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Declarative memory and WCST-64 performance in subjects with schizophrenia and healthy controls

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ABSTRACT

The Wisconsin Card Sorting Test (WCST) is a set-switching task used extensively to study impaired executive functioning in schizophrenia. Declarative memory deficits have also been associated with schizophrenia and may affect WCST performance because continued correct responding depends on remembering the outcome of previous responses. This study examined whether performance in visual and verbal declarative memory tasks were associated with WCST performance. Subjects comprised 30 patients with schizophrenia or schizoaffective disorder (SCZ) and 30 demographically matched healthy controls (CON) who were tested on the WCST, the Benton Visual Retention Test (BVRT), the California Verbal Learning Test (CVLT), and the Continuous Performance Test (CPT). SCZ subjects showed significant correlations between visual and verbal declarative memory and performance on the WCST-64 that were in the hypothesized direction such that worse memory performance was associated with worse performance on the WCST. CON subjects did not show a significant relationship between visual or verbal memory and WCST-64 performance. Fisher's r to z transformations indicated that the associations between declarative memory and WCST-64 performance in the SCZ subjects differed significantly from those of CON subjects. The findings suggest that interpretations of WCST-64 scores for subjects with schizophrenia should be considered in light of their declarative memory functioning.

1. Introduction

1.1. The WCST/WCST-64 in the study of schizophrenia

Impaired cognitive function in schizophrenia is receiving increasing attention as the link with impaired functional outcomes has come to light (Green, 1996; Green et al., 2000). Cognitive deficits in areas such as attention, memory, visual-motor speed, and executive functioning are frequently reported (Braff et al., 1991; Reichenberg and Harvey, 2007) and are thought to represent a core feature of the illness (Green et al., 2004). Two of the most popular tests of executive function, the 128-item Wisconsin Card Sorting Test (WCST) and its 64-item version (WCST-64) have been used in well over 250 studies of schizophrenia. The WCST was developed in 1948 as a measure of abstract reasoning and the ability to shift cognitive sets (Kongs et al., 2000). The WCST-64, an abbreviated version of the WCST, is highly correlated with the longer original version (Spearman's correlations of 0.90 for raw scores, 0.80 for T-scores, Kongs et al., 2000). Most studies have demonstrated impaired WCST performance in subjects with schizophrenia compared to healthy controls (Reed et al., 2002; Goldberg and Green, 2002; Prentice et al., 2008).

The WCST-64 manual indicates that the WCST is a measure of executive function because it requires the ability to use an appropriate problem-solving strategy across changing stimulus conditions to obtain a goal (Kongs et al., 2000). Research suggests that WCST performance reflects a function of the dorsolateral prefrontal cortex (Ritter et al., 2004). In a study comparing the WCST performance of patients with schizophrenia with patients with brain tumors, only patients with right frontal lobe tumors showed deficits similar to that of patients with schizophrenia, namely, significantly more perseverations, longer strings of perseverations, and poorer conceptual level response scores (Haut et al., 1996). In examinations of the factor structure of WCST deficits in schizophrenia, perseveration (which is the behavioral result of a lack of appropriate set switching) has been found to be the most diagnostically useful and characteristic WCST feature distinguishing schizophrenia subjects from controls (Koren e al., 1998). However, a number of studies

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have not found that subjects with schizophrenia make significantly more perseverative errors on the WCST than do healthy controls (Braff et al., 1991; Mattes et al., 1991; Saykin et al., 1994; McGrath et al., 1997; Stratta et al., 1997).

1.2. Declarative memory and schizophrenia

Declarative memory (the retrieval of factual information) is one of the most consistent and severe cognitive deficits in schizophrenia (Cirillo and Seidman, 2003; Reichenberg and Harvey, 2007). Deficits in declarative memory in schizophrenia subjects have been found in both verbal and visual tasks (Tracy et al., 2001).

Despite the prominence of declarative memory deficits in schizophrenia, the relationship of declarative memory to WCST performance has received little attention. Stimuli from the WCST were used to create a declarative memory task (the Paired Associate Recognition Test, PART) using WCST stimuli (Ragland et al., 1995). In a study of 30 subjects with schizophrenia and 30 healthy matched controls, Ragland et al. (1996), found that the schizophrenia group was equally impaired in the PART and the WCST. The CATIE study examined 1263 subjects with schizophrenia in multiple sites across the United States and found a significant correlation ($r = 0.27$, $P<0.0001$) between the Hopkins Verbal Learning Test (HVLT) (Brandt, 1991) and the WCST-64 scores in subjects with schizophrenia (Keefe et al., 2006).

1.3. Cognition and fronto-temporal dysfunction in schizophrenia

Recent functional imaging studies implicate neurocircuitry dysfunction in schizophrenia that is consistent with a potential relationship between executive function and declarative memory. Executive function performance as measured by the WCST depends heavily on the frontal cortex (Milner, 1963; Berman et al., 1988), although not exclusively (Nyhus and Barcelo, 2009), whereas declarative memory is a function most dependent on the temporal lobe (Squire et al., 2004). In a twin study, it was shown that the hippocampal volume of the twins with schizophrenia was strongly related to prefrontal activation during the WCST (Weinberger et al., 1992). Replacing earlier ideas of an isolated frontal lobe or temporal lobe dysfunction in schizophrenia, current models of cognition in schizophrenia have proposed dysfunction of distributed fronto-temporal networks that link frontal and temporal lobes (Friston et al., 1992; Friston and Frith, 1995; Ragland et al., 2007).

