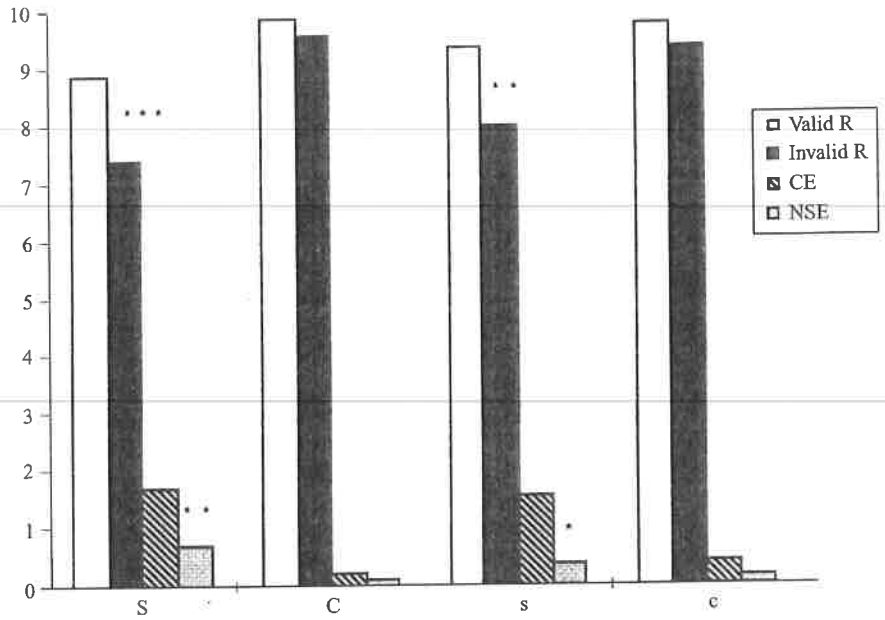

FIG. 1. Mean number of correct sequences obtained by each group of subjects divided by the 'valid' and 'invalid' conditions. Mean number of capture errors (CE) and non-specific errors (NSE) during the invalid conditions. (Total population: S, all schizophrenic subjects; C, all control subjects. Selected population: s, treatment-free schizophrenic subjects; c, control subjects with IQ < 105.) Paired Student *t* test: *** $P < 0{\cdot}001$; ** $P < 0{\cdot}01$; * $P < 0{\cdot}05$.

Table 4. *Correlation coefficients between global IQ and its subtests (vocabulary, picture arrangement and block design) and time scores in Trail Making Tests A and B (TMT A/B) valid (VT) and invalid (IT) total time required to complete the sequences for the schizophrenic subjects* (N = 37) *and the control subjects* (N = 21)

	IQ *r*	Vocabulary *r*	Picture arrangement *r*	Block design *r*	Arithmetic *r*
Schizophrenic group					
VT	−0·51**	−0·57***	−0·53**	−0·35*	NS
IT	−0·57***	NS	−0·38*	−0·56*	NS
TMTA	−0·45**	NS	NS	0·50**	−0·35*
TMT B	−0·68***	−0·49**	−0·60***	0·54***	−0·37*
Control group					
VT	NS	0·47*	NS	NS	NS
IT	NS	NS	NS	NS	NS
TMTA	NS	NS	NS	0·52*	NS
TMT B	0·56*	NS	0·77***	0·51*	NS

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$; NS = not significant.

the sequencing task (group effect: *F* ratio (26·08); $P < 0{\cdot}001$). The interaction effect failed to reach statistical significance (group × condition: *F* ratio (1·62); $P = 0{\cdot}205$).

To control for the possible effects of IQ and medication, a subgroup of 10 treatment-free schizophrenic and 12 control subjects with an IQ lower than 105 was analysed. Table 3 shows the neuropsychological results in these subgroups. The interaction was significant for the number of correct responses in the sequencing test (group × condition: *F* ratio (6·41); $P = 0{\cdot}014$) but not for the response time. *Post hoc* tests revealed that, in this subpopulation, schizophrenic patients differed from control subjects only in invalid conditions. Furthermore, the

IVdif and the number of specific errors (CE) in invalid conditions were significantly higher in the schizophrenic group than in the control group.

