RANDOM NUMBER GENERATION DEFICIT IN EARLY SCHIZOPHRENIA

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Summary.—Random number generation with a written response mode provides a potentially appealing marker for executive processes. Impaired performance on written random number generation tasks has been reported in chronic schizophrenic patients. However, no study has investigated whether such a deficit occurs in early schizophrenia and whether its profile and severity are similar to those in patients with chronic illness. This study investigated the ability to generate random numbers in patients with early schizophrenia (n = 44) and a healthy control group (n = 48). Patients were less able to maintain several production strategies and generated more stereotyped response sequences, whereas their abilities to identify randomness with an even-handed treatment of digits and to monitor the equality of occurrence of single digits appeared to remain intact. These results provide evidence that some aspects of the deficits in random number generation among chronic schizophrenic patients are also present at early psychotic episode, while some other aspects are relatively less affected in the early years.

A random number generation task consists of producing at random a long sequence of numerical digits (Ginsburg & Karpiuk, 1994). The process involves continuously selecting a new response from the set of possible alternatives and inhibiting prepotent response patterns such as repetitions and counting (Baddeley, 1966; Baddeley, 1996; Jahanshahi, Profice, Brown, Ridding, Dirnberger, & Rothwell, 1998; Daniels, Witt, Wolff, Jansen, & Deuschl, 2003). Studies have shown that the ability to generate randomness is related to higher cognitive and executive processes such as retaining task-related instructions in memory, handling information in real time, avoiding interference, monitoring output, and switching response-generation strategy (Sunderland, Watts, Baddeley, & Harris, 1986; Baddeley, Emslie, Kolodny, & Duncan, 1998; Salamé, Danion, Peretti, & Cuervo, 1998; Jahanshahi, Saleem, Ho, Dirnberger, & Fuller, 2006).

Random number generation has been used to examine cognitive impairment in various mental and neurological disorders, including schizophrenia (Peters, Giesbrecht, Jelicic, & Merckelbach, 2007; Salamé & Danion, 2007). The distinct features of random number generation are its

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resistance to practice effect (Evans, 1978; Harrell & Evans, 1978; Horne, et al., 1982) and lack of influence of the education level of the participants (Brugger, 1997), both of which make the task a potentially appealing cognitive marker in schizophrenia research.

Regardless of the significant variability in experimental design and procedures, results from prior studies have been strikingly similar: sequences generated by schizophrenic patients have been less random compared to those generated by healthy controls. Recent neuroimaging studies have investigated the anatomical-functional correlates of this deficit in patients with schizophrenia. These studies have shown that random number generation performance is related to functioning of the cinguloparietal lobe and dorsolateral prefrontal cortex (Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004), which is known to be affected in schizophrenia (Manoach, Gollub, Benson, Searl, Goff, Halpern, et al., 2000; Meyer-Lindenberg, Olsen, Kohn, Brown, Egan, Weinberger, et al., 2005). A positron emission tomography study has shown different covariation patterns between response randomness and activation in the anterior cingulate cortex and superior parietal regions in patients with schizophrenia compared to healthy controls, suggesting a cinguloparietal dysfunction underlying the impairment of working memory control processes during random number generation in patients (Artiges, et al., 2000).

The two modes of oral and written responses have been commonly employed in random number generation experiments, and response modality has been identified as a factor that affects task performance (Brugger, 1997; Towse, 1998; Shinba, et al., 2000). Given that phonological working memory dysfunction has been implicated in performance of this task (Salamé, et al., 1998), it is not surprising that patients have exhibited impairments in verbal performance (Ramsay & Broadhurst, 1968; Horne, et al., 1982; Okura & Ikuta, 1987; Rosenberg, et al., 1990; Hornero, Alonso, Jimeno, Jimeno, & Lopez, 1999). However, even with a written response mode, with presumably less working memory load owing to previous responses remaining visible and the participant being able to make use of these to guide the next response, studies have indicated the presence of deficit in random number generation in these patients (Shinba, et al., 2000). It would be of interest to use the written response mode, with its lighter demand on working memory, to assess the specific effects of executive control rather than working memory.