1.4. Goal of the present study

The hypotheses underlying this article stemmed from clinical observations that schizophrenia patients with deficits in the WCST also tended to show memory deficits, as well as from the development of the fronto-temporal network dysfunction model of schizophrenia as described earlier. Since the WCST/WCST-64 requires subjects to recall previous trial results in order to perform subsequent trials correctly, it would seem reasonable that declarative memory ability as well as executive function skills could affect the test results. Although the WCST is mainly a visual test, instructions and feedback are presented aurally, which suggests that verbal as well as visual declarative memory could affect test performance. The goal of this study was therefore to examine the impact of verbal and visual declarative memory on WCST-64 performance. Specifically, we hypothesized that better memory performance would be positively correlated with better WCST-64 scores, and that this relationship would be more robust in subjects with schizophrenia than in healthy controls. The Perseverative Errors and the Categories Completed scores were the targets of this study because these scores are the scores most frequently analyzed in studies of schizophrenia (Reichenberg and Harvey, 2007). However, other scores from the WCST-64 were also analyzed for comparison. In addition, because attentional deficits are frequently seen in schizophrenia and can also affect cognitive performance across a variety of domains, the relationship of a test of attention to the WCST-64 was also examined.

2. Methods

2.1. Subjects

Subjects comprised 30 subjects with schizophrenia or schizoaffective disorder (SCZ) and 30 healthy control subjects (CON) matched to the SCZ group in age, sex, and race. These subjects were part of a larger study on heritability of sensorimotor gating in schizophrenia (Hasenkamp et al., 2010). All subjects indicated their informed consent for their participation by signing a consent form approved by the Emory University Institutional Review Board and the Atlanta Veterans Administration Research and Development Committee. A screening interview was conducted on all participants to obtain demographic data and determine eligibility for the study. A urine drug screen was performed to rule out recent substance use that might affect test performance.

The patient edition of the Structured Clinical Interview for DSM-IV (SCID-P) was used to confirm a diagnosis of schizophrenia or schizoaffective disorder in the patient group (First et al., 1998). In the SCZ group, current symptoms were evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall and Donald, 1962) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988). Although the PANSS incorporates the BPRS items, the subscales and summary scales of the two scales are based on somewhat different items. Results of both scales are provided for the convenience of readers who are more familiar with one scale than the other. Potential CON subjects were excluded for current or past diagnosis of any Axis I disorder as confirmed by the non-patient edition of the SCID (SCID-I/NP) (First et al., 2007). Subjects were also excluded from the CON group if any of their first-degree relatives had been diagnosed with a psychiatric disorder.

Potential subjects in both groups were excluded if they met any of the following criteria: history of mental retardation, a head trauma with loss of consciousness for greater than 5 min, current unstable clinically significant medical problems, substance dependence (except for tobacco) during the prior 3 months, significant hearing or visual problems, or colorblindness.

The Mini-Mental Status Exam (Folstein et al., 1975) was used as a screener to examine both groups for the possibility of mental retardation. In addition, the two subtest form of the Wechsler Abbreviated Scales of Intelligence (WASI) (Psychological Corporation, 1999) was also administered to the SCZ group to verify that none of these subjects had a general intellectual deficit. The two-subtest form of the WASI consists of the Vocabulary and the Matrix Reasoning subtests and provides a Full Scale IQ estimate.

2.2. Cognitive measures

The hypotheses of this study were examined using the following tests of cognitive function:

1) The Benton Visual Retention Test—Fifth Edition (BVRT), Administration A (10 sec exposure) (Sivan, 1991). The BVRT is a test of visual memory in which subjects are shown a geometrical figure for 10 sec and are then asked to draw the figure immediately after the presentation. A total of 10 figures are shown. The total number correct (BVRTNumCorr) and the total number of errors (BVRTNumErr) are used as measures of visual declarative memory performance. A larger number on BVRTNumCorr signifies better performance; a larger number on BVRTNumErr signifies worse performance. The BVRT takes about 15–20 min to administer.
2) The California Verbal Learning Test—Second Edition, Short Form (CVLT-II SF), (Delis et al., 2000). The CVLT-II is a test of verbal memory in which subjects are read nine words and are then asked to recall the words in any order. This immediate recall procedure is repeated four times and results in a composite score. This composite score for the four trials (CVLT4Trials) was used as a measure of verbal declarative memory performance and was chosen because it resembles the short term recall involved in going from trial to trial during performance of the WCST-64. A larger number on this variable signifies better performance. The CVLT-II SF takes about 15 min to administer.
3) Conner's Continuous Performance Test (CPT), computerized AX version. The CPT AX is a visual test of attention in which subjects are asked to press a key when they see the letter "X" preceded by the letter "A" (Conners and Staff, 2000). The d′ (Attentiveness) score, CPTd, was used as the target variable and measures how well subjects discriminate between the target and non-target letters and takes into account both commission and omission errors. A larger number on this variable signifies better performance. This test takes about 14 min to administer.
4) The WCST-64 card version (Kongs et al., 2000). This version typically takes about 10–15 min to administer. The variables used to assess performance on the WCST-64 in this study are:

a) The number of categories completed (WCSTCat), the number of blocks of 10 consecutive correct matches. A larger number on this variable signifies better performance.
b) Nonperseverative Error Score (WCSTNPErr), the number of incorrect responses that do not match the perseverated-to principle. A larger number on this variable signifies worse performance.