What can eye movements tell us about Symbol Digit substitution by patients with schizophrenia?

Ava Elahipanah a,⁎, Bruce K. Christensen b, Eyal M. Reingold c

a Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada
b Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
c Department of Psychology, University of Toronto, Mississauga, Ontario, Canada

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A B S T R A C T

Substitution tests are sensitive to cognitive impairment and reliably discriminate patients with schizophrenia from healthy individuals better than most other neuropsychological instruments. However, due to their multifaceted nature, substitution test scores cannot pinpoint the specific cognitive deficits that lead to poor performance. The current study investigated eye movements during performance on a substitution test in order to better understand what aspect of substitution test performance underlies schizophrenia-related impairment. Twenty-five patients with schizophrenia and 25 healthy individuals performed a computerized version of the Symbol Digit Modalities Test while their eye movements were monitored. As expected, patients achieved lower overall performance scores. Moreover, analysis of participants’ eye movements revealed that patients spent more time searching for the target symbol every time they visited the key area. Patients also made more visits to the key area for each response that they made. Regression analysis suggested that patients’ impaired performance on substitution tasks is primarily related to a less efficient visual search and, secondarily, to impaired memory.

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1. Introduction

1.1. Cognitive impairment and substitution task performance in schizophrenia (SCZ)

Cognitive impairment is a core feature in schizophrenia (SCZ), and closely related to functional outcome (Green, 1996; Heinrichs and Zakzanis, 1998). Therefore, measurement of cognitive impairment has become an increasingly important part of neuropsychological evaluation and research among patients with SCZ, with the objectives to detect cognitive dysfunction in individual patients and to specify the aspects of cognition that are most impaired in SCZ.

Symbol substitution or coding tasks, which involve the matching of a symbol and a digit, are among the most sensitive tests of cognitive dysfunction (Lezak et al., 2004; Ryan and Kreiner, 2006). Moreover, a recent meta-analysis revealed a substantial SCZ-related impairment on substitution tasks and that these tasks discriminate patients with SCZ from healthy individuals better than other common neuropsychological instruments; that is, they yield effect sizes that are significantly larger than other measures and are not sensitive to study design, medication status or symptomatology (Dickinson et al., 2007). However, due to the multifaceted nature of substitution tests, overall performance scores, per se, fail to pinpoint the precise mechanisms of impaired performance, and poor performance may result from impairment in a variety of cognitive operations. Consequently, experimental paradigms that allow for the dissection of operations underlying substitution performance will shed light on specific mechanisms as they relate to particular populations.

1.2. Parsing substitution performance into its components

Performance on substitution tests requires the integrity of a number of different cognitive abilities. This multifaceted nature
of substitution tests makes it a highly sensitive tool for the
detection of cognitive dysfunction, because the aggregated
deficit across a number of cognitive processes facilitates
detection of cognitive impairment. However, for the same
reason, substitution tasks lack specificity; that is, a low
performance score can be the result of impairment in a number
of different operations such as visual scanning, attention
shifting, memory, and motor output.

