

WE investigated the hypothesis that explicit cognitive processing is impaired in schizophrenia, while implicit processing is left largely intact, using a single sequence learning paradigm that simultaneously measures surface and abstract structure learning. Surface structure is the serial order of sequence elements. Abstract structure is defined in terms of the relationships between repeating elements. Sequences ABCBAC and DEFEDF thus share the same abstract structure, with different surface structures. Learning abstract structure requires explicit processing, while surface structure can be learned in implicit conditions. We predict however, that in explicit conditions, schizophrenics should learn surface structure but not abstract structure. Indeed, schizophrenic patients learned surface structure, but failed to learn abstract structure, demonstrating that implicit sequence processing is spared in schizophrenia while explicit sequence processing is impaired.

**Key words:** Analogical transfer; Schizophrenia; Sequence learning; Serial reaction time

## Schizophrenics learn surface but not abstract structure in a serial reaction time task

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### Introduction

While the cognitive performance of schizophrenic subjects is largely preserved in implicit or automatic cognitive tasks such as word-stem completion, repetitive priming and procedural learning,<sup>1–6</sup> it is impaired in explicit or effortful cognitive tasks such as the Wisconsin Card Sorting Task.<sup>7,8</sup> It has been suggested that various cognitive impairments in schizophrenia may be related to a more central dysfunction, such as an impairment in maintaining and using contextual information,<sup>9</sup> or an impairment in conscious awareness.<sup>10</sup> Several cognitive models of schizophrenia attempt to integrate such anomalies in the framework of the control of action related to dysfunction of a comparator,<sup>11</sup> monitoring of action<sup>12</sup> or planning and executive functions.<sup>13</sup>

It is likely that the processing deficits described by these models are linked to brain abnormalities revealed in studies of neuropathology and functional imaging. Schizophrenics show a hypofrontality of regional cerebral blood flow in a resting state,<sup>14,15</sup> and when performing the Wisconsin Card Sorting Test their dorsolateral prefrontal regional blood flow is not increased as it is in control subjects engaged in the same task.<sup>16,17</sup> It is of interest that in a recent blood flow study of sensorimotor sequence learning in normal subjects, explicit awareness of the sequence was correlated with increased blood flow in dorsolateral prefrontal cortex.<sup>18</sup> In contrast, in the same task in which the sequence was learned implicitly (as

revealed by reaction time reduction) but not in terms of reaching explicit awareness, increased blood flow in the dorsolateral prefrontal cortex was absent. This suggests that the hypofrontality in schizophrenic patients may be causally linked to their impairment in tasks that require explicit processing, while leaving implicit processing largely intact. It is likely that the perturbation of dopaminergic function in the frontostriatal and related systems is a contributing factor to this explicit processing dysfunction.<sup>11</sup>

One might ask however, whether the implicit *vs* explicit processing distinction in these subjects is simply due to differences in the format or complexity of the respective tasks, or whether there are fundamental processing differences. Part of the difficulty is that, until now, these processes have been measured in separate tasks. To address this problem, we use a task that simultaneously quantifies the subject's learning for surface and abstract sequence structure that have been shown to be treated by dissociable cognitive processes that operate in implicit and explicit modes, respectively.<sup>19</sup> We define the surface structure of a sequence in terms of the serial order of sequence elements, and the abstract structure in terms of relations between repeating elements. Thus the sequences ABCBAC and DEFEDF have different surface structures, but identical abstract structure (123213), and are by our definition 'isomorphic'. For any sequence based on the abstract structure 123213, we can see that the elements '213' are entirely predictable by the preceding elements '123', which

are in contrast unpredictable. Thus, given the fragment GHI of a new isomorphic sequence, based on the abstract structure we can predict the next three elements HGI. In other words, knowledge of abstract structure transfers to isomorphic sequences.

Numerous studies have demonstrated that normal subjects in implicit conditions can learn the surface structure, i.e. the succession of sequence elements.<sup>20,21</sup> We have recently demonstrated that learning the abstract structure does not occur in implicit conditions. Indeed, only when subjects have been explicitly informed about its possibility are they able to learn the abstract structure.<sup>19</sup> More generally, for a sequence that contains both surface and abstract structure, subjects in implicit conditions learn only the surface structure, while subjects in explicit conditions learn both.<sup>22</sup>

We have also demonstrated from a theoretical perspective that a neural network model of the frontostriatal system<sup>23</sup> is able to learn surface but not abstract structure, which can only be achieved by an 'evolved' version of the model.<sup>19,24</sup> These observations suggest that in implicit conditions, processes are available that are adequate for acquiring surface structure, but that abstract structure can only be acquired by processes invoked in explicit conditions.

