

Wisconsin Card Sorting Deficits and Diminished Sensorimotor Gating in a Discrete Subgroup of Schizophrenic Patients

Robert W. Butler, Melissa A. Jenkins, Mark A. Geyer, and David L. Braff¹*

It has long been suspected that frontal-lobe dysfunction may play a role in schizophrenia (1,2). Most recently, Weinberger (3) has presented a neurodevelopmental model of schizophrenia that predicts dorsolateral prefrontal dysfunction in schizophrenia through complex feedback mechanisms and interactions between the mesolimbic and mesocortical dopamine systems. The theory suggests that many of the "negative" symptoms of schizophrenia, such as inertia, would be a function of frontal-lobe-mediated deficits while "positive" symptoms, such as hallucinations, are more subcortically mediated. Central to Weinberger's theory is the need for empirical evidence of frontal-lobe deficits in schizophrenia.

A number of studies have documented abnormal frontal-lobe activity in chronic schizophrenia. It has been observed that frontal-lobe metabolism is less active in chronic schizophrenic patients during cognitive tasks when compared with normal subjects using both positron emission tomography (PET) and regional cerebral blood flow (CBF) methodologies (4,5). In addition to metabolic studies of brain function, researchers have investigated the neu-

ropsychology of frontal-lobe function in schizophrenia.

Neuropsychological tests measure cognitive abilities that have been empirically associated with cortical brain functioning. One of the more widely used neuropsychological measures of frontal-brain integrity is the Wisconsin Card Sorting Test (WCST; refs 6,7). The standard WCST consists of 128 cards, each of which contains geometric figures that may vary along several dimensions (eg, color, form, number; see "Methods" below). Patients are instructed to place each card below one of four target or key cards using some principle to guide them. They are not informed of the correct principle but are told whether they are correct or incorrect after their placement of each card. The initial sorting principle is to match according to color. Once a criterion of ten correctly sorted cards is attained, the principle is changed, although the patient is not informed of this change. The test proceeds until the patient has completed six sorting categories of ten cards each or has sorted all 128 cards, whichever occurs first. The type of errors that are elicited may vary, although the most sensitive error type with respect to frontal-lobe dysfunction is the perseverative response, reflecting subjects' difficulty in shifting their strategies or cognitive sets. Although the WCST persever-

¹Department of Psychiatry, University of California at San Diego, La Jolla, CA 92093.

erative response score is often impaired in brain-damaged patients with varying pathology, it has been shown to be particularly sensitive to frontal-lobe dysfunction (8,9).

A relatively large number of studies have reported that patients with schizophrenia perform in an impaired range on the WCST (10-13). None of these studies, however, definitively addressed the possibility that poor WCST performance might be a function of generalized performance deficits in schizophrenia as opposed to relatively discrete frontal-lobe impairment. Directly investigating this possibility, Goldberg and associates (14) attempted to teach chronic schizophrenic patients how to successfully complete the WCST. They found that considerable instruction did not result in improved WCST performance even though the patients were able to improve their performance on a control task of verbal learning. It should be noted that apparently not all of the subjects completed the Mini-Mental State Examination (MMSE), and the reported group means reflect at least mild to moderate deficits on this test. Also supportive of specific frontal-lobe involvement in schizophrenia are two studies that documented frontal cerebral blood flow (CBF) abnormalities during performance on a modified WCST task (15,16). These studies compared medication-free chronic schizophrenic patients to normal controls and, while failing to demonstrate increased frontal metabolic activity during WCST administration in schizophrenia, reported that posterior resting CBF (rCBF) activity increased in an expected direction during a control task. Nonschizophrenic psychiatric control patients were not tested.