Only two studies of random number generation characterized by written response mode in schizophrenia (Shinba, et al., 2000; Shinba, et al., 2004) can be identified in the literature. Little is known about the psychopathological underpinnings of the patients’ impairment in this type of task. In addition, patients included in previous studies were suffer-
ing from chronic schizophrenia, so it is thus unclear whether in the early course of the illness, the impairments in this type of task are similar to those seen in patients with more chronic illness. A limitation of previous studies is that the randomness of the generated sequences (i.e., the dependency between one response and the next) has been evaluated by a limited set of analyses. For instance, the frequency distribution of the first-order difference—the arithmetic difference between each response and the preceding value—was evaluated in Shinba, et al. (2000). However, this measure is not sensitive enough, as the same arithmetic difference can be produced by different pairs of digits (e.g., the interdigit intervals in “3, 5” and “7, 9” are both −2). A more informative measure of the sequential randomness would be to assess the distribution of response pairs (Evans, 1978), which measures the extent to which the 2-digit permutations actually generated (e.g., “3, 5,” “5, 7,” “7, 9,” etc.) exhaust the 100 possible alternatives.

This study aimed to better understand the nature of random number generation deficits in schizophrenia by following up on the previous findings. Impaired performance on written random number generation tasks reported in chronic schizophrenia (Shinba, et al., 2000) does not indicate whether such a deficit might be observable in early schizophrenia. The current study characterized written random number generation in early schizophrenia by using a comprehensive set of measures to reflect different aspects of random number generation performance and analyze deficits with regard to the potential influence of factors including (a) usage of previously learned and automatized schemas; (b) usage of a wrong concept of randomness; (c) monitoring of response redundancies; and (d) variability of response-production strategies.

It was hypothesized that random number generation performance would be impaired in patients early in the course of schizophrenia. However, some aspects of these participants’ random number generation performances were expected to be better preserved than others. In particular, it was expected that observed differences between patients and controls would correspond to higher-order indexes of random number generation.

Method

Population and Sample

In this study, 44 patients were recruited from a specialized early psychosis intervention service in Hong Kong (Wong, Hui, Chiu, Lam, Chung, Tso, et al., 2008). The inclusion criteria were as follows: (1) duration of illness, defined as the length of time since the first hospitalization, less than three years; (2) primary diagnosis of schizophrenia according to the DSM–IV (American Psychiatric Association, 1994); and (3) between ages of 18 and 65 years. The exclusion criteria were as follows: (1) presence of current or past DSM–IV diagnosis of organic brain disorder, mental re-
tardation, or mood disorder; (2) presence of serious physical illness; (3) presence of harmful psychoactive substance (including alcohol) use and dependence in the past three months; and (4) a history of brain trauma or neurological disease. The healthy control group (n = 48) consisted of volunteers from the general public. Potential participants with any personal or family history of psychiatric illness, history of substance abuse, history of brain trauma or neurological disease, mental retardation, or current use of any medication were excluded from the present study. Table 1 provides demographic information for the two groups. All participants gave written informed consent after the procedure had been fully explained. Approval of the relevant institutional review boards was obtained before the study commenced.

Assessments

Diagnostic and clinical assessments.—Diagnoses were made according to the DSM–IV (American Psychiatric Association, 1994) based on a standard clinical interview, informant histories, and review of all available clinical material. An inter-rater agreement of 86% for diagnosis was obtained in an independent validation sample of 38 patients. The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of symptoms in the patients (Kay, Fiszbein, & Opler, 1988). Assessment and scoring were based on the original training manual. The inter-rater reliability of the three raters was .83 for the PANSS positive symptoms subscale and .73 for the PANSS negative symptoms subscale (by intra-class correlation coefficient). See Table 1 for a group comparison of mean scores.

Random number generation.—The verbal instructions presented to participants were as follows: “Please write down numerical digits one after another as they come to your mind spontaneously, try to make it as random as possible and avoid predictable patterns. There are 500 trials in total. In each trial, fill in any number between 0 and 9 inclusive. Fill the blanks in from left to right, row by row (10 cells × 50 rows). Try to avoid

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schizophrenic Group (n = 44)</th>
<th>Control Group (n = 48)</th>
<th>t_{90}</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex ratio, female/male</td>
<td>22/22</td>
<td>29/19</td>
<td>1.01</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Age, yr.</td>
<td>26.90</td>
<td>23.70</td>
<td>1.69</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Education, yr.</td>
<td>13.74</td>
<td>16.79</td>
<td>−5.93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of illness, yr.</td>
<td>2.30</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>PANSS Total score</td>
<td>59.87</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Note.—PANSS = Positive and Negative Syndrome Scale. *Effect size (Cohen’s d) = 1.25.
familiar sequences such as your phone number or identity number. Remember to make it as random as possible.” To avoid any effect because of speed difference, number generation was self-paced and no pacemaker (e.g., metronome) was used (Thomas, 1962; Rosenberg, et al., 1990; Azouvi, Jokic, Van Der Linden, Marlier, & Bussel, 1996; Persaud, 2005). However, participants were asked to proceed at a regular pace.