A dysfunction in the explicit processing capacities of schizophrenic patients would predict that even in explicitly informed conditions, they would be capable of learning only the surface structure and not the abstract structure of a sequence. We tested this prediction with a protocol that simultaneously measures the two types of learning. This new protocol is of particular interest for this patient group as by comparing surface and abstract structure learning in the same experiment it allows for within-subject control of factors such as motivation, medication effects and general cognitive level.

## Materials and Methods

**Subjects:** The study was performed in a group of six patients (one woman, five men), who met DSM-IV<sup>25</sup> criteria for schizophrenia and were recruited from an out-patient population of a local psychiatric hospital (The Vinatier Hospital). Patients were screened for medical and neurological conditions. Exclusion criteria for patients included history of medical or neurological illness or trauma which could affect the nervous system, age > 55 years and history of learning disability. They were also excluded if they met DSM IV R criteria for alcohol and drug abuse, and substance dependence, or if they received lithium, benzodiazepines or antidepressants. The schizophrenic patients had a mean age of  $29 \pm 7.13$  years (range 21–41), and a mean educational level of

$12 \pm 1.67$  years (range 10–14). The mean average disease duration was  $10 \pm 6.29$  years (range 2–21), the mean average age of symptom onset was  $19 \pm 1.78$  years (range 16–21). Patients were classified as paranoid (2), disorganized (1) or undifferentiated (3) according to DSM IV criteria.<sup>25</sup> All patients were clinically stable at the time of evaluation and testing, and all were volunteers who gave written informed consent before testing began, and after the procedure was fully explained. All patients were receiving neuroleptic medication and were stabilized on medication with an average daily chlorpromazine equivalent dose of  $390.83 \pm 64.53$  mg (range 310–500). Four patients received also anti-Parkinsonian treatment (tropatepine, mean dose  $12.5 \pm 5$  mg).

Psychiatric symptomatology was assessed by the Brief Psychiatric Rating Scale (BPRS)<sup>26</sup> and the Positive and Negative Syndrome Scale (PANSS). Symptom severity was measured by the BPRS total score (mean BPRS score  $45.66 \pm 4.13$ , range 40–51). The mean PANSS positive score was  $19 \pm 5.17$ , the mean negative score was  $26.66 \pm 7.89$ . Patients were classified as positive (2), negative (3), and mixed (1).

The control group comprised 10 age-matched ( $28.3 \pm 3.1$  years) subjects, recruited from the hospital community. Exclusion criteria for controls were history of medical or neurological illness or trauma which could affect the CNS, current or past psychiatric illness, history of mental illness in their first-degree family members, stroke, seizure disorders, head injury, severe medical disorder (e.g. cardiac, hepatic, endocrine or renal disease), or substance abuse.

**Apparatus:** Subjects were seated in front of a touch sensitive computer screen (MicroTouch) on which the sequence elements (2.5 cm<sup>2</sup> blue squares on a light green background) were displayed and the response time (from target onset until subject's contact with the screen) was recorded. The eight sequence elements (referred to as A–H) were spatially distributed in a pseudo-random fashion in a  $25 \times 25$  cm surface of the screen. The task was piloted by a PC using Cortex software (NIH/Robert Desimone). The task is based on the SRT protocol<sup>20</sup> and involves pointing to successively illuminated sequence elements on the touch-sensitive screen as quickly and accurately as possible. In a given trial, one of the eight sequence elements is illuminated. After it is touched, it is extinguished, the reaction time is recorded and the next element is displayed.