Attempts have been made in the past to determine the
contribution of different operations to substitution perfor-
mance by using tasks or methods that test the respondent on
an isolated component of the task. For example, the Digit
Symbol-Incidental Learning and Digit Symbol-Copy tests
(Kaplan et al., 1991; Wechsler, 1997) were devised as
complementary or satellite tests to determine the contribu-
tion of memory dysfunction and graphomotor slowing,
respectively, to poor performance on the Digit Symbol Coding
task. Using the Digit Symbol-Copy satellite test, it has been
found that copying speed accounts for at least 50% of the
variance of scores on the Digit Symbol test (Joy et al., 2000;
Kreiner and Ryan, 2001; also see LeFever, 1985; Storandt,
1976). The contribution of memory to coding performance
among healthy participants, on the other hand, seems less
significant. Data from the Digit Symbol- incidental Learning
procedures suggest that memory accounts for only 5% of
coding score variance (Joy et al., 2000; Kreiner and Ryan,
2001). Joy et al. (2003) further investigated the contribution
of visual scanning efficiency to Digit Symbol Coding perfor-
mance by creating a new test – the Symbol-Scan test – that
consisted of a completed Digit Symbol form containing a
number of errors. Participants were required to mark the
incorrect responses as quickly as possible. The Symbol-Scan
test was presumed to reduce the psychomotor aspect of
coding performance, while retaining its other aspects includ-
ing visual scan efficiency. Joy et al. (2003) found a strong
correlation (r = .50) between Digit Symbol-Coding and
Symbol-Scan scores. Moreover, some clinicians record the
respondent’s score at certain intervals (e.g., 30, 60, and 90 s)
during test completion to evaluate variability in the rate of
progress, which in turn could be affected by variables such as
motivation, distractibility, fatigue, or short-term memory
(Kaufman and Lichtenberger, 1999, 2006). A study of thirty-
second interval performance patterns among healthy young
adults during the Digit Symbol test has revealed a slight
decrease in performance (i.e., number of boxes completed) in
the second interval, followed by a gradual improvement in
the third and fourth intervals, although performance in the
fourth interval did not reach that of the first interval (Ryan
et al., 2006). In addition, the contributions of motor and
cognitive aspects of substitution test performance have been
more accurately determined using the digitized tablet
method (van Hoof et al., 1998). Using this technique for
computerized analysis of writing movements, van Hoof et al.
found that SCZ patients differed from healthy controls in the
amount of time they spent ‘not writing’ – referred to as
matching time. Compared to a group of patients with
depression, patients with SCZ demonstrated slower matching
but faster writing times. In fact, SCZ patients in this study did
not differ in writing time from healthy controls. In a more
recent study, Bachman et al. (2010) used a computerized
Digit Symbol Coding task designed to allow for the manip-
ulation of visual scanning and relational memory demands.
On each trial, participants were presented with a reference
set of nine digit-symbol pairs and one target digit-symbol
pair, and were instructed to indicate if the target pair was
identical to one of the pairs in the reference set. Two different
conditions were used. In the fixed pairing condition the digit–
symbol pairing did not change across the trials. In the random
pairing condition, the digit–symbol pairings in the reference
set were changed from trial to trial; therefore, predictable
target information was not available and task performance
was primarily dependent upon visual scanning. Bachman
et al. (2010) found a significant group by condition inter-
action whereby control participants displayed a greater ad-

tage in the fixed condition over the random condition
compared to patients with SCZ, demonstrating that patients
benefited less from a fixed and predictable reference set due
to a deficit in relational memory. However, there was still a
substantial between-group difference in the random pairing
condition, indicating a possible role for visual scanning abil-
ities in patients’ impaired substitution performance.

The described measures provide insight into the more de-
tailed aspects of individual performance on substitution tasks
and are consistent with the quantified process approach to
clinical neuropsychological assessment (for a review, see Ryan
and Kreiner, 2006). These measures also provide an opportunity
to detect specific performance patterns among different
groups of clinical populations who may otherwise be indiscriminable
from each other based on global performance scores alone.
However, performance on substitution tasks involves a greater
number of cognitive functions that cannot be separated using the
described measures. For example, while the digitized tablet
method can parse substitution performance into writing and
matching components (i.e., motor and cognitive aspects of the
task), it cannot separate the contribution of different cognitive
functions that occur during matching time (e.g., encoding the
test symbol, retaining it in working memory, and searching for
the test symbol among the key items). Similarly, the Symbol-
Scan test, devised by Joy et al. (2003) to measure visual scanning
ability, involves all components of the Digit Symbol-Coding task
except the writing aspect. In addition, while Bachman et al.
(2010) convincingly demonstrate the importance of relational
memory in SCZ-related impairment on Digit Symbol substitution
tasks, extracting the relative importance of memory and visual
scanning abilities from their results is less straightforward, as one
might contend that performance on the fixed pairing condition
depends on visual scanning as well as relational memory
abilities. Consequently, other methods are required to provide a
more direct analysis of substitution performance in its original
form and further parse it into narrower areas of cognitive
functioning in order to identify possible specific differences
between patients with SCZ and other clinical and healthy
populations. We believe that monitoring eye movements during
substitution test performance may be an excellent tool to achieve
this goal.