Indices of Randomness

Five measures to indicate randomness of generated numerical series were used: (1) Redundancy score (Towse & Neil, 1998); (2) Random Number Generation Index (RNG Index; Evans, 1978); (3) Guttman’s Null Score Quotient (NSQ; Guttmann, 1967, cited in Brugger, Monsch, & Johnson, 1996); (4) Counting Bias score (Brugger, 1997); and (5) Repetition Bias score (Brugger, et al., 1996). In brief, the Redundancy score addressed the bias for selection of specific digits by calculating the relative frequency with which individual numbers were used. The more unbalanced the frequencies for individual digits, the more redundant was the sequence. A Redundancy score of 0% indicated perfect equality of response alternative frequencies, whereas a Redundancy score of 100% indicated a single response choice was used throughout the task. Based on digit pairs, the RNG Index and the NSQ were used as sequential randomness measures. The RNG Index reflected the disproportion of a number following another number; it ranged from 0 (i.e., ideal randomness in the case of an infinite series) to 1 (i.e., perfect predictability). Structurally related to the RNG Index, the NSQ represents the total percentage of consecutive-digit pairs never named by the participant; it ranged from 0 to 100%. The first-order difference between a random number and the immediately preceding response was calculated for each number in the generated series, and the respective frequencies of interdigit intervals 0 and +1 were obtained as the Repetition Bias score and the Counting Bias score. The respective theoretically expected frequencies of the interdigit interval 0 (immediate repetitions; e.g., 1, 1 or 4, 4) and +1 (forward counting steps; e.g., 1, 2, 4, 5, or 8, 9) were 10 and 9% (Brugger, Milicevic, Regard, & Cook, 1993; Brugger, Monsch, Salmon, & Butters, 1996).

Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, Windows Version 16.0). The two participant groups were compared concerning demographic variables by using independent samples t test and the Pearson’s chi square, as appropriate. Group differences in indices of randomness, with \( p < .05 \), were tested in one-way analyses of covariance (ANCOVAs), with the demographic variable(s) differing between the two participant groups as the covariate(s). One-sample t tests were used to test whether the Repetition Bias score and the Counting Bias score
differed from their respective theoretically expected frequencies. Pearson correlations were used to analyze relationships of demographic variables to random generation performance of participants.

**Results**

**Participants**

The patient sample consisted of 44 participants (22 men, 22 women) with a mean age of 26.9 yr. (SD = 9.4). All but one of these patients were medicated at the time of assessment; 26 were taking atypical antipsychotics (i.e., amisulpride, clozapine, olanzapine, risperidone, and quetiapine) and 17 were taking conventional antipsychotics (i.e., haloperidol, sulpiride, stelazine, fluanxol, and chlorpromazine). The nonmedicated patient had been medicated in the past and was not antipsychotic-naïve. The healthy control group consisted of 48 participants (19 men, 29 women) with a mean age of 23.7 yr. (SD = 8.6). The characteristics of the two participant groups are shown in Table 1. The two groups were matched for age and sex but not years of education: the schizophrenic group had significantly fewer years of education (p < .001).

**Written Random Number Generation Measures**

Indices of random number generation performance in the schizophrenic and control groups are presented in Table 2. In general, the departure from randomness was greater for the schizophrenic group than for the control group. The random number generation performance of the schizophrenic group was significantly worse than that of the control group as measured by the Repetition Bias score, the RNG Index, and the NSQ. The Repetition Bias score of the control group was statistically smaller than the theoretically expected value (p < .001). On the other hand, the Counting Bias scores of both groups were statistically smaller than the theoretically expected value (p < .001).