**Protocol:** The protocol is divided into 10 successive blocks of 108 trials. In blocks 1–6 and 8 the 12-element sequence 'ABCBACDEFEDF' repeats nine times to yield 108 trials per block. In addition to its

12-element surface structure, this sequence also has an embedded abstract structure of the form 123213 (or u, u, u, n-2, n-4, n-3 where 'u' indicates unpredictable, and 'n-2' indicates predictable by the element two places back). This abstract structure recurs twice in the 12-element sequence. In other words, each exposure to the sequence contains two repetitions of the abstract structure and one repetition of the surface structure. Block 7 is a random series of elements. Blocks 9 and 10 each use 9 repetitions of a new, 12-element sequence, isomorphic to that used in blocks 1–6 and 8 (i.e. with the same abstract structure, but with a different surface structure). Note that switching to an isomorphic sequence allows a test of the capacity to learn and transfer knowledge of the abstract structure that is common to the isomorphic sequences. The delay between a response and the next stimulus (RSI – response to stimulus interval) was 200 ms within a 6-element subsequence, and 500 ms between subsequences.

The six schizophrenic subjects were explicitly informed about the existence of the abstract structure. They were shown a schematic diagram depicting the abstract structure ABCBAC, and were able to successfully supply (by pointing) the missing fragment (BAC) once shown the initial fragment ABC, where the letters correspond to spatial targets as on the touch-sensitive screen. Five control subjects were tested under identical explicit conditions, and the five remaining control subjects were tested in implicit conditions in which they were simply told to point to the spatial targets as quickly and accurately as possible.

**Data analysis:** The analysis focused on the RT data for predictable and unpredictable events (in terms of the abstract structure as defined above) in the initial sequence blocks, the random block and the transfer blocks with the isomorphic sequence. It is important to recall that predictable and non-predictable here refer to the abstract structure. Thus a given element may be non-predictable by the abstract structure, but show a reduced RT since it is part of the repeating, learnable surface structure.

The current task provides two concurrent measures of learning that can be compared within a given group. Surface structure learning is quantified by RT reductions for sequence elements that are not predictable by the abstract structure *vs* RTs for random elements. Abstract structure learning is quantified by the difference between RTs for elements that are predictable *vs* non-predictable by the abstract structure. Thus the primary analysis compares the surface *vs* abstract learning measures within the schizophrenic group. A secondary analysis makes between-group comparisons.

Learning of the surface structure is measured in a one-factor (block) ANOVA on the RTs for the unpredictable elements in sequence blocks 6 and 8 *vs* random block 7. By definition, the unpredictable elements are unpredictable in terms of the abstract structure and thus their RTs can only be reduced by learning the surface structure. Learning of the abstract structure is assessed by two measures. If the abstract structure is learned, then there should be a reduction in RTs for predictable *vs* non-predictable elements in the sequence but not random blocks. This is measured by introducing the predictability factor in a two-way (block  $\times$  predictability) ANOVA. In addition, knowledge of the abstract structure should transfer to the new isomorphic sequence in blocks 9 and 10, as revealed by a block  $\times$  position ANOVA comparing performance in the random block 7 with the transfer blocks 9 and 10.

## Results

The mean RTs for predictable and unpredictable responses in blocks 1–10 are presented in Fig. 1. The schizophrenic subjects displayed progressively reducing RTs in blocks 1–6. The RTs then increased in the random block 7, indicating that the surface structure had been learned. In contrast, there was no advantage for the predictable *vs* unpredictable elements, indicating that the schizophrenic patients failed to learn the abstract structure. While all three groups profited from the surface structure, only the explicit group benefited additionally from the abstract structure. All three groups displayed negative transfer to random material in block 7, and positive transfer to block 8, which is constructed as blocks 1–6. The crucial test of transfer involves new material with different surface structure but the same abstract structure in blocks 9 and 10. The schizophrenic group showed no evidence of use of the abstract information in blocks 9 and 10, as was also the case for the implicit group. While these two groups displayed improvement in these two blocks, the performance did not approach that seen in block 6 and, on the contrary, the performance in blocks 9 and 10 did not appear to differ greatly from that for random material in block 7. In contrast, the explicit group regained the reduced RTs for predictable elements in block 9 and approached its best performance (seen in block 6) for these elements in block 10, while at the same time improving also for the unpredictable elements.