Considerable evidence has been amassed to implicate frontal lobe impairment in schizophrenia, chronic schizophrenia in particular. Much of this evidence, however, has been collected on hospitalized patients who were moderately to severely ill, and in some cases WCST administration methods were modified and altered. Braff and co-

workers (17) collected extensive neuropsychological data, including WCST scores, on a group of mild to moderately ill chronic schizophrenic patients who were not hospitalized. Of the 40 schizophrenic patients tested, only five showed significant impairment on the WCST. These authors concluded that, while the specificity of their results remains unclear given that psychiatric controls were not tested and patients were receiving neuroleptic medication, nevertheless, the chronic schizophrenic patients in their study exhibited low-normal performance in conjunction with relatively poorer performance on a variety of other neuropsychological tasks. This pattern of results, when coupled with previously cited studies, supports the possibility that, while deteriorated "Kraepelinian" chronic schizophrenic patients may have frontal-lobe impairment, this may not be true of *all* chronic schizophrenic patients. These conclusions led us to suspect that impaired WCST performance in chronic schizophrenia may be a marker for a relatively discrete subgroup. If so, we would expect this subgroup to show greater evidence of global cognitive dysfunction, a more deteriorated course of illness, and perhaps increased abnormalities on measures of information processing.

Information processing refers to the process by which sensory stimuli are acted on by the central nervous system (CNS) and encoded in ways that are meaningful to humans (18). Abnormalities on information-processing paradigms have been a fairly consistent characteristic of at least some schizophrenic patients (see ref 18). One particularly attractive method of assessing the individual's ability to successfully gate sensory information is the degree of prepulse inhibition of the startle reflex. Weak prestimuli induce a centrally mediated prepulse inhibition of the startle reflex, which is thought to be an important index of central inhibitory processes and effective sensorimotor gating. This paradigm has a number of theoretical and methodological

strengths, including relative independence of attentional shifts, automated measurement, and well-known monoaminergic modulation (19). Although impaired prepulse inhibition (PPI) is present in some chronic schizophrenic patients, it is not a ubiquitous phenomenon. The clinical significance of impaired PPI is that it reflects a failure of sensorimotor gating, a process that normally insulates individuals from being overwhelmed by sensory stimuli (18). The possibility that it may be a correlate of poor performance on the WCST has some theoretical support from research that implicates frontal-lobe involvement in perceptual organization (20,21).

We have collected data to investigate the possibility that WCST impairment is present in some but not all chronic schizophrenic patients. Additionally, we have hypothesized that patients who perform in an impaired range on the WCST will also exhibit increased sensorimotor gating abnormalities and a more deteriorated course of symptomatology.

METHODS

Subjects included three groups consisting of 21 RDC-defined chronic and subchronic paranoid schizophrenic patients, 15 psychiatric control patients, and 20 normal control subjects. All psychiatric subjects were inpatients at the time of testing. A number of the psychiatric subjects had histories of substance abuse, but none met criteria for active alcohol dependence at the time of testing. Eleven of the schizophrenic patients were drug-free for at least 3 months prior to testing, and all psychiatric subjects were drug-free for at least 2 weeks. The schizophrenic patient and psychiatric control groups were not significantly different on the MacAndrews Alcoholism Scale. All of the schizophrenic subjects were receiving neuroleptic medication and were in a state of relative clinical stability at the time of testing. The psychiatric control group

consisted of six patients with unipolar depression, six patients with bipolar disorder, one patient with borderline personality disorder, and two patients with posttraumatic stress disorder. All subjects reported a negative history for head trauma or other significant neurological involvement.

The three groups were not significantly different in age. The normal control subjects had significantly more years of education (mean = 15.0, SD = 2.1), greater Digit Span Scores for the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (mean = 14.8, SD = 2.2) and WAIS-R Vocabulary Scores (mean = 11.5, SD = 2.1) than the two patient groups. The schizophrenic group was not significantly different from the psychiatric control group in education or the WAIS-R variables. The schizophrenic group had a significantly higher Brief Psychiatric Rating Scale (BPRS) score (mean = 33.6, SD = 9.4) than the psychiatric controls (mean = 20.2, SD = 8.6).