1.3. Eye movements and cognition

Since over a century ago, eye movements have been used as
an indirect measure to investigate different cognitive
processes (for a review, see Rayner, 1998). A growing body of
research has suggested that whereas attention can be shifted
covertly in the absence of eye movements, there is often a natural concurrence between attentional shifts and saccadic eye movements (for a review, see Hoffman, 1998). The link between the oculomotor and attentional systems is also supported by neurophysiological data (e.g., Kustov and Robinson, 1996; Wurtz and Goldberg, 1972). Although the coupling between attentional shifts and saccadic eye movements is not complete, it is maximized in complex tasks or when the stimuli to be processed are smaller and fixation is required to identify an item (Irwin, 2004; Rayner, 1998). Thus, in a typical substitution task, eye movements can be considered valid indicators of attention allocation. In addition, eye movement parameters (e.g., number and duration of eye fixations) can provide valuable information about cognitive processing during substitution task performance.

1.4. Objectives of the current study

The current study aimed to specify the cognitive processes involved in substitution task performance using eye movement recording techniques. The Symbol Digit Modalities Test, oral version (SDMT; Smith, 1991) was chosen because it yields scores that are highly correlated with scores on the more commonly used written version ($r > .78$ for healthy adults; Smith, 1991) and it eliminates the motor writing response. This is desirable as it allows the performance of the SDMT task on a computer with minimal deviation from the original form of the test. According to previous research, patients with SCZ do not significantly differ in writing time from healthy control participants (van Hoof et al., 1998); therefore, using the SDMT oral version allows us to focus on the aspects of substitution performance that appear to be most impaired in SCZ. Despite the elimination of the writing motor response, however, the SDMT oral version remains a multifaceted task that requires the encoding and retaining of a test symbol in working memory, and searching for that symbol in the key area to find its matching number. The purpose of the current study was to investigate possible differences in eye movement patterns between SCZ patients and healthy control participants. Given the close link between eye movements and cognitive processing, eye movements can provide valuable insight into how processing of information during substitution task performance differs between patients with SCZ and healthy individuals, and to what degree these differences contribute to SCZ-related impairment on these tasks. More specifically, it is possible to analyze eye movement patterns for evidence of impaired encoding of the test symbols (i.e., prolonged examination of the test items), impaired memory (i.e., excessive referral to the key area), visual search impairments (i.e., prolonged and inefficient search of the key area), and general slowness (i.e., prolonged latencies and fixation durations). The existence of an isolated or disproportionate impairment in one or more of these variables would help identify the exact mechanisms underlying SCZ-related impairment on the SDMT.

2. Methods

2.1. Participants

Twenty-five patients diagnosed with SCZ or Schizoaffective Disorder (Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-IV) and 25 healthy individuals participated in the study. Patients were recruited from the Schizophrenia Research Registry at the Centre for Addiction and Mental Health (CAMH) and their diagnosis was confirmed using the Structured Clinical Interview for Diagnosis of DSM-IV Axis I Disorders Patient Edition (SCID-P; First et al., 2001a). All, but three, of the SCZ participants were outpatients; all were clinically stable and were receiving second-generation antipsychotic medication. Patients receiving medications with known cognitive effects (i.e., benzodiazepines, tricyclic antidepressants, anticonvulsants, analgesics, anticholinergics) were excluded from the study. Healthy control participants were recruited from the community via newspaper advertisements and were matched to the patient participants based on age and sex. They were confirmed as free of Axis I psychiatric disorders using the SCID Non-Patient Edition (SCID-N/P; First et al., 2001b). In addition, individuals who reported a lifetime history of an Axis I disorder or had a first-degree relative with SCZ or other psychotic disorders were excluded from the study. All participants were between 18 and 60 years old, had normal/corrected to normal visual acuity, and reported having acquired English as a primary language before the age of 5. Individuals were excluded from participating in the study if they reported using illicit drugs within the past month or if they met criteria for lifetime history of substance dependence. They were also excluded if they had a self-reported history of a learning disability, neurological injury/ disease (including a history of head injury with loss of consciousness more than half an hour), or any other medical condition known to have cognitive effects (e.g., severe heart or pulmonary disease, insulin-dependent diabetes, thyroid disease, epilepsy, neurological illness such as Parkinson’s or Huntington’s disease).