The observations about learning in blocks 1–6 that resulted in negative transfer to the random block 7 were confirmed in the schizophrenic group by a two-factor (block: 6–8) ANOVA on RTs for unpredictable elements. The significant block effect ( $F(2,51) = 6.69$ ,  $p < 0.005$ ) reflects the increased RT for

## Abstract and Surface Structure in Sequence Learning

A-B-C-B-A-C-D-E-F-E-D-F

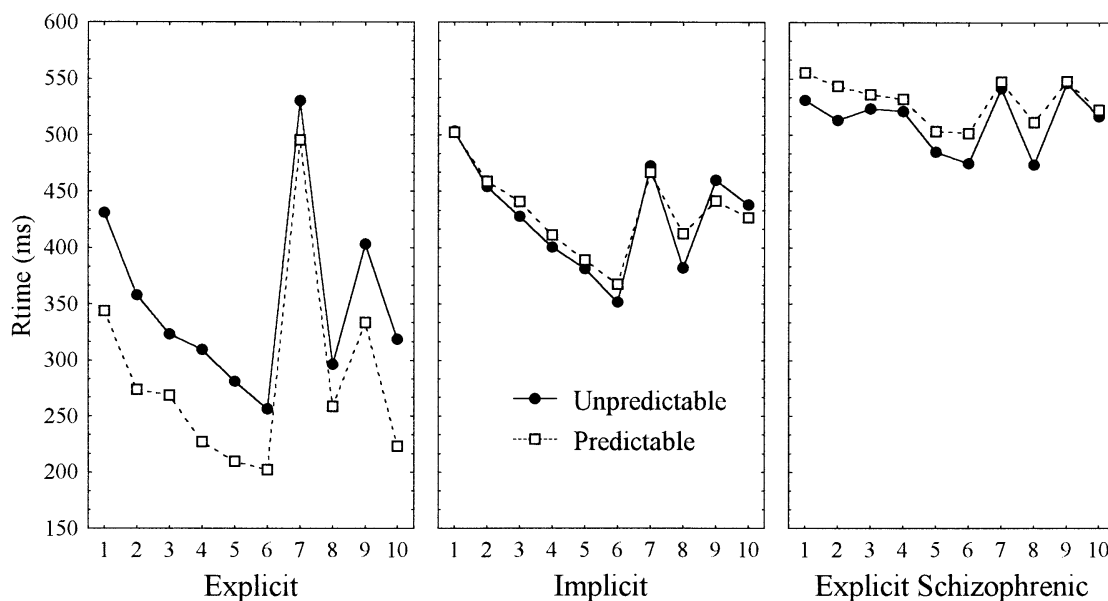


FIG. 1. Abstract and surface structure in sequence learning. Mean reaction times for 10 blocks of 108 trials. RTs for elements that are predictable and unpredictable by the abstract structure shown separately. Data from schizophrenic patients in explicit conditions compared with that from healthy control subjects in explicit and implicit conditions. Schizophrenics learn surface structure (sequence vs random difference) but fail to learn abstract structure (predictable vs non-predictable difference).

random *vs* sequence blocks for elements that are unpredictable by the abstract structure, and that can, therefore, be learned only in terms of the surface structure. When compared with the implicit group in a two (group: schizophrenic, implicit)  $\times$  two (block: 6–8) ANOVA, the significant effect for group ( $F(1,93) = 42.5, p < 0.0001$ ) and block ( $F(1,93) = 16.2, p < 0.0001$ ) and lack of significant group  $\times$  block interaction ( $F(4,96) = 1.2, p > 0.1$ ) indicates while the implicit group had overall reduced RTs, the random *vs* sequence RT difference (i.e. the measure of learning) was independent of group for the schizophrenic and implicit groups. When the explicit group was included, the interaction became quite significant ( $F(4,135) = 8.3, p < 0.0001$ ), reflecting the increased learning observed in the explicit group.

The observation that no processing advantage for predictable *vs* non-predictable elements was seen in the schizophrenic subjects was confirmed in a group  $\times$  predictability  $\times$  block ANOVA. The significant group  $\times$  predictability interaction ( $F(4,270) = 5.67, p < 0.005$ ) reflects the presence of a predictable *vs* non-predictable advantage in the explicit but not the implicit or schizophrenic groups. This was confirmed by planned comparison that revealed a significant reduction for predictable *vs* non-predictable RTs only for the explicit group.