As shown in Fig. 1, the schizophrenic patients showed significant differences in the number of correct responses divided according to the conditions valid/invalid (paired t test: $t = 4{\cdot}62$, $P = 0{\cdot}001$ and for the 10 selected schizophrenic subjects $t = 3{\cdot}27$, $P = 0{\cdot}009$). The difference was not significant for the control group (paired t test: $t = 2{\cdot}03$, $P = 0{\cdot}055$ and for the 12 selected control subjects $t = 1{\cdot}82$, $P = 0{\cdot}09$). The schizophrenic patients produced significantly more capture errors than non-specific errors in the invalid conditions (paired t test: $t = 3{\cdot}41$, $P = 0{\cdot}002$ and for the 10 selected schizophrenic subjects $t = 2{\cdot}57$, $P = 0{\cdot}03$). This was not the case for the control subjects (paired t test: $t = 0{\cdot}81$, $P = 0{\cdot}42$ and for the 12 selected control subjects $t = 1{\cdot}39$, $P = 0{\cdot}19$).

Table 4 shows correlations between the neuropsychological test results. In the control group, IQ only correlated with Trail B. In contrast, in the schizophrenic group IQ correlated with all the parameters in the sequencing task and with trails A and B. The only significant correlation with clinical symptoms was between the disorganized dimension and the mean total time required to complete the 10 invalid sequences ($r = 0{\cdot}35$, $P < 0{\cdot}05$).

DISCUSSION

Fuster (1985) suggested that the prefrontal cortex is particularly involved in unpredictable or unforeseen events, i.e. events or actions that have a low probability of occurring in the context in which the behaviour takes place. This assumption is compatible with the putative supervisory system (Shallice & Burgess, 1991*b*) and its role in the inhibition of ongoing activity involving routine schemata that are inappropriate to the task.

Clinical observation of schizophrenic subjects suggests that many such patients have problems with daily life activities, particularly those involving non-automatic actions. A recent review of the literature showed that among the neurocognitive deficiencies from which schizophrenic patients suffer, verbal processes and particularly verbal memory are the best predictors of defective functional and social activities (Green, 1996). An impairment of executive functions has often been described in schizophrenia, on the basis of tests like the Wisconsin Card Sort Test, verbal fluency test and Tower of Hanoi task (for a review see Elliot & Sahakian, 1995); to our knowledge, however, such an impairment has never been observed in a verbal sequencing task designed to accentuate 'capture errors'.

We used such a paradigm in this study, in which subjects had to rearrange words into correct sentences. The words of each sentence were presented to all subjects in the same jumbled order. The first two words, presented side by side, were characterized by a strong semantic link. In certain cases the subject had to use this pair automatically to construct the sentence (valid conditions), while in others the 'automatic' association had to be broken, thereby calling on a supervisory process (invalid conditions).

The schizophrenic subjects differed significantly from the healthy controls in their capacity to arrange the words into correct sentences, both in 'valid' and 'invalid' conditions. The control subjects showed no difference between the number of correct sentences found in valid and invalid conditions, while the schizophrenic patients found significantly fewer correct sentences in invalid conditions. In addition, the number of 'capture errors' specific to the supervisory system failure was significantly higher in the schizophrenic group. In invalid conditions the 'capture error parameter' may conceivably increase the overall difficulty of the task. This hypothesis was evaluated with the difference (IVdif) between the number of correct responses in invalid conditions minus that in valid conditions. IVdif was significantly higher in the schizophrenic subjects. These results were confirmed in a comparison of two subgroups of controls and schizophrenic patients with the same mean IQ. In addition, the two subgroups differed only in the number of correct responses in invalid conditions. It should, however, be noted that the schizophrenic subjects obtained a relatively large number of correct responses. This reveals a defect in the test, which may be too simple and, therefore, generate a 'ceiling effect'.