The demographic information for the two participant groups is shown in Table 1. The control group was on average 2 years more educated than the patient group and their IQ – estimated from scores on the Matrix Reasoning and Information subtests of the WAIS – was on average 15 points higher. The groups were equivalent across other demographic variables.

2.2. Experimental apparatus

The experiment was built using the Experiment Builder Software (SR Research Ltd.). Stimuli were presented on a 22”
(20° viewable) Viewsonic Professional Series P225fb monitor. A chin-rest was used to keep the participants' viewing distance fixed at 60 cm from the monitor. An Eyelink 1000 eye tracker was used to record participants' eye movements.

2.3. Stimuli and design

The experiment was based on the Symbol Digit Modalities Test, oral version (Smith, 1991). The test was displayed on the computer monitor for viewing and completion by the participants. At a viewing distance of 60 cm, the SDMT sheet subtended a visual angle of 21° horizontally and 26° vertically, while each individual box subtended a visual angle of 1.24° horizontally and 0.85° vertically. Participants were asked to use the key area to find the number corresponding to each of the symbols and say the number out loud. Participants' voice and eye movements were recorded.

2.4. Procedure

After acquiring written consent and general demographic/clinical information, participants' vision was tested using a Snellen acuity chart. Next, participants were interviewed using the SCID, after which they completed the substitution task. At the onset of the SDMT display, only the key and practice areas (i.e., the first 10 boxes) were visible and the symbols constituting the test area were masked. Participants were instructed to find the matching number for each of the symbols and say the number out loud. After each number spoken by the participant, the experimenter pressed a button on her keyboard to insert a cross in the completed box on the participant’s display. After successful completion of the practice boxes, the participant was instructed to fixate the first test box and start completing the boxes as soon as the masks were removed. Participants were instructed to complete as many boxes as possible within 90 s. During this time, participants' eye movements were recorded using an eye-tracker and their voice was also recorded for later scoring of task performance. After 90 s, the experiment terminated automatically. After the completion of the experimental task, a cognitive assessment was performed using the Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997), and the reading subtest of the Wide Range Achievement Test (WRAT). Finally, participants in the patient group were also interviewed using the Positive and Negative Symptoms Scale (PANSS; Kay et al., 1992).

3. Results

3.1. SDMT scores

Patients with SCZ had significantly lower performance scores (mean score = 45.0) compared to healthy controls (mean score = 60.7), t(48) = 7.92, p < .001, Cohen's d = 2.24. This part of the analysis replicates previous findings of impaired performance of patients with SCZ on symbol substitution tasks. Accuracy rates were high and similar across the two groups: SCZ = 97.9%, HC = 98.5%, t(48) = 0.92, p = .36.

3.2. Eye movement indices

Eye movement data were analyzed using the Eyelink Data Viewer software. To study the participants' scanning behaviour, the SDMT display was segregated into two areas of interest: the key and test areas (see Fig. 1). The number and duration of fixations in each of these areas, the number of transitions between the two areas, and the time spent in each of these areas during each visit were analyzed using independent samples t-tests. Table 2 shows a summary of the results. The results showed that compared to healthy participants, patients with SCZ made on average 22% more visits to the key area for each response made, t(48) = 4.49, p < .001, Cohen's d = 1.27. Schizophrenia patients also spent on average 134 ms longer examining the key area every time they visited this area, t(48) = 4.94, p < .001, Cohen's d = 1.40 and made 19% more fixations compared to healthy participants every time they visited the key area, t(48) = 3.81, p < .001, Cohen's d = 1.08.