<table>
<thead>
<tr>
<th>Random Number Generation Measures</th>
<th>Schizophrenic Group (n = 44)</th>
<th>Control Group (n = 48)</th>
<th>ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>1. Redundancy score, %</td>
<td>2.65</td>
<td>4.99</td>
<td>2.51</td>
</tr>
<tr>
<td>2. Repetition Bias score, %</td>
<td>9.46</td>
<td>7.96</td>
<td>5.79</td>
</tr>
<tr>
<td>3. Counting Bias score, %</td>
<td>3.83</td>
<td>2.17</td>
<td>3.27</td>
</tr>
<tr>
<td>4. RNG Index</td>
<td>0.52</td>
<td>0.07</td>
<td>0.49</td>
</tr>
<tr>
<td>5. NSQ, %</td>
<td>12.74</td>
<td>13.80</td>
<td>7.74</td>
</tr>
</tbody>
</table>

*Note.—All random number generation measures were controlled for years of education. RNG = Random Number Generation; NSQ = Guttman’s Null Score Quotient. *p < .05.
Table 3 shows the intercorrelations between random number generation measures for each group. In the schizophrenic group, the Redundancy score showed a positive correlation with the Repetition Bias score \((p = .038)\), the RNG Index \((p = .002)\), and the NSQ \((p < .001)\). The Counting Bias score correlated with the RNG Index \((p < .001)\) and the NSQ \((p = .024)\). There was a positive correlation between the RNG Index and the NSQ \((p < .001)\). Similar to the schizophrenic group, positive interrelations of the Redundancy score with the Counting Bias score \((p < .001)\), the RNG Index \((p < .001)\), and the NSQ \((p < .001)\) were found in the control group. Significant positive correlations of the Counting Bias score with the RNG Index \((p < .001)\) and the NSQ \((p < .001)\) were also observed among controls. Besides, the RNG Index showed a positive correlation with the NSQ \((p < .001)\).

Age (absolute \(r\) ranged from .05 to .09), duration of illness (absolute \(r\) ranged from .02 to .09), medication dose (absolute \(r\) ranged from .01 to .08), years of education (absolute \(r\) ranged from .02 to .07), and PANSS scores (absolute \(r\) ranged from .08 to .31) showed no significant correlation \((p > .05)\) with any of the randomness measures in the present study.

**TABLE 3**

**Pearson Correlations For Random Number Generation Measures**

<table>
<thead>
<tr>
<th>Random Number Generation Measures</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Redundancy score</td>
<td></td>
<td>.31*</td>
<td></td>
<td>.46†</td>
<td>.67†</td>
</tr>
<tr>
<td>2. Repetition Bias score</td>
<td>.02</td>
<td></td>
<td>.02</td>
<td></td>
<td>.18</td>
</tr>
<tr>
<td>3. Counting Bias score</td>
<td>.77†</td>
<td>.11</td>
<td></td>
<td>.64†</td>
<td>.34*</td>
</tr>
<tr>
<td>4. RNG Index</td>
<td>.70†</td>
<td>-.04</td>
<td>.77†</td>
<td></td>
<td>.91†</td>
</tr>
<tr>
<td>5. NSQ</td>
<td>.56†</td>
<td>-.12</td>
<td>.59†</td>
<td></td>
<td>.91†</td>
</tr>
</tbody>
</table>

*Note.*—Schizophrenic group \((n = 44)\) above diagonal; Control group \((n = 48)\) below diagonal. RNG = Random Number Generation Index; NSQ = Guttman’s Null Score Quotient. *\(p < .05\). †\(p < .01\).
The present study appears to be the first to provide data about random number generation performance in early schizophrenia. Results indicate a performance deficit in a written random number generation task in a group of patients with early schizophrenia. The absence of group difference in the Redundancy score, a zero-order measure, suggests that selection of digits was not biased in the patients. The present findings can be explained by the schizophrenic patient group identifying randomness with even-handed selection of digits, and being able to monitor the frequency of occurrence of single digits. In contrast, significantly elevated first-order redundancy scores (namely, RNG Index and NSQ) in the patient group suggest a higher tendency to generate stereotyped response sequences which contain fewer different permutations, likely due to reduced ability to shift from one response schema to another and limited availability of production strategies in patients with schizophrenia (Spatt & Goldenberg, 1993).