Regardless of the population, the mean time required to find the correct sentences was twice

as long in invalid conditions than in valid conditions, clearly showing that the former sentences were more difficult to find. Furthermore, relative to the controls, the schizophrenic subjects took far longer, on average, to find the correct sentences, even in valid conditions. Finally, regardless of the conditions (valid/invalid), the time required to do the word sequencing test correlated with the results of Trail Making test A and B, pointing to a possible underlying attention impairment that might explain the poor performance. The correlations with IQ were not specific to the sequencing task but also applied to the other neuropsychological parameters. Only in the least severely impaired subjects would it be possible to observe isolated defects specifically affecting higher control mechanisms such as the supervisory system. In this study we only delineated such defects in the subpopulation analysis.

Two points help to understand the relationships between IQ and the sequencing task performance. First, the short-form of the WAIS (Silverstein, 1982) used in this study included four subtests. Two of them ('vocabulary' and 'picture arrangement') are directly linked to the mechanisms of the verbal sequencing task. It was, therefore, predictable to find correlations between these subtests and the sequencing test. Furthermore, these correlations were expected in both parts of the test. Indeed, the task in invalid conditions included not only the capture error paradigm, but also other basic and non specific verbal mechanisms. Secondly, Tracy *et al.* (1996) recently demonstrated that IQ estimates based on verbal tasks like the National Adult Reading Test may not only reflect the degree of pre-morbid functioning but also the subject's current status. In the overall population, there was no difference in the educational status (number of years) between the 37 schizophrenic and 21 control subjects. This must also be taken into account when interpreting the links with IQ.

According to Stuss *et al.* (1995), the control of attention by the supervisory attentional system is shown in the following type of tasks: sustaining, concentrating, sharing, suppressing, switching, preparing and setting of attention. At least one of them could be related to the processes involved in the sequencing test. Indeed, 'suppressing attention' is required 'when automatic processes select schemata that are inappropriate to task requirement'; Stroop-related tasks generate such a situation, in which the supervisory system must suppress the incorrect schemata in order to generate context-appropriate responses. Nathaniel-James & Frith (1996) demonstrated that schizophrenic subjects had difficulties with the Hayling test, which requires suppression of inappropriate responses. In the same way, observation of the schizophrenic patients during the sequencing task suggested that they had difficulties in inhibiting the attraction resulting from the strong association between the two words in invalid conditions. This led to difficulties in focusing attention on alternative strategies of response. Interestingly, two studies (Liddle & Morris, 1991; Joyce *et al.* 1996) examined the links between schizophrenic clinical dimensions and Stroop test results, and revealed a negative correlation between the disorganized dimension and Stroop performance. We did not use the Stroop test in this neuropsychological evaluation, but it is noteworthy that the only correlation between the clinical disorganized dimension and the neuropsychological test results was with the total time required to process invalid sequences. This could be interpreted as revealing an indirect link between suppressing attention and the capture error sequencing task.

The model proposed by Shallice is based on two major premises: first, this system is modular, and second, there is a hierarchy of functions. At the first level, simple or complex operations are overlearned, automatic and rapid. The second level corresponds to the supervisory system, which adjust and direct the ongoing automatic behaviours of the lower level. It is involved in various specific subfunctions such as global anticipation, plan formulation and sequential behaviour.

Our experimental paradigm and the results it generated may have practical implications. Indeed, precise location of impaired processes is important for choosing the most appropriate therapeutic approaches, such as behavioural relearning and social skill training (Kane & McGlashan, 1995). On the one hand, a major routine deficit would necessitate compensatory strategies acquired through teaching of specific routine tasks (Stuss *et al.* 1994). On the other

hand, an isolated, non-routine impairment would require the use of step-by-step approaches. Shallice's theory is also a good example of the model that attempts to link the neuropsychological and the anatomical terms, the supervisory system appears to belong to the frontal association cortex (Shallice, 1982); failure of this system can be seen in disorders affecting both the frontal cortex and its output pathways via the striatum (Owen *et al.* 1990). New functional brain imaging research (Andreasen *et al.* 1996) has indicated that schizophrenic disorders could also be linked to dysfunction of the frontal cortex–thalamus–cerebellum circuitry.

In conclusion, these findings suggest that both routine and non-routine behaviours, but particularly the latter, are impaired in schizophrenia. This impairment could be understood in terms of dysfunction of the supervisory attentional system.

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