3.3. Correlation between SDMT score and eye movement variables

So far the analyses revealed significant between-group differences in the number of visits to the key area for each response, and longer time spent and a greater number of fixations during each visit to the key area. To investigate the relationship between each of these variables and SDMT performance (i.e., score), bivariate correlation analyses were conducted. There was a significant negative correlation between the number of key area visits per response and SDMT score, r(48) = −.58, p < .001; between the time spent in the key area and SDMT score, r(48) = −.73, p < .001; and also between the number of fixations during each visit to the key area and SDMT score, r(48) = −.64, p < .001. As expected there was a positive correlation between the time spent in the key area and the number of fixations in this area during each visit, r(48) = .64, p < .001. To investigate the contribution of these variables to differences in the groups' performances, regression analyses were performed in three steps. First, a simple regression analysis was conducted with SDMT score as the dependent variable and Group as the sole predictor variable. Group alone accounted for 55.8% of the variance in SDMT score, R2 = 55.8% (adjusted R2 = 53.5%). Next, Group was added to this one-predictor model. The addition of group membership to the model as a predictor variable resulted in an increase of 16.4% (adjusted R2 = 70.2%) in the amount of total score variance explained by the model, indicating that 90% of the amount of variance in SDMT score that was initially attributed to group membership, could be accounted for by the number of visits to the key area for each response, and the time spent in the key area during each visit; that is, between-group difference in SDMT performance scores could largely be
explained by between-group differences in these two predictor variables.

3.4. Relationship between SDMT performance and clinical variables

The relationship between SDMT performance and clinical variables such as positive and negative symptoms and illness duration was investigated using Pearson correlation analysis. There was no correlation between SDMT score and positive symptoms, negative symptoms or illness duration. However, there was a moderate relationship between SDMT score and general psychopathology, \( r(23) = -0.48, p = .01 \). Likewise, there were moderate relationships between the number of visits to the key area for each response and general psychopathology, \( r(23) = .55, p = .004 \), and between the number of key visits for each response and positive symptoms, \( r(23) = .41, p = .04 \). All other correlations were of smaller magnitudes and statistically nonsignificant.

4. Discussion

The present study investigated eye movements during substitution test performance in order to pinpoint possible mechanisms of SCZ-related impairment on substitution/coding tasks. The results indicate that prolonged search times in the key area during each visit and a greater number of visits to the key area per response distinguish patients with SCZ from healthy participants. These results suggest that SCZ-related impairment on the SDMT is linked to impairments in visual search and memory. The finding of inefficient search of the key area by patients with SCZ on the SDMT is consistent
with previous findings of impaired visual search among these patients (e.g., Carr et al., 1998; Elahipanah et al., 2010; Fuller et al., 2006; Lieb et al., 1994; Mori et al., 1996). It is not surprising that patients with SCZ would manifest the same impairment when searching among the symbols in the key area. However, it is interesting that impairment in visual search would turn out to be the most important factor resulting in patients’ impaired performance on the SDMT. On the other hand, the finding of an increased number of visits to the key area for each response among patients with SCZ implicates the role of memory deficits in SDMT performance. This may appear in contrast with other findings that memory for digit–symbol associations has a subsidiary or even negligible role in substitution performance among healthy participants (e.g., Joy et al., 2000; Knier and Ryan, 2001). It is important to note, however, that studies that have not found a role for memory have investigated Digit Symbol coding tasks. Symbol Digit and Digit Symbol substitution tasks yield highly correlated scores (with correlations as high as .91; Morgan and Wheelock, 1992) and thereby appear to measure similar, if not identical, constructs; therefore, it is reasonable to assume that memory and visual search impairments also contribute to patients’ impaired digit symbol substitution. Nevertheless, it is important to bear in mind that the current data are derived using the Symbol Digit substitution task and, therefore, results are most generalizable to testing or experimental situations using this measure. In digit symbol substitution, remembering the associations would be a mixture of perceptual, attention, and working memory deficits. However, it is important to note that alternative interpretations for the observed eye movement patterns are possible. For example, while an excessive number of transitions between the key and test areas could reflect a memory problem, it might also result from a poorly defined mixture of perceptual, attention, and working memory deficits. Finer decomposition of the observed effects awaits further investigation.