With regard to the Counting Bias scores, no group difference was found, suggesting preserved ability in the schizophrenic group to suppress the overlearned sequential arrangement of digits. This is contrary to previous studies (Horne, et al., 1982; Shallice, 1982; Rosenberg, et al., 1990) showing pronounced excessive ordinal sequencing in schizophrenic patients. When contrasting observed and expected frequencies of the inter-digit interval +1, both participant groups had significantly more forward counting steps than theoretically expected, suggesting that both patients and controls overlearn some groupings of digits but inhibit interference from such highly automatized production schema to a similar extent.

As to the Repetition Bias scores, it is interesting to note a difference between groups, despite the score of the schizophrenic group being statistically equivalent to the theoretically expected value (Brugger, et al., 1993; Brugger, et al., 1996). Thus, the control group’s results seem not to reflect a genuine bias but instead are likely guided by a wrong concept of randomness. This is in agreement with previous studies (e.g., Wagenaar, 1970; Lopes, 1982; Neuringer, 1986; Lopes & Oden, 1987; Treisman & Faulkner, 1987; Kareev, 1992; Rapoport & Budescu, 1992) which suggest that human random number generation behavior deviates from randomness in a number of aspects. For instance, subjective random number sequences generated by humans show a marked avoidance of immediate repetitions of the same number (Spatt & Goldenberg, 1993).

The current findings are consistent with previous cognitive research in schizophrenia, showing executive impairments of cognitive flexibility as important target markers for schizophrenia (Johnson-Selfridge & Zalewski, 2001; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2004; Bur-
gess & Simons, 2005; Chan, Chen, Cheung, Chen, & Cheung, 2006; Chan, Chen, & Law, 2006). Particularly, the current evidence showing a deficiency in inhibiting the tendency to produce stereotyped sequences in schizophrenia is in line with the cognitive psychological approach to schizophrenic symptoms as deficient formation of adaptive behavioral patterns resulting from inappropriate selecting, ordering, and sequencing behavioral elements (Paulus, Geyer, & Braff, 1996). Future research is warranted to elucidate the relationship between the deficits in random number generation and psychotic symptoms such as loose associations, scrambled language, and disordered thinking (Goldman-Rakic & Selemon, 1997; Artiges, et al., 2000).

Several limitations should be addressed. First, the schizophrenic group had significantly fewer years of education than the control group. However, while this education difference potentially confounds the results, the schizophrenic group showed a compromised random number generation performance even after controlling for years of education, suggesting that education did not fully account for the group differences. Second, the present study focused on one specific psychological measurement only. Thus results can only be applicable to the specific components of executive functions measured by a written random number generation task, and generalization of the present findings remains to be explored. It would be helpful to include other neuropsychological tests in future studies of random number generation. Third, most patients included in this study were medicated at the time of assessment, so that medication effects cannot be excluded. However, since the duration of illness and medication dose at the time of assessment showed no correlation with any of the indices in the present study, and previous studies have shown that there are no significant main effects of either medication dose or group on executive function (Heinrichs & Zakzanis, 1998; Aleman, Hijman, De Haan, & Kahn, 1999) and random number generation (Shinba, et al., 2000) in schizophrenic patients, the findings are unlikely to be explained by medication.

Conclusion

The findings support deficits in random number generation in early schizophrenia and specifically link these deficits to exhibition of more stereotyped response sequences and impairments in shifting from one response schema to another and maintaining several production strategies. Following Shinba, et al. (2000), who reported that chronic schizophrenic patients demonstrated impairments of interference inhibition from highly overlearned and automatized production schema during random number generation, the current findings suggest that some of these deficits are present even during early psychotic episodes. Yet, prior to any authorita-
tive conclusions, the study must be replicated with first-episode medica-
tion-naïve patients with schizophrenia.

Studies to date have adopted a cross-sectional design to investigate
random number generation performance in patients with schizophrenia. There have been no longitudinal studies of random number generation. In view of this deficiency, future prospective longitudinal studies tracking patients with schizophrenia from euthymia through symptomatic periods and charting longitudinally the clinical course (including random num-
ber generation and neurocognitive performance, symptoms, and treat-
ment responsiveness) on a case-by-case basis are needed to acquire inform-
ation regarding the rate of progression and selectivity in the range of
deficits. The key questions include: what subdomains of random number
generation are predominantly involved, whether it is a static or a progres-
sive process, whether deficits fluctuate in relation to psychotic episodes,
whether there are identifiable patterns of evolution, whether there is dif-
ferential progression in different subdomains, and to what extent the sub-
domains are influenced by medication.

REFERENCES


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