All subjects were administered the WCST in the standard manner (7). On the same day, subjects were tested for PPI of the startle reflex according to our current methods (22). As part of this paradigm, a series of 31 40-msec, 30-psi tactile stimuli (air puffs) were presented at random intervals, with the average interstimulus interval of 15 msec (9 to 23-msec range) through a tube at the subject's neck. Eyeblink startle was measured by electromyogram (EMG) of facial muscles. Half of these stimuli were preceded 120 msec by an 85 dB, 20-msec acoustic prepulse stimulus.

RESULTS

An ANOVA with post hoc testing indicated that the normal control group had significantly fewer perseverative responses on the WCST (mean = 2.8, SD = 6.4) than the two patient groups. The schizophrenic group (mean = 25.0, SD = 15.8), however, was not significantly different from the psy-

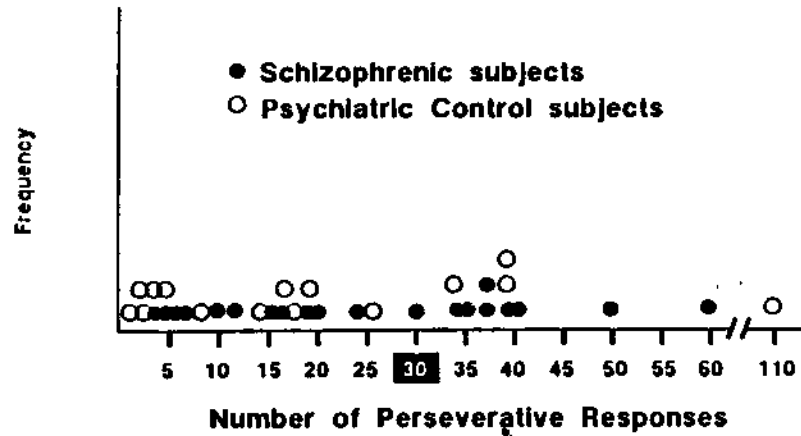


FIG. 1. Frequency distribution of WCST scores Mann-Whitney U-Test ($U' = 22, p < .001$).

chiatric control group (mean = 22.6, SD = 27.7) in perseverative responding on the WCST. On closer inspection, however, it appeared that the distributions of perseverative responses were significantly different. These distributions are presented in Fig. 1. A test for homogeneity of variance

across these two was significant ($F = 3.06$ (20,14); $p < .05$), confirming the violation of the assumption required for parametric statistical analysis. We then conducted a Mann-Whitney U-Test (see Fig 1) that was highly significant, indicating that the frequency of individuals obtaining greater

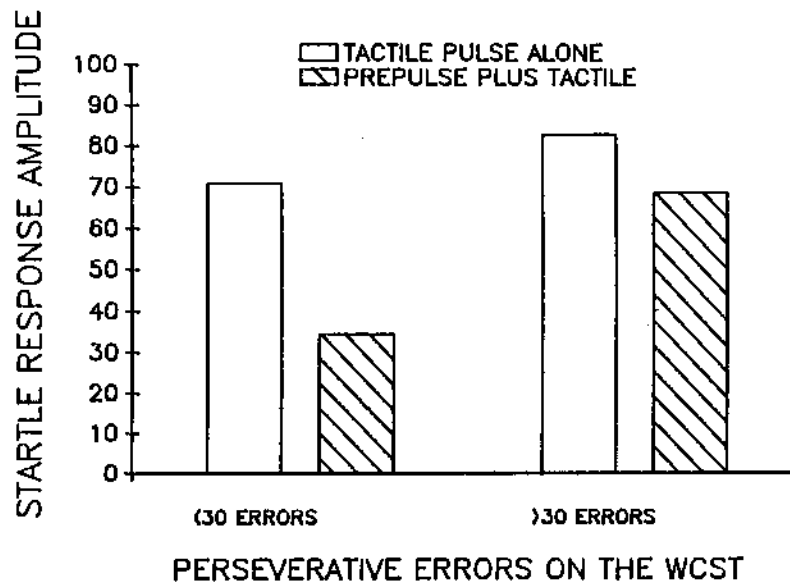


FIG. 2. Tactile prepulse inhibition as a function of perseverative responding on the WCST in schizophrenia. Non-impaired (< 30 errors), $N = 9$; impaired (> 30 errors), $N = 6$.

numbers of perseverative responses on the WCST was higher in the schizophrenic group when compared with the psychiatric control group.