The observation in the schizophrenic group of a lack of transfer of acquired knowledge to the new

sequence was confirmed by a two (predictability)  $\times$  3 (block: 7,9–10) ANOVA. The lack of a block effect ( $F(2,102) = 1.7, p > 0.1$ ) indicates that RTs for the isomorphic sequence in blocks 9 and 10 do not differ from those in random block 7. When compared with the implicit group, the lack of group  $\times$  block interaction ( $F(2,186) = 0.9, p > 0.1$ ) indicates that the failed transfer does not differ for these groups. This interaction becomes highly significant when the explicit group is added to the analysis ( $F(2,270) = 22.9, p < 0.0001$ ) corresponding to the observed RT reduction in Blocks 9 and 10 for the explicit group that results from transfer of the abstract structure.

## Discussion

In a task that permits the simultaneous learning of surface and abstract sequential structure, schizophrenic subjects acquired only the surface structure. This is despite the fact that these patients were fully informed, in an 'explicit' experimental condition. While the repeating abstract structure was six elements in length, the repeating surface structure was twice that, at 12 elements. Thus, from a length-related measure of difficulty or complexity, the abstract task was no more difficult than the surface task. The difference, as revealed by simulation and experimental psychology testing<sup>19,22,24</sup> is that learning abstract structure requires memory and recognition

processes, in addition to those required for learning surface structure. More importantly, these processes appear to be available only in explicit conditions. Thus, though explicitly informed, the schizophrenic patients behave as if they were in implicit conditions, without access to the required explicit processes. While the implicit group had RTs that were faster overall than those for the schizophrenic group, there was no significant group  $\times$  block interaction in either the measure of surface structure learning, or in the failed transfer to the isomorphic sequence. In other words, apart from a global vertical displacement on the time axis, the learning of the schizophrenic group did not differ from that of the implicit group.

These data support our hypothesis that in sensorimotor sequence learning, explicit controlled processes are perturbed in schizophrenia, while implicit automatic processes remain intact. The current results are all the more interesting in the sense that the two capacities are measured in the same task. Thus we can reject the arguments that either the subjects are entirely incapable of learning sequential structure in this type of task, or that they have motivational or drug-therapy related problems since they demonstrate significant learning of the surface structure. Indeed, it has been shown that neither neuroleptics<sup>27</sup> nor anticholinergics<sup>28</sup> are responsible for cognitive dysfunction in these patients.

The nature of the deficit behind the failure of explicit processing in schizophrenia remains to be explored, but appears causally related to the observed hypofrontality. From this perspective it is of interest to contrast these patients with parkinsonian patients. With respect to the current processing dissociation, these patient groups are almost mirror images of each other. Patients with Parkinson's disease are characterized by impairments in implicit learning processes, and greatly benefit when tasks become explicit, returning to near normal performance.<sup>29</sup> Indeed, while PD patients are significantly impaired in learning surface structure under implicit conditions<sup>29-31</sup> we have recently demonstrated that they maintain a significant capability for learning abstract structure in explicit conditions,<sup>32,33</sup> essentially the inverse of the behavioural profile identified for schizophrenic patients in the current study.

This contrast is all the more interesting in that several studies have demonstrated abnormalities in the basal ganglia in schizophrenic patients.<sup>34-40</sup> Combined with the observed hypofrontality, this suggests a functional impairment of the frontostriatal system potentially linked to alterations in dopamine regulation.<sup>11,17,41-43</sup> Several investigators have proposed that frontostriatal dysfunction leads to a variety of symptoms in schizophrenia such as the positive and negative symptoms of the disease, as

well as disorders of motor programming, eye movements and directed attention.<sup>11,37,44</sup> Although it may seem initially somewhat paradoxical, it is not surprising that manipulations of the same (frontostriatal) system in different fashions can lead to quite different results. Indeed, the further study of patients with Parkinson's disease and those with schizophrenia in parallel protocols may lead to a better understanding of the underlying neurophysiology of the disorders, and thus to a clearer understanding of the frontostriatal system.

## Conclusion

We set out to test the hypothesis that schizophrenics would be impaired in a sequence learning task that requires explicit, conscious, processing, and unimpaired in an implicit sequence learning task. We tested this hypothesis in a single sequence learning protocol that simultaneously measures the ability to learn serial order or surface structure (implicit) and an underlying abstract structure or rule (explicit). Despite the fact that they were in fully informed, explicit conditions, the schizophrenic reliably learned the surface structure but failed to learn the abstract structure. This failure in explicit sequence processing is probably due to cortical hypofrontality resulting in part from pathological alteration of frontostriatal dopamine regulation.

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