In conclusion, the results of this study suggest that impaired performance on the Symbol Digit Modalities Test by patients with SCZ is primarily attributable to less efficient visual search for the target symbol among the key items and secondarily to memory deficits. The precise nature of the revealed memory deficits is yet to be determined and may

### Table 2
Eye movement indices [mean (SD)].

<table>
<thead>
<tr>
<th></th>
<th>Patient (n = 25)</th>
<th>Control (n = 25)</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT score</td>
<td>45.0 (6.3)</td>
<td>60.7* (7.6)</td>
<td>.001</td>
<td>2.24</td>
</tr>
<tr>
<td>Total number of fixations</td>
<td>362 (46)</td>
<td>363 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion fixations made in the key area</td>
<td>53.2% (4.9%)</td>
<td>48.6%* (5.1%)</td>
<td>.002</td>
<td>.93</td>
</tr>
<tr>
<td>Proportion time spent in the key area</td>
<td>51.9% (7.4%)</td>
<td>47.0%* (8.7%)</td>
<td>.04</td>
<td>.60</td>
</tr>
<tr>
<td>Number of fixations in the key area</td>
<td>194 (35)</td>
<td>177 (33)</td>
<td>.08</td>
<td>.51</td>
</tr>
<tr>
<td>Number of fixations in the test area</td>
<td>166 (22)</td>
<td>186* (30)</td>
<td>.01</td>
<td>.74</td>
</tr>
<tr>
<td>Duration of first fixation (latency)</td>
<td>1049 ms (698)</td>
<td>1818 ms* (1736)</td>
<td>.05</td>
<td>.58</td>
</tr>
<tr>
<td>Average duration of fixations in the key area</td>
<td>208 ms (28)</td>
<td>206 ms (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average duration of fixations in the test area</td>
<td>222 ms (43)</td>
<td>225 ms (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of visits to the key area</td>
<td>51.8 (7.6)</td>
<td>57.3* (10.2)</td>
<td>.03</td>
<td>.62</td>
</tr>
<tr>
<td>Number of visits to the key area for each response</td>
<td>1.14 (18)</td>
<td>.93* (14)</td>
<td>&lt;.001</td>
<td>1.27</td>
</tr>
<tr>
<td>Average number of fixations during each visit to the key area</td>
<td>3.75 (43)</td>
<td>3.15* (66)</td>
<td>&lt;.001</td>
<td>1.08</td>
</tr>
<tr>
<td>Average number of fixations during each visit to the test area</td>
<td>3.28 (68)</td>
<td>3.31* (84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average time spent in the key area during each visit</td>
<td>772 ms (79)</td>
<td>638 ms* (110)</td>
<td>&lt;.001</td>
<td>1.40</td>
</tr>
<tr>
<td>Average time spent in the test area during each visit</td>
<td>736 ms (251)</td>
<td>743 ms (285)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SDMT = Symbol Digit Modalities Test.
* p < .05.
include impairments in learning the symbol-digit associations or more general working memory deficits that compromise the encoding, retention, or retrieval of individual items (i.e., the test symbol or target digit). Moreover, studying eye movements among patients with cognitive dysfunction from other etiologies may reveal distinct differences and therefore provide a means of discriminating populations with impaired performance on substitution tasks.

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Contributors
This study was conducted in partial fulfillment of Ava Elahipanah’s PhD thesis requirements. Accordingly she was responsible for all aspects of study design, data collection, statistical analysis, and manuscript preparation. The research was conducted under the supervision of Bruce Christensen who participated directly in all aspects of the study. Eyal Reingold served as a thesis committee member and an expert consultant with regard to task design, experimental methods and data interpretation. All authors contributed to and approved the final manuscript.

Conflict of interest
All authors declare that they have no conflict of interest.

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