Given that the schizophrenic group appeared to be approximating a bimodal distribution, we then separated this group into two subgroups, impaired ($N = 8$) and non-impaired ($N = 12$) using 30 perseverative responses on the WCST as the criterion cutoff for impairment (7) and the observation that none of our normal control subjects had obtained a score of greater than 29 perseverative responses. One schizophrenic patient was excluded because of inability to complete the WCST. The two groups were not significantly different in duration of illness, number of previous hospitalizations, age, education, alcohol consumption or on the Scale for the Assessment of Positive Symptoms (SAPS). With regard to PPI of the tactile- (but not auditory) startle reflex, however, the WCST impaired group consistently exhibited less PPI than the nonimpaired group. These data are presented in Fig 2. Statistical analysis was deferred on these measures since individuals who did not exhibit responsivity to the paradigm were removed, which left the sample sizes quite small (WCST impaired, $N = 6$; WCST nonimpaired, $N = 9$).

DISCUSSION

Data are supportive of possible increased sensorimotor gating abnormalities within the subgroup of paranoid schizophrenic patients who demonstrate greater perseverative responding on the WCST. This may reflect a central role of frontal brain dysfunction in some schizophrenic patients that mediates both impaired mental flexibility (eg, WCST) and perceptual disorganization (e.g., decreased sensorimotor gating).

These data are rather intriguing for sev-

eral reasons. First, researchers have tended to ask whether "schizophrenic patients" show hypofrontality on the WCST or PET. It is more appropriate to ask, which subgroup of schizophrenic patients shows these deficits, and are there markers of this impaired subgroup that can be reliably identified? It is likely that multiple converging methods will give us a fuller picture of these schizophrenia-linked deficits in a subgroup of schizophrenic patients. Certainly, the identification of a schizophrenic subgroup with correlated deficits on the WCST, sensorimotor gating, and PET would be very useful. Would such patients have excess negative symptoms and a Kraepelinian picture? Only future research will answer this question. We will also need to examine the relationship of correlated deficits (of, for example, the WCST and gating) and the issue of possible common underlying mechanisms. Might defective sensorimotor gating in schizophrenic patients result from impaired frontal-lobe inhibitory function, as is hypothesized for perseverative errors on the WCST? This is certainly a possibility and one that will need empirical verification. Future research needs to utilize converging methods regarding this potentially distinct subgroup of schizophrenic patients. Specifically, we will need to administer additional tests of frontal-brain functioning to patients in order to determine the degree of concordance that these independent variables hold. We hypothesize that our WCST and gating-impaired subjects will show frontal brain abnormalities on metabolic measures such as PET, rCBF, and poor performance on other neuropsychological tests sensitive to frontal-lobe integrity (e.g., Auditory Consonant Trigrams, Fluency Measures).

Second, the WCST data are of intrinsic interest. In the current study, nonparametric methods were used due to the violation of parametric assumptions and the small sample sizes. Beyond these issues, on a conceptual basis, nonparametric analyses

may be more generally appropriate for these sorts of data. Our study suggests that a central question involves the percentage of schizophrenic patients that perform in an impaired range on the WCST. If schizophrenic patients are indeed characterized by a bimodal-like distribution of WCST perseverative responses, then traditional descriptive and parametric statistics may provide misleading pictures, and non-parametric or nonlinear, topographic measures of complexity analysis may prove more useful. These considerations lead us to ask *which specific subgroups* of schizophrenic patients show increased perseverative errors on the WCST. Currently, it seems as if schizophrenic outpatients have relatively normal performance on the WCST (17). Schizophrenic inpatients have more perseverative errors linked to more generalized impairments and also, perhaps, to greater specific frontal-lobe impairment. The next few years should allow researchers to begin providing answers to the question of which schizophrenic patients under which conditions have the greatest impairments on the WCST, gating measures, and other probes of frontal and general brain function.

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